Tuesday June 2

14:00-18:30	**Registration**	
19:30	**Welcome reception**	

Wednesday June 3

08:00-09:00	**Registration**	
09:00-09:15	**Welcome and Introduction**	
09:15-10:45	**Targeting Ebola**	*Chair: Steven Kern*
09:15-09:30	*Steven Kern*	Conducting clinical trials in challenging environments
09:30-09:55	*France Mentré*	Estimating an effective dose for a repurposed drug to treat Ebola: the case of favipiravir
09:55-10:20	*Matthias Machacek*	Estimating an effective dose for a new drug to treat Ebola with incomplete information: the case of Zmapp
10:20-10:45	*Scott Berry*	An Adaptive Platform Trial for Ebola: Application to Future Epidemics
10:45-12:15	**Coffee break, Poster and Software session I**	
	Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter	
12:15-12:55	**Diabetes**	*Chair: IñakiTrocóniz*

12:15-12:35	*Roberto Bizzotto*	A model of glucose clearance to improve the description of glucose homeostasis
12:35-12:55	*Rada Savic*	A longitudinal HbA1c model elucidates genes linked to disease progression on metformin therapy
12:55-14:25	**Lunch**	
14:25-15:15	**On the 20th anniversary of 'Nonlinear models for repeated measurement data'**	*Chair: France Mentré*
14:25-14:50	*David Giltinan*	Why write a book in 1995 on nonlinear mixed effects modeling?
14:50-15:15	*Marie Davidian*	Subsequent developments in nonlinear mixed effects modeling
15:15-16:40	**Tea break, Poster and Software session II**	
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter	
16:40-17:40	**Other diseases**	*Chair: Ana Ruiz*
16:40-17:00	*José David Gómez-Mantilla*	Towards patient stratification and treatment in the autoimmune disease lupus erythematosus using a systems pharmacology approach
17:00-17:20	*Gopichand Gottipati*	Modeling of a composite score in Parkinson's disease using item response theory
17:20-17:40	*Emilie Hénin*	Determination of effective blood concentrations of cyclosporine in pediatric severe aplastic anemia based on a time-to-response model

Thursday June 4

09:00-10:20	**Lewis Sheiner Student Session**		*Chair: Rada Savic, Steven Kern and Michael Looby*
09:00-09:25	*Huixin Yu*	Development of a tumour growth inhibition model to elucidate the effect of ritonavir on intratumoural metabolism and anti-tumour effect of docetaxel in a mouse model for hereditary breast cancer	
09:25-09:50	*Shan Pan*	Automated proper lumping for simplification of systems models	
09:50-10:15	*Adrien Tessier*	Modelling pharmacogenetic data in population studies during drug development	
10.15-10.20	**Presentation of Lewis Sheiner student session awards**		
10:20-11:45	**Coffee break, Poster and Software session III**		
	Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter		
11:45-12:50	**Applied Bayesian Inference for Pharmacometrics**		*Chair: Paolo Magni*
11:45-12:30	*Michael Betancourt and Sebastian Weber*	Building Robust PK/PD Population Models with Bayesian Inference	
12:30-12:50	*Thierry Wendling*	Application of a Bayesian population approach to physiologically-based modelling and simulation of mavoglurant pharmacokinetics	
12:50-14:10	**Lunch**		
14:10-15:10	**PKPD and drug resistance in infectious diseases**		*Chair: Oscar Della Pasqua and Jonathan Mochel*
14:10-	*Rong Deng*	Towards Model-Based Drug Development of	

14:30		New Therapeutics for Hepatitis C Virus	
14:30-14:50	*Joe Standing*	Treating resistant Gram-negatives: bedside to bench and back	
14:50-15:10	*Anders Kristoffersson*	A PKPD model characterizing resistance for predictions of bacterial kill in vivo	
15:10-15:15	**Announcement of WCoP 2016**		*Nick Holford*
15:15-16:30	**Tea break, Poster and Software session IV**		
	Posters in Group IV (with poster numbers starting with IV-) are accompanied by their presenter		
16:30-17:30	**Stuart Beal Methodology Session**		*Chair: Pascal Girard*
16:30-16:50	*Andrew Hooker*	Preconditioning of nonlinear mixed effect models for stabilization of the covariance matrix computation	
16:50-17:10	*Eric Strömberg*	Simulated model based adaptive optimal design of adult to children bridging study using FDA stopping criteria	
17:10-17:30	*Sebastian Ueckert*	Alternative to resampling methods in maximum likelihood estimation for NLMEMs by borrowing from Bayesian methodology	

Friday June 5

09:15-10:15	**Infectious diseases**		*Chair: Marylore Chenel*
09:15-09:35	*Joel Tarning*	Semi-mechanistic time-to-event modelling in malaria	

09:35-09:55	*Natalie Filmann*	Modeling the PK/PD of hepatitis B immunoglobulin after hepatitis B induced liver transplantation by an extended target mediated drug disposition model
09:55-10:15	*Dimitra Bon*	Multiscale modelling for hepatitis C treatment
10.15-10.25	**Preview of PAGE 2016**	
10:25-10:55	**Coffee break and Software session**	
10:55-12:15	**Modelling in oncology**	*Chair: Dinesh De Alwis*
10:55-11:15	*Nadia Terranova*	Analysis of individual target lesions for tumor size models of drug resistance: a new methodology encompassing signal processing and machine learning
11:15-11:35	*Nelleke Snelder*	PKPD modelling of the relationship between testosterone and PSA in patients with prostate cancer during treatment with leuprorelin – What is the optimal testosterone level?
11:35-11:55	*Anna Georgieva Kondic*	Model-based analysis of the relationship between pembrolizumab exposure and efficacy in patients with melanoma and NSCLC: across indication comparison
11:55-12:15	*Pauline Mazzocco*	Modeling the emergence of resistance in low-grade glioma patients treated with temozolomide, and simulations using a stochastic approach
12.15-12.25	**Closing remarks**	
12:25-12:45	**Audience Input for the PAGE 2016 Program**	

Steven Kern Conducting clinical trials in challenging environments

Steven Kern
Gates Foundation

The recent Ebola crisis in West Africa incited an accelerated effort to bring new therapeutics, diagnostics, and vaccines to the region in hopes of mitigating the tremendous lethal impact of the outbreak. For therapeutics, both new entities that had not been tested in humans and drugs that had been used or approved for other indications that showed some experimental impact against Ebola virus, were accelerated forward for clinical trials. A challenge to this process was estimating effective doses to trial in the unfolding epidemic with these agents. For the new agents, evaluations in nonhuman primates provided the best estimate for scaling to effective human doses based on allometric principles. For the agents repurposed from other indications, combining human pharmacokinetic information in other disease populations, with in vitro assay data or in vivo data from experiments in murine models provided the only guidance for dosing. Pulling together the appropriate evidence to justify evaluating a compound in the midst of this crises presented challenges based on the information gaps that existed. Additionally, conducting a clinical evaluation in an environment where physical case report forms and traditional means of gathering supportive data for post trial analysis was non-existent creates an extreme situation where making the best inferences and decisions with limited data must occur. This is an area where pharmacometric analysis can provide structured process

for best estimated effective dose to assess in a trial where likely only one trial attempt at assessment can be made.

France Mentré Estimating an effective dose for a repurposed drug to treat Ebola: the case of favipiravir

France Mentré (1), Anne-Marie Taburet (2), Jeremie Guedj (1), Naïm Bouazza (3), Jean-Marc Treluyer (3,4),Xavier Anglaret (5), Sakoba Keïta (6), Xavier de Lamballerie (7), Pierre Frange (8), Denis Malvy (5)

(1) INSERM, IAME, UMR 1137, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France, (2) Assistance-Publique Hôpitaux de Paris, Hôpital Bicêtre, Univ Paris-Sud; INSERM U1012; DHU Hepatinov, Kremlin Bicêtre, France, (3) Unité de Recherche Clinique, Assistance Publique – Hôpitaux de Paris (AP-HP), Hôpital Tarnier, Paris, France; EA08, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, (4) Service de Pharmacologie clinique, AP-HP, Groupe hospitalier Paris Centre, Hôpital Cochin, Paris, France; CIC-0901 INSERM, Cochin-Necker, Paris, France, (5) UMR 897, INSERM, F-33076 Bordeaux, France, (6) Ministry of Health, Guinea, (7) UMR_D 190, Aix-Marseille Univ, Institut de Recherche pour le Développement, F-13005 Marseille, France, (8) Laboratoire de Microbiologie, AP-HP, Hôpital Necker – Enfants malades, Paris, France; EA 7327, Université Paris Descartes, Sorbonne Paris Cité, Paris, France

Objectives: Although several antivirals demonstrated an effect against Ebola Virus (EBOV) in vitro or in animal models, none of them were evaluated in humans with Ebola Virus Disease (EVD) when the outbreak started. Potential drug candidates included favipiravir [1], a nucleotide analog approved for novel or re-emerging influenza in Japan. Two studies in EBOV infected mice

showed that the initiation of favipiravir within 6 days of infection induced a rapid virus clearance, and led to 100% survival [2,3]. Moreover favipiravir showed a good safety profile in thousands of patients worldwide, was immediately available and can be used orally. The objective of this work was to propose a dosage regimen of favipiravir in adults and in children for the JIKI trial conducted in Guinea.

Methods: Our approach combined data on favipiravir efficacy against EBOV in vitro and in vivo with data provided by the manufacturer on favipiravir pharmacokinetics in uninfected mice and humans. First we used the dosage regimen in successfully treated mice to estimate plasma favipiravir concentrations to be targeted in humans. Second we used the pharmacokinetic model developed by the manufacturer in humans with the parameters values estimated in US healthy volunteers to evaluate dosage regimen that could achieve these targeted concentrations in adults. Simulations were performed with various loading and maintenance doses. For children, there was no clinical experience about favipiravir. Maturation profiles of enzymes (mainly aldehyde oxydase) involved in the metabolic pathway of favipiravir are fully achieved at the age of 12 months [4,5]. Therefore, the same population PK model was used to predict the disposition in pediatric patients, over one year, using weight-based allometric scaling [6].

Results: The proposed regimen of favipiravir in adults was a loading dose of 2400/2400 /1200 mg every eight hours on day 1, and a maintenance dose of 1200 mg bid afterwards [7]. This dosage regimen is 50% greater than the one in the Phase 3 trials of favipiravir for influenza in US. To limit the chance of relapse in EVD, we decided to give the treatment for 10 days, which corresponds to the time needed for an effective antibody response [8]. For children over on year, a weight-band dosing table was defined [9].

Conclusions: Modelling was used to define the first dosage regimen of favipiravir in in adults and children with EVD. Tolerance, virological and pharmacokinetic data are collected in the JIKI trial and their analysis will help refining the dosage regimen.

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Matthias Machacek Estimating an effective dose for a new drug to treat Ebola with incomplete information: the case of Zmapp

Matthias Machacek (1), Larry Zeitlin (2), Steven Kern (3), Peter Lloyd (4)
(1) LYO-X GmbH, (2) Mapp Biopharmaceutical, (3) Bill & Melinda Gates Foundation, (4) KinDyn Consulting

ZMapp is an experimental drug for the treatment of Ebola virus disease (EVD) and is currently being tested in patients in a phase II study. ZMapp is a cocktail of three IgG1 monoclonal antibodies (mAbs) that are specific to different sites of the viral surface glycoprotein (GP). The currently tested clinical dose regimen is 50 mg/kg given three times at an interval of three days. The acute clinical need and the limited stocks of drug material necessitated an effort to better understand the dose response to see if lower doses with an equivalent clinical outcome would be feasible.

The available data were from studies investigating 50 or 25 mg/kg ZMapp in an EVD model in rhesus monkeys (NHP). ZMapp was administered intravenously twice or three times at a three-day interval. There was no clear difference in the survival rate between the 50 or 25 mg/kg dose levels or between the two or three administrations. Thus the data were not sufficient to identify the minimal effective dose.

In the absence of any PD data that could inform the dose selection, PK considerations were used to rationalize a dose selection. From a rat GLP toxicology study in non-infected animals a population PK model was built and scaled to humans using established allometric scaling parameters for mAbs. PK simulations of different scenarios showed that the 3x50 mg/kg dosing led to a consecutive increase in cmax at each of the administration. In a successful therapy the viral load will have an inverse trend with the highest load at the first dose. Thus accumulation of drug would be unnecessary. An alternative dose regimen was proposed with 50 mg/kg at day one and 25 mg/kg at days four and seven. The alternative dose regimen had the advantage of maintaining a comparable exposure over the 14 days period, critical for the survival of the animals, while saving 1/3 of the drug material meaning that 30% more patients could be treated.

The ongoing study in patients with EBV will provide the PK of ZMapp in infected humans validating the scaling and provide the data if ZMapp PK is altered through binding to the virus. In addition, a new NHP study was proposed to investigate doses of 1 or 10 mg/kg given once or thee times at days one or days one, four and seven to identify a minimal effective dosing that can help to support a lowering of the second and third dose in patients from 50 to 25 mg/kg.

Scott Berry An Adaptive Platform Trial for Ebola: Application to Future Epidemics

Scott Berry
Berry Consultants

In this talk I will present an adaptive platform trial design for ebola. The trial design combines together the innovative trial aspects of platform trials (master protocols) and adaptive designs. The design allows multiple agents and their combinations to be studied simultaneously in a single trial. The trial utilizes adaptive randomization to efficiently find the most effective treatments and combinations for treating ebola. The design allows greatly increased ability to find the most effective treatments, while simultaneously treating patients in the trial effectively. The design is prospectively designed to add new/subtract agents and combinations seamless as the science inside and outside the trial evolves.

The trial design can provide a standing framework and trial design for a possible future pandemic – which can speed up the process of having incredibly efficient clinical trials immediately at the ready.

Roberto Bizzotto A model of glucose clearance to improve the description of glucose homeostasis

Roberto Bizzotto (1), Andrea Natali (2), Amalia Gastaldelli (3), Elza Muscelli (2), Attila Brehm (4), Michael Roden (5,6,7), Ele Ferrannini (2), Andrea Mari (1)

(1) Institute of Biomedical Engineering, National Research Council, Padova, Italy; (2) Department of Internal Medicine, University of Pisa School of Medicine, Pisa, Italy; (3) Institute of Clinical Physiology, National Research Council, Pisa, Italy; (4) Medical Department, Hanusch Hospital, Vienna, Austria; (5) Department of Endocrinology and Diabetology, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany; (6) Institute for Clinical Diabetology, German Diabetes Center, Düsseldorf, Germany; (7) German Center of Diabetes Research, Partner Düsseldorf, Germany

Objectives: Glucose homeostasis models have been developed as tools for the clinical development of glucose-lowering drugs [1]. The description of the known dependence of glucose clearance (GCL) on glycaemia [2] was however not included in these models and never quantitatively analysed. This work aims at modelling GCL in a wide range of clinical settings and individual phenotypes.

Methods: Data were obtained from a three-step hyperglycaemic clamp (N=8) [3], a two-step euglycaemic hyperinsulinaemic clamp (N=8) [4], paired oral glucose test (OGTT) and euglycaemic hyperinsulinaemic clamp in the same volunteers (N=8), a mixed-meal test (N=91) [5], and paired mixed-meal test and hyperinsulinaemic hyperglycaemic clamp in the same volunteers

(N=8) [6]. The participants involved in the tests had normal or impaired glucose tolerance or type 2 diabetes. A model (A) was developed based on a circulatory model of glucose kinetics [3] and a model for GCL based on basic notions of glucose transport. Glucose utilization was modelled as a Michaelis-Menten function of glucose concentration with constant K_m and insulin-controlled V_{max}. V_{max} was expressed as a Hill function of insulin at the site of action. Population and individual model parameters were estimated on glucose tracer data with Monolix 4.3.2. A prototypical glucose homeostasis model (B) was then set up by adding a b-cell [7] and an insulin kinetics [8] submodel. Model B was used to simulate an OGTT and a constant insulin infusion (310 pmol min^{-1} m^{-2}), including or excluding the glucose effect on GCL from model A.

Results: Estimation of model A parameters provided a good fit of the data. Individual parameter estimates were similarly distributed in the different tests. GCL suppression with high glycaemia was in qualitative agreement with the literature. In the typical subject, glucose clearance at an insulin concentration of 500 pmol/l was reduced from 227 to 148 ml $min^{-1}m^{-2}$ when glucose was raised from 5 to 10 mmol/l. Including vs. excluding the glucose effect on GCL produced an increase in maximum glucose during OGTT of 0.6 mmol/l and a decrease in steady state glycaemia after insulin infusion of 1.0 mmol/l.

Conclusions: In contrast to classical models that ignore the effects of glucose on GCL, our model reproduces specific and relevant features observed with concomitant hyperinsulinaemia and hyperglycaemia. This model is expected to improve the representation of glucose homeostasis, and to produce more reliable predictions of drug effects.

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Rada Savic A Longitudinal HbA1c Model Elucidates Genes Linked to Disease Progression on Metformin Therapy

Srijib Goswami, Sook Wah Yee, Kathleen M. Giacomini, Radojka M. Savic
University of California, San Francisco

Objectives: Metformin is first-line therapy for Type 2 diabetes, and is one of the most commonly prescribed drugs worldwide [1-3]. Glycosylated hemoglobin (hbA1c) is the primary surrogate biomarker for long-term glycemic control and drug response [4]. There is high variability in both baseline HbA1c and long-term HbA1c dynamics over time [5,6]. Our research aim is to converge multiple genetic methodologies to identify genes linked to the long-term dynamics of metformin response.

Methods: First, we developed a model for disease progression (DP) and metformin response using non-linear mixed-effects modeling. In the second part of the analysis, a genetic model was built using HyperLasso (HL) and model-based methods. A total of 7822 HbA1c measurements from 1056 patients were used to develop the model. Available PK information was taken into consideration in the model structure. Inter-individual variability (IIV) was estimated for baseline HbA1c, the magnitude of metformin's effect, and the DP parameter. Demographic and clinical covariate selection was performed using a stepwise analysis. For the genetic analysis, variants within 50 kilobases of 267 genes selected from literature were investigated. A

penalized regression based approach was used (HL) to select variants statistically associated with individual parameters outputted from the model [7,8]. The top variants from HL were investigated using a model-based approach.

Results: A turnover model with a symptomatic metformin effect on the synthesis rate of HbA1c best characterized the data. In the model structure, K_{IN} increase was influenced by the DP parameter in a nonlinear manner. Metformin surrogate drug exposure (steady-state serum creatinine level) was a significant predictor on the metformin effect parameter. From the HL step, 16 variants were linked to DP, of which 11 were intronic, 1 was missense, and 4 were located within 50 kilobases of the gene. Of the prioritized 16 variants from HL, a model-based approach subsequently selected 9 significant variants within the model structure that had strong effect sizes. The top 9 variants accounted for approximately 1/3 of the entire variability in the DP model parameter. Minor alleles of SNPs in CSMD1 and SLC22A2 were most influential on DP.

Conclusions: Overall, our study has successfully integrated model-based approaches with genetic analyses methods to uncover genes linked to the long-term progression of HbA1c on metformin therapy. Genetic variants in 2 genes: *CSMD1*, and *SLC22A2*, were identified as influencers of DP with a potential for genetic interaction.

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José David Gómez-Mantilla Towards Patient Stratification and Treatment in the Autoimmune Disease Lupus Erythematosus using a Systems Pharmacology approach.

José David Gómez-Mantilla(1), Itziar Irurzun-Arana(1), Leire Ruiz-Cerdá(1), Ignacio González-Garcia(1)(2), Chuanpu Hu(3) , Honghui Zhou(3) , An Vermeulen(4), Iñaki F. Trocóniz(1).
(1) Pharmacometrics & Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona 310890, Spain. (2) Pharmacy and Pharmaceutical Technology Department. University of Valencia. Valencia, Spain. (3) Model Based Drug Development, Janssen Research and Development, LLC, Spring House, PA 19477, USA (4)Janssen Research and Development, a division of Janssen Pharmaceutica NV, Beerse B-2340, Belgium

Objectives: Systemic lupus erythematosus (SLE) exhibits very heterogeneous manifestations among patients [1], consequently, all the patients may not share the same molecular alterations in their immune response. Therefore, specific patient subpopulations may respond differently to the same therapeutic agent. This project aims to: 1) identify plausible altered pathways of the immune response that may explain the different and heterogeneous alterations in SLE patients, 2) classify patients according to their alterations, and 3) identify an optimal therapy for each patient subpopulation.

Methods: Due to the complexity associated with SLE, together with the lack of in vivo quantitative longitudinal data, the described aims were approached through developing a systems pharmacology framework. The immune response after production of autoantigens was modeled by Boolean networks [2,3]. Networks were built based on a rigorous bibliographic review, focused on the components of the immune response that have been reported to be altered in autoimmune diseases patients. Simulations of the immune response were performed perturbing the network by simulated upregulation or downregulation of different nodes in the network in order to identify which ones, if perturbed may trigger alterations similar to those observed in SLE patients. Clustering analysis was performed to group the network nodes according to the alterations these nodes may trigger after being up or downregulated. Network implementation and all simulations and analyses were performed in R.

Results: Different clinical manifestations were linked to different altered pathways of the immune response. Virtual lupus patients were classified into five major categories, according to common manifestations reported in the literature and five group-specific therapies were identified. Manipulation of the PD1-PD1L, CD45, IL23, GMCSF and CD40-CD40L pathways were able to reduce the disease alterations for each patient subpopulation. No single treatment was able to reduce the manifestations in all patient subpopulation, advocating the need of personalized therapies.

Conclusions: Heterogeneity of SLE manifestations can be modeled by different underlying altered pathways of the immune system. Patients can be classified into different categories according to their alterations and optimal treatments can be identified for each patient subpopulation.

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Gopichand Gottipati Modeling of a composite score in Parkinson's Disease using Item Response Theory

Gopichand Gottipati, Mats O. Karlsson, Elodie L. Plan
Dept of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.

Objectives: Traditionally, the disease status in Parkinson's Disease (PD) is quantified using Unified Parkinson's Disease Rating Scale (UPDRS) and more recently, it was revised to Movement Disorder Society (MDS) sponsored – UPDRS [1]. The MDS-UPDRS scale includes a mix of 68 items rating motor or non-motor aspects of experiences of daily living, assessments and complications. The objective of the current analysis was to model MDS–UPDRS through the application of Item Response Theory (IRT) methodology.

Methods: Data used in this work were obtained from the Parkinson's Progression Markers Initiative (PPMI) database [2]. Longitudinal MDS–UPDRS records were available from (up to) 60-week observational clinical study in 196 healthy controls (HC), 423 (de novo) PD subjects (diagnosed for ≤ 2 years and not taking any PD medication) and 64 SWEDD subjects (consented as PD subjects but not showing evidence of dopaminergic deficit). An IRT model was applied and the reported MDS–UPDRS responses were assumed to be related to an unobservable (latent) disease status variable. Modeling was performed using NONMEM 7.3 and simulation-based diagnostics were conducted using PsN and R.

Results: The final IRT model included 66 ordered categorical and 2 binary items, and a total of 337 item-specific parameters that were estimated using all the data. Item characteristic curves describing the probability of observing a specific score for an item were also constructed. The subject-specific disease status distribution of the PD subjects was used as a reference for the shifts in mean and variance for individuals of the HC and SWEDD cohorts. Typical individuals of the HC and SWEDD cohorts had a less severe disease status but a larger variability than the PD cohort, with an overlap between PD and SWEDD distributions more important than with the HC. Simulations with the IRT model were in good accordance with the observed MDS–UPDRS item level data. The time course of the disease status was described with different functions for each cohort, and only the PD patients displayed a significant linear increase over time.

Conclusions: It is the first time that PD is described using IRT methodology, although it has been applied in therapeutic areas such as Alzheimer's disease [3], Multiple Sclerosis [4], and Schizophrenia [5]. IRT was shown to be more advantageous than conventional methods using total scores and can provide a framework for investigating disease progression and drug effects in PD.

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Emilie Hénin Determination of effective blood concentrations of cyclosporine in pediatric severe aplastic anemia based on a time-to-response model

Michael Philippe (1,2), Sylvain Goutelle (2,3), Yves Bertrand (4), Dominique Plantaz (5), Nathalie Bleyzac (1,2), Emilie Hénin (2,6)
(1) Département de Pharmacie, Service d'Hématologie et Oncologie Pédiatrique, IHOP, Lyon, France (2) UMR CNRS 5558 – Equipe Evaluation et Modélisation des Effets Thérapeutiques, Université Claude Bernard Lyon 1, France (3) Département de Pharmacie, Groupement Hospitalier de Gériatrie, Hospices Civils de Lyon, France (4) Unité de Transplantation, Service d'Hématologie et Oncologie Pédiatrique, IHOP, Lyon, France (5) Service d'Hématologie et Oncologie Pédiatrique, CHU Grenoble, France (6) Service de Pharmacologie Clinique et Essais Thérapeutiques, Hospices Civils de Lyon, France

Objectives: Optimal immunosuppressive therapy in acquired severe aplastic anemia (SAA), a rare disease affecting children, remains to be defined. Current recommendations state that cyclosporine (CsA) trough blood concentrations (TBC) should be maintained between 200 and 400 ng/mL, but there is a lack of data supporting this target. Our study aimed at quantifying relationships between exposure to CsA and hematological response, and at determining the effective CsA TBC target range in a cohort of children with SAA.

Methods: Data from 23 pediatric patients with SAA treated with CsA were retrospectively analyzed to develop a population

PK/Interface/Time-to-event model, linking CsA doses, TBC, effective concentration and time-to-hematological response (TTR). The effective concentration profile was driven by CsA TBC through an interface compartment[1].The input function of the interface compartment was adapted to estimate a lower and an upper bound of effective CsA TBC, thus defining an effective range. A time-to-event model linked effective concentration profile to TTR, defined as two successive neutrophil counts > $0.5x10^9$ cells/L. TTR was prospectively predicted in three additional patients not included in the model building**.**

Results: Fifteen out of 23 patients (65.2%) had a hematological response with a median TTR of 69 days (min 19- max 182). The median (min-max) age and weight were 8.5 (8-15) years and 34 (9.8-79.3) kg respectively. CsA TBC profiles were adequately described by an allometrically scaled two-compartment model with first-order absorption with a lag-time and a linear elimination. The effective target range of CsA TBC was estimated at 87 - 120 ng/mL (relative standard error < 5%). Simulations showed that the optimal CsA TBC target would be 100 ng/mL resulting in maximal response rate. TBC values above or below the 87-120 ng/mL range would be associated with lower response rate. Moreover, for three new patients, TTR predicted distribution from their TBC values was remarkably consistent with the observed TTR values (57, 41 and 61 days respectively).

Conclusions: This original modeling approach was successful in describing the relationships between CsA TBC and the hematological response in patients with SAA. While further research in a larger population is necessary to confirm our findings, this work suggests that a CsA TBC target of 100 ng/mL, much lower than that currently recommended, would be associated with a better response rate in children with SAA.

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Huixin Yu Development of a tumour growth inhibition model to elucidate the effect of ritonavir on intratumoural metabolism and anti-tumour effect of docetaxel in a mouse model for hereditary breast cancer

Huixin Yu (1), Jeroen J. M. A. Hendrikx (1), Alfred H. Schinkel (2), Sven Rottenberg (2), Jan H. M. Schellens (3,4,5), Jos H. Beijnen (1,4,5), Alwin D. R. Huitema (1,4)

(1) Department of Pharmacy & Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands; (2) Department of Molecular Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands; (3) Department of Medical Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands; (4) Department of Clinical Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands; (5) Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.

Objectives

Docetaxel, administered intravenously, is widely used as anti-cancer agent [1]. An oral formulation of docetaxel has been successfully developed in our group [2]. One major limitation for oral administration of docetaxel is its low bioavailability due to its affinity for P-glycoprotein and Cytochrome P450 (CYP) 3A [3-4]. Ritonavir strongly inhibits CYP3A4 and thereby proved to be a

potent booster of docetaxel exposure in both mice and human [5-6]. Phase I trials with oral docetaxel and ritonavir showed the feasibility of this oral treatment [7-8].

Although ritonavir is primarily used as exposure booster, it has also been suggested that ritonavir may have an anti-tumour effect itself [9-13]. In order to explore the effect of ritonavir on docetaxel metabolism as well as anti-tumour effects of ritonavir, we performed an allograft study in mice [14]. The results suggested that co-treatment of docetaxel and ritonavir significantly prolonged survival and substantially reduced average tumour size compared to that of docetaxel only-treated mice. However, from the empirical data analysis, it could not be definitively concluded whether this was only the consequence of decreased docetaxel metabolism in tumours or additional factors, e.g. direct anti-tumour effect of ritonavir.

The aims of the current study were: (1) to develop a pharmacokinetic (PK)- pharmacodynamic (PD) model based on central and tumour exposure of docetaxel and tumour size measurements from this previous study; (2) to further evaluate and quantify the effects of ritonavir on systemic and intratumoral exposure and anti-tumour effects of docetaxel when combined.

Methods

Data

70 host mice lacking Cyp3a (*Cyp3a*$^{-/-}$) with implanted tumour tissue presenting inherent Cyp3a expression were divided randomly over 4 groups [14]. Group I was not treated and used as control for tumour growth (control group, n=20). Group II was treated with 12.5 mg/kg oral ritonavir (ritonavir only-treated group, n=20), group III was treated with 20 mg/kg intravenous docetaxel (docetaxel only-treated group, n=30), and group IV was treated with both 20 mg/kg intravenous docetaxel and 12.5 mg/kg oral ritonavir (co-treated

group, n=30). Docetaxel and ritonavir PK were measured in both plasma and tumour. PK samples (n=5 per time point) were collected on day 2, 9 and 16 at approximately 24 hours after docetaxel administration. Tumour volumes were measured daily in all groups.

PK model

A previously established two-compartment model was used for docetaxel plasma PK [15]. Although Cyp3a-/- mice were studied, it was hypothesized that ritonavir might still influence docetaxel plasma PK. Docetaxel tumour concentrations were described with a separate compartment with a first-order absorption rate from the system, and a first-order elimination rate from the tumour. Ritonavir systemic PK was fixed with a one-compartment model similar as used in a previous study [15]. Measured ritonavir tumour concentrations were modelled analogously to docetaxel. In the co-treated group, the inhibition of docetaxel tumour metabolism by ritonavir was explored with ritonavir tumour concentrations by an Emax-type inhibition model. The ritonavir tumour concentration that inhibits half of Cyp3a enzymes ($IC50_{RTV}$) was fixed according to the literature as 2.5 ng/g [16].

PK/PD model

Non-perturbed tumour growth in untreated mice was described by an exponential net tumour growth rate. In docetaxel treated mice, a progression factor that represents the increase in tumour growth rate over time was considered. Docetaxel anti-tumour effect was described by a delayed effect model using transition of cells from the proliferative pool to an apoptotic pool. This transition of tumour cells was described with a first-order rate constant and was dependent on the docetaxel tumour concentration using an Emax-type model. The cells in the apoptotic compartment were eliminated by a first-order rate constant.

Hypothesis tests

Firstly, docetaxel effect parameters were estimated based on the

docetaxel only-treated group. Secondly, these parameter estimates were used to predict tumour size profiles in the combined treatment group taking only the increased docetaxel tumour concentrations as a result of ritonavir co-administration into account. Subsequently, it was explored whether ritonavir had an additional anti-tumour effect independent from the increased tumour docetaxel concentrations.

Sensitivity tests
A sensitivity analysis was conducted to explore whether the assumed value for $IC50_{RTV}$ influenced the final outcome (±10% difference from fixed $IC50_{RTV}$ parameter).

Results

PK model
The final PK model adequately described the observed data. In the *Cyp3a*$^{-/-}$ host, ritonavir slightly decreased docetaxel systemic clearance by 8% (relatively standard error (RSE) 0.4%) in the co-treated group. As expected, docetaxel tumour exposure was increased with mean area under the concentration-time curve 2.5-fold higher when co-treated with ritonavir.

PK/PD model & Hypothesis tests
Firstly, effect parameters in the docetaxel only-treated group were successfully estimated. A model improvement with a drop of objective function value (OFV) of 30 points ($p < 0.001$) was found when an increased tumour growth rate over time was considered.

Secondly, these effect parameters from docetaxel only-treated group together with increased docetaxel tumour concentration were used to predict the tumour growth profiles in the co-treated group. This resulted in a slight underestimation of the time to tumour re-growth in the co-treated group. Also in early phases of treatment the anti-tumour effect was underestimated. This

indicated that the observed enhanced anti-cancer effect in the co-treated group, compared to the docetaxel only-treated group, could not be fully explained by the increased docetaxel tumour concentrations alone.

Subsequently, a potential ritonavir anti-cancer effect was modelled analogously to that of docetaxel. Inclusion of this effect of ritonavir resulted in drop of OFV of 59 points ($p < 0.001$). Bias in the model predictions of the co-treated group disappeared by inclusion of this effect.

In the final PK/PD model, non-perturbed tumour growth was estimated with a net growth rate of 1.32 $week^{-1}$. This rate exponentially accelerated with 0.06 $week^{-1}$ in treated groups. Docetaxel tumour concentration with 50% of maximum anti-tumour effect was estimated as 307 ng/g.

Sensitivity tests
Difference of ±10% on fixation of $IC50_{RTV}$ suggested no influence on the final model parameters.

Conclusions

A PK/PD model has been successfully built describing the complex interaction between docetaxel and ritonavir when co-administered in a mouse model for hereditary breast cancer. We showed that the increased tumour growth inhibition in co-treatment of docetaxel with ritonavir is mainly caused by boosting the tumour exposure to docetaxel and to a minor extent by a direct tumour growth inhibitory effect of ritonavir.

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Shan Pan Automated proper lumping for simplification of systems models

Shan Pan, Stephen Duffull
School of Pharmacy, University of Otago, Dunedin, New Zealand

Background: Systems pharmacology models are created to explore detailed mechanisms of drug behaviour. However due to large dimensionality and complexity they cannot be easily utilised as the basis for modelling of data-driven pharmacokinetic-pharmacodynamic (PKPD) studies. With model order reduction methods systems models can be simplified into simpler structures while retaining similar input-output relationships. Lumping is one model order reduction technique that merges original states into fewer pseudo-states in a reduced system. Proper lumping as a special case of lumping that merges one or more original states into one pseudo-state in the reduced system. The reduced states after proper lumping retain their physical meaning as in the original system. Recently a proper lumping technique has been used for the simplification of a large-scale systems pharmacological model [1]. Other complex systems such as physiologically based pharmacokinetic (PBPK) models have been lumped by merging the tissues with similar specification (i.e. in serial or parallel connection) [2]. Automating the process of system simplification represents a large combinatorial search problem.

Aims: The overall aim of this work was to develop an automatic process for the simplification of a complex model. Specific objectives were to: (1) develop an automatic proper lumping

technique, (2) apply the automated process for the simplification of a PBPK model.

Materials & Methods: A PBPK model for fentanyl was identified from the literature [3] and used as the application example. This model predicted the arterial fentanyl concentrations over time in humans after an intravenous infusion of fentanyl. In total there were 17 states with liver as the site of metabolism. The PBPK system was written as ordinary differential equations (ODEs). For this example application of model simplification, it was considered desirable that the arterial concentration-time curve from the lumped model shows good agreement with the original profile. The criterion for an acceptable lumped model was defined as the total area under the arterial concentration-time curve (AUC) between lumped and original models was set to differ by 0.002% at maximum (termed ARD% for absolute value of the relative difference expressed as a percent). Note this criterion is arbitrary.

Proper lumping has previously been described by Dokoumetzidis and Aarons [4]. A general form of the model for a vector of model predictions (y) is given by

$$dy/dt = K \times y.$$

Here K is the micro-rate constant matrix. In this technique the lumped micro-rate constant matrix (K_L) can be obtained by the relationship of K, the lumping matrix (M) and the pseudo-inverse of lumping matrix (M^+) by

$$K_L = M \times K \times M^+.$$

The resulting lumped micro-rate constant matrix is then used to simulate the concentration-time profile of the lumped system. The lumping matrix (M) is a user defined m × n matrix composed of 0s and 1s, where m is the number of lumped states and n is the

number of original states. The M matrix transforms the states between the original and lumped systems. Note the M matrix for the setting where the lumped model equations are the same as the original model is the identity matrix (I_n) of dimension n (i.e. m = n).

The M matrix is specified where the sum of each column is 1 and the sum of each row ≤ n. The optimal M matrix is defined as having the minimum number of states (min(m); m ∈ {1,2,…,n}) that satisfies the criterion.

Methods of searching the matrix developed in this work included: (1) full enumeration, (2) non-adaptive random search (NARS), (3) scree plot plus NARS.

Full enumeration: all legal lumping matrices were exhaustively searched. The search started from the fully lumped matrix (m = 2) and then incremented one row each time until the criterion was accepted.

NARS: legal lumping matrices were constructed randomly. The search started from the fully lumped matrix (m = 2) and m was incremented by one after each NARS was completed or until the criterion was accepted. Number of random samples per increment in m was tested with 10, 100, 1,000 or 10,000 or 100,000 or 1,000,000.

Scree plot plus NARS: A scree plot was used to visualise the influence of the compartmental structures. In the scree plot, the eigenvalues of the K matrix were plotted in rank order against the ranked state number. Either a cut-off point of an eigenvalue of 1 or a change in the slope of the scree plot indicated an initial estimate of the number of states in the reduced model. This was used as the starting point for NARS.

The automatic methods described above were tested individually for simplification of original fentanyl PBPK model. In all methods it was constrained that the artery as the output state was unlumped during the search process.

Results:

Full enumeration: a 4-state lumped model was found after 40 minutes where ARD% was 0.0001% satisfying the exploratory criterion (i.e. ARD% < 0.002%). The minimum ARD% for all lumped models with m = 4 took more than two days.

NARS: Stationary ARD distribution was formed until 10,000 random samples and lower ARD was shown with the increment in m.

With 10 and 100 samples the random searched did not find a lumped model that satisfied the criterion (i.e. the full model was the only acceptable model). With 1,000 samples, a 14-state lumped model was found after 15 seconds. With 10,000 samples, a 6-state lumped model was found after one minute and after 100,000 samples per iteration a 5-state lumped model was found after five minutes. With 1,000,000 samples, a 4-state model was found after 30 minutes.

Scree plot plus NARS: The eigenvalues of the first four states were above 1 and therefore may provide the basis of those that are informative and could be left unlumped as the first iteration. The slope in the scree plot clearly levelled off up to the fourth state and also indicated four or five states in the lumped model. ARD% for both lumped models were above 38%. The lumped states were gradually unlumped and a lumped model within the ARD% criterion was not found.

In NARS the search then started from four states with 10,000 samples, and a 7-state lumped model was found after 40 seconds.

Conclusions: We have demonstrated that different automatic processes can be applied to simplify an existing PBPK model. It is evident that full enumeration for anything other than a simple model is not practical. The scree plot approach although informative was not optimum. In this (relatively) straightforward example, NARS with 1,000,000 samples per iteration was both relatively quick and found the optimum. The methods described here are general and more specific and efficient methods may be required for large scale problems ($n > 50$).

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Adrien Tessier Modelling pharmacogenetic data in population studies during drug development

Adrien Tessier (1,2,3), Julie Bertrand (4), Marylore Chenel (3) and Emmanuelle Comets (1,2,5)
(1) INSERM, IAME, UMR 1137, F-75018 Paris, France. (2) Université Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, F-75018 Paris, France. (3) Division of Clinical Pharmacokinetics and Pharmacometrics, Institut de Recherches Internationales Servier, Suresnes, France. (4) Genetics Institute, University College London, London, UK. (5) INSERM CIC 1414, Université Rennes 1, Rennes, France.

Introduction

Pharmacogenetics (PG) studies the proportion of interindividual variability (IIV) in drug response explained by genetic variation, investigating the link between genotype and pharmacokinetic (PK)/pharmacodynamic (PD) phenotypes [1]. In the hopes to personalise therapy, genetic data are now collected in many clinical trials in large arrays. For instance, the pharmaceutical company Servier developed a microarray that informs on metabolism enzymes and transporters polymorphisms. In early PK studies, genetic variation is often tested for an association with phenotypes estimated using noncompartmental analysis (NCA) [2], although nonlinear mixed effects models (NLMEM) are increasingly used in clinical trials. Currently, there is no consensus on methods to study the PG of drugs in clinical development. We investigated the

methodology of PG analysis in PK early phase studies, to propose approaches enhancing the detection of genetic effects.

Objectives

1. To compare the ability of different PK phenotypes to detect genetic effects.
2. To assess the performance of different association tests.
3. To improve PG analysis in small samples with large genetic arrays, through combined analysis of phase I and II data or using a PK phenotype enrichment approach.

We performed this study through simulations.

Motivating example

A case-study from Servier concerning a drug under phase I development was the setting for a series of simulation. The PK of this drug exhibited nonlinear bioavailability and a double absorption process. In the clinical studies, 176 Single Nucleotide Polymorphisms (SNPs) were genotyped through the microarray developed by Servier.

Methods

We used the genetic array and the PK model developed to simulate genotypes and PK profiles under the null (H_0, no genetic effect) and an alternative hypothesis (H_1). Under H_1, 6 SNPs were drawn randomly to affect the log-clearance (CL) through an additive linear model. Each SNP explained a different proportion of CL IIV (between 1 and 12%, totally 30%).

First, we simulated two phase I studies: one inspired from the real-case example with extensive sampling (16 observations per subject) of 78 subjects and an “asymptotic” version with the same rich

design of 384 subjects. The PK phenotypes were two observed concentrations (C24h and C192h), the area under the curve (AUC) estimated by NCA, and CL Empirical Bayes Estimates (EBE) estimated using Monolix [3]. The four association tests applied to the 4 PK phenotypes were a stepwise procedure [2] and three penalised regressions: ridge regression [4], Lasso [5] and HyperLasso [6]. The 16 combinations of 4 PK phenotypes and 4 association methods were compared on the two phase I studies in terms of probability to detect genetic effects, computed as the percentage of data sets simulated under H_1 where one to six of the six causal variants were selected [2].

Second, we moved on to the next phase of clinical development, exploring realistic ways of increasing the amount of PK information by combining phase I data with data collected in sparse phase II studies. To investigate the influence of the design and of the amount of information, we simulated three phase II studies with sparse sampling (1 to 3 observations per subject, 306 subjects), optimising the three samples designs [7]. We focussed on the EBEs of CL as the phenotype and two association tests were considered: a stepwise procedure and Lasso. The probability of detection was compared and related to estimated shrinkage [8].

Finally we investigated a new approach for PK phenotype enrichment to increase the amount of information in sparse designs [3]. We used imputations randomly drawn in the conditional distribution of CL using Monolix. We compared applying a linear mixed model to handle the correlation in imputations of a same subject, to a linear model on the CL EBEs. The alternative hypothesis was simulated as one genetic marker affecting CL in two phase I studies of 78 subjects with rich or sparse sampling. In both cases, we estimated the probability to detect the genetic variant.

Results

Interestingly, in the presence of nonlinearity and/or variability in bioavailability, model-based phenotype allowed a higher probability to detect the SNPs than other phenotypes. When PK was simulated without nonlinearity and variability in bioavailability, the tests based on AUC and CL had a similar power. None of the penalised regressions or the stepwise procedure showed a much higher power than the others, but ridge regression had the best probability to detect SNPs, with also a higher number of false positives. This result holds regardless the number of subjects. In this realistic phase I setting with a limited number of subjects, the probability to detect genetic effects was low regardless of the method. As expected it increased with the number of subjects for all methods.

Compared to phase I data alone, additional phase II data, even with sparse sampling, increased markedly the detection probability due to the larger sample size, showing that rich PK information is only required in a subset of subjects. A direct relationship was observed between the design of the phase II study, the shrinkage in the individual CL estimates and the probability of detection. Optimising the phase II design reduced the shrinkage and allowed the highest probability to detect the genetic variants. But this gain was low compared to the one due to the sample size increase.

Imputations allow a better description of the uncertainty of the estimated parameters and reduced the shrinkage when compared to using only the EBEs. With this approach the probability of detection improved marginally (less than 10%).

Conclusion

The present work focussed on PG studies performed during the clinical development of a drug. It shows how, in contrast to what is done in most early phase studies, modelling approaches should generally be preferred to estimate PK phenotypes, in particular in the presence of complex PK involving non-linearity. Our results also

reinforce the importance of the sample size in PG studies, and show that phase I trials are underpowered to detect even strong genetic effects and/or genetic effects due to rare alleles. To improve their detection, we propose to play on two aspects: the increase in sample size, combining data from phase I and II studies, and PK phenotype enrichment. Phase II data is needed to confirm the impact of genetic variants on drug response and design optimisation improves the power of the studies. We also show that a new imputation-based approach provides a slight gain of the same order than design optimisation.

To conclude we recommend the combined analysis of phase I and II data for the exploration of genetic associations and to prospectively optimise the phase II study design accordingly. Increasing the sample size is the main driver of genetic association analyses power.

Acknowledgment:
We are grateful to Marc Lavielle for help implementing the imputations in the conditional distribution of the parameters.

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Oral: Modelling using Bayesian Analysis | C-06 | Thursday 11:45-12:30

Sebastian Weber Building Robust PK/PD Population Models with Bayesian Inference

Michael Betancourt (1) and Sebastian Weber (2)
(1) University of Warwick and (2) Novartis Pharma AG

Because clinical data is often limited in the number of patients or observations
per patient, PK/PD analyses that don't model the complexity in the data compromise
our ability to make robust inferences, especially when trying to characterize variation
amongst a population of patients. In this talk we will discuss how Bayesian inference is the
natural framework for modeling these complexities and building robust PK/PD
population models, ending with a contemporary example to demonstrate the
power and clinical relevance of this approach.

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Thierry Wendling Application of a Bayesian population approach to physiologically-based modelling and simulation of mavoglurant pharmacokinetics

Thierry Wendling (1, 2), Swati Dumitras (2), Ralph Woessner (2), Etienne Pigeolet (3), Kayode Ogungbenro (1) and Leon Aarons (1)
(1) Manchester Pharmacy School, The University of Manchester, Manchester, United-Kingdom, (2) Drug Metabolism and Pharmacokinetics, Novartis Institutes for Biomedical Research, Basel, Switzerland, (3) Pharmacometrics, Novartis Pharma AG, Basel, Switzerland

Objectives: Mavoglurant (MVG) is an antagonist at the metabotropic glutamate receptor 5 currently under clinical development at Novartis Pharma AG for the treatment of CNS diseases. The aim of this work was to develop and optimise a population physiologically-based pharmacokinetic (PBPK) model for MVG to predict the impact of drug-drug interaction and age on its PK.

Method: A whole-body PBPK model for drug disposition was first developed and optimised with data from a Phase-I study of intravenously administered MVG using a Bayesian approach. We developed a three-stage hierarchical model to describe both uncertainty and inter-individual variability (IIV) in the drug-specific parameters. Prior information on the system-specific parameters was extracted from the physiology literature. For drug-specific

parameters, prior distributions were constructed based on the results of *in vitro* and animal experiments. A sensitivity analysis was performed prior to model fitting to identify the parameters that could be updated just by plasma data. Parameters' posterior distributions were approximated by random draws using MCMC simulations in NONMEM. Three chains of 10^6 iterations were computed. Convergence to the equilibrium distribution was monitored using the potential scale reduction statistic [1]. The optimised model was then used together with a mechanistic absorption model to predict MVG PK when orally co-administered with ketoconazole in adults or administered alone in children. The predictive performance of the model was evaluated using data from three other clinical studies.

Results: The population PBPK model allowed good description of MVG plasma PK data following IV administration in healthy adults. Prediction of the MVG-ketoconazole interaction was consistent with results of an in-house non-compartmental analysis of the clinical data (3-fold increase in systemic exposure). Finally, scaling of the PBPK model allowed reasonable extrapolation of MVG PK from adults to 3 to 11 year-old children.

Conclusions: Population PBPK modelling and simulation for MVG provided further insight into its PK, including the source and magnitude of IIV. The Bayesian approach allowed uncertainty in some of the drug-specific parameters to be reduced. The model can be used to predict plasma and brain (target site) PK profiles following oral administration of various immediate-release formulations of MVG alone or when co-administered with a perpetrator, in adults as well as in children.

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Rong Deng Towards Model-Based Drug Development of New Therapeutics for Hepatitis C Virus

Rong Deng, Brinda Emu, William Capra, Jin Y. Jin
Genentech, Inc., South San Francisco, CA, US

Objectives: The FDA "critical path" document characterizes model-based drug development (MBDD) as the development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge, management and decision-making. One of the frequent and well established applications of MBDD is utilization of mathematical models of disease progression to test different study designs in silico via clinical trial simulations. In the past few years, MBDD has been a unique and useful tool to inform drug development strategy and decision-making in various therapeutic areas, such as metabolic, neurological, and cardio-vascular diseases, and we believe it can be similarly useful in infectious diseases.

Methods: The life cycle of Hepatitis C virus (HCV) has been studied extensively in the past decade, from which mathematical models have been developed to quantitatively describe both viral dynamics as well as existing and potential therapeutic interventions. The models have also been well validated against the rich clinical data of patient viral load reduction upon receiving the standard of care (SOC)(ribavirin+ peginterferon). We propose to utilize and modify these models to assist the design of clinical trials of an HCV entry inhibitor by testing different input clinical parameters (choice of

antiviral therapy, viral load, known characteristics of patient population), to inform selection of virologic endpoints, sample size, and patient population.

Results: We have developed and validated a modified HCV dynamic model that incorporates resistance to SOC and use of an HCV entry inhibitor for treatment. This model suggests HCV entry inhibition may increase cure rate and decrease treatment duration when combined with current SOC or direct-acting antiviral agents, with or without interferon. In additional, an HCV entry inhibitor is likely to show larger added benefits in patients not responding well to SOC. Based on the model, a phase I study is proposed in HCV patients, regardless of baseline viral load, designed to show evidence of viral load decline, and the PKPD relationship of a novel HCV entry inhibitor.

Conclusions: MBDD has been successfully applied to develop a study design for HCV in the early drug development stage.

Joe Standing Treating Resistant Gram-Negatives: Bedside to Bench and Back

Lynette Phee (1,2), Yucheng Sheng (3), David Wareham (1,2), Joseph F Standing (4,5)

(1) Antimicrobial Research Group, Blizard Institute, Barts and The London School of Medicine and Dentistry, UK (2) Division of Infection, Barts Health NHS Trust, UK (3) School of Pharmacy, University College London, UK (4) Institute of Child Health, University College London, UK (5) Great Ormond Street Hospital, London, UK

Objective: London is a culturally diverse city, and this extends to diversity in bacterial pathogens. Multi-drug resistant (MDR) Gram-negatives are an increasing problem. We started at the bedside identifying a number of MDR *A. baumannii* clinical isolates. Moving to the bench, potentially synergistic combinations were identified with in vitro models and then tested in an invertebrate model of infection (*G. mellonella*). Returning to the bedside, we have used the identified combination to treat patients infected with extensively resistant strains of *A. baumannii*. Here we focus on the development of simple, identifiable mechanistic models which allowed for quantifying antimicrobial synergy and dose optimisation.

Methods: Colistin disrupts the outer membrane of Gram-negatives; it was therefore screened in combination with a range (10 agents) of Gram-positive agents using disk diffusion screening assay. Potential synergy was confirmed with checkerboard assays (1) and

modelled with a response surface approach. Then ascending concentration 24 hour time-kill experiments with each drug alone and a range of combination concentrations was performed. Differential equation models (2) of colony-forming unit (CFU) concentration with time were extended to two drugs and simultaneous analysis of six strains (population approach) using NONMEM 7.3 (FOCE). A colistin concentration-dependent mechanistic synergy function was tested. Confirmation of combination efficacy was sought from *G. mellonella* infected with *A. baumannii* with survival modelled by time-to-event. Published PK models were used to optimise dose defined with a model-based utility function. Clinical outcome can be reported for two patients so far.

Results: Colistin-fusidic acid was identified as the optimal combination in initial screening. A simple model with time-varying effect adequately described time and concentration dependant resistance development. Adding a synergy term on resistance development rate significantly improved model fit (delta OFV 118). Preliminary exploration of methods for dose optimisation by utility function have been explored.

Conclusions: We have shown both in vitro and in vivo that fusidic acid can be combined with colistin to treat MDR *A. baumannii*. Fusidic acid is potentially colistin-sparing and future work will investigate the combination activity versus other organisms.

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Anders Kristoffersson A Pharmacokinetic-Pharmacodynamic (PKPD) Model Characterizing Resistance for Predictions of Bacterial Kill in vivo

Anders Kristoffersson (1), Pascale David-Pierson (2), Neil J. Parrott (2), Olaf Kuhlmann (2), Thierry Lave (2), Lena E. Friberg (1), Elisabet I. Nielsen (1)

(1) Department of Pharmaceutical Biosciences, Uppsala Universitet, Uppsala, Sweden, (2) Hoffmann LaRoche LtD., Basel, Switzerland

Objectives: Within the infectious disease area, the pharmacokinetic (PK) -pharmacodynamic (PD) characterization is generally limited to the establishment of the so called PK/PD indices or drivers [1]. PK/PD indices are summary endpoints assessed at a single time point and can therefore not accurately describe emergence of resistance. This study aims to predict bacterial kill and resistance development *in vivo* based on a PKPD model characterizing the *in vitro* time course of meropenem activity against *Pseudomonas aeruginosa*.

Methods: A semi-mechanistic PKPD model described the *in vitro* effect of meropenem on two strains of *P. aeruginosa* (wild type, and resistant clinical isolate) [2]. Each strain was modelled as consisting of compartments for susceptible and resting bacteria. Regrowth after initial kill was explained by a pre-existing subpopulation with greatly reduced meropenem susceptibility (>200 × higher EC50). The model was evaluated for *in vivo* conditions by replicating a murine

PKPD study [3] using PK established in mice [4], and applied to make predictions of efficacy in humans [5].

Results: The murine *in vivo* study results were well replicated with the same PK/PD index selected, with similar magnitude required for efficacy. Contrary to expectation [6], the clinical isolate required concentrations above the minimum inhibitory concentration (MIC) for twice as long as the wild type (30 vs. 63 % of the dosing interval). In order to suppress emergence of resistance to meropenem concentrations greatly exceeding the MIC over a large part of the dosing interval are expected to be needed, hence prolonged infusions were required in patients with short meropenem half-life. As expected [7], the clinical maximum daily dose was predicted not to be sufficient to treat the resistant isolate.

Conclusions: An *in vivo* murine dose finding study was successfully replicated *in silico* using a PKPD model based on *in vitro* data. The magnitude of the PK/PD index was found to be sensitive to the susceptibility of the strain. Simulations illustrated that combination therapy is expected to be required to treat infections by the resistant strain. Contrary to the PK/PD indices, a PKPD modelling approach naturally lends itself to investigation of effect from drug combinations. The ability to integrate *in vitro* findings on resistance with *in vivo* PK data to provide dosing recommendations is of great potential for dose finding of antibiotics and to guide improved treatment.

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Nick Holford Announcement of WCoP 2016

Nick Holford

Invitation to attend From WCoP Executive Committee and the WCoP 2016 Organizing Committee

On behalf of the WCoP 2016 organizing committee, it is our great pleasure to invite you to the second World Conference on Pharmacometrics (WCoP) to be held in Brisbane, Australia from 21 to 24 August 2016.

The Population Approach Group of Australia and New Zealand (PAGANZ) will be your host for WCOP 2016 and will be supported by the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT). Together, with the WCoP Executive we will join forces to produce a 2016 conference that is innovative and promotes pharmacometrics research and methodology globally.

Being the gateway to Australia's most popular tourist region, we encourage you to bring your family and explore all that is on offer. With over 200 direct international flights into Brisbane each week, access from Asia, Europe and USA is easy.

Thank you in advance for your participation and support. We are looking forward to welcoming you to Brisbane in 2016.

Who should attend?

WCoP 2016 will bring together leading national and international researchers, academics, clinicians and educators from various arenas, including:

- pharmacokinetics and pharmacodynamics
- population modelling and simulation
- clinical and experimental pharmacology
- systems pharmacology
- medical, pharmaceutical and other healthcare disciplines
- pharmaceutical industry
- governmental and non-governmental organizations from around the globe.

NOTE: IT IS IMPORTANT THAT YOU APPLY FOR YOUR VISA WELL IN ADVANCE OF YOUR DEPARTURE DATE. Please see the General information page for further information about visas

Please visit www.wcop2016.org for further details

Andrew Hooker Preconditioning of Nonlinear Mixed Effect models for Stabilization of the Covariance Matrix Computation

Yasunori Aoki, Rikard Nordgren, and Andrew C. Hooker
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: As the importance of pharmacometric analysis increases, more and more complex models are introduced and computational stability starts to become a bottleneck. We can observe such instability, for example, in the computation of the covariance matrix with the error message "R MATRIX ALGORITHMICALLY NON-POSITIVESEMIDEFINITE" in NONMEM. In this work, we present a preconditioning method for nonlinear mixed effect models to increase the computational stability of the covariance matrix computation.

Methods: Roughly speaking, the method re-parameterizes the model with a linear combination of the original model parameters so that the R-matrix of the re-parameterized model becomes close to an identity matrix. This approach will reduce the chance of the R-matrix being non-positive semi-definite due to computational instability and gives a clear indication when the R-matrix is fundamentally non-positive semi-definite (e.g., if the model is not identifiable). Based on the re-parameterized model results, the

parameters and covariance matrix in the original parameterization can be calculated.

Results: We have conducted a number of stochastic simulation and estimation experiments, using three published models [1,2,3] and NONMEM. We have simulated various datasets and then estimated both parameters and covariance matrices using the published parameterizations. In these studies there were 85/200, 30/50, and 69/200 of cases where the covariance step failed. However, after preconditioning the covariance matrices were successfully computed for all these cases. In addition, to illustrate the danger of computational instability, we have conducted a similar test using an unidentifiable model. Surprisingly, covariance matrices could be computed for 48/100 cases with reasonable relative standard errors (RSE). However after preconditioning, the RSE typically grew by a few orders of magnitude (e.g., 47% to 1243%) clearly indicating identifiability problems with the parameters.

Conclusions: Computational instability can potentially influence pharmacometric analyses and we propose a preconditioning method to reduce that instability and increase the chances of getting a covariance matrix in NONMEM (if the model parameters are identifiable). The method is automated and made available as a part of PsN [4,5]. Computational instability can also influence the parameter estimates and an investigation of this correlation using the preconditioning method is presented in a separate abstract [6].

Acknowledgement: This work was supported by the DDMoRe (www.ddmore.eu) project.

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Eric Strömberg Simulated model based adaptive optimal design of adult to children bridging study using FDA stopping criteria.

Eric A. Strömberg, Andrew C. Hooker
Department of Pharmaceutical Biosciences Uppsala University, P.O. Box 591, SE-751 24 Uppsala, Sweden

Objectives: In traditional design, the size of the study population is regularly calculated *a priori* using power calculations which are dependent on the prior information. Wang *et al.* has previously suggested a precision criteria for sample size determinations based on derived variability in clearance and volume of distribution for design of pediatric PK studies [1]. Model based adaptive optimal design (MBAOD) has been shown to be less sensitive to initial model misspecification in the design stage. This can be useful in bridging studies where the prior information on model and parameters from the original population may differ greatly from the target population [2,3]. In this work we apply the Wang et al. precision criteria as a stopping criteria for a MBAOD of an adult to children bridging study where the estimates of variability for the parameters of interest are taken directly from the target population.

Methods: An adaptive optimal design of an adult to children bridging study was simulated 25 times using the MBAOD package in R [4]. The true model was assumed to be a one-compartment model with linear elimination. The volume of distribution in children was

scaled by a weight covariate model and clearance was driven by weight and age using a size and maturation model. Two levels of misspecification on the scaling parameters were investigated. A simulated pediatric population with children of age 3 months to 18 years was split into 6 age groups. The first cohort of children was fixed to 9 children from the age group with the oldest children. To avoid moving into age groups with poor estimates of parameters the design space for each new cohort of patients was restricted to only add children from age groups for which the stopping criteria had already been reached. In each adaptive cohort the design was optimized for which age group from which to add 2 children to the study. Once the stopping criteria were reached for all age groups, the MBAOD ended.

Results: The stopping criteria was for the small and large misspecifications reached after 2-5 and 4-8 cohorts of children, which corresponded to a total of 11-17 and 15-23 pediatric subjects.

Conclusions: The criteria for population size determination as described by Wang *et al.* was successfully implemented as stopping criteria for a MBAOD simulation study. The stopping criteria was reached in the MBAOD simulations with fewer individuals than required by a traditional design with the same initial misspecification in the prior information.

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Acknowledgement: This work was supported by the DDMoRe (www.ddmore.eu) project.

Sebastian Ueckert Alternative to Resampling Methods in Maximum Likelihood Estimation for NLMEMs by Borrowing from Bayesian Methodology

Sebastian Ueckert (1,2), Marie-Karelle Riviere (1), France Mentré (1)
(1) IAME, UMR 1137, INSERM and University Paris Diderot, Paris, France; (2) Pharmacometrics Research Group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Asymptotic theory-based statistics such as confidence intervals (CI) from the covariance matrix (COV) and p-values (PVAL) from the Wald test (WALD) are the basis for most model-driven decisions in drug development. For small sample sizes these approximations do not hold and resampling methods like bootstrap (BOOT) or permutation tests (PERM) are employed. Sampling from the Bayesian posterior distribution represents an alternative, if uniform priors are used, as posterior and likelihood become proportional to each other [1]. With the development of Hamiltonian Monte-Carlo (HMC) methods, this approach becomes computationally attractive for hierarchical models [2]. The objective of this work was therefore to compare HMC-based calculation of CI and PVAL with existing approaches.

Methods: The following HMC-based methodologies were used:

CI: Starting at the maximum likelihood (ML) estimate, 8000 posterior samples were obtained through HMC and used for the calculation of parameter confidence intervals.

PVAL: Posterior samples obtained for multiple permutations of the covariate vector were pooled and the PVAL calculated as the percentile of the ML covariate effect in the posterior distribution.

Both methods were evaluated through simulations with different PK/PD models under different study designs (large & small, sparse & rich). For CI, the results were compared to BOOT and COV in terms of density distribution and coverage. For PVAL, the results were compared to PERM and WALD in terms of power and type-I error.

The HMC methods were implemented in R [3] using STAN [4] with improper priors for sampling. Asymptotic theory and resampling-based results were obtained in NONMEM 7.3 [5] using PsN 4.3.17 [6].

Results: The simulations showed good agreement between COV, BOOT and HMC based CIs for large sample sizes. For small sample sizes, COV CIs deviated considerably from CIs obtained with BOOT or HMC. Results for PVAL were similar, with type-I error rates close to the nominal ones for all three methods at large sample sizes, but deviations for WALD at small sample sizes. In terms of computation time the HMC-based methods were >30 times faster than resampling methods.

Conclusions: In this comparison the HMC based methods appear as a very promising approach, showing good agreement with asymptotic results for large and equal or better performance than resampling methods for small sample sizes as well as drastically shorter run times.

This work was supported by the DDMoRe project.

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Joel Tarning Semi-mechanistic time-to-event modelling in malaria

Joel Tarning (1,2), Praiya Thana (1), Palang Chotsiri (1), Issaka Zongo (3), Nicholas Day (1,2), François Nosten (1,2), Nicholas J White (1,2).
(1) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, (2) Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK, (3) Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso.

Objectives: Dihydroartemisinin-piperaquine is a promising antimalarial treatment of *P. vivax* and *P. falciparum* malaria. *Falciparum* malaria causes the majority of deaths but *vivax* malaria causes substantial morbidity with frequent relapses due to the reactivation of latent parasites in the liver. The objective of these studies was to evaluate the PK/PD of piperaquine in patients with *vivax* and *falciparum* malaria.

Methods: Study 1) 250 patients with *P. vivax* malaria in Thailand received a standard 3-day regimen of dihydroartemisinin-piperaquine. Plasma samples were collected in 116 patients at 6 random time points and at the time of recurrent malaria. Study 2) Sparse piperaquine plasma sampling in 183 children (age between 2.33-58.1 months) were obtained after monthly dihydroartemisinin-piperaquine prophylactic treatment of *falciparum* malaria in Burkina Faso. In both studies, PK/PD properties of piperaquine were evaluated with nonlinear mixed-effects modelling. Recurrent

malaria were modelled with a time-to-event approach for both *falciparum* and *vivax* malaria.

Results: Piperaquine population pharmacokinetics were described by a 3-compartment disposition model with transit-absorption for both children and adults, supported by prior information in the sparse data in children. Study 1) The biology of relapsing *vivax* malaria was accommodated by a constant baseline hazard with the addition of multiple surge functions that increased the hazard of relapse with an estimated 123% in fixed 3 week intervals. Study 2) Parasite density at the time of malaria detection was used for extrapolation of the likely time interval of *falciparum* malaria acquisition in children. The protective effect of piperaquine was implemented as an inhibitory E_{MAX} function. Dose-optimization using the final PK/PD model suggested that small children had lower exposure to piperaquine after a standard body weight-normalised dose. A prospective dose increase predicted a 34% decreased malaria incidence in small children.

Conclusions: PK/PD modelling conducted here demonstrated that both the biology of relapsing *vivax* malaria and the acquisition of new *falciparum* infections were successfully described by a time-to-event approach. The results suggest that a large proportion of the first *vivax* relapses were suppressed completely by residual piperaquine concentrations, and that small children are under-dosed in preventive treatment of new *falciparum* infections.

Natalie Filmann Modeling the PK/PD of hepatitis B immunoglobulin after hepatitis B induced liver transplantation by an extended Target Mediated Drug Disposition Model

N Filmann (1), J Rosenau (2), MP Manns (3), H Wedemeyer (3), E Herrmann (1)
(1) Goethe University Frankfurt, Germany, (2) University of Kentucky Hospital, (3) Medical School Hannover

Objectives: Although hepatitis B immune globuline (HBIg) administration in combination with hepatitis B virus (HBV) polymerase inhibitors is the standard of care for prophylaxis of reinfection after liver transplantation (LTX) for HBV–related liver disease in many transplant centers worldwide, no rational basis for individualized HBIg doses schedules exists until today.
The objective of the present study is the analysis of the virus kinetics after HBV-induced LTX and pharmacokinetics (PK) of HBIg after LTX.

Methods: To analyze the HBsAg- and HDV RNA kinetics and the anti-HBs PK after liver transplantation, we developed and evaluated virus kinetics models based on existing models for chronic HBV or chronic HBV/HDV [1, 2, 3] and the general Target Mediated Drug Disposition Model (TMDD-Model) of [4]. The TMDD-Model is used for the analysis of the pharmacokinetics and pharmacodynamics (PK/PD) of drugs where a significant proportion relative to dose is bound with high affinity to the pharmacological target, such that

this is reflected in the PK of the drug. Model parameters were estimated by non-linear fitting of individual patient data (serial quantifications of 67 patients of anti-HBs, HBsAg, and -if present- HDV RNA).

Results: The application of the general TMDD-model led to systematic deviations between data and fits, especially, because a decreasing effect after repeated HBIg doses could not be modeled adequately. Our extension of the TMDD-model proposed here therefore also takes account of the binding of anti-HBs and HBsAg antigens to anti-HBs-HBsAg-immune complexes and the ratio of antigens and antibodies.

Our findings confirm a strong correlation between HBsAg- and HDV decline, anti-HBs increase and HBIG dosing schemes, which was already described by [5]. Global sensitivity analysis indicates that, besides the volume of distribution and baseline HBsAg-levels, the elimination of immune complexes has large influence on the PK/PD, too.
Different therapy regimes were analyzed by means of simulations. The simulation results indicate that treatment classification according to baseline HBsAg-levels is reasonable with regard to minimization of the HBIg doses and concurrent HBsAg elimination.

Conclusion: We propose an approach to model the PK/PD of HBIg after HBV-induced LTX by an extension of the general TMDD model. The modeling results form a basis for treatment individualization.

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Dimitra Bon Multiscale modelling for hepatitis C treatment

Dimitra Bon, Eva Herrmann
Goethe University Frankfurt

Objectives: In parallel to the beginning of a new era of HCV treatment with direct-acting antivirals (DAAs), new models where developed in order to describe the viral kinetics. Clinical data with such new drugs showed a triphasic decay with a rapid first phase, a moderate second phase decay and a relatively slow third phase decay during the first few weeks. Therefore, classical biphasic models may not been suitable. Some recently proposed models take into account the dynamics of intracellular replication, which is the main target of the DAAs.

Methods: Here we describe a new variant of a multiscale model that describes both, intracellular and cellular dynamics, with an ordinary differential equation system. We compare our model with two multiscale models, the ICCI model [1] and the age-structured multiscale model [2,4]. We evaluate all three models with the design of the SYNERGY study [3]. In some cases, patients showed a three phase viral decline and we analysed if such a decline could be modelled with biologically reasonable parameters.

Results: Only the new multiscale model and the age-structured multiscale model could reasonably describe this three phase viral decline. The rapid first phase is associated with viral clearance, the

intermediate second phase is only visible if the effect of blocking vRNA packaging is close to 1 and the third phase reflects infected cell clearance. In contrast to the other two models, the age-structured multiscale model is relatively complicated to analyse. There exist easy approximations but those cannot be easily adapted for modelling full PK-PD.

Conclusions: The new variant of a multiscale model proposed here is able to describe the viral kinetics of HCV under these new treatments without a computational effort.

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Nadia Terranova Analysis of individual target lesions for tumor size models of drug resistance: a new methodology encompassing signal processing and machine learning

N. Terranova (1), P. Girard (1), U. Klinkhardt (2, 3), A. Munafo (1)
(1) Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland, (2) Merck KGaA, Darmstadt, Germany, (3) Current affiliation: CureVac GmbH, CureVac GmbH, Paul-Ehrlich-Str. 15, Tübingen 72076, Germany

Objectives: Exploratory data analysis is a fundamental step in the model development effort. It becomes even more relevant when, for developing semi-mechanistic tumor size models of drug resistance, we consider individual target lesions rather than their sum [1]. In this work, we propose a new methodology, inspired by signal processing and machine learning, for clustering classified individual tumor lesions according to the degree of similarity in their dynamics. Resulting information can drive the modeler in rationally selecting the most appropriate modeling strategy for describing the tumor resistance profile of cancer patients.

Methods: A new classification of tumor individual target lesions, based on functional and location criteria, was defined, validated by a clinical expert and applied to clinical studies in metastatic colorectal cancer (mCRC). This classification was implemented in SAS® software through keywords recognition on the lesion

description recorded by physicians. When lesions were similarly classified for one patient, the sum of tumor measures was computed. Cross correlation (CC) was used to measure the similarity among classified lesion dynamics by also considering potential delays. Resulting correlations were clustered with K-means to obtain a straightforward and overall interpretation. Both methods are part of the *Stats* package in R [2].

Results: We have classified 2038 individual target lesions, selected and measured according to the WHO criteria, of 642 mCRC patients from two Phase II studies. CCs have been estimated for 216 patients with multiple classified individual lesions, and clustered. Results from both studies are consistent across tested scenarios and highlight a similar tumor dynamics in about the 60%-70% of classified lesions. The degree of similarity decreases when computed without considering any delay between lesion dynamics.

Conclusions: The proposed methodology, by integrating knowledge from other fields, provides a novel and suitable workflow for the non-parametric analysis of individual target lesions prior to any modeling step. Our approach is flexible enough to be applied to any case study. Moreover, by coupling the information on the target tumor metastases along with the lesion dynamics, it enables the modeler to precisely evaluate the maximum information gain obtainable by considering individual tumor lesions in tumor size modeling of resistance to anticancer drugs.

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Nelleke Snelder PKPD modelling of the relationship between testosterone and PSA in patients with prostate cancer during treatment with leuprorelin – What is the optimal testosterone level?

N. Snelder(1), H. Drenth(1), K. Bergmann(1), N. Wood(2), M. Hibberd(2), and G. Scott(2)
(1) LAP&P Consultants BV, Leiden, The Netherlands, (2) Takeda Development Centre Europe Ltd, London, United Kingdom

Objectives: The main goal in the treatment of prostate cancer with gonadotropin-releasing hormone (GnRH) agonists is to achieve and maintain testosterone concentrations below castration level. However, this level is based on available, and improving, measurement techniques, while a relationship between testosterone and clinical outcome, i.e. survival [1], is lacking. Prostate specific antigen (PSA) serum concentrations are used as a surrogate marker for disease control in clinical practice [2]. This investigation aimed to characterize, in a quantitative manner, the relationship between leuprorelin (a GnRH agonist), testosterone and PSA concentrations over time in order to aid identification of a target testosterone concentration which optimises the balance of the benefits of testosterone suppression whilst reducing the risks of futile oversupression.

Methods: Data from a single dose study to investigate the effect of leuprorelin in a 6 month depot formulation on testosterone and PSA in prostate cancer patients were analysed using a population

pharmacokinetic-pharmacodynamic (PKPD) modelling approach. The developed model was qualified using external data from two clinical studies, in which the effect of different formulations of leuprorelin on PSA and/or testosterone was evaluated in healthy elderly male volunteers and in prostate cancer patients, respectively.

Results: The effect of leuprorelin on the relationship between testosterone and PSA was adequately characterized by the Romero model [3] with minor modifications, combined with a turnover model to describe the delay in response between testosterone and PSA. A model based on the assumption that PSA concentrations do not decrease anymore even when testosterone concentrations would go to zero resulted in a significantly better description of the data, than a model assuming that both PSA and testosterone concentrations could go to zero.

Conclusions: The model-based analysis suggests that reducing testosterone concentrations below 35 ng/dL does not result in a further decrease in PSA levels (>95% of the minimal PSA level is reached). More data is required to support this relationship in the lower testosterone and PSA range. Since the absolute minimal PSA concentration reached during treatment with GnRH agonists is largely determined by the PSA concentration before treatment, the percentage reduction in PSA may be a better criteria for response to treatment than the he absolute minimal PSA concentration.

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Anna Georgieva Kondic Model-based analysis of the relationship between pembrolizumab exposure and efficacy in patients with melanoma and NSCLC: across indication comparison

M. Chatterjee*, D.C. Turner*, M. Ahamadi*, Dinesh de Alwis*, J. Elassaiss-Schaap**, T. Freshwater*, R de Greef***, C. Li*, K. Mayawala*, J. Stone*, A. Kondic* (presenting author)
-Merck Sharp and Dohme, 126 E Lincoln Ave, Rahway, NJ 07065; ;PD Value; ***--Quantitative Solutions;Pivot Park Molenweg 79, 5349 AC Oss The Netherlands*

Objectives: To quantify the relationship between exposure to the Programmed Cell Death 1 (PD-1) inhibitor pembrolizumab in serum (AUC over 6 weeks at steady state) and the anti-tumor response in patients with melanoma and Non-Small Cell Lung Cancer (NSCLC), measured as the sum of the longest dimension (SLD) of the tumor lesions. An additional goal is to create a modeling framework that can quantify the time course of tumor growth and shrinkage and characterize potential differences between melanoma and NSCLC indications.

Methods: Non-linear mixed effects modeling approach was used, where the structural model was parameterized with both first-order tumor growth and shrinkage rates. As pembrolizumab binds to immune cells rather than tumor cells, its effect was linked to shrinkage rate. In addition, the model assumes that some fraction of the tumor mass to be accessible for immune-mediated antitumor

effect with the remaining tumor portion insensitive to treatment. Population parameter values and inter-individual variability were estimated from the available data via NONMEM 7.2, using SAEM for parameter estimation, and importance sampling (IMP) estimation method for likelihood evaluation. Simulations were conducted with final parameter estimates and compared to clinical data. .

Results: A total of 897 melanoma and 496 NSCLC patients were analyzed. Observed tumor size data showed a wide-range of longitudinal response patterns, well-characterized by the model. Model parameters were estimated with good precision. The analysis demonstrates an esseintially flat relationship between exposure and reduction in tumor size in the dose range studied. Comparing model parameters between the two indications suggest that the tumor growth characteristics are indication-specific with the growth term for melanoma predicted to be half of that for NSCLC. The model predicts that the drug effect on antitumor response is similar across indications, consistent with its pharmacological mechanism (binding to systemic T-cells that elicits a downstream tumor cell clearance).

Conclusions: The exposure-response modeling approach applied to pembrolizumab has been an important component in optimizing the current clinical dose of 2 mg/kg Q3W, demonstrating comparable efficacy to 10 mg/kg Q3W. The model presented here shows promise as a tool in providing an integrative look across indication, delineating system-specific properties from drug-specific properties. While the results are premature with two indications analyzed thus far, this approach will also be extended to other solid tumors.

Pauline Mazzocco Modeling the emergence of resistance in low-grade glioma patients treated with temozolomide, and simulations using a stochastic approach

P. Mazzocco (1), F. Ducray (2), A. Leclercq-Samson (3)
(1) Inria, Project-team NUMED, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, 69007 Lyon Cedex 07, France ; (3) Hospices Civils de Lyon, Hôpital Neurologique, Neuro-oncologie,Lyon, 69003 France; Inserm U1028 ; CNRS UMR5292 ; LyonNeuroscience Research Center, Neuro-oncology and Neuro- inflammation team, Lyon,F-69000, France; University Lyon 1, Lyon, F-69000, France (3) Université Joseph Fourier, Grenoble, UFR IM2AG, Laboratoire Jean Kuntzmann, UMR CNRS 5224; 38 041 Grenoble Cedex 09.

Objectives: To develop a mixed-effect modeling framework to describe the emergence of resistance in low-grade glioma (LGG) patients treated with temozolomide (TMZ).

Methods: We analyzed a dataset containing mean tumor diameters (MTD) in 77 LGG patients, treated with first-line TMZ, representing a total of 952 observations. TMZ is known to induce DNA mutations that decrease chemo sensibility of the tumor. Almost half of the patients (n = 34, 44%) experienced tumor progression during treatment.
We proposed a mixed-effect model, using ordinary differential equations (ODE), to describe the observed MTD, especially the resistance phenomenon. To this purpose, we modified a previously

published model [1] and added a sub-population of resistant cells to describe the emergence of resistance in a more mechanistic manner. We tested different hypotheses for the emergence of resistance, including mutations due to TMZ and random mutations that can occur at any time. The best model was chosen according to the regular selection criteria. Model parameters were estimated in a population context, using Monolix [2] (Lixoft [3]).
ODE model parameter estimates were then used to simulate tumor dynamics through a stochastic approach. That later introduced some randomness that compensated effects of factors that were not included in the model, such as environmental factors. We implemented stochastic differential equations (SDE) in Matlab to allow for some randomness in the processes involved in tumor evolution, before, during and after the treatment.

Results: We found that the best ODE model includes mutations due to TMZ, as well as random mutations that can occur before, during and after treatment. The model reproduced the different tumor dynamics observed in our population, including tumor progression during treatment.
We then added noise on the TMZ clearance and on the mutation parameters. Empirical distributions for time to progression, time to tumor growth and minimal tumor size were then derived from these distributions.

Conclusions: Our results indicated that two different processes were involved in the emergence of resistance: random mutations and mutations due to TMZ chemotherapy. Thanks to simulations with SDEs, empirical distributions were build for time to tumor growth, time to progression and minimal tumor size. This modeling framework could be used to test different therapeutic protocols for TMZ administration, in order to delay the emergence of resistance and prolong tumor response to treatment.

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Jae Eun Ahn Modelling and Simulation of Motor Symptom Measurements in Parkinson's Disease after L-Dopa Administration

Jae Eun Ahn (1), Sridhar Duvvuri (1), Danny Chen (1), and David L. Gray (2)
(1) PTx Neuroscience Clinical Pharmacology, Pfizer, Cambridge, MA; (2) Neuroscience Research Unit, Pfizer, Cambridge, MA

Objectives: To simultaneously characterize multiple motor symptom measurements such as Movement Disorder Society's Unified Parkinson's Disease Rating Scale Part 3 (UDPRS motor) scores, finger tapping speed (root mean square angular velocity) measured by Kinesia Technology, and patient's reported diary (ON/OFF-state times) after L-Dopa administration in Parkinson's Disease (PD) patients.

Methods: L-Dopa exposure-responses were obtained as a part of a phase 1B, randomized, subject and investigator-blind, sponsor-open, placebo controlled, cross-over efficacy, safety, and tolerability study of a novel compound in Parkinson's patients. L-Dopa was administered in the form of Sinemet during the open label period 1. Analysis data consisted of 11 per protocol analysis subjects. Pharmacokinetic and pharmacodynamic data were simultaneously analyzed using NONMEM 7.3 [1].

Results: UPDRS motor score *and* finger tapping speed data were adequately described by an inhibitory Emax *and* linear model with effect compartments [2], respectively. Unlike motor scores, baseline dependency in response was not apparent in finger tapping speed. The equilibrium half-life for delay in effects was slightly shorter for motor scores than finger tapping speed (0.74 hr vs. 1.2 hr). Patient dairy records consisted of sleeping, off, on without dyskinesia, on with non-troublesome dyskinesia, and on with troublesome dyskinesia. Proportional odds model was initially applied with an assumption that such data are ordered categorical with respect to L-Dopa exposure but the description of such model to the data was inadequate. % off time (wake) appeared to be proportional to baseline motor scores.

Conclusions: Motor symptom measurements in PD patients were characterized with respect to L-Dopa exposures. Although motor responses such as UDPRS motor scores and finger tapping demonstrated exposure-related changes, patients' report on when they feel "ON" or "OFF" was hard to correlate or quantify with PK exposure or other motor response in this small data set and study design.

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Mona Alameddine Optimal phase 2 dose selection based on the relationship between exposure and target occupancy

Mona Alameddine, Christophe Boetsch, Ronan Carnac, Patricia Sanwald-Ducray and Nicolas Frey
Clinical Pharmacology, Roche Innovation Center Basel, F.Hoffmann-La Roche

Objectives: Target occupancy is a useful metric to confirm drug engagement with the target in early clinical phase and to potentially predict the expected clinical response in the target patient population. For most first in class compounds in Neuroscience there is usually a high uncertainty on the link between TO and the clinical response and it is a challenge to determine which doses should be tested in Phase 2. To help the project team to address this challenge for our drug X, a CNS small molecule currently in phase 1, we proposed to build a population pharmacokinetic (PK) model and an exposure-TO model and to combine them to determine using simulations the optimal number of doses that should be investigated in Phase 2.

Methods: Using Phase 1 PK data a Population PK model was build using NONMEM (Version 7.2.0). Using Phase 1 PET data an exposure- TO model was build using Phoenix NLME (Version 1.2). By combining those 2 models, 24-h steady-state TO time profiles were simulated for 7 different doses. For each dose, the percentages of

hourly TO measurements within expected relevant region of interests, three non-overlapping 3 predefined ranges of TO (10-30%, 30-50%, 50-80%) were calculated and were used to select the number of doses to be investigated in Phase 2 to get an optimal coverage of the TO range and to properly characterize the TO-clinical response relationship.

Results: Rich Pharmacokinetic (PK) data from 95 individuals were adequately described by a two-compartment Population PK model with first order absorption and elimination. Body weight significantly impacted Inter-compartment Clearance and peripheral volume while age significantly affected peripheral volume. An Emax model adequately described the PKTO relationship using sparse PK and PET scans data in 9 individuals. TO simulations were performed using a distribution of covariate from a historical trial in the same target patient population in order to properly account for the covariate impact on PK. By comparing the results of the 7 simulated doses using graphical illustration, we determined that at least 3 doses should be investigated in Phase 2 to get an appropriate coverage of the overall TO range compared to 2 doses.

Conclusions: We successfully leveraged the target occupancy information collected in Phase 1 to identify the optimal number and strength of doses to be evaluated in Phase 2 to properly characterize the target occupancy-efficacy relationship that ensures later a robust dose selection rationale for the confirmatory trials.

Hesham Al-Sallami Development of a population pharmacokinetic-pharmacodynamic model of a single bolus dose of unfractionated heparin in paediatric patients

Hesham S Al-Sallami (1), Fiona Newall (2,3,5), Paul Monagle (2,3,5), Vera Ignjatovic (2,3), Noel Cranswick (2,4), Stephen Duffull (1)
(1) School of Pharmacy, University of Otago, Dunedin, New Zealand (2) Department of Paediatrics, University of Melbourne, Australia (3) Murdoch Children's Research Institute, Melbourne, Australia (4) Department of Pharmacology, University of Melbourne, Melbourne, Australia (5) Clinical Haematology, Royal Children's Hospital, Melbourne Australia

Objectives: Unfractionated heparin (UFH) is the anticoagulant of choice in paediatric patients undergoing a variety of cardiac procedures. The ability to predict the dose-response relationship of UFH is essential in order to optimise its dosage. There are currently no population pharmacokinetic-pharmacodynamic (PKPD) models for UFH in paediatrics. The objectives of this work are to develop and evaluate a PKPD model to predict the dose-response relationship of UFH in paediatrics. Also, to explore the use of fat-free mass (FFM) to guide dose-individualisation of UFH in this population.

Methods: Data from 64 infants and children who received 75-100 IU/kg of UFH during cardiac angiography were analysed. Four

plasma samples were collected at baseline and at 15, 30, 45, and 120 minutes post-dose. UFH concentration (231 measurements) was quantified using a protamine titration assay. UFH effect (164 measurements) was quantified using activated partial thromboplastin time (aPTT). A PKPD model was fitted to the data using the non-linear mixed effects modelling software NONMEM v7.2. Various patient covariates such as age, weight (Wt), and FFM were tested. The final model was evaluated using the likelihood ratio test and visual predictive checks (VPCs).

Results: A one-compartment model with linear elimination provided the best fit for the dose-concentration data. Wt and FFM had substantial influence on model fit; FFM was preferred statistically. A linear model provided the best fit for the concentration-effect data using the PPP&D sequential estimation method. Censored PD data (above the upper limit of quantification) were accounted for using the M3 method. The PKPD model performed well using visual predictive checks.

Conclusions: A PKPD model to describe the time-course of UFH effect was developed in a paediatric population which received a high single prophylactic bolus dose. FFM was shown to describe drug disposition well and can potentially be used in dose calculation after appropriate evaluation.

Oskar Alskär Interspecies scaling of the integrated glucose insulin model

Oskar Alskär (1), Mats O. Karlsson (1), Maria C. Kjellsson (1)
(1) Pharmacometrics research group, Department of Pharmaceutical biosciences, Uppsala University, Sweden

Background and objective: The integrated glucose insulin (IGI) model is a semi-mechanistic model that describes glucose and insulin concentrations in humans during glucose tolerance tests [1]. The objective of this work was to investigate if the model can be scaled to describe intravenous glucose tolerance test (IVGTT) data from several preclinical species.

Methods: Glucose and insulin concentrations from IVGTTs performed in rats, mice, dogs, cats and humans as well as the body weight of each subject was available for analysis [2-7]. In the first step allometric scaling based on body weight was investigated. The most suitable value for the allometric exponent was investigated for all parameters in the model, based on objective function value, parameter uncertainty and model complexity. In the second step species adaptations was investigated by scaling parameters with the weight of organs relevant to that parameter in each species. The cat data showed substantially different glucose and insulin profiles. For this reason the cat data was excluded from model development to not distort the allometric scaling relationship. The glucose and insulin baselines as well as the residual error were estimated for all species.

Results: Estimating one allometric exponent for clearances (0.85), one exponent for volumes (0.9), one exponent for first phase secretion (0.79) and fixing the exponent of rate constants to -0.25 described the data well and kept the scaling complexity low. Estimating an allometric exponent for the power functions for glucose effect on glucose production and insulin secretion (GPRG, IPRG) did not improve the fit and they were fixed to the human values. Dogs showed lower first phase secretion and stronger second phase secretion of insulin than the model predicted and these two parameters (IFST, IPRG) were estimated for dogs. Of the investigated scaling relationships with species specific organ weights only liver weight on insulin clearance improved the fit. The final model was applied to the cat data and IFST and IPRG was estimated and displayed under prediction of glucose concentrations.

Conclusions: The allometrically scaled IGI model can accurately preclinical IVGTT data. The omnivores (mouse, human, rat) show different insulin response to an intravenous glucose bolus dose compared to carnivores (cat, dog). The allometrically scaled IGI model can be used in drug development to facilitate better translations of preclinical research into clinic.

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Robert Andersson Dose-response-time modelling - Second generation turnover model with integral feedback control

Robert Andersson (1,2) Mats Jirstrand (2) Lambertus A. Peletier (3) Michael J. Chappell (1) Neil D. Evans (1) and Johan Gabrielsson (4)
(1) University of Warwick, Coventry, United Kingdom (2) Fraunhofer-Chalmers Centre, Gothenburg, Sweden (3) Leiden University, Leiden, The Netherlands (4) Swedish University of Agricultural Sciences, Uppsala, Sweden

Objectives: To demonstrate the utility of a dose-response-time (DRT) model using a large preclinical biomarker dataset of nicotinic acid (NiAc) induced changes on free fatty acids (FFA).

Methods: Data were collected from studies where different rates, routes, and modes of NiAc provocations on the FFA time course had been tested [1]. All information of the exposure were excluded in order to use a DRT approach. Different models structures, describing the biophase kinetics, were assessed and quantitatively and qualitatively compared. The modeled biophase drug amount was assumed to act as the `driving force`of an inhibitory Imax-model which acted on the turnover of FFA. An integral feedback controller was used to model the slow adaptation process that forces FFA levels back to baseline values under long-term NiAc provocations. Finally, new numerical algorithms were applied, which rely on sensitivity equations to robustly and efficiently

compute the gradients of the approximate population likelihood function in mixed-effects modelling [2].

Results: The DRT model successfully captured the behaviour of all FFA time courses. The model predicted 90% adaptation within four days of constant-rate infusions of NiAc, using rates that lead to therapeutic concentrations. High consistency of the pharmacodynamic parameters was shown when compared to an exposure-driven study by Tapani et al. [3].

Conclusions: The versatility of the DRT approach was shown by successfully fitting a DRT model to all FFA time courses. Different feedback mechanisms were described, using moderator compartments and integral feedback control. The consistency in the pharmacodynamic parameters, when comparing to an exposure-driven approach, demonstrates the utility of DRT analysis in a wider context.

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Yusuke Asai Mathematical modeling by random ordinary differential equations and their numerical schemes

Yusuke Asai and Eva Herrmann
Goethe-University Frankfurt

Objectives: Random ordinary differential equations (RODEs) are introduced to build mathematical models with noise processes. Numerical schemes for RODEs are developed via RODE-SODE transformation and they are applied to biological models. The accuracy of the schemes as well as their computational costs are compared.

Methods: Lotka-Volterra model and virus kinetic model are randomized by adding two different types of noise processes. In the first case, a Wiener process is adopted to make the predatory rate fluctuated and noisy switching scenario is described in simple prey-predator system. The explicit numerical schemes, namely RODE-Taylor schemes, stochastic linear multi-step methods (SLMMs) and the averaged schemes, are applied to the model. The second example is a three compartment virus kinetics model with spatial dependence. An Ornstein-Uhlenbeck process is taken as a stochastic process and the loss rate of virus is randomized. The random partial differential equation (RPDE) is discretized with respect to space and implicit schemes are tested to the corresponding system of RODEs.

Results: Two steady states, which have been reported in multiple preys models, could be observed in the simulations. The averaged schemes show the same convergence rate with 1-step and multi-step 1-order schemes. Their computational costs are quite small while the accuracy is relatively low comparing to higher order schemes. The dimension of first example is low and no big difference in computational cost is observed between Ito-Taylor schemes and SLMMs. On the other hand, the second example is of high dimension due to the spatial discretization and computational costs, especially between 1.5-order Ito-Taylor scheme and SLMM, is quite apparent.

Conclusions: The SLMMs have big advantage from the point of computational costs especially when they are applied to large systems. The implicit schemes are stable and can be applied to stiff systems or spatially discretized RODEs. Choosing appropriate type of noise is still an open question and further investigation will be necessary.

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Hyun-moon Back A Mechanistic multicompartmental Pharmacokinetic model for food effect of fenofibrate

Hyun-moon Back (1), Byungjeong Song (1), Hwi-yeol Yun (1), Jung-woo Chae (1), Kwang-il Kwon (1)
(1) College of Pharmacy, Chungnam National University, Korea

Objectives: Fenofibrate is a prodrug of the active metabolite fenofibric acid and it is used for hypercholesterolemia and hypertriglyceridemia. Absorption of fenofibrate is significantly different after consumption of food [1]. The aim of this study was to develop a mechanistic population pharmacokinetic model of fenofibrate following food consumption in human.

Methods: A randomized, three-way crossover trial study was conducted in 24 healthy Korean subjects (13 male, 11 female). PK data collected after administration of fenofibrate 250mg and different food type on three occasions, with a 1-week wash out period between each drug administration. A mechanistic multicompartmental PK model was developed in NONMEM 7.3.0 [2]. Linear and nonlinear effect were evaluated for explaining impact of food intake measured by calorie on fenofibrate absorption. For explaining change of gastric emptying time of fenofibrate affected by food, MTIME option in *ka* was assessed. For evaluating the final PK model, visual predictive check was performed.

Results: Multi-compartment model with two physiological compartments for fenofibrate and two additional compartments for food consumption best described fenofibrate pharmacokinetics. Amount of calorie intake was used to explain food effect and in our final model. The absorption of fenofibrate was stimulated depending on the amound of calorie in duodenum compartment. The visual predictive check (VPC) was performed and the prediction power of final model was acceptable.

Conclusions: A mechanistic multicompartmental PK model was successfully developed and acceptable parameters were obtained for explaining fenofibrate absorption variation after food intake. Using this final model, we can simulate PK of fenofibrate following food intake and make a quantification of fenofibrate concentration depending on the amount of calorie.

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Kathryn Ball Semi-physiological population pharmacokinetic modelling of renal transporter-mediated clinical drug-drug interactions

Kathryn Ball (1), Sylvain Fouliard (1), Yannick Parmentier (2), François Bouzom (2), Marylore Chenel (1)
(1) Clinical Pharmacokinetics and Pharmacometrics Department, Institut de Recherches Internationales Servier, Suresnes, France, (2) Nonclinical Pharmacokinetics and Biopharmaceutical Research Department, Technologie Servier, Orleans, France

Objectives: The once-separate disciplines of population pharmacokinetic (Pop PK) modelling and physiologically based pharmacokinetic modelling (PBPK) are becoming more and more frequently entwined. A population semi-physiological PK model for a Servier compound (S1) was built in order to (i) simulate renal drug-drug interactions (DDI) prior to a clinical study, and (ii) to estimate the inhibition constant K_i from the clinical data.

Methods: A semi-physiological PK model was built for S1 as a victim of DDI, with a separate compartment to represent renal tubule cells [1]. The kinetic parameter of transporter-mediated active secretion was estimated by fitting the model to Phase I clinical study data (plasma and urine concentrations simultaneously). A PK model for probenecid was constructed to provide the time course of inhibitor concentrations, and the *in vitro* K_i was used to provide the inhibition potential and simulate the DDI with S1. The data from the

subsequent clinical DDI study was then used to estimate the model parameter K_i (resulting in a so-called '*in vivo* K_i') and compare with the previously used *in vitro* value.

Results: The extent of DDI predicted using the model and *in vitro* K_i was a 2-fold increase in plasma AUC of S1 and a 2.5-fold reduction in S1 renal clearance. This was in agreement with the observed interaction ratios (2-fold increase in plasma AUC, 2.5-fold reduction in renal clearance). The '*in vivo*' K_i (6.9 µM) was estimated with a good precision, and was similar to the *in vitro* value of 7.5 µM.

Conclusions: A good agreement was obtained between the *in vitro* (experimentally measured) and *in vivo* (model-estimated) inhibition parameter, which could give confidence in using this approach to predict renal DDI *a priori*. Although there are relatively few examples of renal DDI modelling in the literature, the extent of renal transporter-mediated DDI is generally low, so physiologically-structured population PK modelling could be used to replace clinical DDI studies when a negligible interaction is predicted [2].

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Guillaume Baneyx Population PK model describing multiple peaks after a single oral administration of buparlisib in healthy volunteers.

G. Baneyx (2), P-H. Huang (3), C. Meille (1) and V. Duval (2)
Novartis Pharma AG, Translational Clinical Oncology (1) and Oncology Clinical Pharmacology (2), Basel, Switzerland. (3) Novartis Pharmaceuticals Corporation, Oncology Clinical Pharmacology, East Hanover, New Jersey, USA.

Objectives: Buparlisib is an anticancer drug inhibiting the PI3K pathway [1] and presently in Phase 3 development. Visual inspection of buparlisib plasma PK profiles showed multiple peaks after oral administration in healthy volunteers (HVs) and cancer patients. The objective of this study was to develop a PK model able to describe the observed multiple peaks in healthy volunteers and quantify the contribution of this phenomenon.

Methods: In a first step, plasma concentrations of 60 HVs from 3 Phase 1 studies collected up to 240h after a single oral administration were used to develop a PK model structure including a drug recirculation component. Then based on modeling results, an additional sampling time was added to the design of a fourth Phase 1 study enrolling 16 HVs in order to confirm drug recirculation hypothesis and better characterize this phenomenon. Finally, a pooled analysis was performed with all PK data from these studies.

Model parameters were estimated using population approach with Monolix 4.3.2 [2].

Results: A third compartment representing the gallbladder was added to a classical 2 compartment disposition model in order to mimic a potential biliary excretion of buparlisib. The release of buparlisib amount stored in the gallbladder compartment was assumed to occur only at 3 meal times per day and directly in depot compartment. Meal times were estimated at 3, 9 and 21h post dose which is in agreement with theoretical lunch, dinner and breakfast times, respectively. Contribution of biliary excretion to buparlisib PK is suggested to be an important component since the fraction of dose excreted in bile was estimated to 10-30%.

Conclusions: Buparlisib multiple peaks occurring around meal times were well described by the proposed PK model suggesting an entero-hepatic circulation which is in agreement with preclinical results. This model will be applied to PK data in cancer patients obtained after continuous daily dosing.

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Charlotte Barker Population pharmacokinetics of benzylpenicillin in neonates in routine care

Charlotte I.S. Barker (1,2), Iblal Rakha (2), Karin Kipper (1), Mark A. Turner (3), Mike Sharland (1), Joseph F. Standing (2)
(1) Paediatric Infectious Diseases Research Group, St George's, University of London, (2) UCL Institute of Child Health, (3) Department of Women's and Children's Health, University of Liverpool

Objectives: Penicillin G remains widely used in neonates and, with gentamicin, it forms the mainstay of standard treatment for early onset sepsis in the UK. Despite widespread usage, the pharmacokinetic/pharmacodynamic (PK/PD) data to support current neonatal dosing regimens are limited. NAPPA is a population-PK study utilizing opportunistic sampling strategies to study the PK of penicillins during routine care of neonates/children. This interim analysis aimed to investigate the population PK of penicillin G in the first cohort of neonatal participants.

Methods: Eligible neonates, receiving intravenous penicillin G as part of routine care, were recruited at participating sites. The dosing regimen was as per normal local NHS (National Health Service) practice. After informed consent was obtained, study blood samples (0.5mL each) were obtained by clinical staff at the time of routine blood tests or blood gases. Samples were frozen at -80 degrees Celsius and analysed retrospectively. The plasma samples were analysed using high-performance liquid chromatography with

tandem mass spectrometry. A population-PK model was fitted simultaneously to the measured drug concentration-time data using non-linear mixed-effects modelling software (NONMEM v7.3, Icon plc). The study protocol was approved by an NRES Research Ethics Committee.

Results: For the interim analysis, 102 evaluable samples were available from 45 neonates (22 term; 23 preterm). Using NONMEM v7.3, one-, two- and three-compartment models were tested, using FOCE-I method, and the objective function values were compared. A two-compartment model was most suitable for these data; the final parameter estimates were 0.10 L/h for clearance (CL) and 0.34 L for central volume of distribution, 0.03 L/h for intercompartmental CL and 0.72 L for volume of the peripheral compartment.

Conclusions: In conclusion, a population PK model was developed based on interim neonatal penicillin G data. A two-compartment model resulted in the best fit to the data. Future work will include the addition of allometric scaling and a function describing the maturation of the glomerular filtration rate. Covariate analysis will also be performed, to assess factors including birth weight, gestational age, and renal function.

Christian Bartels Relation of FEV1 to COPD Patient Outcomes: A patient level pooled analysis of COPD clinical trials

Christian Bartels(1), Peter D'Andrea(2), Donald Banerji(2), Robert Fogel(2), Francesco Patalano(1), David Morris(1), Jessica Marvel(2)
(1)Novartis Pharma AG, Basel, Switzerland; (2)Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Objectives: The measurement of lung function by spirometry (specifically FEV_1) is routinely used to measure the efficacy of bronchodilators. However, measurement of patient's outcomes is also important as it directly reflects the patient's quality of life. Previous studies have shown FEV_1 can be a good predictor of future morbidity, and mortality, patient reported outcomes (PROs) and exacerbation frequency [1][2]; however, they did not include information on COPD patients treated with a LABA/LAMA combination.

This patient level pooled analysis of COPD clinical trials further characterizes the correlation between FEV_1, and patient outcomes as measured by St Georges Respiratory Questionnaire (SGRQ) in COPD patients treated with LABA (indacaterol), LAMA (glycopyrronium) and LABA/LAMA dual bronchodilator, QVA149 (fixed-dose combination of indacaterol maleate and glycopyrronium bromide).

Methods: Pooled data from twenty-three randomized, parallel-group, placebo- or active-controlled studies (3 to 18 months duration; 23,213 patients) on FEV_1 and SGRQ scores in COPD patients was analyzed using descriptive statistics of correlations. Linear mixed effect models were used to determine, if changes in FEV_1 can predict improvements in patient outcomes.

Results: Summary statistics showed statistically significant correlations between FEV_1 and SGRQ. Compared to patients with a small response in FEV_1, patients with larger response in FEV_1 had on average better SGRQ scores.

Longitudinal mixed effects models demonstrated that the change in FEV_1 from baseline was predictive of change in SGRQ. The models attributed part of the treatment efficacy in SGRQ to improvements in FEV_1.

Analyses of simulated data generated assuming a strong association of SGRQ and FEV1 and taking into account variability of the FEV1 measurements illustrated that due to regression dilution bias[3] the mixed effects models underestimate correlations.

Conclusions: The analysis showed that there is a statistically significant correlation between the average change in FEV1 from baseline and change in SGRQ from baseline. FEV1 change from baseline has been shown to be a predictive marker in assessing the effectiveness of bronchodilation treatment in COPD patients. Due to variability of FEV_1 measurements, correlations with other endpoints are underestimated. Efficacy in SGRQ may be primarily due to bronchodilation which is measured by FEV_1.

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Ana Bastos A joint population pharmacokinetic model of total and unbound temocillin serum concentrations in hemodialysis patients

Miranda Bastos AC (1,2,3) , Vandecasteele SJ (4), Capron A (5), Tulkens PM (1,3), Spinewine A (2,3), Van Bambeke F (1,3)
(1) Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium (2) Clinical Pharmacy Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium (3) Center for Clinical Pharmacy, Université catholique de Louvain, Brussels, Belgium (4) Department Nephrology and Infectious Diseases, AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium (5) Department of Clinical Chemistry, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

Objectives: Temocillin is a narrow-spectrum anti-gram-negative beta-lactam antibiotic. Its pharmacokinetics in hemodialysis patients have not been investigated yet. The purpose of this study was to develop a model describing the pharmacokinetics of total and unbound temocillin serum concentrations in end stage renal disease patients undergoing hemodialysis. In addition, this study aims to evaluate by simulation, the clinical performance of current dosing regimens, considering that β-lactam efficacy is best predicted by the proportion of the dosing interval during which unbound concentrations remain above the MIC (minimal inhibitory concentration) of the offending organism.

Methods: 16 patients were administered a dose of 1, 2, or 3g of temocillin (total of 61 doses) followed by an interdialytic period (off-dialysis) of 20, 44, or 68h, respectively, and dialysis period of 4h. 429 serum samples were collected to measure total and unbound concentrations. A population PK model was constructed and evaluated by a bootstrap analysis (internal evaluation, 1000 runs) and visual predictive check. A 1000-subject Monte Carlo simulation was conducted to determine 95% probability of target attainment (PTA95) versus MIC, based on 40% time above MIC (ƒT > MIC) for measured unbound (free) drug. Data analyses were performed using NONMEM 7.3, Pirana, PsN and R.

Results: Temocillin pharmacokinetics was best described by a two-compartment model, non-linear binding to albumin (Langmuir model) and mixed order elimination. Base PK parameters were allometric weight scaled. Temocillin dialysis unbound clearance was estimated to be 6.16 L/h resulting in marked reduction of temocillin serum concentrations. PTA95 was obtained for a MIC up to 8mg/L, for a typical thrice weekly hemodialysis regimen, with temocillin administered immediately after dialysis.

Conclusions: A joint model has been developed to describe the non-linear PK of total and unbound temocillin concentrations. Once the total temocillin serum concentrations are known, the unbound concentrations, which are pharmacologically active, can be predicted. This model might serve as a useful tool to provide guidance in the optimization of temocillin dosing regimens in hemodialysis patients.

Stephan Benay Linear compartmental pharmacokinetic models : from continuous-time differential form to discrete time auto-regression with extra inputs. Application to system identification.

Stephan Benay and Athanassios Iliadis
Dpt. of Pharmacokinetics, Aix-Marseille University, Inserm, CRO2 U 911, 13385 Marseille, France.

Objectives: Even for the simplest pharmacokinetic model, the state variable is a nonlinear function with respect to the model parameters. For this reason, given observations, parameter values cannot be directly computed, but must be estimated by using iterative optimization algorithms. Our proposal is to obtain linear expressions of the state variables for the common pharmacokinetic models, allowing computation of parameter values without using iterative optimization algorithms.

Methods: The one- and two-compartment models with infusion have been transformed from their initial form in continuous time (set of first-order linear differential equations) to a new form in discrete-time (linear transfer function between inputs and states). The transform results in a polynomial form of the transfer function called ARX (Auto-Regression with eXtra inputs) involving a set of new parameters obtained from the parameters involved in the compartmental configuration. In the discrete-time ARX model, the state variables are linear with respect to the parameters. Therefore,

the parameter estimation has been performed straightforwardly without requiring an iterative algorithm. The ARX model parameters have then been estimated using a least squares estimator [1], either on the whole set of data, or recursively by incorporating new data to the set as it becomes available. The ARX and the compartmental parameters are linked by simple algebraic relationships.

Results: The method was applied on real pharmacokinetic data and allowed to successfully estimate parameters of one compartment (fotemustine) and two-compartment (mitoxantrone) models without using any optimization algorithm. Additionally, data was simulated using a one-compartment model with Michaelis-Menten elimination. Using the ARX recursive least squares estimator, the model with linear elimination revealed able to track the time-varying elimination, and correlate it with the drug concentration to discover the Michaelis-Menten nonlinear relationship.

Conclusions: The approach allows estimation of the system parameters through direct, non-iterative calculation. It also has the potential to track apparent time-varying parameters and detect nonlinearities in the process. These kinds of discrete-time, linear-in-parameters models should be proposed to be applied in the population approaches for mixed-effects modeling or in the optimization of experimental designs.

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Poster: Drug/Disease modeling - Safety | I-14 | Wednesday 10:45-12:15

Linnea Bergenholm Population PKPD modelling of QRS and PR intervals in conscious dogs.

Linnéa Bergenholm (1,2), Neil Evans (2), Michael Chappell (2), Teresa Collins (3), Joanna Parkinson (4)
(1) Discovery Safety, Drug Safety and Metabolism, iMED, AstraZeneca, Mölndal, Sweden, (2) Systems Modelling and Simulation, School of Engineering, University of Warwick, Coventry, UK, (3) Translational Safety, Drug Safety and Metabolism, iMED, AstraZeneca, Alderley Park, UK, (4) Early Clinical Development, Quantitative Clinical Pharmacology, iMED, AstraZeneca, Mölndal, Sweden.

Objectives: To develop population PKPD models for describing baseline and drug-induced changes in QRS and PR intervals in dogs using standard telemetry data accessible in drug development. Compare modelling results for a selection of compounds with different mechanism of action.

Methods: Cardiac effects of three antiarrhythmics (AZD1305, flecainide and quinidine) and two anticholinergics (AZD8683 and AZD9164) were investigated in conscious dogs. Plasma concentrations were quantified. Cardiac effects were monitored using surgically implanted telemetry devices. Mixed effects PKPD models were developed sequentially. Individual PK models were used to drive PD modelling of vehicle and treatment QRS and PR interval data. RR interval correction and circadian rhythm models were investigated for identification of appropriate baseline models.

Linear and non-linear direct and link models were tested to describe the drug-induced effects on QRS and PR intervals.

Results: (preliminary) Prolongation of QRS ranged from 9-16% in AZD1305, flecainide and quinidine and prolongation of PR from 21-34% in for AZD1305, AZD8683, AZD9164 and flecainide. Population PK models were able to characterise the drug exposures well. Preliminary results suggest that RR correction and circadian rhythm improve fit to PR but not QRS interval data. Also, drug effects on PR and QRS are best explained by linear models rather than power and Emax models. The slopes of the PK-QRS relationships varied from 2-7 ms/uM unbound drug, while the slopes of the PK-PR relationships were larger.

Conclusions: Baseline and drug-induced effects on QRS and PR intervals were successfully described for five compounds. These models improve our understanding of the concentration-effect relationships and as such add value to the project teams and decision-makers. Also, these analyses could be used to investigate the translational relationship between dogs and humans, potentially improving the prediction of QRS and PR effects in humans before clinical trials.

Aliénor Bergès Time-to-event (TTE) modelling in drug safety evaluation: a case study

Alienor Berges (1), Marc Cerou (1), Claire Ambery (1), Lia Liefaard (1), Stefano Zamuner (1), Emilie Hénin (2), Chao Chen (1)
(1) Clinical Pharmacology Modelling and Simulation, GSK, UK. ; (2) Université Claude Bernard Lyon1, Lyon, France ; UMR CNRS LBBE 5558 – équipe Evaluation et Modélisation des Effets thérapeutiques. Hospices Civils de Lyon, Service de Pharmacologie Clinique et Essais Thérapeutiques.

Objectives: The no-observed-adverse-effect level (NOAEL) of a drug defined from animal studies is crucial for inferring a maximal safe dose in human. However, several issues are associated with its concept, determination and application. For example, simulations showed that the NOAEL value which is identified for a given study highly depends on dose and sample size. [1-3]. We explored how modelling the probability of toxicity as a continuous function of time and dose across studies could potentially overcome these limitations.

The objective of this current work is to apply a TTE approach to histopathology toxicology data in rats for a test compound.

Methods: Binary histopathology data (presence/absence of toxicity, but not severity) from 7 studies (from 6 to 26 week study duration) were combined to develop a time-dose-toxicity model. The data were collected from each animal (n=137) once, at the time of

terminal sacrifice. Parametric hazard modelling was conducted using the *surv* package in the R software (version 3.1.2) [4]. Model selection was mainly based on biological plausibility, AIC criteria, standard error values and simulation-based diagnostic plots. Covariates like dose level were tested in a univariate and multivariate manners.

Results: Due to the nature of data, the exact time of toxicity event was unknown, and all events were left- (toxicity appeared between the study start and sacrifice) or right-censored (toxicity had not appeared at the time of sacrifice). Hence time of observation was limited to a single time point per study, which resulted in 5 main time points in the total dataset. There were 6 dose groups with various sample sizes (from 9 rats in the lowest dose group to 136 in the control group). The model of choice was a time dependent hazard model with a weibull distribution and dose as significant covariate. The diagnostic plots showed a satisfactory fit of the data, despite the high degree of left censoring.

Conclusion: The diagnostic performance of the TTE model was similar to a previous logit model applied to the same data [3]. However, the TTE approach (including time as part of its definition) showed a more mechanistic description of the time impact on toxicity than the logit approach (including time as a covariate). Provided sufficient number of time points, the TTE approach would allow a better prediction of event incidence across study durations and would better inform the choice of experimental toxicity study designs.

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Jan Berkhout Systems pharmacology modeling describing osteoporotic disease progression in a population of postmenopausal women receiving placebo or alendronate

Jan Berkhout (1,2) , Julie A. Stone (3), Katia M.C. Verhamme (1), Bruno H.C. Stricker (4,5), Miriam C.J.M. Sturkenboom (1), Meindert Danhof (2) and Teun M. Post (6)

(1) Department of Medical Informatics, Erasmus Medical Centre, Rotterdam, The Netherlands, (2) Leiden Academic Centre for Drug Research, Division of Pharmacology, Leiden, The Netherlands, (3) Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA, (4) Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands, (5) Drug Safety Unit, The Health Care Inspectorate, The Hague, The Netherlands, (6) Leiden experts on Advanced Pharmacokinetics and Pharmacodynamics (LAP&P), Leiden, The Netherlands

Objectives: A complete mechanism-based model describing osteoblast and osteoclast activity has been reduced in order to apply it in a population-approach. It was shown that the model reduction did not jeopardize the dynamical properties of the model. The reduced model was successfully applied to describe responses in treatment with various doses of tibolone and/or calcium in postmenopausal women. The objective of this study is to use the previously established systems pharmacology model to test whether it can also adequately describe the placebo and

alendronate treatment response in BMD and other bone turnover markers in an external population of postmenopausal women.

Methods: Data were obtained from the Early Postmenopausal Intervention Cohort (EPIC) study, a 4-year clinical trial of oral alendronate in 1609 postmenopausal women randomly assigned in a double-blind manner to receive 2.5 or 5.0 mg alendronate once daily or placebo to evaluate the potential to prevent osteoporosis [1]. The model used is a mechanism-based disease systems model based on [2]. While maintaining the original model structure and system parameter values, we added the alendronate treatment function (as a disease independent proportional symptomatic effect) and updated the BMD dynamics equation (to an indirect-response model) of this model and implemented this in the population approach (NONMEM).

Results: The updated systems pharmacology model was shown to adequately describe the alendronate and treatment response. The final model yielded realistic parameter values that could be estimated with good precision. Visual predictive checks of the final model revealed that the dynamics of all biomarkers for all treatment arms could be described to very good approximation during the four study years. The final model allowed for simulations of the dynamics in BMD and biomarkers and revealed a symptomatic treatment effect for BSAP and a disease modifying effect for NTX and BMD.

Conclusions: We have successfully extended a mechanism-based osteoporosis model based on an external dataset with a different mechanism of action. Developing a robust model to describe the treatment response is of high importance to enable quantification of drug effects, and eventually to guide the design of clinical trials for osteoporosis treatment. Finally, this study shows the strength of a systems pharmacology approach, which could also be of great importance for other degenerative diseases.

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Marival Bermejo Level A IVIVC for Carbamazepine IR formulations and in vitro dissolution specifications using one-step approaches

I Gonzalez-Garcia (1, 3), V Mangas-Sanjuan (2), M Merino-Sanjuán (3), C Alvarez-Alvarez (4), J Diaz-Garzon (4), A Rodriguez-Bonnin (4), JJ Torrado-Duran (4), A García-Arieta (5), IF Troconiz (1), M Bermejo (2)

(1) Pharmacometrics and Systems Pharmacology. Pharmacy and Pharmaceutical Technology Department. University of Navarra; (2) Pharmacy and Pharmaceutical Technology Area. Miguel Hernandez University; (3) Pharmacy and Pharmaceutical Technology Department. University of Valencia; (4) Department of Pharmacy and Pharmaceutical Technology, Complutense University of Madrid; (5) Head of Service on Pharmacokinetics and Generics, Division of Pharmacology and Clinical Evaluation, Department of Human Use Medicines, Spanish Agency for Medicines and Health Care Products.

Introduction: *In vitro-in vivo* correlations (IVIVC) are defined, almost identically, by Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and a relevant *in vivo* response. IVIVC can be useful in product development for quantifying the *in vitro* release, evaluating formulation related effects on absorption, supporting in quality control for certain scale-up and post approval changes, and as a tool for setting *in vitro* dissolution specifications.

Objectives: The purpose of this work is to establish standard dissolution specifications based on a novel approach to ensure *in vivo* bioequivalence for a drug using simulated data.

Methods: A level A IVIVC was developed using differential equations. A one compartment model was assumed for drug disposition. Absorption and elimination were defined as first order processes.The internal validation of the IVIVC was performed using a VPC (n=1000) Then, new formulations were tested using stochastic simulations in order to establish the dissolution specification limits based on the 90% confidence interval of the p50 of the Cmax and AUC. Simulated data were fitted using non-linear mixed-effects modelling implemented in NONMEM 7.2. Simulations were performed using PsN and the R software.

Results: Differential equations method was successfully applied to establish a level A IVIVC and internal was achieved according to FDA and EMA limits. AUC and Cmax results from the 500 simulations of the new formulations were represented. *In vivo* predicted profiles based on each formulation were plotted. Dissolution specification limits were calculated based on the formulations which successfully achieved the 90% CI.

Conclusions: A new method to establish *in vitro* dissolution specifications has been developed incorporating *in vitro* and *in vivo* interindividual and residual variability. This method is more restrictive, but guarantees bioequivalence standards for the new formulations developed based on the IVIVC previously established.

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Julie Bertrand Bayesian Variable Selection for high-throughput genetic association analysis in population pharmacokinetics.

Julie Bertrand (1), Maria de Iorio (2), Celine Verstuyft (3), Monidarin Chou (4), Anne-Marie Taburet (5), David Haas (6) and David J Balding (1).

(1) University College London Genetics Institute, London, UK, (2) University College London Statistical Science Department, London, UK, (3) Departments of Molecular Genetics, Pharmacogenetic, and Hormonology, Assistance Publique Hopitaux de Paris, Hopital Bicetre, Paris, France, and Univ Paris-Sud, EA2706, France, (4) Rodolphe Merieux Laboratory, Faculty of Pharmacy, University of Health Sciences, Phnom Penh, Cambodia, (5) Clinical Pharmacy Department, Assistance Publique Hopitaux de Paris, Hopital Bicetre, Paris, France, (6) Center for Human Genetics Research, Departments of Medicine and Pharmacology, Pathology, Microbiology & Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.

Rational: In population pharmacokinetics (PK), the standard genetic association analysis is a stepwise procedure. We have shown that an integrated approach, simultaneously estimating the PK parameters and the genetic effect sizes, is as powerful in large samples and more powerful to detect single nucleotide polymorphism (SNP) associations with multiple PK parameters [1]. Bayesian Variable Selection (BVS) is growing in importance in high-throughput genetic

association studies, and represents another attractive alternative which can manage both complex study designs and missing genetic data.

Objectives: i) to compare in a simulation study BVS with a stepwise procedure and an integrated approach and ii) to apply BVS to the analysis of nevirapine pharmacogenetics on data from the PECAN ANRS 12154 study.

Methods: BVS was implemented, using the r2jags package, as described by Kuo and Mallik [2]: an indicator variable dictates which SNPs are associated with the PK parameter of interest. We used Bernoulli and Normal priors for the SNPs indicators and effect sizes respectively. SNPs are selected based on the posterior probability distribution of their indicator approximated by means of the Markov chain Monte Carlo algorithm.

In the simulation study, we analysed 200 data sets of N=300 subjects with n=6 concentrations from a two compartments PK model and the genotypes for 1227 SNPs, where 6 unobserved causal variants were associated to the drug oral clearance.

In the PECAN ANRS 12154 study, we analysed 129 patients with trough concentrations on two occasions (after 18 and 36 weeks of treatment) among which 10 patients also had complete PK profiles (6 samples) and the genotypes for 134 SNPs.

Results: BVS detected 216 of the 1200 true signals in the simulation versus 367 and 340 for the stepwise procedure and the integrated approach and 21 false positives versus 34 and 13, respectively.

Using BVS, we found the clearance of nevirapine in HIV-infected Cambodians to be associated with the rs7246456 (in linkage disequilibrium with rs3745274 at $r^2 > 0.6$) and with the rs2279343. Thus, we replicated two out of the three associations found in [3],

where a stepwise procedure was performed using the oral clearance empirical Bayes estimates as phenotypes.

Conclusion: Although simulation study results were not yet competitive, this was an initial attempt and we will explore further developments [2].

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Shanshan Bi Model-Based Meta-Analysis (MBMA) for direct-acting antiviral (DAA) agents in the Treatment of Chronic HCV

Shanshan Bi, Jenny Zheng, Liang Li, Hechuan Wang, Zheng Guan, Fengbo Xie, Gailing Li

Objectives: To understand the underlying mechanisms of each class of direct-acting antiviral (DAAs) agents and/or their interplay when co-administered for the treatment of chronic HCV and also to predict long term efficacy from early clinical outcome, using Model-Based Meta-Analysis.

Methods: A mechanism-based PK/PD model was developed to model the dynamics of hepatitis C virus and the antiviral effect of selected DAAs. 3 DAAs (NS3/4A and NS5A inhibitor) were selected to build the dynamic model. The data sources are collected from extensive literature search based on PUBMED and http://www.natap.org from year 2007 to 2013. The final model described the viral kinetic in hepatitis C via a biphasic decline in viral load with a rapid first phase lasting 1-2 days followed by a slower phase [1]. We learned that the initial rate of viral decline did not depend on the DAAs dose from the published representative data. A linear model with a breakpoint for the beginning time of the HCV relapse was used. A parameter of inhibitions for the virus production was estimated to describe the DAAs effect for these 3

compounds, respectively. The comparison of the potency for the 3 DAAs was evaluated.

Results: The model was developed using summary levels data from 5 clinical trials, 17 unique arms, and assessed by internal evaluation techniques. The beginning time for the relapse after virological response were estimated to be 2.75 days (NS3/4A), 2 days (NS5A) and 2.31 days (NS5A) for these 3 DAAs, respectively. The drug effect for the rapid first phase were different from the slower phase. The coefficient for the inhibition of the virus production of the NS3A/4A inhibitor was estimated to be 0.234 and 0.32 for the biphasic decline, respectively. And the NS5A inhibitors have ~4/2-fold greater drug potency than the NS3A/4A inhibitor.

Conclusions: This study demonstrates the application of MBMA in the field of HCV treatment. The modeling and simulation results will be used to improve confidence in the selection of DAA combinations.

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Andrzej Bienczak Population Pharmacokinetic/Pharmacogenetic Analysis of Nevirapine in African Children

Andrzej Bienczak (1), Sandra Castel (1), Quirine Fillekes (2), Lubbe Wiesner (1), Andrew Owen (3), Sarah Walker (4), Diana Gibb (4), David Burger (2), Helen McIlleron (1), Paolo Denti (1) and CHAPAS1/CHAPAS3 Study Teams

(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; (2) Department of Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; (3) Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom (4) MRC Clinical Trials Unit, London, United Kingdom;

Objectives: Nevirapine is a NNRTI widely used for treatment of HIV-infected adults and children. It is metabolised by *CYP3A4* and *CYP2B6* [1]. *CYP2B6* polymorphisms significantly influence the disposition of the drug and their prevalence differs between populations [2].

The aim was to characterise the pharmacokinetics (PK) of nevirapine in African children and to identify patient characteristics influencing its disposition**.**

Methods: Data were pooled from two clinical trials in HIV positive children at four sites in Uganda and Zambia. In the CHAPAS1 study,

7 samples were collected at a single PK visit in 84 children (aged 0.25-15 yrs). In the CHAPAS3 study, 2 samples were collected on 4-7 PK visits, in 334 children (aged 0.45-12.35 yrs) followed longitudinally for 2 years. Concentrations below the lower limit of quantification (LLOQ; 0.0195 mg/L) were imputed as LLOQ/2 [3].

Model building was conducted using NONMEM 7.3 (FOCE-I) following an approach previously suggested to combine intensive and sparse data [4]. Allometric scaling [5] was conducted to account for the effect of body size, and the influence of age and *CYP2B6* genotype on CL were investigated.

Model building was guided by differences in objective function value (OFV) and diagnostic plots, including visual predictive checks.

Results: A total of 2989 nevirapine concentrations were included in the analysis and were best described using a 1-compartment model with absorption through a series of transit compartments and first-order elimination [6].

Besides the effect of weight through allometric scaling, the most significant determinant of nevirapine PK was *CYP2B6* 516|983 genotype on CL [2]. Patients were allocated to 4 metaboliser groups based on their genotype: fast (CL=1.87 L/h, for a 15.4 kg child), intermediate (1.40 L/h), slow (0.87 L/h), and ultra-slow (0.51 L/h). Children with no available genotype information (n=79) were assigned to a group using a mixture model reflecting the prevalence in the rest of the cohort [7].

Including terms to correct for the increased uncertainty in the time of unobserved doses preceding the sparse samples improved fit, leading to an increase in RUV and BOV in bioavailability.

No effect of maturation was detected.

Conclusions: Nevirapine metabolism in children is affected by a composite effect of 2 SNPs in CYP2B6: 516GT (rs3745274) and 983TC (rs28399499). The lack of significance of a maturation effect could be due to small numbers under 2 years of age.

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Konstantinos Biliouris MatVPC: A User-friendly Matlab Tool for the Automatic Construction of Visual Predictive Checks and Quantified Visual Predictive Checks of Systems Pharmacology Models

Konstantinos Biliouris (1), Marc Lavielle (2), Mirjam N Trame (1)
(1) Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, USA, (2) Inria Saclay, POPIX team, Saclay, France

Objectives: Quantitative Systems Pharmacology (QSP) models are progressively entering the arena of contemporary pharmacology [1]. The efficient implementation and evaluation of complex QSP models necessitates the development of flexible computational tools that are built into QSP mainstream software. The objective of this study was to develop a versatile Matlab-based tool that accommodates complex QSP models and executes Monte Carlo simulations as well as automatic construction of Visual Predictive Checks (VPCs) [2] and Quantified VPCs (QVPCs) [3].

Methods: A computational tool, dubbed MatVPC, was built in Matlab 2013a for the simulation and automatic construction of VPC and QVPC plots of QSP models. In this tool, the user simply inputs i) the NONMEM-like dataset with observations, ii) the model equations, iii) the model parameters, and MatVPC outputs VPCs, QVPCs and Monte Carlo simulation plots at will. Unlike comparable computational tools, MatVPC is a unique all-in-one package that integrates the following: 1) it is publicly open, 2) it constructs VPC

plots of complex QSP models, 3) it offers automatic data binning using a rigorous approach [4], 4) it constructs QVPC plots of complex QSP models, 5) it performs Monte Carlo simulations of the model and plots the results with any requested summary statistics and 6) it provides the option of post-plotting modification of graphical settings.

Results: Two models were implemented in MatVPC to illustrate its functionality: i) a three compartment pharmacokinetic model with oral and intravenous bolus dosing and ii) a pharmacodynamic model describing the body weight time course. These models were inserted in MatVPC and the respective VPCs and QVPCs were generated. The VPCs constructed with MatVPC were validated against VPCs constructed with the gold standard tools in pharmacometrics community [5], PsN/Xpose (coupled with NONMEM) and Monolix.

Conclusions: MatVPC is publicly available at https://sourceforge.net/projects/matvpc/ and can be utilized by users with little or no prior Matlab experience. Collectively, MatVPC constitutes a useful addition to the openly available toolboxes exploited by quantitative as well as clinical pharmacologists.

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Sofia Birgersson New micronized formulation does not affect the population pharmacokinetic properties of artemisinin.

Sofia Birgersson
University of Gothenburg

Objectives: Malaria is still a major health problem in the poorest parts of the world. The highly effective first line treatment recommended by the WHO is artemisinin-based combination therapy. However, the emergence of multidrug-resistant *Plasmodium falciparum* parasites has started to diminish the efficacy of these available drugs (1, 2). A new combination of artemisinin with the long acting drug piperaquine has shown high efficacy and tolerability in patients with uncomplicated *Plasmodium falciparum* infections (3). The aim of this study was to characterize the population pharmacokinetics of single doses of artemisinin in various formulations in healthy male Vietnamese volunteers and to evaluate specifically the relative bioavailability of two different formulations.

Methods: Fifteen subjects received four different dose regimens of a single dose of artemisinin; the micronized test formulation, 160 mg (T1), the conventional formulation, 160 mg (T2), the conventional formulation, 250 mg (T3), and the micronized test formulation, 160 mg, in combination with piperaquine, 360 mg, (T4). Between each period there was a washout period of three

weeks (i.e. four-way cross-over). Venous plasma samples were collected frequently up to twelve hours after dose in each period. Artemisinin was quantified in plasma using liquid chromatography coupled with tandem mass spectrometry. A nonlinear mixed-effects modeling approach was utilized to evaluate the population pharmacokinetic properties of the drug and to investigate the clinical impact of different formulations.

Results: The plasma concentration-time profiles for artemisinin were adequately described by a transit-absorption model with a one-compartment disposition, in all four sequences simultaneously. Influence of formulation, dose and possible interaction of piperaquine was evaluated as categorical covariates in full covariate approaches. No clinically significant differences between formulations were shown.

Conclusions: In conclusion, this is the first population pharmacokinetic characterization of artemisinin in healthy volunteers. The new micronized formulation, dose or concomitant piperaquine administration did not affect the pharmacokinetic properties of artemisinin. The developed final model may be an important tool to investigate new dosing regimens *in silico* and to be implemented in clinical trial simulations for informative design of future clinical trials.

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Henrik Bjugård Nyberg Influence of Covariance Step Success on Final Parameter Estimates

Henrik Bjugård Nyberg (1,2), Andrew C. Hooker (1), Yasunori Aoki (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (2) Mango Solutions Ltd, Chippenham, United Kingdom

Objectives: To determine if computational stability influences final parameter estimates, and if so how we can assess the quality of the parameter estimates from NONMEM output. Specifically we want to determine whether a completed covariance step in NONMEM has any bearing on the quality of the final parameter estimates.

Background: For years there has been debate in the pharmacometric community around whether the different success criteria in NONMEM have any bearing on the quality of the final parameter estimates. One study by Holford et al. using bootstrap methodology concluded termination status was not an indicator of the quality of parameter estimates [1]. Preconditioning [2] lets us generate linearly reparameterized models resulting in different computational stability. As the likelihood of the nonlinear mixed effect model is invariant under linear re-parameterization, the minimum OFVs of these models are the same.

Method: As an initial example, data for a single dose experiment with 8 samples for each of 32 individuals were simulated with a

two-compartment, linear absorption PK model. We generated 10,000 reparameterised models with various levels of computational stability using the precond tool in PsN [3,4]. The condition number of the theoretical variance covariance matrix was varied between 10^6 to 10^15. In addition, we perturbed the initial estimates with a random uniform distribution within +/-20% of the theoretical maximum likelihood parameters. Two groups of runs were analyzed: 1. Minimization and Covariance step successful. 2. Minimization successful and Covariance step failed. A Wilcoxon rank sum test was performed to determine if groups 1 and 2 differ in OFV and theoretical condition numbers.

Results: The OFV of runs in group 2 differed significantly from those in group 1 with a p-value < 2.2e-16. Group 2 also represents a significantly higher theoretical condition number with p=1.1e-5. Mean OFVs for the groups were -79.6 for group 1 (n=7997) and -36.2 for group 2 (n=116). Mean condition numbers were 2.8e+18 (group 1) and 2.1e+20 (group 2).

Conclusion: The quality of parameter estimates is clearly influenced by computational stability, as measured by theoretical condition number. Our investigation shows that a failed covariance step in NONMEM estimation is a good predictor of lower quality parameter estimates.

Acknowledgement: This work was supported by the DDMoRe (www.ddmore.eu) project.

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Irina Bondareva Population modeling of changes in steady–state pharmacokinetics of carbamazepine (CBZ) due to antiepileptic drug-drug interactions from therapeutic drug monitoring (TDM) data

Irina Bondareva
The Research Institute of Physical – Chemical Medicine, Russia

Objectives: Epilepsy is a chronic disease requiring long term treatment with antiepileptic drugs (AEDs). While monotherapy is considered as the gold standard, patients who don't respond are prescribed AED polytherapy. So called old AEDs are involved in many interactions due to their pharmacokinetic (PK) properties. Although the PK interactions are well documented in general, their magnitude varies among studies. The objective of the study is to evaluate changes in the CBZ population PK due to AED interactions and to develop a nonlinear model describing CBZ heteroinduction when another AED is added to a CBZ monotherapy from repeated TDM data.

Methods: TDM data were routinely collected in the Laboratory of Pharmacokinetics of Moscow Medical University. Levels of anticonvulsants were measured by high performance liquid chromatography. The nonparametric population PK analysis was performed using the USC*PACK software based on 460 TDM (peak-trough strategy) data files of adult epileptic patients who received chronic CBZ-monotherapy or duotherapy. In the nonlinear model of

CBZ heteroinduction, the metabolic rate of elimination asymptotically changes from a monotherapy value (D) during time-lag (Lamda) to a value (D+A) after heteroinduction. The model was fitted by the NPEM to the multiple TDM data of 24 patients for whom measured CBZ levels related to both CBZ-mono and polytherapy.

Results: The steady-state CBZ- monotherapy half-lives were estimated as 3.2 – 50.6h (median = 10h) using a one-compartment model and TDM data of 100 adult epileptic patients. Great interindividual variability of CBZ PK for both mono- and polytherapy was observed (70 – 95% for the metabolic rate). Heteroinduction effects of CBZ metabolism by phenytoin and phenobarbital were clearly demonstrated. The lack of significant influence of valproate on CBZ total levels was obtained. The population parameter estimates are in good agreement with those reported in the literature. Individual serum CBZ level/dose ratios in patients taking CBZ plus AED were changed compared to the CBZ alone values.

Conclusions: The study demonstrated wide inter- and intraindividual variability of CBZ pharmacokinetics due to AED interactions and, taking into consideration narrow therapeutic range, the need for individualizing when an AED is added to a pre-existing AED regimen. Estimation of individual PK parameters might help to optimize CBZ polytherapy in epileptic patients based on thoughtful TDM data.

Jennifer Bonner Building of a virtual paediatric cancer population for physiologically-based pharmacokinetic modelling and simulation in neonates, infants, and children

Bonner J (1), Walsh C (1), Johnson T (2), Neuhoff S (2), Greystoke A (1), Veal G (1)
(1)Northern Institute for Cancer Research, Newcastle University, Newcastle, UK (2) Simcyp Limited (Certara), Sheffield, UK

Objectives: Determination of appropriate dosing of many anticancer agents in neonates and infants is a difficult task. Doses are routinely reduced but little pharmacokinetic data exists to act as guidance as to the magnitude of the reduction[1]. Physiologically-based pharmacokinetic (PBPK) modelling and simulation may assist in dose selection but requires a virtual paediatric population containing information on parameters that may affect PK that are known to change with age[2]. However, physiological changes affecting PK may also occur in cancer and these alterations may change typical ontogeny functions. The aim of this work is to build a virtual paediatric cancer population for use in PBPK modelling and simulation.

Methods: Anonymised patient data/plasma samples from 153 paediatric cancer patients were used (age range 1 month to 19.8 years). Plasma alpha-1 acid glycoprotein (AAG) concentrations were measured in 120 samples by ELISA. Relationships between height

and age, weight and height, and AAG and corrected GFR (cGFR) and age were assessed by nonlinear regression. The slope and intercept values from the height and weight curves were used to simulate height and weight values for 2,000 virtual paediatric subjects within Simcyp version 14.1. Comparison of patient ages, BSA, AAG, and cGFR by cancer type were performed by the Kruskal-Wallis test with Dunn's multiple comparisons test.

Results: The relationship between height and weight was described by a second order polynomial and weight vs. height by an exponential function. Heights and weights in simulated individuals created using the fitted equations did not differ significantly from those produced by use of a virtual healthy volunteer population. Plasma AAG concentrations in the paediatric cancer patients were significantly higher than the normal range (Mean AAG concentration in males was 2.24 mg/mL (64%CV) and in females 2.35 mg/mL (67%CV)) and no significant correlation with age was seen as exists in healthy subjects. There was no significant correlation between cGFR and age. No differences were observed in AAG concentrations or cGFR between cancer types.

Conclusions: These results show that while functions for height and weight do not differ greatly from those observed for healthy children, typical ontogeny functions for AAG and cGFR do not apply to this paediatric cancer population, underscoring the need for a special virtual population for modelling and simulation in children with cancer.

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Ohk Boram Population pharmacokinetics of Fimasartan

Boram Ohk, Joomi Lee, Sook-Jin Seong,Mi-Ri Gwon, Hae Won Lee, Young-Ran Yoon
Clinical Trial Center, Department of Biomedical Science and BK21 plus program, Kyungpook National University Hospital and School, Daegu, Korea

Objectives: Fimasartan, a novel angiotensin II receptor blocker that has been used for hypertension, is known to have inter-individual pharmacokinetic(PK) variability. The aims of this study were to develop a population PK model of Fimasartan in healthy Korean subjects.

Methods: A randomized, open-label, two-period, crossover bioequivalence study in 49 healthy male adults was performed. All subjects were received either the test or reference formulation as repeated 120-mg oral dose of Fimasartan, followed by a 1-week washout period and administration of the alternate formulation. Blood samples were drawn at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dosing. Plasma Fimasartan concentrations were analyzed using API 3200. A population PK analysis was conducted using NONMEM (Ver. 7.1).

Results: A 2-compartment model with first-order absorption provided the best fit from healthy subjects. Estimates of the population PK parameter were as follows; *CL*, 85 L/h; V_c, 350 L; K_a, 5

h^{-1}; V_p, 205 L/h; Q, 25 L/h. The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model.

Conclusions: A population PK model was successfully developed and reasonable parameters were obtained. Further study will be required to find out covariates affecting the PK parameters.

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Elisa Borella Predictive assessments of pharmacokinetic alterations in subjects with renal disease

Elisa Borella (1), Italo Poggesi (2), Paolo Magni (1).
(1) Dipartimento di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Italy; (2) Quantitative Sciences/Model-Based Drug Development, Janssen-Cilag SpA, Italy.

Objectives: To find a model capable of predicting, relying on a minimum amount of PK information in normal subjects, the effect of renal impairment on the exposure of a drug. Three categories of renal impairment (mild, moderate and severe) were considered according to the KDIQO guideline.

Methods: For a list of 64 marketed drugs, PK descriptors and recommended dosage adjustments for subjects with renal impairment were obtained from the literature and other public resources [1]. The considered PK descriptors were: clearance, bioavailability, oral clearance, amount excreted unchanged in urine (Ae), binding to plasma protein (ppb) and hepatic extraction ratio. The PK changes due to the renal dysfunction were summarized using the ratio between the AUC computed in subjects with renal impairment and the AUC in healthy subjects. Two different types of analyses were performed. The first one consisted in exploring, for each level of renal impairment, the potential correlations between the AUC ratios and the PK variables, implementing in R different

methods, from multiple linear regression (MLR) to partial least squares (PLS). The second approach consisted in classifying the drugs, basing always on their PK parameters, in different levels of risk of administering wrong dosage to renal impaired patients. Different data-mining and machine-learning methods were tested using Orange 2.7 [2].

Results: A multiple regression (regressors selected by a stepwise procedure) gave results with a reasonable degree of accuracy. Besides, the regressors selected (Ae for mild and moderate, Ae and ppb for severe renal impairment) find a physiological explanation. The results of the regression analysis were summarized in a sort of "traffic-light" histograms which could become an immediate clinical decision-making tool. As regards the classification problem, for a binary class (risk and no-risk) the best results in term of accuracy were given by Naïve Bayes, Classification Trees and SVM. Setting a threshold to discern risky and not-risky administering situation, the AUC predicted by the MLR were discretized and the percentage of misclassifications was compared to those produced by the best classificators.

Conclusions: This model can be considered a smarter statistical analysis, which may provide a useful guidance for designing the studies of new compounds, highlighting those cases that may need additional investigations.

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Jens Borghardt A New Parameterisation to Describe Parallel Absorption Processes After Drug Inhalation

J.M. Borghardt (1, 2), B. Weber (2), A. Staab (2), C. Kloft (1)
(1) Dept. Clinical Pharmacy & Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany; (2) Dept. Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Objectives: Pulmonary absorption of inhaled drugs is a complex process influenced by pulmonary deposition patterns and dissolution (1, 2). Parallel first-order absorption processes were demonstrated for inhaled drugs applying empirical models (3, 4). In those models the total estimated fraction absorbed (lung dose) was constrained to be between zero and one. Proportionality factors for each absorption process (PF_i) were estimated. The contribution of each process to the lung dose was calculated as $PF_i/sum(PF_{1-n})$. Variability of PF_i was assumed to be log-normally distributed before normalisation, which is in contrast to the usually applied logit-transformation, for which variability is assumed to be normally-distributed on the logit-scale. The objective was to develop an alternative parameterisation applying logit-transformations, which allow modelling fractions directly on a zero to one scale.

Methods: The new parameterisation for pulmonary absorption was inspired by “Advanced Compartmental Absorption and Transit“ models applied to describe gastrointestinal (GI) absorption (5). In these models, transport through transit GI absorption

compartments is described by transit rate constants. In the lung, inhaled particles have to pass different airways, possibly represented by multiple absorption compartments. In contrast to the GI tract, drug distribution across pulmonary absorption compartments was assumed to be instantaneous. Hence, fractions (F_i) on a logit-scale were estimated instead of transit rate constants. While F_i represented drug input to absorption compartment i, $1-F_i$ represented the remaining amount of drug available for subsequent absorption compartments. The lung dose was estimated as a fraction of the nominal inhaled dose. The new and previously proposed parameterisations were applied to data (plasma and urine) of inhaled olodaterol.

Results: Without allowing for interindividual variability (IIV), both parameterisations provided numerically identical description of the data. This was expected since it can be shown that the parameterisations are mutually transformable functions. When including IIV, the new parameterisation provided a numerically better description of the data.

Conclusions: A new parameterisation for parallel pulmonary absorption processes was successfully developed. The parameterisation allowed to adequately describe PK data after olodaterol inhalation. Additionally the new parameterisation might also facilitate interpretation of parameters.

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Rolien Bosch A mechanism-based model is able to simultaneously explain the effect of rhLCAT and HDL mimetics on biomarkers of reverse cholesterol transport

Rolien Bosch (1), Kirsten Bergmann (1), Paul Baverel (2), David Fairman (2)*, Peter Vis (1), Balaji Agoram (2)
*1 LAP&P Consultants BV, 2 MedImmune, Cambridge, UK *Current affiliation: GSK, Stevenage, UK*

Objectives: To develop a mathematical model that describes the effect of IV administration of recombinant human Lecithin-cholesterol acyltransferase (rhLCAT) and HDL mimetics on biomarkers of reverse cholesterol transport (RCT) in humans.

Methods: The systems model was built using NONMEM v.7 with clinical data combining in-house individual rhLCAT [1,2] exposure, lipid biomarkers (high density lipoprotein-cholesterol HDLc, and cholesteryl-ester CE) and summary level data of HDL mimetics derived from literature [3,4,5]. The model was evaluated using VPCs plus sensitivity analyses and was externally qualified using two independent clinical studies of HDL mimetics [5, 6].

Results: Although stimulation of RCT by HDL mimetics and rhLCAT are related to different mechanisms of action, the developed eight compartment mechanistic model was able to adequately describe both the observed plasma rhLCAT concentrations and the time-

course of relevant biomarkers, including the fraction of esterified and unesterified cholesterol within HDL particles. Both internal and external model validation using VPC showed adequate model fit and good predictive performance. HDLc AUC showed high correlation with the amount of cholesterol movement from the peripheral tissue and can be used to compare the effects of HDL mimetics with rhLCAT on RCT.

Conclusions: We have generated a model that describes the time-dependent dynamics of lipid biomarkers within HDL particles by integrating literature and study data from two compounds with different mechanisms of action. This is the first to integrate the effects of HDL mimetics and rhLCAT preparations on RCT and describes both the conformational change of the HDL particle from pre-β-HDL to αHDL as well as the effect of this conformational change on the efflux of cholesterol.

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Marion Bouillon-Pichault Longitudinal Model-Based Meta-Analysis in Type 2 Diabetes: Assessment of link between fasting plasma glucose and Hba1c.

Marion Bouillon-Pichault, Bernard Sebastien, Clemence Rigaux
Sanofi R&D

Objectives: The link between fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c) has previously been described using empirical correlations at steady state and semi-mechanistic modeling for few anti-diabetic compounds. In particular, the correlation between HbA1c and FPG has been established in several studies (1)(2). Although these correlations or models have been calculated or developed on large populations of subjects, they have generally not been assessed and compared across different types of treatments. To that end, a model based meta-analysis was performed to assess the link between FPG and Hba1c over a large set of anti-diabetic drug class.

Methods: The analysis database was made of publicly available summary results from Type 2 Diabetes clinical trials published in the medical literature. Only monotherapy treatment arms from randomized controlled studies with at least 12 weeks duration, with documented HbA1bc with fasting plasma glucose data, were included in the analysis database. Only drug classes including more than 5 trials were kept, to ensure a sufficient representation of each drug class. The data were analyzed in the non-linear mixed effect

model framework, using Monolix 4.3.3, considering trial arm as individual, with mean change (from study baseline) HbA1c as dependent variable and mean change in FPG as explanatory variable (3)(4).

Results: A general empirical model was established linking FPG to HbA1c. Trial arms were used as ID and the residual variability was weighted by the square root of the number of measurements at each time point, to account for summary data precision. Several covariates were integrated in the model: treatment drug class, washout, gender and age. The model was qualified, using Goodness of fit plots, Visual Predictive Checks and other classical diagnosis criteria generated from an external database made of 100 studies previously removed from the model development database for model qualification.

Conclusion: By predicting long term HbA1c response given shorter terms glycemia, this work will help phase 2 decision making and designing phase 3 in T2DM.

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Karl Brendel How to consider microdosing data in a population PK analysis?

Brendel K.(1), Tessier A(2), Chenel M(1).
(1)Department of Clinical Pharmacokinetics and Pharmacometrics, SERVIER, France. (2)INSERM, IAME, UMR 1137 France

Introduction: Human microdosing (MD) studies are used in the context of drug development in order to have a better knowledge of pharmacokinetics (PK) of a drug (i.e. absolute bioavailability determination)(1). MD studies are usully performed in a limited number of volunteers. However the integration of MD data in PK models can significantly improved modelling by decreasing the number of assumptions made.

Objectives: To develop a population PK model of a BCS class 2 compound (drug S) taking into account MD data to better understand absorption process (non-linearity due to the dissolution process) and the presence of a second peak in the concentration-time profile.

Methodology: Data came from 10 phase I studies, including 257 healthy volunteers, who received a single or repeated oral administration (tablet) and 10 who received single MD iv perfusion also or single MD oral solution.

First a population PK model was built using MD data from iv and oral solution administration, especially to estimate the absolute

bioavailabity and to fit the absorption process independently of tablet dissolution.

Secondly a model with all data was developed by fixing parameters obtained previously with MD data. The adequacy of the model to describe the data was assessed based on uncertainty on parameter estimates (RSE), and on advanced evaluation methods such as VPC and NPDE.

Estimation of the population parameters was performed using NONMEM 7.3 and FOCE algorithm.

Results: Informations from the MD data were used to identify the dissolution process from the absorption, bioavailability and to explain the presence of a second peak due to the EHC (after iv and oral solution administrations).

All data were described by a 2-compartments model with first-order absorption and linear elimination; the second peak in concentrations was described using EHC. A fraction of drug S was excreted from the central into a gall bladder compartment with a first-order constant, while a periodic drug release from the gall bladder to depot compartment was used through MTIME. Some parameters of EHC and dissolution were fixed due to model identifiability.

A non-linear dose relationship was also added in the absorption process. The RSE, VPC and NPDE were satisfactory for both MD and therapeutic doses models.

Conclusion: Informations from the MD data were used to explain non-liearity to the dose due to the dissolution process, and to confirm the presence of a second peak due to the EHC.

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Annika Brings Modelling and simulation of adverse drug effects on heart rate in the anaesthetized mouse

Annika Brings, Eric Martel, Wolfgang Rist, Robert Augustin, Stefan Scheuerer and Brian Guth
Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany

Objectives: To develop a PK/PD model of adverse, drug-mediated increase in heart rate in the anaesthetized mouse in order to determine a dose with acceptable heart rate alterations (defined as < 10% increase relative to baseline).

Methods: PK data were obtained in C57BL/6NCrl or Rj:SWISS mice following an i.v. bolus injection of drug A, B or C. For assessment of cardiovascular effects, arterial blood pressure, heart rate (HR) and body temperature were continuously measured in anaesthetized, male Swiss mice for up to 95 min. Baseline values were collected for 5 min prior to i.v. injection of drug A, B, or C, or vehicle. Plasma samples for exposure measurements were obtained for 1-3 time points in this study. Plasma concentrations were fitted to a pharmacokinetic model using non-linear modelling with the naïve pooled approach implemented in Phoenix WinNonlin 6.3. Heart rate data were fitted either to a turnover model with saturable stimulation of build-up, or to a receptor binding model [1].

Results: PK data could be described with a one-compartment (drug A) or two-compartment model (drugs B+C). Due to the low drug clearance (~0.01 L/hr/kg) a step-wise increase in plasma

concentrations could be achieved using sequential, escalating i.v. bolus doses (3, 10, 30 and 100 µg/kg at 0, 15, 30 and 45 min) to study the concentration dependence of cardiovascular effects. This showed a dose-dependent increase in HR and a time delay between plasma concentration and effect, suggesting that the emergence of HR effects takes longer than 15 min. The time delay could be described by a turnover model, which was used to predict the time and magnitude of the maximum effect and to plan a further study with HR monitoring for up to 90 min following a single i.v. injection of compound C at 6 different doses. In this study the maximum HR effect occurred at ≥ 60 min after drug administration. HR effects were emerging slower than predicted by the turnover model and were described more adequately by a receptor binding model. Turnover and distributional delay models yielded poorer fits as assessed by predictive check. The receptor binding model predicted an acceptable dose of 40 µg/kg.

Conclusion: The observed time delay between plasma concentration and HR increase was best described by a receptor binding model, suggesting that receptor binding kinetics may be responsible for the slow emergence of HR effects. Further studies would be required to investigate the mechanism of HR increase.

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Jantine Brussee Population modeling of cytochrome P450 mediated drug metabolism and oral absorption in preterm neonates receiving intravenous and oral midazolam in a cross-over study

Janneke M. Brussee (1), Saskia N. de Wildt (2), Meindert Danhof (1), Catherijne A.J. Knibbe (1,2,3)
(1) Division of Pharmacology, LACDR, Leiden University, Leiden, The Netherlands, (2) Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands, (3) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands

Objectives: Midazolam is a benzodiazepine which is often used for sedation in neonatal and pediatric intensive care units orally or intravenously. For sedation of preterm neonates, the use of midazolam is largely off-label. This project aims to describe and predict CYP3A mediated clearance and oral bioavailability of midazolam in preterm neonates using data from a cross-over study on oral and intravenous midazolam.

Methods: Patients included 38 preterm neonates (postnatal age ranging between 3-46 days, birth weight 745-2135 grams) from the neonatal intensive care unit of the Sophia's Children Hospital in Rotterdam [1,2]. They were randomly assigned to receive midazolam orally (n=13) or via an half-hour infusion (n=25), and they received midazolam via the alternate route after >72 hours, if they still met the inclusion criteria (n=13). A sequential drug-

metabolite population pharmacokinetic model for midazolam and its primary metabolite, 1-OH-midazolam, was developed using NONMEM 7.3. CYP3A mediated formation clearance of 1-OH-midazolam was assumed to be a fraction of 60% of total midazolam clearance [3,4]. Birth weight, body weight during the study, postnatal age and gestational age were considered as potential covariates. A non-parametric bootstrap was performed to evaluate the model.

Results: A two-compartmental PK model with values for clearance and central volume of distribution of 0.135 L/h and 0.542 L, respectively, was used to describe the plasma concentrations of midazolam. Oral absorption was best described by a first-order process with an absorption rate of 2.05 hr(-1) and bioavailability of 0.72. Plasma concentrations of 1-OH-midazolam were described by a 1-compartment model with an estimated clearance of 0.48 L/h and a volume of distribution equalized to the volume of distribution of midazolam. No significant covariates were found, likely because the studied population was very uniform.

Conclusions: Based on data from a cross-over study on oral and intravenous midazolam, a pharmacokinetic model for midazolam and metabolites was identified for preterm neonates. Compared to adults, clearance of midazolam seems lower and bioavailability higher. In the combined oral and intravenous model, there was no evidence for pre-systemic formation of the CYP3A mediated metabolite (1-OH-midazolam) [5] after oral administration in preterm neonates.

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Simon Buatois Using Item response theory to yield information from the MDS-UPDRS items in Parkinson's disease clinical trials

S.Buatois (1), S.Retout (1), R. Gieschke (1), S.Ueckert (2,3), N.Frey (1)
(1) Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, Switzerland; (2) IAME, UMR 1137, INSERM, F-75018 Paris, France; (3) Pharmetheus AB, Uppsala, Sweden

Objectives: Item response theory (IRT) has been recently introduced in pharmacometrics by Ueckert et al. to model the Alzheimer's disease progression based on the ADAS-Cog scale [1]. It permits a more precise analysis by integrating the whole available items information, it increases the probability to detect changes due to a drug effect and helps to determine the most informative items of the global score in function of the population of interest. The aim of this work was to apply IRT to the MDS-UPDRS scale to better assess the natural disease progression of Parkinson's disease (PD) patients.

Methods: First, a baseline IRT model was built to analyze baseline data from the Parkinson's Progression Marker Initiative (PPMI) database [2]. The dataset includes 431 de novo idiopathic PD patients, 199 healthy controls and 65 PD patients with Scans without Evidence of Dopaminergic Deficit. This work focus on the MDS-UPDRS score [3], which consists of 65 items measuring the disturbance of non-motor experiences of daily living (i.e. sleep,

cognition, mood) as well as motor experiences (i.e. Tremor, Rigidity, Bradykinesia) and motor complications. All item-specific-parameters were implemented as fixed effect via ordered categorical models and the baseline hidden neuronal disability as a random effect. In a second step, a longitudinal model was used to describe the neuronal disability time course [4,5]. Visual predictive checks both on the item as well as on the MDS-UPDRS score level were used to evaluate the model.

Results: We were able to describe the evolution of the neuronal disability over time using a longitudinal IRT modeling approach, for a better leverage of the whole MDS-UPDRS items information. The developed IRT model allowed also to rank the information provided by each item with respect to different severity of patient population and could be useful afterwards to derive simplified but informative MDS-UPDRS sub-scores according to the targeted patient population.

Conclusions: IRT is a powerful tool which enables to yield information from the MDS-UPDRS scale used in clinical trials, therefore maximizing the likelihood to bring new medicine to Parkinson's disease patients.

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Núria Buil Bruna Population PK/PD modelling of the biomarker and progression free survival effects of Lanreotide Autogel in patients with non-functioning gastroenteropancreatic neuroendocrine tumors

Núria Buil-Bruna (1), Marion Dehez (2), Amandine Manon (2), Thi Xuan Quyen Nguyen (2), Iñaki F. Trocóniz (1)
(1) Pharmacometrics & Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona 31080, Spain, (2) Clinical Pharmacokinetics, Pharmacokinetics and Drug Metabolism, Ipsen Innovation, Les Ulis, France

Objectives: To develop a PK/PD model for the somatostatin analogue Lanreotide Autogel® (LA) in patients with non-functioning gastroenteropancreatic neuroendocrine tumours (GEP-NETs) establishing the relationship between serum concentrations of LA, biomarker Chromogranin A (CgA) serum levels, and progression free survival (PFS).

Methods: Data came from a phase III, randomized, double-blind, placebo-controlled study [1] conducted in 204 patients over 96 weeks where deep subcutaneous injections of LA 120 mg (n=101) or placebo (n=103) were administered every 4 weeks. The PK/PD model was established based on 810 serum samples of LA and 1298 (n=632 placebo and n=666 LA) serum samples of CgA; during the course of the study 76 patients experienced disease progression

(n=49 placebo and n=27 LA).
The analyses were performed sequentially with NONMEM v7.2 [2]. First the PK model was selected and the corresponding empirical Bayes parameter estimates were used to describe the time course of CgA and its effects on PFS, the latter modelled as a time to event response variable.

Results: Serum profiles of LA were described with a one-compartment disposition model and with an absorption process characterized by two parallel absorption pathways following first and zero order kinetics.
Results shown PFS data had to be considered as informative drop-outs, and therefore CgA and PFS responses were modelled jointly. CgA levels were Box-Cox transformed for the analysis. Disease progression was characterized in the placebo group with a linear model (in Box-Cox scale). LA induced a decrease in CgA levels described by an inhibitory E_{MAX} model. Inter-patient variability in the rate of disease progression and pharmacodynamic parameters was high (130%). C_{50} was estimated to be 7.8 ng/mL.
The Weibull model characterized the PFS hazard. A decrease on CgA with respect CgA_0 reduced significantly the hazard ($p<0.001$). The covariates primary tumor location in pancreas, and baseline tumor hepatic load were associated with a higher risk (i.e., lower probability of PFS) ($p<0.001$).

Conclusions: A model linking in a mechanistic way drug exposure, biomarker and clinical endpoint could be established in patients with non-functioning GEP-NETs receiving LA. Our results indicate that there is a direct link between LA exposure and CgA levels, and that CgA levels in serum could be a good marker for the follow-up of the patients i.e. to monitor disease progression in this type of patients.

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Theresa Cain Application of Simcyp's R Library Package in Simulation and Prediction of Metoprolol Compliance Using a Single Plasma Concentration Sample

Theresa Cain (1), Adrian Barnett (1), Masoud Jamei (1)
(1) SIMCYP Limited (a Certara Company), Sheffield, UK

Objectives: To develop a Simcyp R library package facilitating the simulation of virtual clinical trials using the Simulator via R. To use the R package to predict the compliance of Metoprolol from a patient's single PK sampling point, and to determine the optimal time point for correctly identifying the compliance scenario in two populations of CYP2D6 Extensive Metabolisers (EM) and CYP2D6 Poor Metabolisers (PM).

Methods: We developed an R library package where Simcyp is run via R and facilitates simulating various compliance scenarios. The Barriere et al. [1] method, incorporating a Bayesian framework, was used to predict patient's compliance after a scheduled 100 mg Metoprolol BID for 6 days. Prior in vitro and physicochemical parameters for Metoprolol and the Healthy Volunteer population were used to generate plasma concentration profiles of 500 CYP2D6 EM and PM patients. The first 10 doses were taken and the final two doses varied over five scenarios: full compliance, missing the first dose, missing the second dose, taking both doses together and missing both doses. Compliance scenarios were predicted for each patient using plasma concentrations taken at 0, 12, 24, 36, 48, 60

and 72 hours after the scheduled final dose. A ROC curve was used to determine the optimal sampling time for predicting compliance scenarios.

Results: The probability of a true positive in the EM population was greatest at the time of the final dose for all scenarios and decreased over time. In the PM population the probability of a true positive is lowest at the time of the final dose, increases rapidly by 12 hours and then remains fairly constant over the remainder of the sampling times. In both populations, the probability of a true negative is high for all sampling times. The ROC curve shows that for the EM population, the concentration taken at 12 hours is the best at predicting all compliance scenarios apart from where two doses are taken together; in this case the 0, 12 and 24 hour samples are all equally good predictors. For the PM population the optimal times varied by compliance scenario.

Conclusions: An R library package for Simcyp is developed that enables running virtual clinical trials from within R. This was used to show that the optimal time for correctly predicting compliance in the EM population is 12 hours after the final dose. However, the optimal sampling time in the PM population depends on the compliance scenario.

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Sophie Callies Dose projection and prediction of PK/PD response - a bench to bedside example for LY drug.

Sophie Callies, Elizabeth Smith LaBell, Enaksha Wickremsinhe, Vijay Reddy, Ji Lin, Gregory Donoho, Volker Wacheck, Johan Wallin
Eli Lilly and Company

Background: Small molecule (LY) is an inhibitor leading to a decrease in biomarker X levels in preclinical model. We hypothesize LY could lead in human to disease control (DC) as observed in non-clinical disease mode**l.**

Objectives: to predict human efficacious dose range through modeling analysis of non-clinical data, to design the first in human dose (FHD).

Material Methods: Data available were: in mice, pharmacokinetic (PK, intravenous IV and oral PO administration), biomarker inhibition (BI) and disease control (DC) data; in dog PK data (n=45, n=11 IV/PO, n=34 PO); in rat PK data (n=21 PO); in human PK, BI data (n=38). Allometric scaling was used to predict human PK based on non-clinical PK data. Mice PK, BI and DC data were modelled to determine the biologically relevant LY exposure range. Based on this information, the relevant dose range to be investigated in FHD study was determined with support of the toxicology studies. NONMEM (version VII) was used for the analysis. Text regarding methods.

Results: Allometric scaling predicted an IV and PO LY clearance (CL, CL/F) of 41.9 (34.0-51.7) and 55.9 (45.3-68.9) L/h in human (mean (90% CI), assuming bioavailability (F) 0.75 and body weight 70 kg). The non-clinical DC versus exposure relationship was modelled using an Emax model. This model indicated an IC50 of 95.1 ng/mL (CV 40 %), corresponding to daily exposure of 2280 ng*h/mL following a 3 mg/kg BID dose, which was considered a minimally efficacious dose in mice. Efficacious dose range in mice was determined to be 6 -10 mg/kg BID leading to daily exposure of 5380-9110 ng*h/mL. To reach 2280 and 5380-9110 ng*h/mL in human, the model predicted that LY dose range of 100-150 and 250-600 mg daily would be needed, respectively. The proposed dose range for FHD was 20 mg (starting dose) to possibly 600 mg maximum daily dose. Observed human CL/F was 64 L/h (CV 45.6%, 90%CI 60-70, n=38) after repeated doses in the 20 to 325 mg dose range. A two compartmental model, with first order absorption, adequately fit LY clinical exposure. A sigmoidal Emax model adequately fit the BI versus LY exposure relationship with mean AUCdaily50 and Caverage50 (leading to 50 % of maximal inhibition) of 1090 ng.h/mL and 45.4 ng/mL, respectively (CV=44%, n=19).

Conclusions: The integration of the non-clinical data, using modelling, enabled the prediction of the relevant biological dose range to be investigated in human.

Elisa Calvier Extrapolation potential of semi-physiological covariate models to newborns: a simulation-based study

Elisa Calvier (1), Elke H.J. Krekels (1), Catherijne A.J. Knibbe (1,2)
(1) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands; (2) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands

Objectives: Semi-physiological covariate models (SPCMs) describe the maturation of plasma clearance (CLp) for specific metabolic or elimination pathways [1,2]. These models are obtained in PK studies of model drugs that are mainly eliminated through one specific pathway. It has been suggested that SPCMs can be extrapolated between drugs sharing an elimination pathway [1,2]. In this work we investigate the extrapolation potential of SPCMs between drugs undergoing hepatic metabolism, when predicting CLp in newborns based on CLp information in adults.

Methods: In R, the dispersion model [3] was used to simulate CLp of hypothetical drugs with different unbound fractions, microsomal unbound intrinsic clearances (CLintu), and blood to plasma ratios. Regarding CLintu in newborns, two scenarios were investigated: 1) enzyme maturation completed at birth, 2) enzyme maturation not completed at birth, with changes in CLintu derived from a published SPCM [4] by retrograde calculation. Physiological parameters for

scaling between adults and newborns were compiled from literature [5-9]. SPCMs were derived from the CLp simulated in adult and newborns for each hypothetical drug and scenario. Within each scenario, SPCMs were extrapolated between hypothetical drugs to predict CLp in newborns from CLp values in adults. The prediction error (PE) of the predicted CLp in newborns was computed.

Results: Patterns in PE were best summarized using extraction ratios (ER). The PE of SPCMs was higher in scenario 2 compared to scenario 1. For both scenarios, SPCMs over-predict or under-predict CLp in newborns when extrapolated to drugs with a lower or a higher ER, respectively, than the model drug from which they are derived. SPCMs developed using drugs with a low ER have the best extrapolation potential (maximum PE of -47% and -83% for scenario 1 and 2, respectively), while SPCMs developed using model drugs with a high ER have the poorest extrapolation potential (maximum PE of 89% and 475% for scenario 1 and 2).

Conclusions: SPCMs reflect not only physiological and enzymatic maturation processes, but also drug specific properties. Their predictive properties are dependent on the properties of their model drugs, while their extrapolation potential depends on the differences in properties between the model drug and the drugs the SPCM is extrapolated to, and on the extent of enzyme maturation. SPCMs developed on model drugs with low ER have the best overall extrapolation potential.

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Tim Cardilin Modelling and Analysis of Tumor Growth Inhibition for Combination Therapy using Tumor Static Concentration Curves

Tim Cardilin (1,5), Alexandre Sostelly (2), Johan Gabrielsson (3), Samer El Bawab (2), Christiane Amendt (4) and Mats Jirstrand (5)
(1) Department of Mathematical Sciences, Chalmers University of Technology and Gothenburg University, Gothenburg, Sweden, (2) Merck Serono, Global Early Development - Quantitative Pharmacology, Darmstadt, Germany, (3) Division of Pharmacology and Toxicology, Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences, Uppsala, Sweden, (4) Merck Serono, Translation Innovation Platform Oncology, Darmstadt, Germany, (5) Fraunhofer-Chalmers Centre, Gothenburg, Sweden

Objectives: To develop and analyze a Tumor Growth Inhibition (TGI) model for combination therapy based on experimental data using Tumor Static Concentration (TSC) curves.

Methods: Patient-Derived xenograft data on Erbitux-Cisplatin combinations were obtained from mice. Drug exposure profiles were generated based on literature data. Time series of efficacy data were modelled based on the *in vivo* TGI model with simultaneous cytostatic and cytotoxic drug action. Model parameters were estimated using a mixed-effects approach implemented in Mathematica 10 [1]. The models were then

investigated using an analytical approach to obtain Tumor Static Concentration [2] curves, which should be compared with the established concept of isobolograms [3].

Results: The TSC condition for the combination of a cytostatic (*A*) and a cytotoxic (*B*) drug can be expressed mathematically as

$$k_{growth}\, I(C_A) = k_{kill}\, S(C_B),$$

where C_A and C_B are the plasma concentrations of drugs *A* and *B*, respectively. *I* and *S* are an inhibitory and a stimulatory function acting on the proliferating cell compartment. k_{growth} and k_{kill} are the cell growth and kill rates. This can be visualized as a curve in the C_AC_B-plane. Keeping the concentrations above this curve gives tumor shrinkage, while falling below it gives tumor growth.

The Erbitux-Cisplatin combination data were adequately modelled with Erbitux as the cytostatic and Cisplatin as the cytotoxic compound, under the assumption of independent action. TSC curves were generated and compared with the exposure profiles of all test compounds. This provided visualization of when and to what extent the concentrations were at a sufficiently high level for tumor shrinkage and helped to suggest times when either a higher or additional dose would be necessary.

Conclusions: The graphical TSC presentation of two compounds proved to be a useful tool for presentation of drug combinations tumor growth/kill interventions.

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Letizia Carrara Modelling the effect of Sunitinib given alone and in combination with CPT11 on the tumor growth in xenografted mice

L. Carrara (1), B. Ribba (2), M. Tod (3), M. Wei (4), B. You (5), G. Freyer (5), P. Magni (1)

(1) Dipartimento di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Pavia, Italy, (2) INRIA Grenoble Rhône-Alpes, Montbonnot-Saint-Martin, Grenoble, France, (3) EMR3738, Université Claude Bernard Lyon-1, France, (4) CellVax Laboratory facility, Bâtiment Marcenac, aile Est, Ecole Nationale Vétérinaire d'Alfort, 7 avenue du Général de Gaulle, 94704 Maisons Alfort cedex, France, (5) EMR UBCL/HCL 3738; Université Claude Bernard Lyon-1; France; Centre d'Investigation des Thérapeutiques en Oncologie et Hématologie de Lyon (CITOHL); Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL); Service d'Oncologie Médicale Lyon, Lyon, France.

Objectives: Nowadays anti-angiogenic drugs are considered one of the cornerstore of the anticancer therapy. Limiting oxygen and nutrient supplies to tumor, angiogenesis inhibitors cause tumor stasis but they do not exert a direct tumor cells kill effect. For this reason they are usually administered in combination with chemotherapy.
The aim of this work is to study the effects of Sunitinib on tumor growth in xenograft mice both in the case of single drug experiment

and in combination regimens with cytotoxic drug (CPT11) to assess the type and the strength of the interaction.

Methods: Data were obtained from CellVax (France) and relate to 2 different experiments both on athymic nu/nu mice xenografted with human colonrectal cancer cells. When tumor volume reached 200-300mm^3, the treatment started. Data were modeled starting from the Rocchetti TGI model [1].

Single agent experiment

The single agent experiment involves 1 control arm and 2 arms treated with Sunitinib following different schedules of administration. A naïve pool analysis, considering average data, was performed in Matlab 2010a fitting simultaneously control and treated arms, while a population approach with non-linear mixed effect model was implemented in Monolix 4.3.2.

Combination experiment

The combination experiment, besides the control arm and 2 single agent arms, also involves 5 combination arms in which both Sunitinib and CPT11 were administered to the animals. Both naïve pool and mixed effect approaches were implemented as for the single agent experiment. The assessment of the type of interaction between the 2 drugs is mainly investigated by using the pool approach.

Results:

Single agent experiment

A modified version of the Rocchetti TGI model was proposed to describe the action of Sunitinib. In particular, an effect compartment was added to the original model because of the faster PK of Sunitinib compared to Avastin (drug used in [1]). The model successfully describes the experimental data.

Combination experiment

A joint model that integrates the action of the 2 drugs was used. Difference between model predicted tumor growth curves under

the null interaction hypothesis and experimental data suggests a negative interaction between Sunitinib and CPT11.

Conclusions: The new TGI model seems to be adequate to describe the action of Sunitinib, while the co-administration with the cytotoxic drug shows a negative interaction.
This work was supported by the DDMoRe project (www.ddmore.eu).

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Massimo Cella Use of a TMDD model in the translational development of a BDNF-neutralizing monoclonal antibody

Massimo Cella(1), Emma Hawkins(1), Grace O'Leary(1), Rie Suzuki(2), Pinky Dua(1)
(1) Pharmatherapeutics Research Clinical Pharmacology, Pfizer Neusentis, Cambridge, UK. (2) Pfizer Neusentis, Cambridge, UK.

Objectives: Drug X is a humanized IgG1 monoclonal antibody (mAb) that is able to neutralize the Brain-derived neurotrophic factor (BDNF) by inhibiting interaction with its receptors. In sensory neurons, application of BDNF causes acute sensitization of peripheral nociceptors, leading to enhanced neuronal excitability and pain sensitivity, whilst promoting chronic pain processing via mechanisms involving gene transcription and alterations in the innervation pattern of sensory neurons.
The aim was to 1) build a mechanistic target-mediated drug disposition (TMDD) model and 2) use the model to influence the design of pre-clinical experiments and predict the relationship between mAb dose and BDNF suppression across species.

Methods: Plasma levels of mAb and total BDNF were measured after intravenous and subcutaneous administration of various drug amounts in rats (0.1 and 1 mg/kg) and cynomolgus monkeys (0.03 and 0.3 mg/kg). Using Matlab R2012b software a TMDD model was developed using rat data. This model was subsequently used to

predict mAb PK and design the PK study in cynomolgus monkeys. Data from cynomolgus monkeys were then used to refine the model and extrapolate mAb PK and BDNF suppression over time at different doses in humans. All simulations were performed using Berkeley Madonna 8.3.18 software.

Results: In rats, the minimum dose that resulted in measurable efficacy 5 days post-dose was 0.03 mg/kg, which according to model simulation was predicted to cause an average free BDNF suppression of 37%. In cynomolgus monkeys, doses predicted to produce a range of free BDNF suppressions were identified (e.g. average 30, 70 and 90% over the considered interval). These doses were 0.03, 0.15 and 0.6 mg/kg for an 8 weeks dosing regimen. Finally, the same levels of suppression extrapolated to humans were obtained with 0.008, 0.03 and 0.125 mg/kg, respectively.

Conclusions: A TMDD model adequately described drug X pharmacokinetics and pharmacodynamics (defined as free BDNF concentration in central compartment). This analysis provides an example in which TMDD models were used to predict PKPD properties of a mAb across species, helping the design of preclinical studies and the mechanistic extrapolation of results to humans.

Dong Woo Chae Mechanistic Modeling of Telmisartan Blood Pressure Lowering Effect in Human

Dong Woo Chae (1,2), Mijeong Son (1,2), Yukyung Kim (1,2), Hankil Son (1,2), Nick Holford (3), Kyungsoo Park (1,2)
(1) Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea (2) Brain Korea 21 Plus Project for Medical Science, Yonsei University, Seoul, Korea (3) Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

Objectives: Telmisartan, a potent angiotensin II type-1 (AT1) receptor blocker (ARB), is indicated for the treatment of essential hypertension. Its effect is classified into rapid response due to vasodilation and slow response due to volume loss steming from natriuresis [1]. PK-PD models of telmisartan have been published in rats [2,3], but no such model reported in human. This study aimed to develop a mechnitic model of telmsartan drug effect in human using non-invasive markers, which can be readily applicable in real clinical situations.

Methods: Data was acquired from a previous PK study where telmisartan 80 mg was given once daily for 6 days. Systolic and diastolic blood pressure and heart rate (HR) were measured before dosing for Day 1 to 5 and serially after the last dose. PK was modeled with weight incorporated using allometry. With posthoc estimates of PK parameters, a mechanistic PD model was built considering followings: (i) MAP formulated as MAP = C·TPR·PP·HR,

based on MAP = CO·TPR, CO = SV·HR, and C = SV/PP, with CO, TPR, SV and C being cardiac output, total peripheral resistance, stroke volume and compliance, respectively, where C = SV/PP is a simplified version of Windkessel model and C assumed to be constant over the study period; (ii) negative feedback of MAP on turnover rates of PP, HR and TPR; (iii) a common circadian rhythm with MAP, HR and CO in parallel fluctuations and TPR in the mirror image of the others; (iv) drug plasma concentration linked through a first-order process to Cb, the effect site concentration binding to AT1 receptor; (v) drug effect, a function of Cb, assumed to inhibit turnover rates of TPR (rapid effect) and PP (slow effect), with no influence on HR. The prediction of MAP was computed using the estimates of C·TPR, PP and HR, where C·TPR was estimated from 'derived' data. The model was validated using a visual predictive check (VPC) and analyses were made using NONMEM 7.3.

Results: Two compartment model with 1st order absorption and lag time was chosen for PK. Feedback of MAP was negligible in PP and HR, and an inhibitory I_{max} model successfully described the time courses of C·TPR, PP and HR (and MAP accordingly). VPC showed 95% of observations lied within 95% prediction interval.

Conclusions: This work demonstrated the feasibility of using non-invasive cardiac indices in deriving a mechanistic model of telmisartan effect in human. The developed model can be applied to antihypertensive drugs other than ARBs.

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Pascal Chanu Model-based simulation assessment of Personalized Healthcare strategies. A case for siponimod in multiple sclerosis.

P. Chanu (1), F. Mercier (1)
(1) Pharsight Consulting Services, Pharsight, a CertaraTM Company

Objectives: The "One dose fits all" concept still dominates in clinical development. Pharmacometrics could definitely contribute to implement Personalized Healthcare (PH). S1P (Sphingosine 1-phosphate) receptor modulators prevent the egress of lymphocytes from lymph nodes, reducing the amount of circulating lymphocytes and their potential to transit to the brain and damage neurons in relapsing forms of multiple sclerosis (RRMS). As a consequence of their therapeutic effect, S1P receptor modulators induce lymphopenia. Siponimod, is a S1P receptor modulator currently in Phase 3. Model-based simulations were performed to investigate how dose individualization could improve its efficacy and safety.

Methods: A simulation framework using public-domain information was developed to describe the clinical effect of siponimod. A PK model and a drug-specific model linking siponimod concentration to lymphocyte count [1] were implemented in Pharsight® Trial Simulator™. Model-based simulations were performed targeting lymphocyte count between 0.2 to 0.5 10^9/L. Four different daily siponimod dose regimens were tested: 1 mg; 2 mg; 1 mg starting dose with one dose adjustment (-50% or +100% when above or

below the target) 2 weeks after treatment initiation; and 1 mg starting dose with two dose adjustments 2 and 4 weeks after treatment initiation. Drug-independent models linking lymphocyte count to lesion count [2], and lesion count to relapse rate [3] were used to simulate clinical efficacy.

Results: Simulations results showed a clear benefit of both dose-adjustment scenarios over both fixed-dose scenarios with approximately 25% of subjects within target after 7 weeks versus 12% respectively. Simulations results showed a reduction of the risk of grade 4 lymphopenia (9/L) by 50% with dose-adjustment scenarios. Simulated clinical efficacy (lesion count and relapse rate) was similar for the four dosing regimens though with less variability with those using dose adjustments.

Conclusions: Simulations showed the benefit of dose adjustments during the first weeks of treatment with siponimod using a simple dose adjustment algorithm. This is particular interesting for drug classes where efficacy and safety can be monitored by the same biomarker and model-based simulations can help delineate best dosing strategies to maximize therapeutic index.

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surrogate for relapses in multiple sclerosis: a meta-analytic approach. Ann Neurol (2009) 65: 268–275.

Aziz Chaouch Approximate prediction percentiles for non-linear mixed effects models with continuous response

Aziz Chaouch (1,2), Thierry Buclin (2) and Valentin Rousson (1)
(1) Statistics Unit, Institute for Social and Preventive Medicine, University Hospital, Lausanne, Switzerland, (2) Division of Clinical Pharmacology and Toxicology, University Hospital, Lausanne, Switzerland

Objectives: Prediction percentiles for non-linear mixed effect models are commonly calculated using a large number of Monte Carlo simulations. In some applications (e.g. implementation of population pharmacokinetic models on miniaturized systems or calculation of confidence intervals for predicted quantiles), the computation time is critical and it is desirable to develop approximation methods to obtain such quantiles.

Methods: We present a general methodology to approximate the conditional predictive distribution (i.e. given covariate values) of the continuous response in a non-linear mixed effects model at a given time point by considering the distribution of a second order Taylor expansion of the model. We derive analytically its first four moments and match them with the corresponding moments of a flexible family of parametric distributions [1] which can accommodate different levels of skewness and kurtosis. The proposed methodology is applied to the computation of steady-

state prediction percentile curves for a published population pharmacokinetic model of an anti-fungal agent [2].

Results: The proposed approach performs reasonably well and preliminary results suggest that it is either faster (for the same degree of accuracy) or more accurate (for the same amount of computation time) when compared to Monte Carlo simulations.

Conclusions: The proposed approximation method provides an alternative to Monte Carlo simulations for the computation of prediction percentiles for non-linear mixed effects models. Further validation on different parameter sets is still warranted, using a sufficiently large number of MC simulations as gold standard.

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Christophe Chassagnole Modelling Synergistic Immunotherapy Combinations with Virtual Tumour

Frances Brightman, David Orrell, Eric Fernandez, Christophe Chassagnole
Physiomics plc

Objectives: Immunotherapy has recently developed into a highly active area of anticancer drug development. The field is dominated by immune-checkpoint blockers, which counteract the suppression of the immune response that is often observed in cancer. While early results for monotherapies are promising, the real potential of immunotherapy agents could be in combining them together or with other anticancer treatments. However, there is currently no rational basis on which to select optimal dosing regimens or combination schedules, and a clear unmet need for predictive tools to aid this process[1,2].

Methods: Physiomics has developed a preclinical and a clinical 'Virtual Tumour' ("VT") technology that can predict how a tumour will respond to drug exposure. The VT technology integrates PK and PD effects and models the way individual cells behave within a tumour population. These agent-based methods are particularly suitable for modelling not only tumour cells, but also other cell populations – such as those involved in the immune response – and interactions between cells. Here we describe our recent development and application of the VT technology for modelling preclinical efficacy of immune-checkpoint blockers, with a focus on

agents targeting the PD-1/PD-L1 axis. The VT platform has been extended by the addition of an immunotherapy module, which has been developed and calibrated using data taken from the literature. This module captures the mechanisms by which the immunotherapy activates the antitumor immune response and synergizes with conventional anticancer therapies.

Results: Through a preclinical case study derived from the literature, we demonstrate that the extended VT can be applied to model the efficacy of an anti-PD-L1 antibody in syngeneic mouse xenografts, both alone and in combination with irradiation. The model was calibrated using published PK data for the antibody[3], and tumour growth inhibition data for the monotherapies in two *in vivo* models (TUBO and MC38)[4]. As in a blind validation study, the calibrated model was then used to predict the respective combination efficacies. The predictions were validated against the published experimental data[4], and found to accurately reflect the synergy of the combination treatment.

Conclusions: Through this case study, we demonstrate that our enhanced VT capability represents the first step towards a ground-breaking tool for optimizing dosing and scheduling of immunotherapy, both alone and in combination with conventional anticancer therapies.

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Clarisse Chavanne How to simulate pediatric pharmacokinetic (PK) exposures using a population PK dataset composed of incomplete age groups.

C.Chavanne(1), N.Frey (1)
(1) Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, Switzerland, F. Hoffmann-La Roche Ltd.

Objectives: Conducting clinical trials in the pediatric population is generally a challenge, particularly when trying to ensure that enough patients are recruited to be able to explore the entire age range. Consequently, the collection of information to characterize the impact of the change in demographics and laboratory parameters with age on the drug PK properties, is generally incomplete. Population PK approaches could help by establishing covariate effect relationships to fill those gaps. However when simulations need to be conducted, the lack of covariate information for some age groups may become an issue. The objective of this work is to create a procedure that artificially increases the number of patients from an existing clinical database to get a more complete coverage of the age range. This work was done especially to support the evaluation of a new dosing algorithm for a drug X.

Methods: A covariate database was built with pediatric patients (age < 16 yrs) sourced from five Roche-sponsored and investigator-

initiated trials and treated for the same pathology. The following covariates that influence the PK of drug X were of interest: age, gender, weight, height, CrCl. All sets of covariates from all trial visits were considered. In order to artificially increase the number of patients, each set of covariates at a given visit was considered as being that of a new patient. The Center for Disease Control (CDC) growth charts [1] were used as reference to evaluate if the coverage of the weight and height distribution over the entire age range was optimal. The population PK model of drug X was used to simulate steady-state exposure for the new dosing algorithm. Comparisons were then made between the databases both with and without the artificial increase.

Results: 293 patients were considered from the five clinical trials. Using each set of covariates as being a different patient, increases this number to 1473. The weight and height values were well distributed over the CDC charts. The simulated exposures with the largest dataset allowed for a better evaluation of the properties of the new dosing algorithm across the entire age range.

Conclusions: Considering each set of covariates at a given visit in pediatric clinical trials as being that of a different patient is a very effective procedure to artificially increase the range of covariates that change with age and then conduct simulations in a pediatric population to explore for example the evaluation of a new dosing algorithm.

References:

[1] Center for Disease Control (CDC) growth charts (http://www.cdc.gov/growthcharts/)

Tina Checchio Mixed Effects Analysis of Non-compartmental Pharmacokinetic Parameters of Tofacitinib from 16 Phase 1 Studies.

Tina Checchio (1), Mark Peterson (2) and Sriram Krishnaswami (3)
(1) Pharmacometrics, Global Clinical Pharmacology, Pfizer, Groton, CT, USA, (2) Pharmacometrics, Global Clinical Pharmacology, Pfizer, Cambridge, MA, USA, (3) Specialty Care, Global Clinical Pharmacology, Pfizer, Groton, CT, USA

Objectives: Estimate and summarize effects of intrinsic and extrinsic factors on tofacitinib exposure, an oral Janus kinase inhibitor, in healthy adults by pooling and analyzing individual level metrics from 16 Phase 1 trials.

Methods: Evaluable AUC and Cmax values were included from 356 healthy volunteers (HV). Taking into account the 3 hour half-life of tofacitinib, single-dose and steady-state metrics were pooled. Base model characteristics included a linear model fit to Ln(AUC) vs Ln(Dose) and a sigmoidal E_{Max} dose function model for Ln(Cmax). Intersubject random effects were estimated on the intercept parameters of the models, and a residual error model containing a single additive term was supported. A full model approach was employed to estimate covariate effects. Covariates of interest (age, weight, race, sex, creatinine clearance (CrCL), fed/fasted status, and formulation) entered as power (continuous covariates) and fractional change (discrete covariates) functions. The possible range of exposure values for specific changes in covariates relative to the

reference individual were simulated. A reference individual was defined as a healthy normal volunteer 32 year old, Caucasian, male, weighing 73 kg with baseline CrCL = 109 mL/min, receiving 5 mg tablets of tofacitinib under fasting conditions.

Results: Tofacitinib exhibited approximate dose proportional increases in AUC and Cmax over dose ranges of 0.1 to 100 mg and 0.1 to 50 mg, respectively. Differences in typical AUC were less than 20% across the range of ages, body weights, gender and races studied. Differences in typical Cmax were less than 38% across the ages, gender and races studied. Cmax decreased with increasing body weight. When administered as a solution, tofacitinib AUC and Cmax were estimated to be 15.9% (8.92-23.3%) higher and 17.4% (11.3-24.2%) higher, respectively, relative to tablet. Co-administration of tofacitinib with high fat meal resulted in 13.3% (5.43-21.7%) higher AUC and 30.3% (24.4-36.1%) lower Cmax, relative to fasted state. The model-estimated differences in formulation and food are consistent with the observed results from individual studies.

Conclusion: The magnitude of change predicted in AUC/Cmax in HV did not suggest necessary dose modification or dosing restrictions in adults based on age, body weight, gender, race, or fed status. The approach allowed use of NCA parameters to assess covariate relationships in absence of a population analysis.

Pierre Chelle Assessment of Endogenous Thrombin Potential predictive potential of Thrombin Generation mechanistic models with Hemophilic A patients

P Chelle (1,2), C Morin (1), M Piot (2), A Montmartin (3), N Durrande (1), R Leriche (1), S Laporte (2), X Delavenne (2), E Ollier (2), S Avril (1), B Tardy-Poncet (2,3), M Cournil (1)
(1) Center for Health Engineering, UMR 5307, Ecole Nationale Supérieure des Mines de Saint-Etienne, 42023 Saint-Etienne, France; (2) EA3065, Université Jean Monnet, 42023 Saint-Etienne, France ; (3) Inserm CIC1408, CHU de Saint-Etienne, 42023 Saint-Etienne, France

Objectives: Hemophilia A (HA) is the deficiency of coagulation factor (f) VIII and leads to bleeding tendency. Thrombin Generation (TG), a global PD test of coagulation, may improve management of HA patient substitutive treatment. It describes the thrombin concentration, *[IIa](t)* in a plasma sample and is well correlated with bleeding severity [1]. TG mechanistic model might be a good way to use this biomarker for the prediction of fVIII to reach. The objective is to evaluate the predictive potential of a set of mechanistic numerical models [2-7] to identify if they might be used to predict TG in HA patients.

Methods: Mechanistic models describe the evolution of concentrations of the plasmatic species interacting in the system by stiff non-linear Ordinary Differential Equations (ODE) system. ODE

were implemented in Matlab and solved numerically using ODE15s solver due to ODE stiffness giving *[IIa](t)*. Then, the area under the curve called Endogenous Thrombin Potential (ETP) is calculated from [IIa](t): **ETP=$\int_{t=0}^{\infty}$[IIa](t).dt** and compared with ETP obtained from a study including N=40 HA patients. Estimated ETP from patient *i* is noted *eETPi* and corresponds to the model response to this patient data. Mean Squared Error (MSE) was used to assess the model estimations as well as Stone-Geisser criterion (Q2) a normalized version of MSE [8].

$$Q^2=1-\frac{\sum_{i=1}^{N}(eETP_i-ETP_i)^2}{\sum_{i=1}^{N}(mETPi-ETPi)^2}$$

where *mETPi* is the mean of the N-1 ETP values when ETP_i is omitted. Thus, models with good estimations have Q2 close to 1. If Q2 is negative, using the model is worse than using mean to predict data. To minimize bias, optimization of MSE was realized using genetic algorithm (GA) [9] and gradient method (data not shown).

Results: MSE and Q2 results indicate a poor quality prediction for all the original models (cf Table). For mechanistic models, number of interactions is not necessarily synonymous of better behavior. Best estimations are obtained with models having fewer parameters as Panteleev model [6].

Table: Model performance

Reference	Nb of reactions	Nb of parameters	Q2	Optimized Q2	√MSE (nM.mn)	Optimized √MSE (nM.mn)
Hockin [2]	27	**42**	-1.08	**0.37**	552	304
Bungay [3]	46	105	-1.69	-0.20	628	419
Tyurin and	50	72	-3.2	0.04	792	376

Khanin [4]			9			
Panteleev [6]	51	**65**	-1.94	**0.51**	656	269
Zhu [5]	55	75	-8.21	-0.25	1161	427
Chaterjee [7]	57	105	-0.36	0.17	445	349

Discussion: The predictive potential of mechanistic models is not good enough yet to predict TG in HA patients. Optimization has given significant improvement on ETP estimations. Over-parameterization of models might explain the lack of precision of these models.

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Chunli Chen Application of the Multistate Tuberculosis Disease Model for Studying Pharmacokinetics and Pharmacodynamics in a Chronic Tuberculosis Mouse Model

Chunli Chen (1), Gerjo J. de Knegt (2), Jurriaan E.M. de Steenwinkel (2), Ulrika SH Simonsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (2) Erasmus MC, University Medical Centre Rotterdam, Department of Medical Microbiology & Infectious Diseases, Rotterdam, the Netherlands

Objectives: To use the Multistate Tuberculosis Disease Model for studying pharmacokinetics and pharmacodynamics (PKPD) of rifampicin (RIF) in a chronic tuberculosis (TB) mouse model.

Methods: One PK sample/animal was obtained in both healthy (n= 49) and infected mice (n= 18). Healthy mice were administered RIF (10 or 160 mg/kg) 5 days a week for 3 weeks where after the PK was obtained, which were pooled with PK data from infected mice. BALB/c mice were intratracheally infected with *Mycobacterium tuberculosis* Beijing-1585 strain at day 0 [1]. Rifampicin (5, 10, and 20 mg/kg orally) was administered daily for 4 weeks from day 15 after infection. Pharmacokinetic data was obtained at day 40. Mice were sacrificed at days 21, 28 and 42 and lungs were obtained, homogenized and plated to measure colony-forming unit (CFU) per mouse. Additional CFU were obtained in a separate group of

infected mice treated for 3 weeks, from day 15 after infection, by RIF (80, 160 and 320 mg/kg, no PK) and sacrificed at day 35 after infection. One group of animal (n= 67) received no treatment (natural growth) and were sacrificed at days 1, 3, 7, 14 and 21 after infection. The population PK model was first developed and thereafter a Population PK Parameters and Data approach [2, 3] was used to link PK to the Multistate Tuberculosis Disease model [4] in order to describe the change in CFU in lungs over time using NONMEM [5]. Xpose [6] and PsN [7] was used for data exploration and visualization, model diagnostics, model comparison and visual predictive checks.

Results: A one-compartment model with first-order absorption and elimination provided the best fit to the PK data. Rifampicin oral clearance (CL/F) of infected mice treated 4 weeks was 3 times higher than in healthy mice received 3-week treatment. The Multistate Tuberculosis Disease Model [4] composed by fast- (F), slow- (S), non-multiplying (N) state bacteria and dead bacteria compartments, and drug effects were introduced in the model according to the mechanism of action. Bacterial movement between different states, except for the transfer from F to S, were fixed to corresponding transfer rates estimated in the *in vitro* study using Beijing-1585.

Conclusion: Most probably due to disease related effects, rifampicin CL/F was higher in infected mice, although auto-induction might contribute to a limited degree because of different treatment lengths, showing needs to obtain PK in the same animal as studying drug effects. The Multistate Tuberculosis Disease model successfully described anti-TB effects of RIF in a chronic mouse model.

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Mohammed Cherkaoui Rbati Mechanistic Model to Predict DDIs in the Liver

Mohammed Cherkaoui, Stuart Paine, Cyril Rauch, Peter Littlewood
University of Nottingham

Objectives: To generate a mechanistic dynamic model for the prediction of Drug-Drug Interactions (DDIs), which results from time-processes within hepatocytes, taking into account the spatial distribution of the drugs in a lobule, the uptake at the sinusoidal membrane, the enzyme inhibition/induction [1] and the up-regulation of the enzyme gene.

Methods: Over 70 clinical DDIs [2,3], including inhibitors, inducers and mixed interactions, were compared with the prediction using a static model and the new dynamic model. This was implemented in MATLAB® and inserted into a PBPK model with 4 compartments (Blood/Gut/Liver/Rest).

The Blood and Rest compartments are simple compartments with a physiological volume and a partition coefficient. The Blood compartment has a partition coefficient of one, whereas the Rest compartment depends on the drug.

The Gut compartment comprises two sub-compartments: the first represents the gut wall with a first order absorption for the oral dose and takes into account DDIs within the enterocytes assuming a

well-stirred compartment; and the second represents the portal vein.

The estimations of the drug parameters (inhibition/inactivation/induction/uptake) were obtained with in vitro experiments and adjusted for the human liver size. The PK parameters (clearance/absorption rate) were obtained from the literature [4,5].

For each clinical case, the AUC ratio of the victim drug was estimated with the dynamic model and compared to the static model along with the clinical outcome.

Results: The preliminary results show that the model accurately predicts the DDI of the compounds which are purely inhibitors (reversible or time-dependent) or inducers. For compounds which are both, the prediction is less accurate. Overall, more than 50% of the DDIs have been predicted within 2-fold and more than 89% within 5-fold. The Geometric mean fold error (GMFE) has been estimated as 2.19, which is in the same range as the current static model ([2,3]: GMFE=1.7-2.5).

Conclusions: The model is consistent with those in the literature. It also provides a dynamic description of the DDIs, such as the enzyme level and spatial distribution within a lobule. Furthermore, the perpetrator dose regimen can be changed to observe its influences on the AUC ratio.

Finally, as in the static model [2,3], the DDIs prediction of compounds demonstrating inhibition and induction in-vitro is poor. These could be the result of a more complex mechanism occurring in the liver and/or intestine as an MDR1 induction or the perpetrator metabolite playing a role in the DDI.

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Manoranjenni Chetty Emerging covariates on the pharmacokinetics of monoclonal antibodies: Do current PBPK models account for the covariates identified in POPPK studies?

Manoranjenni Chetty (1), Katherine Gill (1), Krishna Machavaram (1), Linzhong Li (1), Iain Gardner (1), Amin Rostami (1,2), Masoud Jamei (1)

(1) Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK (2) Manchester Pharmacy School, Manchester University, Manchester

Objectives: To identify covariates that impact significantly on the pharmacokinetic (PK) parameters of monoclonal antibodies (mAbs) in population pharmacokinetic (POPPK) studies and to evaluate whether current human physiologically based pharmacokinetic (PBPK) models account for the PK variability due to these covariates.

Methods: A literature review was conducted to retrieve POPPK studies on mAbs. Studies were evaluated to identify covariates tested and those that had a significant impact on the PK variability. Published human PBPK models for mAbs were evaluated for their potential ability to account for variability in PK, with special reference to the significant covariates identified by POPPK studies.

Results: 37 POPPK studies were evaluated. Cumulatively, 59 different covariates were tested and 17 were identified as significant covariates. Weight was found to be significant in 20 studies, with covariates such as serum albumin, antibodies to the mAb, body surface area, sex, concurrent medication, white blood cells, dose, smoking status, aspartate aminotransferase (AST), ethnicity, age, target concentration, formulation, route of administration and glomerular filtration rate reported to be significant in 6 studies or less. PBPK models have the potential to account for the variability due to the majority of these covariates but most of the current models do not focus on sources of variability. Weight, the major covariate identified in POPPK analyses, requires to be considered in PBPK models, although many mAbs are dosed according to the weight of the patient. Antibodies to the mAb were found to be significant in only 16% of the studies. However, this covariate could present some challenges for PBPK modelling.

Conclusions: Weight was the major significant covariate identified. PBPK models generally do not adequately incorporate variability due to the relevant covariates.

Maxwell Tawanda Chirehwa Model based evaluation of higher doses of rifampicin using a semi-mechanistic model incorporating auto-induction and saturation of first-pass hepatic extraction

Maxwell Chirehwa (1), Roxana Rustomjee (2), Thuli Mthiyane (3), Philip Onyebujoh (4), Peter Smith (1), Helen McIlleron (1), Paolo Denti (1)

(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa; (2) Strategic Health Innovation Partnerships (SHIP), South African Medical Research Council, Cape Town, South Africa; (3) South African Medical Research Council, Durban, South Africa; (4) Intercountry Support Team for East and Southern Africa, World Health Organization, Regional Office for Africa, Harare, Zimbabwe

Introduction: Rifampicin is a key drug in the treatment of tuberculosis. It is hepatically cleared and it undergoes extensive first-pass metabolism [1], whose saturation with larger doses has been reported since early pharmacokinetic (PK) studies [2]. Rifampicin also induces its own metabolism via Pregnane X Receptor (PXR) [3]. WHO currently recommends 8-12 mg/kg doses of rifampicin. However, higher doses which are likely to be more effective are being investigated.

Objectives: To develop a population model to describe rifampicin

PK among tuberculosis patients accounting for the auto-induction of rifampicin clearance and saturation of first-pass hepatic extraction.

To explore changes in rifampicin exposures when doses are increased beyond the currently recommended range.

Methods: As previously described, blood samples were collected from 61 HIV/TB co-infected patients in South Africa who had a median age of 32 years (range: 18-47 years) and weight of 55 kg (range: 34-99 kg)[4]. Intensive PK sampling was performed on four occasions after initiation of treatment: day 1, 8, 15, and 29. On each occasion, samples were collected just prior to the dose and at 1, 2, 4, 6, 8, and 12 h after dose. 41 of the patients received efavirenz-based antiretroviral therapy starting on day 15. Weight band-based dosing for antituberculosis treatment was implemented according to WHO guidelines [5]. Plasma rifampicin was quantified using LC-MS/MS. The assay was validated for concentrations between 0.1-30 mg/L.

Data were analysed using nonlinear mixed effects modelling in NONMEM VII using first-order conditional estimation with eta-epsilon interaction (FOCE-I). For absorption, the models evaluated during model building included first-order absorption with and without delay with lag time or a series of transit compartments [6]. With regards to disposition, a one compartment with first-order elimination and a semi-mechanistic well-stirred hepatic model similar to the one used by Gordi *et al.* [7] were assessed. Auto-induction of clearance over time was described using an exponential model. To adjust for body size, allometric scaling [8] was applied to clearance, volume of central and liver compartments, and hepatic blood flow. The M6 method was applied to handle concentrations below the limit of quantification [9]. Model development was guided by change in objective function value (OFV) and diagnostic plots.

The final model was employed to simulate exposures at increasing doses using the demographic data of 870 tuberculosis patients from South Africa and West Africa (200 repetitions). Based on the current weight-bands, exposures were evaluated using doses equivalent to 1.5, 2, and 3.5 times the current dose. Twenty-four hour areas under the curve at steady-state (AUC_{0-24}) were predicted and dose/exposure proportionality was assessed.

Results: Rifampicin PK was best described using a transit compartment absorption and a well-stirred liver model with saturation of (first-pass) hepatic extraction. For a typical individual, volume of the liver compartment was assumed to be 1 L, and the liver plasma flow 50 L/h. Free fraction of unbound rifampicin was fixed to 20% (2). Saturation of first-pass metabolism was parameterized using a Michaelis-Menten saturation model and hepatic metabolism was found to have a maximum CL_{int} of 98 L/h at baseline with a Km of 3.2 mg/L.

Large between-occasion variability was detected for k_a and absorption mean transit time, while between-subject variability was relatively low for both clearance and volume of distribution (<25%). Fat free mass was the best descriptor of body size for all clearance and volume parameters. Increase of hepatic CL_{int} over time was characterised in the model and it was estimated CL_{int} approximately doubles from baseline to steady state with a half-life of the auto-induction of around 4 days.

As expected, the current model predicts that increases in dose of rifampicin result in more-than-linear increases in drug exposures as measured by AUC_{0-24}. Our simulations show that giving patients 20 mg/kg rather than 10 mg/kg results in 3.2 times higher AUC and further increasing the dose to 35 mg/kg (3.5 times), the AUC becomes 8.4 times higher. Simulation results from this study are predictive of the observed exposures recently reported in studies using higher doses of rifampicin by Aarnoutse *et al*. [10]. They

reported a 3.1 times higher AUC when giving patients 1200 mg compared to 600 mg dose, closely in line with our model predictions.

Conclusion: We developed a model for rifampicin PK that characterises auto-induction of clearance and saturation of metabolism, which is evident on first-pass extraction even at the current doses. The model correctly predicts that increasing the dose of rifampicin results in a more than proportional increase in drug exposure. Our simulations with a 20 mg/kg doses produce results closely in line with those from recent clinical trials.

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Jason Chittenden Evaluation of stepwise covariate model selection with Bayesian models

Jason Chittenden (1) and Klaas Prins (1)
(1) qPharmetra LLC, Andover, MA, USA

Objectives: Stepwise covariate modeling (SCM) is a commonly used tool for covariate model selection. Traditionally, SCM as implemented in Perl Speaks NONMEM (PsN)[1] is performed using deterministic estimation methods (e.g. FOCE-I, Laplace). The recent availability of stochastic methods, such as: stochastic approximation EM (SAEM), importance sampling EM (IMPEM), and Bayesian Markov Chain Monte Carlo methods (BAYES) [2] raises the question of how the SCM process fares in the face of stochastic noise in the objective function. Prompted by a real case where SCM failed with FOCE-I and succeeded with BAYES the current simulation-estimation study aims to test the performance of FOCE-I vs. BAYES methods in a hypothetical SCM process and to challenge the model selection criterion used.

Methods: The true model was a one-compartment elimination, 1^{st}-order absorption PK model with body weight proportionally increasing volume of distribution and CL decreasing with age. From this model a data set with 90 subjects with dense sampling was simulated 100 times. Other, non-impactful and highly correlated covariates were added to the data set. Using the correct structural model, an SCM for three scenarios was run on all data sets and the success rate to recover the true model was retained. The three SCM

scenarios were: 1) using FOCE-I and the final objective function value (OFV) as model selection criterion, 2) using MCMC BAYES and the sample mean OFV and 3) using MCMC BAYES and the Deviance Information Criterion[3] (DIC). DIC has been suggested [4,5] as a robust method for model selection in Bayesian analyses. The SCM tool in PsN was modified to compute either the mode of the OFV (current SCM default) or the DIC to be used as model selection criterion. Where SCM failed to identify the true model it was determined if pruning of the selected model by removing non-significant (alpha=5%) effects would arrive at the true model.

Results: Scenario 1 (FOCE_I & mode of OFV) selected the true model in 66% of the cases, with 68% succeeding after pruning. Scenario 2 (MCMC BAYES, mode of OFV) also succeeded 66% of the time, increasing to 78% with pruning. Scenario 3 (MCMC BAYES, DIC) performed worst at 5% success rate, and 25% after pruning.

Conclusion: SCM can be performed using MCMC Bayesian or FOCE-I estimation interchangeably using the OFV as model selection criterion. The DIC criterion was found to be unsuitable for the stepwise covariate search when using Bayesian estimation.

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Palang Chotsiri Population pharmacokinetic and cardiotoxic modelling of the antimalarial drug piperaquine

Palang Chotsiri (1,2), Thanaporn Wattanakul (1,2), Borimas Hanboonkunupakarn (2), Podjanee Jittamala (2), Salwaluk Panapipat (1), Richard Hoglund (1,3), Daniel Blessborn (1,3), Sasithon Pukrittayakamee (2), Nicholas J. White (1,3), Nicholas P.J. Day (1,3)
(1) Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand, (2) Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, (3) Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, United Kingdom

Objectives: This study aimed to characterise the pharmacokinetic properties of the antimalarial drug piperaquine and its propensity for QTc prolongation, and its potential drug-drug interaction with the transmission blocking agent primaquine.

Methods: Sixteen healthy volunteers were recruited to this study and randomly administered primaquine alone, dihydroartemisinin-piperaquine alone, and dihydroartemisinin-piperaquine with primaquine at three occasions. Nonlinear mixed-effects modelling was performed to characterise the pharmacokinetic properties of piperaquine. The effect of primaquine co-administration was evaluated separately as a categorical covariate on all individual pharmacokinetic parameters and by using a full covariate approach.

All remaining covariates were evaluated by a stepwise addition/elimination approach. Double-delta Fredericia-corrected QT measurements (ΔΔQTcF) were modelled as a linear direct-response pharmacodynamic model.

Results: Piperaquine plasma concentrations were best described by two transit-absorption compartments followed by three-disposition compartments. No clinical covariates had a significant impact on the pharmacokinetic parameters, and co-administration of primaquine did not affect the pharmacokinetic properties of piperaquine. ΔΔQTcF increased linearly with increasing piperaquine concentrations. Simulations using the final pharmacokinetic-pharmacodynamic model suggested that 95% of individuals with peak piperaquine concentrations below 850 ng/mL will have a ΔΔQTcF below 60 mSec.

Conclusions: Data presented here demonstrated that co-administration of primaquine did not alter the pharmacokinetic properties of piperaquine. Simulated maximum piperaquine concentrations after a standard 3-day antimalarial therapy of dihydroartemisinin-piperaquine were below that considered to produce a clinically significant QTcF prolongation.

Steve Choy Modelling the disease progression of diabetes from healthy to overtly diabetic in ZDSD rats

Steve Choy (1), Willem de Winter (2), Mats O Karlsson (1), Maria C Kjellsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden, (2) Clinical Pharmacology, Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium

Objectives: Type 2 diabetes (T2DM) is a disease exhibiting a gradual worsening of hyperglycemia, on the timescale of years. Studying the critical transitional phase from healthy to diabetic is of interest, but acquiring such data in humans is not practical due to ethical reasons and the long study duration required.
ZDSD rats, a strain of rats bred specifically to spontaneously develop metabolic syndrome and type 2 diabetic symptoms [1] has been used in a population model to describe the changes in insulin sensitivity (IS), beta-cell function (BCF) throughout different phases of diabetes and their effects on glucose and insulin.

Methods: Body weight (WT), fasting plasma glucose (FPG), and fasting serum insulin (FSI) were collected every 2 weeks for 24 weeks from ZDSD rats (n=23) starting from age 7 weeks. During these 24 weeks the rats' insulin sensitivity is decreased as indicated by hyperinsulinemia with normoglycemia. Eventually the rats become overtly diabetic with hypoinsulinemia and hyperglycemia. The weight of the rats increases due to natural growth and excess growth owing to the strain's propensity for fat storage and obesity.

As the rats become hyperglycemic the weight decreases slightly. A semi-mechanistic model previously developed with human data [2] was adapted to rat data. Baseline IS and BCF were estimated according to the human homeostatic assessment model (HOMA) [3]. Non-linear mixed-effect model estimation was performed with NONMEM 7.3 [4] with first-order interaction.

Results: Baseline estimated IS and BCF were 39% and 41% of normal humans, respectively. Egrowth was best described with a stimulatory effect with a maximum of 1.8, gradually decreasing to 1. BCF was described with a non-linear rise until it reached a mean peak around 14 weeks, before it declined to a negligible level, leading to hypoinsulinemia and hyperglycemia. The FPG-dependent urine effect exerted a 2 to 6-fold increase on the Kout of FPG

Conclusions: A semi-mechanistic model was successfully developed for a rat population to describe insulin and glucose profiles adequately, transitioning from healthy to an advanced stage of diabetes. It is also shown that weight loss can be modeled to mimic "starvation in the midst of plenty" which is a phenomenon related to hypoinsulinemia and hyperglycemia.

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Eirini Christodoulou Pharmacokinetics of Crocus sativus L. aqueous extract after peros and intravenous administration to C57/BL6J mice

Ei. Christodoulou(1), Z.I. Kakazanis(2), N. Kostomitsopoulos(2), A. Dokoumetzidis(1), G.Valsami(1)
(1) Laboratory of Biopharmaceutics-Pharmacokinetics, Department of Pharmaceutical Technology, School of Pharmacy, National and Kapodistrian University of Athens, Greece (2) Center of Clinical Experimental Surgery and Translational Research, Biomedical Research Foundation, Academy of Athens, Greece

Objectives: To develop a PK model to describe serum pharmacokinetics and bioavailability of saffron aqueous extract, and especially the PK properties of crocetin, after peros and intravenous administration to mice.

Methods: A lyophilized aqueous extract of Crocus sativus L. stigmata was administered to 80 C57Bl/6J male mice (dose 60 mg/kg body weight) after reconstitution with sterile water. Mice were divided into groups of five and sacrificed at selected time points for blood and tissue sampling. Serum samples were analyzed with an HPLC-DAD method developed for crocetin (the metabolite of crocin, the main antioxidant component of the aqueous extract) [1]. Crocetin serum concentration data after both iv and peros administration were analyzed in NONMEM to describe serum pharmacokinetics and bioavailability of saffron aqueous extract.

Results: Crocetin serum levels were measured after p.o. and i.v. administration of lyophilized saffron aqueous extract using standardized calibration curves. Mean measured C_{max} value was found 3±0.18 μg/mL (T_{max}=15 min) and 2.7±0.06 μg/mL (T_{max}=30 min) for i.v and peros administration respectively. Serum i.v and peros data were described by a one-compartment model parametrized for i.v. administration as V=33.5 mL, CL=55.2 mL/h and k_{tr}=12.1 h^{-1} representing the rate of crocin to crocetin transformation (%RE 22.1); and for peros administration V=13.0 mL, CL=41.5 mL/h and $k_{a,tr}$=2.01 h^{-1}, representing a hybrid rate of absorption and crocin to crocetin transformation (%RE 25.6). Crocetin bioavailability after peros administration was found comparable to i.v. administration of saffron extract, probably because the intestinal tract serves as an important site for crocin (main saffron constituent precursor of crocetin) hydrolysis to crocetin [1] and thereafter rapid absorption and entrance to blood circulation. However, since crocetin is also metabolized to glucuronides, measurement of total crocetin (free+glucuronide) is required and is in process to fully characterize oral bioavailability.

Conclusions: Both i.v. and peros pharmacokinetics of crocetin after single dose administration to C57Bl/6J male mice as saffron extract was adequately described by a one compartment PK model. After p.o. administration crocin, the main constituent of saffron extract, was rapidly hydrolyzed to its active metabolite crocetin in the GI tract and measured serum crocetin levels were comparable to those after i.v. administration.

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Laurent Claret A comparison of two stage and joint tumor growth inhibition-progression free survival modeling approach to simulate clinical outcome in oncology

Laurent Claret (1), Rene Bruno (1), Bei Wang (2), Mathilde Marchand (1), Chunze Li (2), Sandhya Girish (2), Jin Jin (2), Angelica Quartino (2)
(1) Pharsight Consulting Services, Pharsight, a CertaraTM Company, Marseille, France (2) Genentech Research and Early Development (gRED), Roche, South San Francisco, CA

Objectives: In anticancer drug development, tumor growth inhibition (TGI) metrics have been increasingly used to predict clinical outcomes: overall survival (OS) or progression free survival (PFS) [1]. This approach involves two step modeling (TSM): 1) a longitudinal TGI model to estimate TGI metrics and 2) a time to event model to link TGI to clinical outcome. This TSM approach has been criticized [2] because the uncertainty of the individual TGI metrics estimations is not carried forward in the time to event model likelihood, and it is proposed to use a joint model (JM) fitting simultaneously both dependent variables. If JM cannot be easily applied for OS as longitudinal and time to event data are not recorded simultaneously and TGI models cannot be extrapolated after treatment stop, it can be evaluated on PFS.

Methods: TSM and JM were evaluated on a study comparing two treatments based on PFS hazard ratio (HR) in cancer patients. TSM and JM were implemented in NONMEM 7.2. TGI data are described by a bi-exponential model [3] implemented in a non-linear mixed effect approach and PFS data by a Weibull distribution. PFS models are evaluated in their abilities to simulate distributions and treatment HR.

Results: In the TSM approach the Weibull PFS distribution is defined by patient characteristics and TGI model parameters [3]. The model is qualified to predict PFS in patient sub-groups and treatment HR. The JM model development revealed that TGI metrics provided better fit than hazard as function of longitudinal baseline adjusted tumor size prediction and a Weibull distribution of the intercept was better than a constant one. The final JM got the same structure. Model parameter point estimates and posterior predictive distributions of JM and TSM were similar. PFS model parameters were estimated slightly more precisely with JM.

Conclusions: This comparison, based on an analysis of single study, shows that despite a slightly better precision of JM model parameter estimates, structural models and prediction performances were similar for both approaches. TGI metrics were better than tumor size as function of time to drive PFS hazard function. JM model can be used to predict PFS based on TGI profiles. Ultimately, the goal of the model will have to be accounted for e.g. develop the best model to simulate alternative clinical trial designs, assess an early marker of effect to support decisions or predict individual patient outcomes to support therapeutic decisions.

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Pieter Colin Towards TDM-guided dosing for cefepime in the critically ill

Pieter Colin, Stijn Jonckheere, Hans De Beenhouwer, Nikolaas De Neve, An Vermeulen, Jan Van Bocxlaer
Ghent University

Objectives: Cefepime (CFP), is extensively used for serious infections in the intensive care unit. Several groups described extensive variability in plasma concentrations and a high proportion of ICU patients not achieving suitable PKPD targets following currently used clinical treatment regimens. Nevertheless, due to discrepancies between published models for CFP and uncertainties with respect to the correlation between CFP clearance and different GFR biomarkers, therapeutic drug monitoring is not yet routinely implemented for this compound. We set out to compare the predictive performance of the different published models and propose a new model / sampling strategy to guide CFP dosing in the ICU.

Methods: Plasma and urine samples were obtained from patients who were treated with CFP, per standard of care, in the ICU of the OLVZ hospital in Aalst, Belgium. Patients were treated with a median of 10 doses resulting in a median follow-up of 80 hours. Using NONMEM, median prediction error and root mean square error were chosen as a performance metric to compare the different models. As a step up from the available models we investigated whether adding different biomarkers for GFR as time-

varying covariates could significantly improve the model's predictive performance.

Results: The predictive performance of earlier published models was found unsatisfactory in our patient cohort. Furthermore, the non-renal clearance of CFP, which accounts for approx. 1/3 of CL_{TOT} is frequently ignored, making accurate predictions of CFP clearance impossible. Since, in our institution, 1/5 patients on CFP undergo hemodialysis we developed a PopPK model including in addition to parameters describing the renal and non-renal clearance, a $CL_{Dialysis}$ parameter describing the kinetics of the "on-dialysis" moments. Finally, by incorporating CKD-EPI as a time-varying covariate on the renal CFP clearance, the model's goodness-of-fit was further improved.

Conclusions: A therapeutic drug monitoring-based adaptation of our PopPK model could allow to adequately control the level of variability in this vulnerable patient population. Nevertheless, more accurate, non-serum creatinine related, GFR estimators might be more suitable to follow-up on changes in CFP clearance over time (and are currently under evaluation), reducing the necessity of daily TDM measurements.

Francois Combes Population Pharmacodynamic Modeling and Simulation of Anti-Obesity Clinical Trials to Explore Longitudinal Weight Loss

Combes FP (1), Vakilynejad M (2), Lahu G (3), Lesko LJ (1), Trame MN (1)

(1) Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA; (2) Takeda Pharmaceuticals Research Division, Pharmacometrics, Deerfield, IL, USA; (3) Takeda Pharmaceuticals Research Divsion, Pharmacometrics, Zurich, Switzerland

Objectives: Currently, drugs approved for obesity treatment have shown a wide range of response in clinical trials, even though the dropout rate remains high [1]. The mechanistic reason for non-response or dropout during the treatment period remains unclear. The objective of this study was (i) to develop a Population Pharmacodynamic (PopPD) model describing BodyWeight (BW) time-courses in obese subjects on placebo and LifeStyle Interventions (LSI), (ii) to evaluate the transition probabilities between Responder (R), Non-Responder (NR) and Dropout (D) states using a Markov Model (MM), and (iii) to simulate the outcome of anti-obesity trials using the developed PopPD/MM with regard to R, NR and D rates.

Methods: 1102 obese patients (BMI>30) on placebo, in Phase III naltrexone-bupropion trials, were included in this analysis with up to 60 weeks of BW information. Subjects were instructed on dietary changes (≈-500kcal/d) and encouraged to exercise 3 times/week. To analyze the placebo patient level data, an indirect-response model with 0 and 1st-order rate constants for BW gain and loss, respectively [2], for the purpose of predicting longitudinal BW loss under different LSI, was used.

MM was developed to predict time courses of transition probabilities between R, NR, and D states [3-4]. Longitudinal BW, predicted using the PopPD model, was examined as a covariate on the transition probabilities to explain the D or R pattern.

Results: The PopPD model described the BW change over time adequately for all subjects included in this analysis. The estimated MM probabilities of transitions between R to NR (0.162), R to D (0.048), NR to R (0.195), and NR to D (0.070), concluded that NR are more likely to dropout than R. The predicted longitudinal BW over time when used as a covariate was shown to significantly influence the transition probabilities between all R, NR, and D states. The developed PopPD/MM model was enabled to simulate R, NR, and D rates for anti-obesity clinical trials.

Conclusions: The joint PopPD/MM described longitudinal BW loss and transition probabilities between states in anti-obesity clinical trials well, concluding that BW is a major factor influencing the probabilities. Further research is required to explore other covariate effects such as treatments, and side effects. The developed framework can be utilized for clinical trial simulations to inform go/no-go decisions in anti-obesity drug development [5].

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Emmanuelle Comets Joint modelling of iron and hepcidin during the menstrual cycle

Adeline Angeli (1), Fabrice Lainé (1), Bruno Laviolle (1), Emmanuelle Comets (1,2)
(1) INSERM CIC 1414, Rennes, France; Université Rennes-1, Rennes, France (2) INSERM, IAME UMR 1137, Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, Paris, France

Objectives: Iron is a key element for the organism, involved in many biological processes.Serum iron levels are regulated through digestive absorption from food and sophisticated storage mechanisms Hepcidin is a peptidic hormone regulating iron storage and release. It is synthesised by the hepatocytes, and interacts with ferroportin, a cellular iron-exporter located on macrophages, hepatocytes and intestinal cells, to prevent iron from being released from these cells into the general circulation . A recent analytical method developed to measure hepcidin allows its use in the diagnostic of iron-related pathologies such as iron overload or anaemia. Women lose iron during menstruation, which causes cyclic variations in iron-status variables [1]. The HEPMEN study was designed to follow serum levels of hepcidin and iron during the menstrual cycle.

Methods: Ninety menstruating women between 18 and 45 years of age were recruited in after a screening visit, where demographic covariates were recorded. Six fasting blood samples for determination of iron-status variables were taken in the morning

throughout the cycle, starting on the second day of the period. Non-linear mixed effect models were used to describe the evolution of iron and hepcidin, first separately then simultaneously. Parameters were estimated using the Monolix software [2]. Diagnostics included VPC and npde [3].

Results: A general pattern was observed for both hepcidin and iron, consisting of an initial decrease during menstruation, followed by a rebound, and stabilisation during the second half of the cycle. Considerable fluctuations were observed in both iron and hepcidin levels, as well as in individual profiles.

We developed a joint model of iron and hepcidin. Menstruation induced a decrease of both molecules at the beginning of the menses, and the rebound was modelled as an increased input. Iron stimulated the release of hepcidin. Several covariates, including contraception, amount of blood loss and ferritin, were found to influence the parameters of the model. Simulations were then performed to evaluate the fluctuations of both variables during a typical cycle, and to establish recommendations for time of measurement.

Conclusions: Considerable fluctuations of hepcidin occur throughout the menstrual cycle. Hepcidin should be measured during the second half of the cycle, but the residual variability for hepcidin was large, reflecting daily intraindividual variations.

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Ana Margarita Contreras Sandoval Towards a platform PK/PD model for an anti-PD-L1 monoclonal antibody through a preclinical syngeneic melanoma mouse model

Ana Margarita Contreras S (1), María García-Cremades (1), María Merino (1), Laurent Blom (1,3), Pedro Berraondo (2), Iñaki F. Trocóniz (1), María Jesús Garrido (1).
(1) School of Pharmacy. Department of Pharmacy and Pharmaceutical Technology. University of Navarra. 31008. Pamplona. Spain. (2) Division of Gene Therapy and Hepatology. Center for Medical Applied research (CIMA). University of Navarra. 31008. Pamplona. Spain. (3) Department of Pharmacy and Biomolecular Science (PBS). Liverpool John Moores University. Liverpool, L3 5AF. UK.

Objective. To develop a platform PK/PD model for an anti-PD-L1 monoclonal antibody (mAb). PD-L1 is a ligand over-expressed on tumor cells and is able to down-regulate the immune response to enhance tumor proliferation. This study includes serum and tumor levels of an anti-PD-L1 mAb, as well as measures of tumor size and specifics immune biomarkers to stablish a relationship between the mAb treatment and the effect.

Methods. *In-vitro assay.* The endogenous expression of PD-L1 and the effect over its expression due to different concentrations and times of exposure to an anti-PD-L1 mAb was characterize for B16-

OVA cell line by flow cytometry along 72h. Then, three different mechanism of internalization for the mAb were also explored. *In-vivo assay.* s.c. syngeneic melanoma model was stablish for B16-OVA. Mice were randomly assigned to one control and three different treated groups according to the day when the treatment stars. 100 µg mAb/mouse Q3D x 4 administrations were given i.v. to the treated groups, and tumor growth profiles were recorded. For another group of mice with tumor volume 20-50 mm^3, treatment was given as explained above and at different time points serum and tumor mAb's concentration was measure by ELISA; meanwhile lymphocyte and different immune biomarkers ($CD8^+$-OVA and PD-1) were quantify by flow cytometry. A B16F10 syngeneic melanoma model was used to validate these data. Data from PK/PD assays was analyzed using NONMEM 7.2 and plots were done with R program.

Results. *In-vitro assay.* PD-L1 is expressed in 100% of B16-OVA cells. An anti-PD-L1 mAb treatment is able to block this expression with not dependence on the time of exposure. However, expression's recovery seems to be concentration and time-dependent, which suggest a complex mechanism of internalization different than endocytosis. *In-vivo assay.* One compartmental model describes time profile of an anti-PD-L1 mAb in an *in-vivo* tumor free mouse model. Tumor growth profiles, explored for B16F10 and B16-OVA cell line, were described by Hahnfeldt's model **[7]**. PK/PD analysis is currently ongoing.

Conclusions. Anti-PD-L1 mAb was able to block the PD-L1's expression at the surface of melanoma cells for more than 72h. The presence of the OVA antigen seems to be the main responsible for the efficacy of the mAb over B16-OVA cells, which is even greater when tumors are treated at earlier stages. Immune response can be modulated by an anti-PD-L1 mAb to promote anti-tumor effect.

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Teresa Dalla Costa Population analysis of levofloxacin in plasma, lung and prostrate measured by microdialysis in Wistar rats after intravenous and intratracheal administration

Estevan Zimmermann(1,2); Camila Neris (1); Stephan Schmidt (2); Chakradhar Lagishetty (2); Teresa Dalla Costa (1)
(1) Pharmaceutical Sciences Graduate Program, Federal University of Rio Grande do Sul, Brazil; (2) Center for Pharmacometrics & Systems Pharmacology, School of Pharmacy, University of Florida at Lake Nona, Orlando, USA

Objectives: To evaluate levofloxacin (LEV) lung and prostate interstitial fluid (ISF) concentrations with and without tariquidar (TAR), a P-gp inhibitor, viewing to elucidate this fluoroquinolone penetration mechanism and to develop a population pharmacokinetic (POPPK) model able to describe experimental data simultaneously.

Methods: Wistar rats (300-400 g) were randomly distributed in eight groups (n = 6/groups). For each dose/route of administration, one group was used for total plasma sampling and one for ISF concentrations sampling. Animals received LEV 7 mg/kg intravenously (i.v.) or intratracheally (i.t.) alone or 30 min after TAR 15 mg/kg i.v. dosing. Experiments approved by CEUA/UFRGS 21169. CMA/20 microdialysis probes (4 mm, cutoff 20 kDa), flushed with Ringer´s solution 1.5 µL/min, were used to collect ISF free

concentrations in both tissues. Throughout the experiment, animals were kept anesthetized with urethane and under mechanical ventilation. Total LEV concentrations in plasma and free lung and prostate were investigated up to 12 h. A semi-mechanistic population pharmacokinetic model was developed using NONMEM version 7.2 to simultaneously characterize total plasma and free ISF tissues (lung and prostate) concentrations.

Results: A four compartment model was appropriate to simultaneously characterize and predict concentrations in total plasma and in the ISF of prostrate and lung, target infected tissues treated with this drug [1,2]. Statistically significant differences were observed for three parameters for TAR group compared to control group (*lung penetration*, *prostrate penetration* and *kidney active secretion*). The final model was best in terms of curve fitting, precision of parameter estimates and model stability. The interindividual variabilities were reasonably small for the parameters in the model. The intravenous model was extended and adapted to describe the intratracheal route of administration. The intratracheal model was adequate to fit simultaneously plasma and lung levels in presence and absence of TAR.

Conclusions: A semi-mechanistic POPPK model was successfully developed to describe LEV total plasma and free ISF concentrations in lung and prostate. The results indicate P-gp impact on LEV renal active secretion. Efflux transporters are relevant to pulmonary penetration only after intratracheal dosing. In the prostate, our findings strongly support the role of efflux transporters besides P-gp participating in LEV tissue penetration.

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Andre Dallmann Development of a Physiologically-Based Pharmacokinetic Population Model for Pregnant Women

Andre Dallmann (1), Ibrahim Ince (2), Michaela Meyer (2), Kirstin Thelen (2), Stefan Willmann (2), Thomas Eissing (2), Georg Hempel (1)

(1) University of Münster, Münster, Germany, (2) Systems Pharmacology CV, Bayer Technology Services GmbH, Leverkusen, Germany

Objectives: The goal of this study is to develop a physiologically-based pharmacokinetic (PBPK) model for the prediction of pharmacokinetics (PK) of small molecule drugs in healthy Caucasian pregnant women from conception until term.

Methods: A systematic literature search was carried out to identify and collect study data on pregnancy-related changes of anatomical, physiological, and functional parameters to establish a PBPK population model for healthy Caucasian pregnant woman. Each study was quality appraised and the data were extracted if the study met the inclusion criteria. The extracted data were further analysed and compiled in a database. A set of mathematical functions was fitted to the data and the best performing function was selected based on numerical and visual diagnostics together with literature support. The mathematical functions were implemented in PK-Sim®/MoBi® [1] and the pre-existing PBPK model structure for healthy Caucasian adult women was extended

by pregnancy-relevant compartments to create a prototype whole-body PBPK population model for pregnant women.

Results: The literature search yielded 279 studies with 9409 anatomical, physiological, and functional data on 430 507 healthy Caucasian pregnant women. These data comprised information on 28 out of 50 parameters. Rich data were found for many relevant parameters such as cardiac output, placental volume, and uterine arterial blood flow. Parameters for which minimal or no data could be found, such as brain or bone volume, were set to the values of non-pregnant women and were kept constant throughout pregnancy. The mathematical functions were selected based on numerical and visual diagnostics and described the time-related changes adequately. They were implemented in a prototype whole-body PBPK population model for healthy Caucasian pregnant women.

Conclusions: A set of mathematical functions describing changes in anatomical, physiological, and functional parameters throughout the course of pregnancy is developed and implemented in a longitudinal and time-varying prototype whole-body PBPK model for healthy Caucasian pregnant woman. Ultimately, this model could be applied to investigate *in silico* the PK of small molecule drugs in this vulnerable special population.

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Adam Darwich Gastric emptying and its covariates

Adam S. Darwich (1), Alison Margolskee (1), Kayode Ogungbenro (1), Aleksandra Galetin (1), Leon Aarons (1), Amin Rostami-Hodjegan (1,2)
(1) University of Manchester, Manchester, UK, (2) Simcyp Ltd, Certara, Sheffield, UK.

Objectives: Gastric emptying plays an important role in governing the rate of oral drug absorption of readily absorbed drugs. The aim of this study was to characterise the influence of covariates on gastric emptying in a quantitative manner.

Methods: An extensive literature search was carried out using PubMed (1950-May 2014) in order to identify publications of clinical trials investigating gastric emptying. Quantitative measures of gastric emptying were recorded, including gastric emptying rate, half-life, lag time, and a number of other predefined variables. A statistical meta-analysis approach was applied in order to develop a multivariable linear regression model based on identified significant covariates.

Results: Over 4,000 articles were identified according to the search criteria, out of these over 1,000 publications containing over 3,000 study arms fulfilled the criteria and were included in the meta-analysis. Data analysis concluded general demographics such as age, weight, height and gender, to have little or no impact on gastric

emptying, instead most of the variability was explained by caloric content, meal composition and solid/liquid state.

Conclusions: This work presents a multivariable linear regression model with potential applicability in pharmacokinetic modelling in order to account for covariate effects on gastric emptying.

Camila De Almeida PKPD-efficacy modelling of AZD9496, a novel oral selective estrogen receptor downregulator

Camila de Almeida (1), Klas Petersson (3), Lars Lindbom (3), Peter Ballard (1), Phillip MacFaul (1), Hazel M. Weir (2), Jon Curwen (2), Zena Wilson (2), Michael Hulse (2), Steve Powell (2), Owen Jones (1)
(1) Oncology iMed DMPK, AstraZeneca, Alderley Park, UK; (2) Oncology iMed Bioscience, AstraZeneca, Alderley Park, UK; (3) qPharmetra, Stockholm, Sweden

Objectives: To develop a preclinical PK-PD-Efficacy model for AZD9496, a novel oral selective estrogen receptor downregulator [1]. Using a parent-metabolite PK model for AZD9496, to quantify the relative contributions of both to the pharmacodynamics effects in MCF7 xenografts. To use the predicted biomarker modulation to drive tumour growth inhibition (TGI) in xenografts, integrating diverse endpoints into a single model using nonlinear mixed effect analyis [2, 3].

Methods: Discrete Parent-metabolite PK data pooled with PK info from PD and efficacy studies were analysed in a population model with proportional error using NONMEM.

Progesterone receptor A (PRA) in tumours of male MCF7 xenografts were measured in time course PD studies after oral administration of AZD9496 or its metabolite with doses ranging from 0.2 to 5

mg/kg for three days. Tumour growth inhibition (TGI) data has been generated from MCF7 xenograft studies conducted at a range of doses from 0.02 to 50 mg/kg for 21 days.

A ”PRA driven” TGI model was proposed and the total of data was fitted using an integrated population PK, indirect PD and biomarker driven efficacy model in NONMEM.

Results: A two comparment model for parent and one compartment model for metabolite with proportional error adequately fitted the PK data. The terminal half-lives of both parent and metabolite are around 5 hours.

An indirect response model for inhibition of PRA synthesis adquately described the observed delayed between PK and PD for both parent and active metabolite, predicts PRA degradation half-life to be 24 hours and a maximum of 40% contribution of the metabolite to the observed PD effects in xenografts.

A biomarker-driven efficacy model, with tumour growth proportional to the levels of PRA, adequately descrived the efficacy data. This model was used to predict likely human doses based on PBPK predicted human PK and target PRA inhibition.

Conclusions: Complete integration of preclinical PK-PD and efficacy data into a single model was obtained used nonlinear mixed effect analysis in NONMEM, taking into account the inter-animal variability observed in PKstudies. This is a novel approach that focuses on the mechanism of action of the drug and helps bridge the gap between preclinical and clinical studies, deviating from the traditional PK-efficacy models, for a better estimation of doses in humans [4].

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Pieter De Cock Population cefazolin pharmacokinetics before, during and after cardiopulmonary bypass in children undergoing cardiac surgery

Pieter De Cock (1,2), Hussain Mulla (3), Karen Jacobs (2) Kim Vanderburght (2), Sarah Desmet (1), Brett McWhinney (4), Jacobus Ungerer (4), Filip De Somer (5), Annelies Moerman (6), Hugo Robays (1), Katrien Francois (5), Peter De Paepe (2)
(1) Department of Pharmacy, Ghent University Hospital, Ghent, Belgium, (2) Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium, (3) Department of Pharmacy, University Hospitals of Leicester, Leicester, UK, (4) Department of Chemical Pathology, Pathology Queensland, Brisbane, Australia, (5) Department of Cardiac Surgery, Ghent University Hospital, Ghent, Belgium, (6) Department of Anaesthesiology, Ghent University Hospital, Ghent, Belgium

Objectives: Scarce data are available to guide cefazolin dosing in children undergoing cardiac surgery with cardiopulmonary bypass[1,2]. The objective of this trial is to derive a model-based dosing regimen for cefazolin in this patient population.

Methods: 56 infants and children were included (median age: 0.75 years; range:0.01-15 years) and received following intravenous dosing regimen: 25 mg/kg 30 minutes before surgical incision, just before start weaning of cardiopulmonary bypass, 8 hours after the 2nd dose and 8 hours after the 3rd dose. Blood, auricle and

subcutaneous fat tissue samples were collected before, during and/or after cardiopulmonary bypass. NONMEM ®v7.2 was used for population PK modelling and covariate analysis of plasma and tissue data. Internal validation of the final model was performed using a non-parametric bootstrap and Visual Predictive Check (VPC).

Results: A two compartment model best described bound and unbound plasma concentrations. The effect of cardiopulmonary bypass was modelled using a separate compartment. The relationship between bound and unbound concentrations was described by a saturable binding model, and where plasma albumin levels was a significant covariate on maximum binding capacity (Bmax). Weight was identified as a significant covariate on all plasma and tissue clearance and volume parameters using allometric scaling. Implementation of estimated Glomerular Filtration Rate (eGFR) as a covariate on plasma clearance further improved the model.

Conclusions: The proposed model adequately describes cefazolin plasma and tissue pharmacokinetics in infants and children undergoing cardiac surgery with cardiopulmonary bypass. In a next step, Monte Carlo simulations will be performed to optimize dosing in this vulnerable patient population.

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Sjoerd De Hoogd Population pharmacokinetics of morphine and its metabolites M3G and M6G in morbidly obese patients and healthy volunteers

Sjoerd de Hoogd (1), Pyry Välitalo (2), Albert Dahan (3), Simone van Kralingen (4,5), Eric P.A. van Dongen (4), Bert van Ramshorst (6), Catherijne A.J. Knibbe (1,2)

(1) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands, (2) Division of Pharmacology, LACDR, Leiden University, Leiden, The Netherlands, (3) Department of Anaesthesiology, Leiden University Medical Center, Leiden, The Netherlands, (4) Department of Anaesthesiology and Intensive Care, St. Antonius Hospital, Nieuwegein, The Netherlands, (5) Department of Anaesthesiology, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands (6) Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

Objectives: Morbidly obese patients are at increased risk of side effects of opioids, especially after surgery[1]. While in clinical practice postoperative pain management in adults with morphine is generally fixed dosed[2], the pharmacokinetics of morphine and metabolites in morbidly obese patients are poorly studied[3]. The aim of this study is therefore to investigate the pharmacokinetics of morphine and morphine metabolites (morphine-3-glucuronidate (M3G) and morphine-6-glucuronidate (M6G)) in morbidly obese patients and non-obese healthy volunteers.

Methods: In a prospective study, 20 morbidly obese patients, with a mean BMI of 49.9 kg/m2 (range 37.6 – 78.6 kg/m2) and a mean weight of 151.3 kg (range 112 – 251.9 kg) and 20 healthy volunteers[4] with a mean weight of 70.6 kg (range 58 – 85 kg) were included in the study. Morbidly obese patients received 10 mg intravenous (I.V.) morphine for postoperative pain management after gastric bypass surgery, with additional morphine I.V. doses as needed. Morphine, M3G and M6G blood concentrations were measured at T=0, 5, 15, 30, 45, 60, 90, 120, 150, 240, 420. Healthy volunteers[4] received an I.V. bolus morphine 0.1 mg/kg followed by an infusion of 0.030 mg/kg/hr for 1 hour. Morphine, M3G and M6G was measured at T=0, 5, 10, 20, 40, 60, 65, 80, 100, 130, 180, 300, 420. Population pharmacokinetic modeling and covariate analysis characterizing the influence of body weight was performed using NONMEM 7.3.

Results: A three compartment pharmacokinetic model best described the data for morphine in morbidly obese and non-obese individuals. For both glucuronides, one compartment models were used with multiple transit compartments for the formation of these metabolites with a mean transit time (MTT) for M3G and M6G of 2.98 and 12.6 min, respectively. The covariate analysis identified body weight as covariate for peripheral volume of distribution of morphine (P<.001). With increasing body weight a delay in the formation of M3G was found (P<.001), as well as a decrease in formation clearance of M6G (P<.001) and decrease elimination clearance of M3G and M6G (both P<.001).

Conclusions: No weight-based dosing adjustments are necessary in adult morbidly obese patients in terms of morphine exposure. However, increased concentrations of both M3G and M6G in obese patients could impact the efficacy of morphine and the occurrence of side effects.

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Mailys De Sousa Mendes Prediction of human foetal pharmacokinetic profile using transplacental parameters from ex-vivo human placenta perfusion model and pregnancy-Physiologically Based Pharmacokinetic models

Maïlys De Sousa Mendes, Deborah Hirt, Saik Urien, Cécile Vinot, Elodie Valade, Claire Pressiat, Naïm Bouazza, Frantz Foissac, Stephane Blanche, Jean-Marc Treluyer, Sihem Benaboud
1 EA08 : Evaluation des thérapeutiques et pharmacologie périnatale et pédiatrique, Unité de recherche clinique Paris centre, 75006 Paris, France

Objectives: Pregnant women can be exposed to numerous drugs during the gestational period. Due to obvious ethical reason in vivo studies of foetal exposure to these drugs are limited and information about transplacental transfer prior administration to pregnant women would be highly desirable. This study presents a novel approach to quantitatively predict the fetal exposure of drugs administered to the mother.

Methods: We implemented transplacental parameters values estimated from the ex-vivo human placenta perfusion model in pregnancy-Physiologically Based PharmacoKinetic (p-PBPK) models in order to predict foetal PK profile. With our models we simulated foetal PK for 3 antiretroviral drugs, tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and lamivudine (3TC). We compared

these predictions to observed cord blood plasma concentrations to support the validity of our models.

Results: Simulated foetal PK profiles were in accordance with observed cord concentrations. Moreover sensitivity analyse showed that foetal predictions were sensitive to changes in values of transplacental parameters obtained by the ex-vivo model.

Conclusions: The human placental perfusion study associated with PBPK analysis may be a new approach for predicting human foetal exposure

Elien De Thaye Model-based comparison of modified-release metoprolol formulations in beagle dogs and rabbits

Elien De Thaye (1), Pieter Colin (1)(2), Anouk Vervaeck (3), Jean Paul Remon (3), An Vermeulen (1), Jan Van Bocxlaer (1)
(1)Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Belgium, (2) Department of Anesthesiology, University Medical Center Groningen, Groningen University, The Netherlands, (3)Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Ghent University, Belgium

Objectives: Metoprolol, a selective adrenergic β1-receptor antagonist, is commonly prescribed for a variety of cardiovascular conditions. This drug is available in different salt forms and as different modified-release formulations. In our institution, dogs and rabbits are used interchangeably to study preclinical pharmacokinetics of in-house developed pharmaceutical dosage forms. Purpose of the current study was to investigate absorption kinetics of different metoprolol (model BCS class I compound) modified-release formulations in beagle dogs and rabbits, using compartmental modeling methods.

Methods: Metoprolol tartrate (50 to 200 mg) was administered to 6-8 beagle dogs and rabbits as a single intravenous bolus or oral dose (p.o.). Three modified-release formulations were administered

p.o.: an in-house produced prill formulation and two commercially available formulations, ZOK-ZID® and Slow-Iopresor®. A non-linear mixed-effect model was developed using NONMEM®. Different published absorption model approaches were fitted to the data. Furthermore, the M3 method [1] was used to study the impact of observations below the limit of quantification (BLoQ) on parameter estimates. Consistency in parameter estimates across both species was investigated.

Results: Following intravenous bolus dosing, plasma concentration-time profiles in both species were best described by a two-compartment model with first-order elimination. Plasma concentration-time curves in beagle dogs following p.o. dosing were best described using a sequential zero- and first-order absorption model. The absorption phase in rabbits was best described using a first order absorption process. Compared to rabbits, impact of BLOQ data on parameter estimates in dogs was low. Pharmacokinetic variability in bioavailability and absorption rate constant was observed between oral formulations and across preclinical species.

Conclusions: Our current approach led to different selected absorption models for both preclinical species, thereby hampering a consistent comparison between the different drug products in both species. Research is ongoing to compare our findings in these animals with the pharmacokinetic profile of metoprolol in humans and use of an IVIVC approach will be explored. We expect that these approaches will provide the necessary guidance to establish an experimental design for future studies and motivate our choice of which preclinical species should be included in our routine preclinical testing.

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Femke de Velde Nonlinear absorption pharmacokinetics of amoxicillin

Femke de Velde (1,2), Brenda de Winter (2), Birgit Koch (2), Teun van Gelder (2,3), Johan Mouton (1). on behalf of COMBACTE consortium.

(1) Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands; (2) Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands; (3) Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.

Objectives: Amoxicillin is an aminopenicillin that has been in clinical use for decades. Yet, the pharmacokinetic profile has been poorly described. Some small pharmacokinetic studies have shown nonlinearity in the absorption [1-3]. The aim of this study was to describe the population pharmacokinetics of oral amoxicillin with a focus on absorption and consequences for exposure.

Methods: 28 healthy volunteers received on 2 separate occasions either 2 (b.i.d. 875/125 mg or 500/125 mg) or 3 (t.i.d. 500/125 mg or 250/125 mg) single oral doses of amoxicillin/clavulanic acid at the start of a meal. Blood samples were collected just before administration and after 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h (t.i.d. until 8 h). 140 amoxicillin concentration-time profiles with 1428 samples were available. The data were analyzed with nonlinear mixed effect modeling (NONMEM, version 7.2). Different

absorption models (first-order, zero-order, Michaelis-Menten) with and without lag-time were evaluated in combination with one- and two-compartment disposition models. Model selection criteria were decrease in objective function, diagnostic plots and visual predictive checks.

Results: The increase in mean $AUC_{0\text{-}24h}$ was proportional to the dose for 250/125 mg t.i.d., 500/125 mg b.i.d. and 500/125 mg t.i.d. (750, 1000 and 1500 mg/day amoxicillin, respectively). However, the mean $AUC_{0\text{-}24h}$ of 875/125 mg b.i.d. (1750 mg/day) was equal to 500/125 mg t.i.d. (1500 mg/day), thus nonlinear absorption was to be assumed. As expected, a first-order absorption model did not fit the data. Nonlinear (zero-order or Michaelis-Menten) absorption models showed a significant improvement in diagnostic plots. Pharmacokinetics of amoxicillin was best described by a two-compartment model with time-lagged nonlinear (zero-order or Michaelis-Menten) absorption and first-order elimination. Mean central volume of distribution was 28,1 L and mean clearance was 21,2 L/h. With each concentration-time profile analyzed separately, variability was included for central volume of distribution, clearance, lag-time and the model-specific absorption parameters (duration of the zero-order absorption process and the Michaelis-Menten parameters K_m and V_{max}).

Conclusions: Absorption pharmacokinetics of amoxicillin is dose-dependent and best described by a zero-order or Michaelis-Menten absorption model. These findings may have consequences for the dosing regimen of amoxicillin.

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Brenda de Winter Population pharmacokinetics of intravenous albuterol in children with status asthmaticus

Brenda C.M. de Winter (1), Nienke J. Vet (2), Saskia N. de Wildt (2), Bart C.H. van der Nagel (1), Catherijne A.J.Knibbe (3), Muriel Koninckx (4), Matthijs de Hoog (2), Birgit C.P. Koch (1)
1. Department of hospital pharmacy, Erasmus Medical Center, Rotterdam, the Netherlands, 2. Intensive care and departments of Pediatric Surgery and Pediatrics, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands, 3. Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden, the Netherlands, 4. Pediatric Intensive Care, Middelheim Ziekenhuis, Antwerp, Belgium

Objectives: To develop a population pharmacokinetic model of R-albuterol and S-albuterol for children suffering from status asthmaticus following continuous intravenous administration.

Methods: At the children ICU 19 children suffering from severe status asthmaticus were treated using continuous intravenous albuterol in doses based on clinical symptoms (range 0.1-10 µg/kg/min). During therapy 111 blood samples were collected and analysed for R- and S-albuterol using a validated LC/MS-MS method. A population pharmacokinetic analysis was conducted using non-linear mixed effects modelling (NONMEM 7.2, FOCE+I). Data was logarithmically transformed. Model selection criteria were decrease

in objective function, diagnostic plots and NPDE. The covariates (range) analysed were bodyweight (7.8-70 kg), age (0.8-15.3 years), creatinine concentration (17-70 µmol/L), alanine transaminase (5-29 IU/L), and urea (1.6-4.8 mmol/L).

Results: A two-compartment model with separated clearance for R- (16.3 L/h) and S-albuteroll (8.8 L/h) best described the data. Separated values for central volume of distribution (12.9 L), peripheral volume of distribution (45.2 L) and intercompartmental clearance (20.0 L/h) did not improve the model. Between-subject variability was described for clearance of R-albuterol (42%), clearance of S-albuterol (37%) and central volume of distribution (280%). Weight is a significant covariate using a power function. The exponent of the powerfunction was fixed at 0.75 for clearance and intercompartmental and at 1 for central and peripheral volume of distribution. Estimation of the exponent resulted in similar values and did not improve the model. No other covariates were identified.

Conclusion: The population pharmacokinetics of R- and S-albuterol are described. This model can be used to evaluate the correlation between albuterol pharmacokinetics and effect in a population pharmacokinetic-pharmacodynamic analysis.

Willem de Winter A dynamic population PK/PD model to assess the effect of once daily versus twice daily dosing regimens on the relationship between canagliflozin plasma exposure and HbA1c response

Willem de Winter, Adrian Dunne, Chyi-Hung Hsu, Xavier Woot de Trixhe, Damayanthi Devineni, David Polidori, Jose Pinheiro
Janssen Research & Development LLC

Objectives: Canagliflozin is an orally active inhibitor of SGLT2 for the treatment of patients with T2DM. A dynamic pop PK/PD model was developed to assess the effect of once daily (QD) versus twice daily (BID) dosing regimens of canagliflozin as add-on to metformin on the relationship between canagliflozin plasma exposure and HbA1c response in diabetic patients on metformin background medication.

Methods: A dynamic pop PK/PD model based on a turnover model for HbA1c was implemented in NONMEM 7.2 using observed HbA1c responses and predicted 24 hour individual canagliflozin plasma exposures from 1,347 type 2 diabetic patients on metformin background medication at screening from two placebo-controlled canagliflozin studies: a 12 week Ph 2b study with 50, 100, 200 and 300 mg QD and 300 mg BID dosing arms, a 26 week Ph 3 study with 100 and 300 mg QD arms, and the baseline and placebo-arm data from an 18 week Ph 2 study in patients receiving placebo, 50 and 150 mg BID. 24 hr exposure profiles were predicted using a population PK model for canagliflozin developed on 9,061 PK

samples from 1,616 subjects [1]. An efficient method of averaging was developed for numerically solving the ordinary differential equations of the dynamic model [2]. The final model was validated internally as well as externally on its ability to predict the post-baseline BID dosing observations from the 18 week Ph 2 study.

Results: The pop PK/PD model provided a satisfactory fit to the observed HbA1c data. The combined HbA1c-lowering effects of placebo (study specific) and canagliflozin were found to be baseline dependent. No other significant covariate effects could be identified using this patient population which consisted mostly of subjects with normal to mildly impaired renal function. The model could adequately predict the external data from the 50 and 150 mg BID dosing arms from the 18 week phase 2 study, and was used to demonstrate that the differences in HbA1c reduction between the BID and QD regimens in patients with similar baseline conditions and total daily doses were small and not clinically meaningful [3].

Conclusions: A dynamic pop PK/PD model for the relationship between canagliflozin exposure and HbA1c response was developed and used to support the regulatory approval of the canagliflozin/metformin IR fixed-dose combination for BID administration by bridging efficacy between the QD and BID regimens, thus avoiding the need for an additional clinical trial.

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Wilbert de Witte What is the influence of diffusion-limited binding on in vivo target occupancy profiles?

Wilhelmus E.A. de Witte, Meindert Danhof, Elizabeth C.M de Lange, Piet H. van der Graaf
Leiden University, Division of pharmacology, LACDR, Leiden, the Netherlands.

Objectives: To predict *in vivo* target occupancy profiles and obtain a meaningful incorporation of drug-target binding kinetics in drug discovery, drug target binding kinetics should be integrated with other determinants of target occupancy and effect profiles, including pharmacokinetics, diffusion-limited binding and signal transduction. The aim of this study was to validate and explore previously published models which integrate pharmacokinetics, drug-target binding and diffusion-limited binding.

Methods: Initial simulations were performed in Berkeley Madonna to investigate the potential effect of diffusion-limited binding on target occupancy profiles under various conditions. Subsequently, a NONMEM code was written to describe pharmacokinetics, drug-target binding kinetics and diffusion-limited binding based on literature models[1,2]. Subsequently, the model performance was evaluated by comparing model predictions and published postiron emission tomography (PET) data for 18-F fallypride (a selective, high affinity dopamine D_2 tracer) brain concentrations in plasma, cerebellum and striatum of rhesus monkeys[3]. These literature

data were used to fit the NONMEM model both with and without diffusion-limited binding.

Results: The initial simulations demonstrated that diffusion-limited binding can increase the average target occupancy for drugs with fast drug-target dissociation kinetics. This effect of diffusion-limited binding decreases if the dissociation constant (Kd) increases and if an endogenous ligand is present. The developed NONMEM model enabled the description of *in vivo* brain concentrations of three subsequent injections of radiolabeled and unlabeled fallypride. The obtained model fits demonstrated the capability of both models (with and without diffusion-limited binding) to describe the data. Both models performed similarly in the description of striatum concentrations, but the overall model performance improved without diffusion-limited binding.

Conclusions: Diffusion-limited binding can increase the average target occupancy in a condition-dependent manner. Previously published models which integrate pharmacokinetics, drug-target binding and diffusion-limited binding were unable to demonstrate a significant influence of diffusion-limited binding on the *in vivo* receptor occupancy profile of fallypride.

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Francesca Del Bene Modelling potential drug-drug interaction risks with a combined top-down/bottom-up approach

Stefaan Rossenu, Francesca Del Bene, An Vermeulen, Italo Poggesi
Janssen Research & Development, Beerse, Belgium

Objectives: To develop a PK model combining the use of a top-down (non-linear mixed effects model) with a bottom-up (physiology-based pharmacokinetic model) approach to predict potential drug-drug interactions (DDI), based on the outcome of a single drug-drug interaction trial.

Methods: A PK model for bedaquiline has been reported in the literature [1], based on the outcome of clinical studies in healthy subjects and in subjects with tuberculosis. In the available package of information on bedaquiline, the effect of inhibitors and inducers of CYP3A4 have been assessed following short term repeated doses of bedaquiline and DDI perpetrators [2]. These assessments may not provide the full extent of the DDI due to the inherent long terminal half-life of bedaquiline. To anticipate the level of DDI that can be observed following long term co-medication, simulations were performed based on the non-linear mixed effect PK model developed for bedaquiline. To establish the effect of mild, moderate and potent inhibitors, the physiology-based approach proposed by Ohno [3] was used and the inhibitor parameters reported. For providing different scenarios, different values for the fractional clearance due to CYP3A4 involvement in bedaquiline metabolism

(f_{CYP3A4}) were considered (0.75, 0.90, 0.95), compatible with CYP3A4 being responsible for the majority of the bedaquiline clearance. PK simulations at steady state were performed with bedaquiline clearance modulated by strong, moderate and mild CYP3A4 inhibitors.

Results: The simulations indicated that the exposure after long term administration of the combination with a strong CYP3A4 inhibitor provides an AUC increase of 1.80-2.21 fold, dependent on the assumed f_{CYP3A4} of bedaquiline. As expected, the DDI effect of moderate inhibitors was less extensive than for strong inhibitors, which – considering the observed interindividual variability – appears of minimal or no clinical relevance.

Conclusions: The proposed combination of top-down and bottom-up approaches provides useful information regarding the appropriate use of bedaquiline when clinical data cannot be generated due to logistical/ethical constraints.

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Paolo Denti Population Pharmacokinetics of Ofloxacin in South African children

Lukas Löfling (1), Anthony Garcia-Prats (3), H. Simon Schaaf (3), Sandra Castel (2), Lubbe Wiesner (2), Helen McIlleron (2), Anneke Hesseling (3), Paolo Denti (2)
(1) Department of Pharmaceutical Bioscience, Uppsala University, Uppsala, Sweden (2) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa (3) Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa

Objectives: Multidrug-resistant tuberculosis (MDR-TB) is an emerging problem, increasingly affecting children. Ofloxacin is a fluoroquinolone widely used in the treatment and prophylaxis of MDR-TB, but with limited PK data in children.
The study aim was to describe ofloxacin PK in the paediatric population, to optimise future dosing regimens.

Methods: 88 South African children (age 3.5 yr, 0.5–15, and weight 15 kg, 7–66) were routinely receiving daily ofloxacin as part of MDR-TB treatment or prophylaxis. Blood samples were collected pre-dose, and at 1, 2, 4, and 6-8 or 8-11 hr post-dose. Children were dosed exactly 20 mg/kg of ofloxacin on the day of PK sampling, with smaller children receiving crushed tablets, sometimes by naso-gastric tube.
MONOLIX 4.3.3 was used to analyse the PK data. Allometric scaling

[1] was employed to account for differences in body weight. The effect of age, HIV status, treatment vs. prophylaxis, and drug administration procedure was evaluated using drops in objective function value (OFV) and goodness of fit plots. The final model was then used to optimise doses across different weight bands, targeting previously reported ofloxacin exposures in adults [2, 3].

Results: Ofloxacin PK was best described by a 1-compartment model with 1st-order elimination and 1st-order absorption with a lag time. The inclusion of allometric scaling substantially improved the model. For a 15 kg child, the model estimated CL of 5.2 L/h and V of 25 L. Crushing tablets or use of naso-gastric tube affected the rate of absorption, but not bioavailability. Age, HIV status, and treatment vs. prophylaxis did not significantly affect PK.
Children in this cohort achieved exposures lower than previously reported in adults on the standard 800 mg daily dose (median AUC of 58 mg·h/L vs. roughly 100 mg·h/L). As predicted by allometric scaling, lower weight children achieved lower concentrations. Dose simulations from the model show that to obtain similar median AUCs to those in adults, paediatric doses should be in the range of 25-50 mg/kg, with smaller children receiving higher mg/kg doses.

Conclusions: With the current "constant mg/kg" dosing approach, children achieve ofloxacin exposures considerably lower than adults and smaller children are even more severely under-dosed and exposed. However, allometric scaling does not account for the entire difference with adult exposures. No maturation effect of age on CL was detected in this cohort, possibly due to the low number of children <1 yr.

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Cheikh Diack An empirical drug-disease model to characterize the effect of Ranibizumab on disease progression in wet AMD patients

Cheikh Diack, Dietmar Schwab, Nicolas Frey
F. Hoffmann-La Roche Ltd

Objectives: Ranibizumab, an anti-VEGF is the standard of care for the wet form age-related macular degeneration (AMD). The characterization of the time course of visual acuity with and without anti-VEGF treatment may prove useful for the development of new drugs.

Methods: A drug-disease model for visual acuity was developed on the 24-month patient level data of 2 phase 3 monthly dosing trials of Ranibizumab (~1100 patients including ~230 untreated patients). Adaptations of a model in [1] combined with a K-PD approach to account for the change in dosing frequency over time and an Emax model to represent the drug effect were fitted to the data(cf. (1) and (2)) .

(1) $VAt=VA0-(VA0-VAss).(1-EXP(-kpr.t))+Emax.IR/(E50+IR)$

(2) $VAt=VA0-(VA0-VAss).(1-EXP(-kpr(1-IR/(Ed50+IR)).t))+Emax.IR/(E50+IR)$

VAt, VA0 and VAss are respectively the visual acuity at time *t*, at entry in trial and at steady state when the patient is not treated. *IR* is proportional to the amount of drug a time *t*; *kpr* represents the rate of progression of the disease.

Several baseline covariates were tested on model parameters. The final model was further tested against 2 other phase 3 trials of Ranibizumab with different dosing regimen (including monthly, quarterly and PRN dosing, ~ 1200 patients).

Results: Model (2) was preferred over (1) as it was shown using a deconvolution process, that to adequately describes the data, the model parameter *kpr* is affected by the treatment in a manner which slows down wet AMD progression. It was shown that some baseline covariates have an influence on the model parameters VA0, *Kpr* and E50. The time course of visual acuity from trials not used during model development were adequately described using only the baseline characteristics of patients.

Conclusions: The dynamic of visual acuity for wet AMD patients with or without treatment was characterized using a disease model. The influences of several baseline covariates were tested on model parameters and relevant covariates were included in the final model. The final model suggests two sites of effect of Ranibizumab: an additive (symptomatic) effect and an effect slowing down the progression of the disease (protective effect). The low *E50* compared to *Ed50*, suggests that Ranibizumab is more potent for restoring the visual acuity than for slowing down wet AMD progression. The model was successfully tested against trial data of different dose and dosing regimen to data used for its development. This suggests that the model can suitably be used for clinical trial simulations.

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Emilie Schindler Comparison of item response theory and classical test theory for power/sample size for questionnaire data with various degrees of variability in item discriminatory power

Emilie Schindler, Lena E. Friberg, Mats O. Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Patient-reported outcomes, usually assessed using questionnaires, are increasingly collected during clinical trials to evaluate variables not directly quantifiable such as fatigue, health-related quality of life or pain. Due to their multi-scale nature, their analysis is challenging and item response theory (IRT) in a non-linear mixed effect modeling framework [1] offers an alternative to classical test theory using total score (TS). The aim of this analysis was to compare IRT vs TS approaches for power/sample size calculation based on longitudinal questionnaire data for different magnitudes of variability between the items' discriminating power.

Methods: An IRT model was used to simulate item-level data for a 7-item questionnaire in a parallel-group trial of one placebo and one active dose arm with 1000 patients/arm and 6 occasions per patient. Each item had scores ranging from 0 to 4, the probability of each score being described by a proportional odds model. Discrimination and difficulty parameters used for simulations were obtained from IRT modelling of physical subscale of baseline

Functional Assessment of Cancer Therapy-Breast (FACT-B) in metastatic breast cancer patients [2]. Four scenarios were simulated with 0%, 50%, 100% and 200% of original variability in discrimination parameters. The latent variable D_i was assumed to vary over time according to the following equation: $D_i(t)=D_{i,0}+(\vartheta_1*x_{grp}+\eta_2)*Time$, where $D_{i,0}=D_i(0)$ is a standard normally distributed random variable, $x_{grp}=0$ in the placebo group and $x_{grp}=1$ in the treatment group. Total scores for TS analysis were calculated as the sum of simulated item responses. Monte-Carlo Mapped Power method [3] implemented in PsN software was used for power calculation.

Results: For all four scenarios, IRT approach resulted in smaller sample sizes to achieve 80% power to detect a drug effect compared to TS approach (18%, 20%, 26% and 40% fewer patients for 0%, 50%, 100% and 200% of original variability in discriminatory power, respectively). IRT was less sensitive to variability in discrimination parameters than TS.

Conclusions: The value of IRT modelling over TS approach may increase as variability in discriminatory power across items increases.

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Jan-Frederik Schlender Application of an elderly PBPK model to specify age-dependent changes of active processes

Jan-Frederik Schlender (1,2) Niklas Werner (2) Michaela Meyer (2) Kirstin Thelen (2) Thomas Eissing (2) Stefan Willmann (2) and Ulrich Jaehde (1)
(1) Institute of Pharmacy, Clinical Pharmacy, University of Bonn, Germany (2) Bayer Technology Services GmbH, Computational Systems Biology, 51368 Leverkusen, Germany

Objectives: Recently a novel whole-body physiologically-based pharmacokinetic (PBPK) ageing approach has demonstrated its feasibility to predict the pharmacokinetic disposition of exclusively glomerular filtered drugs in elderly individuals [1]. The aim of this study was to evaluate the influence of age on active processes such as tubular secretion (TS) by applying a lifespan PBPK model for digoxin.

Methods: Age-related parameters deemed necessary for an evaluation of the renal ageing process were identified in a literature search and incorporated into the PBPK modelling software PK-Sim® (Bayer Technology Services GmbH, Leverkusen, Germany) [2]. Digoxin was chosen as test compound as it is mainly cleared renally with a considerable extent of tubular secretion. A digoxin PBPK model was established for young adults based on different pre-clinical and clinical data, validated on additional data sets, and

subsequently scaled to different elderly ages in order to quantify the extent of age-dependent changes of tubular secretion.

Results: The digoxin PBPK model established for young healthy adults described plasma concentration and urinary excretion data of the compound well after intravenous and oral administration. Using relative tissue expression profiles of P-glycoprotein (P-gp) derived from mRNA data [3] the contribution of P-gp to absorption, disposition and excretion was specified. The established PBPK model was used to assess age-related changes of digoxin clearance and thus quantify the percentage related to active elimination processes.

Conclusions: The knowledge-driven PBPK lifespan model offers the unique opportunity to evaluate and specify age-dependency of active processes that are difficult to measure in a clinical setting. Such a model represents a valuable tool for analysing the varying influence of multiple kinetic mechanisms with advancing age and, thus, serves to predict the pharmacokinetics of drugs in elderly.

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Henning Schmidt SBPOP/mPD: Informing dose-concentration-response relationships - Application to study design and information generation based on competitor data

Henning Schmidt
Novartis Pharma AG

Objectives: The main goal of quantitative approaches to drug development is the integration of all available information in order to achieve high confidence in compound and dose selection for Phase III and beyond.

Pharmacokinetic and pharmacodynamic modeling and simulation aim at supporting drug development by characterizing the important relationships between dose, concentration, and clinically relevant response levels. Once models are available and adequately capture the signature of the clinical data, they can be used to efficiently address various questions, e.g., about optimal dose and dosing regimen, profiling against competitors, and study design. Traditional nonlinear mixed-effect modeling, however, is often time consuming and anecdotal evidence indicates that lack of meeting the time constraints often limits the extent of pharmacometric involvement in the industry [1].

Methods: In this work, we propose a methodology for efficient characterization of dose-concentration-response relationships on a

population level. Instead of considering individual level patient data, summary level data are used. Inter-individual variability can be taken into account by bootstrapping and covariates can be considered based on stratification of the individual level patient data. The methodology is implemented in the form of a module within the SBPOP package [2], providing a user-friendly and well-documented framework for model building and trial simulation.

Results and Conclusions: The approach was applied in support of a Phase IV study design, dose-concentration-response analysis of summary level competitor data, and support of a submission project in which a multitude of different endpoints had to be assessed. Available examples show that parameter estimates for fixed effects essentially agree with the ones obtained from nonlinear mixed-effect modeling, but time for model development was only a small fraction of typical NLME modeling efforts.

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Rik Schoemaker PK/PD modeling of brivaracetam in epilepsy using daily seizure counts

Rik Schoemaker (1), Armel Stockis (2)
(1) SGS Exprimo, (2) UCB Pharma

Objectives: To determine the population PK/PD relationship between brivaracetam (BRV) concentration and daily seizure counts in three Phase III studies in the adjunctive treatment of partial onset seizures.

Methodology: A population PK/PD model describing the effect of BRV on daily seizure counts was developed where seizure frequencies were described using a negative binomial distribution taking previous-day seizure frequencies into account [1], and using a mixture model to separate a placebo-like and a responder sub-population. Daily seizure count sequences with dependence on preceding-day seizures were simulated using NONMEM. A covariate analysis was performed to investigate factors influencing the effect of BRV on daily seizure counts.

Results: The population exposure-response model provided an excellent description of the data, where visual predictive checks (VPCs) for median % change in daily seizure frequency from baseline and proportion of subjects with ≥50% reduction in daily seizure frequency from baseline indicated that the model was perfectly capable of simulating the observed outcomes.

Covariate analysis indicated that levetiracetam (LEV) co-administration reduced the fraction of subjects in the mixture-model responder population to close to zero. Covariate analysis also indicated that subjects with high baseline seizure rates had a much lower probability of ending up in the mixture-model responder population. In the absence of LEV co-medication, the probabilities for ending up in the mixture-model responder population were estimated to be 54.8% at 4 seizures/month, 29.3% at the median baseline seizure frequency (0.32 seizures/day), and 0.8% at 6 seizures/day. No further significant covariates influencing BRV effectiveness were detected.

The concentration at half the maximum response (EC_{50}) in the mixture-model responder population was estimated to be 0.57 mg/L in the final model corresponding to the exposures obtained after BRV doses of 50 to 100 mg/day.

Conclusions: A population PK/PD model was developed allowing the mathematical description of the relationship between BRV exposure and its effect on daily seizure counts. Only LEV co-administration and baseline seizure frequency were shown to significantly influence the response to BRV treatment.

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Johannes Schropp Distributed transit compartments for arbitrary lifespan distributions in aging populations

Johannes Schropp (1) and Gilbert Koch (2)-(3)
(1) Department of Mathematics and Statistics, University of Konstanz, Konstanz, Germany (2) Department of Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo NY, USA (3) Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital of Basel (UKBB), Basel, Switzerland

Objectives: In an aging population every individual has its own and unique lifespan, and after expiration the individual has to leave the population. Transit compartment models (TCM) are often used to characterize aging populations [1], e.g. to describe stimulation effects of erythropoietin on cell maturation [2]. However, a serious limitation is the gamma-distributed lifespan in TCMs. In general, lifespans follow e.g. the Weibull or more complex distributions [3]. Therefore, we extend the TCM concept to approximately describe any distribution and call this generalized method distributed transit compartment models (DTCM).

Methods: In general, in the compartment approach every state defines a subpopulation with a certain age range, and the sum of all states describes the total aging population. In DTCMs the transit rate between the compartments is now controlled by the survival function of the lifespan distribution, and the number of

compartments controls the quality of approximation. The DTCM can be equivalently reformulated with the same underlying ordinary differential equations as TCMs and only summation of the states differs.

Results: Convergence investigations of the approximated lifespan distribution towards the original distribution are visualized. An acceptable amount of compartments is sufficient for a convenient approximation quality. A pharmacokinetics / pharmacodynamics (PK/PD) example is presented and data with Weibull-distributed lifespans is fitted.

Conclusion: DTCMs are an extension of TCMs to approximately describe any lifespan distribution. DTCMs are implemented equally as TCMs and only summation of the states differs. Therefore, DTCMs could be applied in any PK/PD software like NONMEM, WINNOLIN or MONOLIX

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Mark Sellors Reproducible Analysis Environments for Pharmacometric modelling and simulation.

Mark Sellors
Mango Solutions

Objectives: To provide an easily reproducible analytical computing environment for pharmacometric modelling and simulation without compromising the speed with which a computational environment can be deployed.

Methods: A suite of common tools such as NONMEM, PsN, R etc. are installed with an operating system and a suite of validation tools, inside an 'image'. The word 'Image' is used to describe a complete description of a working environment, for deployment onto your computing infrastructure. This may be a Virtual Machine, a docker container, or a cloud provider image such as an Amazon Machine Image. The validation tools are made available for running on a scheduled or ad-hoc basis and the final image is validated using these tools before deployment. When a new version of a software component is released, a new version of the image is created. When an image reaches the end of its useful life, for example, if it contains an obsolete piece of software, that image is retired and added to an archive for future use. Any given analysis has the image used recorded against it.

Results: As the results of past analyses are tied to a particular image, we found it simple to run a given analysis again, on the same

image. Over time, a library of images is created and archived. This allows an organisation to effectively go 'back in time' with their analysis environments should a query be made against an earlier analysis. Using the ad-hoc validation tools we demonstrated that it is possible to perform immediate validation of any image deployed from the archive. This provides the user and regulators with assurance that the resulting output of analyses performed using that image are as expected and consistent with any analysis run previously.

Conclusions: We proved that the ability to version control validated analysis environments is a compelling benefit for anyone engaged in pharmacometric computing. We found this to be particularly true where such work is heavily regulated and the ability to quickly and easily re-run an old analysis in a validated manner is essential. Further, we demonstrated that keeping track of the 'library of images' can be difficult and should therefore form part of the overall pharmacometric platform in use. The flexibility provided by such an approach is highly desirable as it frees your compute infrastructure from being a single purpose environment to being able to perform multiple analysis duties using whatever tools are appropriate.

Marina Senek Population pharmacokinetic modelling of Levodopa/Carbidopa Microtablets versus standard formulations of Levodopa/Benserazide and Levodopa/Carbidopa

Marina Senek (1), Dag Nyholm (1), Elisabet Nielsen (2)
(1) Department of Neuroscience, Uppsala University, Sweden (2) Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Objectives: Levodopa is the most efficacious therapy available for Parkinson's disease. The pharmacokinetics (PK) of levodopa becomes especially important when the therapeutic window starts to narrow, and patients develop motor fluctuations. The concept of continuous drug delivery proposes that a smoother plasma concentration profile, and thus a more continuous stimulation of the post-synaptic dopamine receptors, may reduce motor fluctuations [1]. Low dose levodopa/carbidopa microtablets with an automatic dose dispenser have been developed to facilitate individualized treatment. The aim of this study was to characterize and compare the PK of three available levodopa formulations containing one of the two available aromatic amino acid decarboxylase (AADC)-inhibitors; carbidopa and benserazide.

Methods: The population PK analysis involved data from 18 healthy subjects included in a randomized three-way, single-dose and open-label crossover study [2]. The different formulations (immediate

release levodopa/carbidopa tablet, dispersible levodopa/carbidopa microtablets, and dispersible levodopa/benserazide) in a dose of 100 mg/25 mg were administered on three separate occasions with a four day washout period between treatments. Plasma samples (19 per occasion) were analyzed with regards to levodopa and carbidopa. The PK analysis was carried out using NONMEM 7.3. A separate multiple-dose study with levodopa/carbidopa microtablets was used for external model evaluation.

Results: The PK of levodopa was well described by a two-compartment disposition model and a transit absorption model, while carbidopa was well described with a one-compartment disposition model, with a transit absorption model. The PK profile differed between formulations, particularly with regards to the absorption characteristics where levodopa administered with benserazide resulted in a more rapid absorption profile and higher peak concentrations as compared to levodopa administered with carbidopa.

Conclusions: The presented models adequately described the population PK of levodopa as well as carbidopa for three different formulations. The higher absorption rate of levodopa with benserazide may result in a more fluctuating plasma concentration and treatment with levodopa microtablets containing carbidopa may in the future lead to more optimized and individualized treatment regimens for Parkinson's disease patients.

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Kok-Yong Seng Evaluating Ethnicity Differences in the Effect of Ritonavir, Ketoconazole and Rifampicin on Cytochrome P450 3A Induction and Inhibition in the Asian and Western Populations

Kok-Yong Seng (1, 2), Daryl Kim-Hor Hee (1), Boon-Cher Goh (3, 4), Soo-Chin Lee (3, 4) and Lawrence Soon-U Lee (1)
(1) Yong Loo Lin School of Medicine, National University of Singapore, Singapore, (2) Defence Medical & Environmental Research Institute, DSO National Laboratories, Singapore, (3) National University Cancer Institute, National University Health System, Singapore, (4) Cancer Science Institute, Singapore, Singapore

Objectives: The objectives of this analysis were: (i) development of a linked population pharmacokinetic model for midazolam (MDZ) and its two major metabolites, 1'-hydroxymidazolam (1OHM) and 1'-hydroxymidazolam glucuronide (HMG); and (ii) evaluation of ethnicity differences in the modulation of intestinal and hepatic activity of human cytochrome P450 3A (CYP3A) by ritonavir, ketoconazole and rifampicin in healthy Chinese, Malay, Indian and Caucasian adults.

Methods: 52 subjects underwent pretreatments with probe drugs on 4 separate occasions (i) reference (no pretreatment); (ii) ritonavir 100 mg twice daily given for 3 days; (iii) ketoconazole given for 3 days [(ii) and (iii) in a randomised crossover design]; and (iv)

rifampicin 600 mg given nightly for 2 weeks. At the end of pretreatment, each subject received intravenous 0.75mg midazolam and oral 400mg raltegravir followed by oral 1.5mg midazolam 4h later. Plasma concentrations of MDZ, 1OHM and HMG (0–12h) were measured by LC/MS/MS. A pharmacokinetic model of MDZ, 1OHM and HMG was built using nonlinear mixed effect modelling in NONMEM. The covariate model was built using the generalised additive modelling and forward selection-backward elimination [1].

Results: In the final model, the type of probe drug used in pretreatment was a significant covariate for MDZ and 1OHM clearances, and MDZ oral bioavailability. Additionally, MDZ and HMG clearances in Chinese were lower than the other ethnicity groups following ketoconazole pretreatment. Overall, ritonavir reduced hepatic and intestinal CYP3A activity to 0.18-fold (90% CI, 0.15–0.21) and to 0.75-fold (0.73–0.78), respectively. Ketoconazole reduced hepatic and intestinal CYP3A activity to 0.53-fold (90% CI, 0.4–0.66) and 0.76-fold (0.74–0.78), respectively. In agreement with [2], hepatic CYP3A activity in the Chinese was found to be reduced to a greater extent than the rest of the ethnicity groups following ketoconazole pretreatment (0.27 and 0.62, respectively). Rifampicin increased hepatic and intestinal CYP3A activity by 2.92-fold (90% CI, 2.38–3.45) and 1.32-fold (1.25–1.39), respectively.

Conclusions: Ritonavir inhibits hepatic CYP3A activity more profoundly than ketoconazole. Ketoconazole reduces MDZ and HMG clearances to a greater extent in Chinese than Malay, Indian and Caucasian adults. Rifampicin induces intestinal and hepatic CYP3A activity by the same extent among the studied ethnicity groups.

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Yoon Seonghae Population pharmacokinetics/pharmacodynamics modeling of uric acid formation after xanthine oxidase inhibitor administrations

Seonghae Yoon, Jae-Yong Chung, Kyung-Sang Yu, In-Jin Jang
Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea

Objectives: Gout is a common inflammatory arthropathy caused by elevated serum uric acid (hyperuricemia), usually due to reduced excretion [1]. There are several categories of drug to lower serum uric acid level, including a xanthine oxidase inhibitor like allopurinol or febuxostat. The aims of this study were 1) to characterize the population pharmacokinetics(PK) of a newly developed xanthine oxidase inhibitor in healthy volunteers, 2) to find an appropriate pharmacodynamic(PD) model to explain the metabolic process of uric acid, and 3) finally, to recommend an optimal dose of the drug to treat hyperuricemia or gout patients.

Methods: A population PK/PD analysis was performed in 124 healthy volunteers who received single or multiple doses of the drug (10 – 600mg, single dose; 100 – 800mg, multiple doses). For pharmacodynamic analysis, the concentrations of uric acid, xanthine and hypoxanthine of serum and urine were determined. A total of 3,116 drug concentration measurements and 2,590 measurements

of PD markers were analyzed using the nonlinear mixed effect model (NONMEM V7.2) program.

Results: The population PK of the drug was well described by an oral, two-compartment model with first-order absorption and elimination from the central compartment. There was no significant covariate for clearance or volume of distribution. Uric acid formation at baseline was modeled using serum and urine compartments of 3 biomarkers based on known metabolic pathway of uric acid [2]. Indirect response model [3] was used to describe inhibition of xanthine oxidase that metabolizes hypoxanthine to xanthine, and xanthine to uric acid: PK parameters and parameters calculated in uric acid formation model at baseline[j1] were fixed in this model. To investigate the optimal dose of the drug in patient with gout or hyperuricemia, final PK/PD model was used simulate changes in uric acid levels after the drug administrations.

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Maria Sfouni Prediction of subtherapeutic tigecycline plasma levels by model-based Bayesian individualization

Maria Sfouni, Irene-Ariadne Kechagia, Sophia Markantonis, Aris Dokoumetzidis
School of Pharmacy, University of Athens, Greece

Objectives: To investigate the optimal sampling times for estimating posthoc clearance of tigecycline and assess their performance, in terms of predicting response, as early as possible, in the treatment of complicated skin and skin-structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs).

Methods: A large set of combinations of 4 sampling times was evaluated in a dataset of 1000 subjects, generated in MATLAB. For each combination, concentration-time data were simulated in NONMEM 7.3 from a literature two-compartment population PK model [3] and the EBEs of the PK parameters were subsequently estimated. Greater emphasis was placed on systemic clearance (CL), since tigecycline follows linear kinetics and the AUC_{24}/MIC ratio is the PK-PD index predictive of efficacy with breakpoints of 17.9 (cSSSIs) [1] and 6.96 (cIAIs) [2].The optimality criteria were the absolute relative mean prediction error (|MPE%|) and the 90^{th} percentile of the |MPE%| of the AUC_{24} as measures of bias, the relative root mean square prediction error (RMSE%) of the AUC_{24} as a measure of precision and the ETA shrinkage of CL as a measure of

informativeness. In addition to these, the D-optimality criterion of the Fisher information matrix (FIM) of the typical individual was maximized. At a second level, the assessment of predictive performance of the optimal time combinations was based on metrics derived from the confusion matrices corresponding to each MIC of interest [4] for both cSSSIs and cIAIs.

Results: According to the optimality criteria considered, four sampling schemes were chosen to have good performance for estimating the posthoc clearance, hence the AUC_{24}/MIC ratio, taking also into account practical considerations. Up to 72 hours, the scheme 61, 64, 71, and 72 hours is the optimal, however schemes with performance close to that but with earlier sampling times were also identified, that may be more useful. The predictive performance of all sampling schemes varies across the MIC range, still the selected combinations exhibit a comparatively high performance.

Conclusions: Detecting subtherapeutic antibacterial plasma levels as early as possible in treatment, can contribute to the reduction of the development rate of resistance. The results of an optimality study for tigecycline, a mainly bacteriostatic antibacterial, characterized by a long elimination half-life with high inter-individual variability are presented, but the methodology can be expanded to other similar agents.

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Siti Maisharah Sheikh Ghadzi Disease progression in the integrated glucose-insulin model in subjects with impaired glucose tolerance

Siti M. S. Ghadzi1,2, Mats O. Karlsson1, Vanessa D. de Mello3, Matti Uusitupa3, Maria C. Kjellsson1; Finnish Diabetes Prevention Study Group

1Department of Pharmaceutical Biosciences, Uppsala University, Sweden 2Universiti Sains Malaysia, Ministry of Education Malaysia, Malaysia 3Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio Campus, Kuopio, Finland

Objectives: Silber et. al[1] published an integrated glucose-insulin (IGI) model, describing glucose and insulin after various glucose loads in healthy subjects and in patients with type 2 diabetes. This model does not include disease progression (DP) from prediabetes, i.e. impaired glucose tolerance, to overt diabetes, which is driven by decreased insulin sensitivity and relative beta cell failure. The objective of this project was to develop the IGI model to include DP model for glucose and insulin in subjects with impaired glucose tolerance.

Methods: Data was obtained from a substudy of the Finnish Diabetes Prevention Study[2,3], consisting of 101 subjects with impaired glucose tolerance; randomly assigned to control group and lifestyle intervention group with intensive counselling on diet, weight reduction and exercise. At the start and end of the study

most subjects underwent a frequently sampled intravenous glucose tolerance test (FSIGT): 87 subjects at year 0 and 52 subjects at year 4. All subjects also underwent yearly an oral glucose tolerance test (OGTT). Subjects who developed diabetes were excluded from the study at the time of diagnosis. Intense blood sampling was performed after the FSIGT and sparse (0, 30 min, 120 min) after OGTT. Combination of intravenous and oral IGI model was used to fit the data for baseline until the fourth year, incorporating prior information on the parameters from published models using PRIOR functionality in NONMEM[4]. The DP model was investigated on the pathophysiologically most reasonable parameters e.g. insulin-dependent glucose clearance (CLGI). The impact of diet and exercise intervention on the DP was investigated. The best model was chosen based on objection function value, diagnostic plots, and visual predictive check.

Results: For the control group, first phase insulin secretion (IFST), CLGI, and maximum incretin effect (EMAX) were decreased by 7.5%/year, 4.7%/year and 7.4%/year as a consequence of DP. For the intervention group, IFST was marginally decreased by 1.3%. Instead CLGI was increased by 3.1% indicating an improvement of insulin sensitivity, while the DP based on EMAX was similar to the control group.

Conclusions: The DP was successfully included in the IGI model to describe difference seen in a population with impaired glucose tolerance with or without lifestyle intervention. In particular, insulin dependent glucose clearance improved after intensive lifestyle intervention.

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Yucheng Sheng Development of a New Mixed Poisson-Gaussian Model for Count Data from Rodent Brief-Access Taste Aversion Experiments

Yucheng Sheng(1), Jessica Soto(1), Mine Orlu Gul(1), Catherine Tuleu(1), Joseph F. Standing(2)
(1) School of Pharmacy, UCL (2) Institute of Child Health, UCL

Objectives: Rodent Brief-Access Taste Aversion (BATA) experiment is a common in-vivo screening tool to evaluate the taste of a drug [1]. Since the "lick number" data from BATA experiment is not normally distributed, previously published models that based on the "lick ratios" from the means are not ideal for analyzing these data. This work describes a new mixed Poisson Gaussian model development suited for BATA experiments.

Methods: The rodent BATA data were obtained from a series of experiments conducted with a well-known unpleasant taste reference compound, quinine hydrochloride dihydrate (QHD). After scrutinizing the histogram and distribution plot for each concentration of QHD, several single distribution models were tried [2,3]. As the QHD concentration rises,the proportion of first distribution will decrease and the second distribution will increase. Two mixed models, Poisson- Poisson and Poisson-Gaussian, were also tested. The proportion of the first distribution was defined as a logistic function P= EXP(EFF)/(1+EXP(EFF)) and effects(EFF) linked to QHD concentrations through the sigmoid Emax equation.

Categorical VPC was used to assess model fits. Data from 3 other drugs was also used as an external validation.

Results: QHD data from BATA experiments can be well described by the new mixed distribution model with λ=2.73 for the first Poisson distribution and mean=50.5 for the second truncated Gaussian distribution. The changes among different concentrations were captured by the logistic and Emax functions. External validation and VPCs demonstrated that this new model is reasonable for all BATA data.

Conclusions: The New Mixed Poisson-Gaussian Model is well suited for count data from rodent brief-access taste aversion (BATA) experiments .

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Konstantina Soulele Development of a POPPK model for Clopidogrel Acid Metabolite in patients with Acute Coronary Syndrome

K. Soulele(1), Ei. Christodoulou(1), E. Neroutsos(1), G. Valsami(1), A. Dokoumetzidis(1), A. Koniari(2), F. Kolokathis(2), E. Iliodromitis(2), P. Macheras(1)

(1) Laboratory of Biopharmaceutics-Pharmacokinetics, Department of Pharmaceutical Technology, School of Pharmacy, National and Kapodistrian University of Athens, Greece (2) 2nd Cardiological Clinic of Attikon General Hospital, National and Kapodistrian University of Athens, Greece

Objectives: To develop a PopPK model based on the concentration data obtained from an easy to use HPLC-PDA plasma assay method of the inactive carboxylic acid metabolite (CCA) of the antiplatelet prodrug clopidogrel (CLP) in combination with genotyping information (PCR analysis).

Methods: The clopidogrel carboxylic acid metabolite concentration data obtained (HPLC-PDA analysis method) from 50 patients suffering from ACD were analyzed. The covariates including demographic characteristics, laboratory indexes, combined medication, different generic formulations administered and genetic polymorphisms of related enzymes (CYP2C19) were screened for their influence on PK parameters. Population PK data

analysis was performed using NONMEM software to describe the time course of CLP inactive metabolite in plasma.

Results: A one-compartment (1-CMT) PK model with first order absorption and elimination was found to best describe the concentration vs time data of Clopidogrel carboxylic acid metabolite (inactive). The model was parameterized as Cl=1.94 L/h, V=274 L and ka=1.45 h-1. The interindividual variability was 85.8% and 45.2% for Cl and V, respectively. The application of an additive residual error model led to the optimum performance. No significant covariates were identified.

Conclusions: The derived model described adequately the concentration-time data of Clopidogrel carboxylic acid metabolite (inactive). The model is intended to serve as a prior information for the individualization of CCA levels in Greek hospitals. The model will be enriched with more patients till the end of the study, further elucidating the effect of various covariates on PK parameters.

Hanna Silber Baumann Support phase II dose selection of a novel dual GIP/GLP-1agonist using a population PKPD model developed on phase I data

Hanna E. Silber Baumann, Christophe Schmitt and Valerie Cosson
Clinical Pharmacology, Roche Pharma Research and Early Development, Roche Innovation Center Basel, F.Hoffmann-La Roche Ltd

Objectives: The objective of the analyses was to support the Phase II dose selection through the characterization of the non-linear properties of RG7696 PK, the identification of the model describing the effects on mean plasma glucose (MPG) as a function of exposure, and the extrapolation of MPG decrease to 12-week HbA1c reduction.

Methods: Data from 92 individuals which were treated with at least one dose of RG7697 were included in the PK analysis. Doses ranged between 0.03-5 mg (s.c. injection) once daily. Rich sampling was performed on day 1 and 14 with additional sparse sampling. In 54 type 2 diabetics patients receiving 2-week treatment, the pharmacological effect of RG7697 was assessed with repeated meal tolerance tests (MTT). 24-hour glucose profiles were collected on days -1, 1, 7 and 14. MPG was calculated as the average of the collected samples over 24 hours. PK and PKPD models were developed based on 2-week data. Finally, 12-week HbA1c extrapolations were generated based on the 2-week PKPD model,

coupled with a life-span model of HbA1c [1]. The results were compared to literature data of GLP-1 compounds through a model-based meta analysis. Analysis and simulations were performed using NONMEM 7.2.

Results: The PK of RG7697 was described using a 2-compartment model. Non-linear functions were incorporated to account for dose and time-dependent kinetics with respect to bioavailability and duration of absorption. Steady-state was reached after approximately 1 week of treatment. The time course of MPG over 2 weeks was captured using an indirect response model (IDR). Individual predicted RG7697 steady state exposure was included as an Emax function on Kout. Fasting plasma glucose was included as a covariate on the baseline MPG. Predicted 12-week HbA1c reduction across a range of RG7697 doses was compared to prediction from a meta-analysis model of GLP-1 compounds. The results predict that the reduction following RG7697, compared to Liraglutide at the recommended dose, would follow a faster onset and that the HbA1c reduction would be larger with RG7697.

Conclusions: RG7697 non-linear PK could be adequately accounted for by including functions of dose and time on the absorption phase. The reduction in MPG over 2 weeks was adequately described through an IDR model with the drug effect on Kout. The predicted 12-week reduction in HbA1c indicated that well tolerated doses of RG7697 should compare favorably to marketed GLP-1 compounds in Phase II.

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Giovanni Smania Model-based comparison of alternative study designs in paediatric trials

Giovanni Smania (1,2), Paola Baiardi (3), Massimo Cella (1,4), Paolo Magni (2)
(1) Consorzio per Valutazioni Biologiche e Farmacologiche, Via Luigi Porta 14, Pavia, Italy, (2) Dipartimento di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Via Ferrata 5, Pavia, Italy. (3) Direzione Scientifica Centrale, Fondazione Salvatore Maugeri, IRCCS, Via Salvatore Maugeri 4, Pavia, Italy. (4) Pharmatherapeutics Research Clinical Pharmacology, Pfizer Neusentis, Cambridge, UK.

Objectives: The adoption of alternative designs can potentially facilitate the realization of paediatric trials, especially when compared to the standard practice. The objective of this analysis was to compare the performance of the classical parallel design (PaD) with that of a sequential design (based on the Triangular Test (TT) [1]) and of a Bayesian design (BD), exploiting priors from adult data [2], by using PK-PD based clinical trial simulation (CTS).

Methods: A published paediatric PK-PD model of topiramate [3] was used as a paradigm for CTS in epileptic children. 2000 virtual patients were generated based on weight-for-age tables from WHO [4]. Then, for each virtual child, 500 PK profiles were created by using NONMEM version 7.2.0 [5]. Finally, the PD measurement was simulated once for each patient and a design-specific statistical analysis was performed. This procedure was reiterated 1000 times.

R software [6] (version 3.0.1) was used for the generation of virtual patients population, drug effect simulations and statistical analyses. Study designs were evaluated in terms of: type I and type II errors, sample size per arm (SS), trial duration (TD) and precision of treatment difference estimate, assessed through the width of its confidence interval (CIW).

Results: Type I and II errors are close to their predetermined levels of 5% and 20% for all designs except for the BD, whose type I error lies between 18.3% and 23.3%. SS for the PaD and BD was fixed to 121 and 54 respectively, whilst the 50^{th} and 95^{th} percentile of sample sizes distribution in the TT design were 80 and 140, respectively. As to TD, assuming an average enrolment rate of 10 patients/month, the PaD and BD showed a TD of 26.2 and 12.8 months, respectively. In contrast, TT's median TD and its 95^{th} percentile were 32 and 60 months, respectively. Finally, The PaD guarantees the best precision BD and median TT precision are only slightly lower than PaD's one, even though the value of the 97.5th percentile of CIW distribution in the TT suggests this design could lead to very imprecise estimates.

Conclusions: This model-based analysis suggests that if it is reasonable to assume that treatment effect in children is similar to that in adults, a BD allows to streamline paediatric trials. On the contrary, if adult data cannot be leveraged, a TT design appears to outperform a classical PaD, especially if a large effect size is expected.

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Byungjeong Song Application of simplified-ACAT model for specific angiotensin receptor blocker in rats to human

Byungjeong Song, Jung-woo Chae, Byoungyo Lee, Hyunmoon Back, Jaeyeon Lee, Hwi-yeol Yun, Kwang-il Kwon
College of pharmacy, Chungnam National University, Daejeon, Korea

Objectives: The purpose of this study was to establish a simplified-ACAT (advanced compartmental absorption and transit) model of specific angiotensin receptor blocker (ARB) and to applicate this model to human.

Methods: For building the simplified-ACAT model for ARB, rat whole body autoradiography (WBA) data after oral administration was used and for application of the model to human, phase I clinical data of 30 volunteers was used. For applying the simplified-ACAT model to human, only those parameters which represent organ size were scaled up for human. Modeling process was carried out using nonlinear mixed effect modeling (NONMEM®) program. For describing unconventional disposition of drugs to liver, Michaelis-Menten kinetics and fractal kinetics which can explain non-linear kinetics of drugs were used.

Results: : In total, over 60 radioactive concentrations from organ samples in rats and 398 plasma samples in human were collected after oral administration. The final simplified-ACAT model which is

composed of multiple compartment includes stomach, small intestine, large intestine, liver and plasma were successfully established with almost 30 estimated parameters. The kinetics of drugs in plasma was well explained with this simplified-ACAT model. But the non-linear kinetics in the liver compartment still ongoing.

Conclusions: This approach may facilitate prediction of human ARB pharmacokinetics, and may be extended to other study, for examples, drug-drug interaction study. As a matter of fact, this simplified-ACAT model still have limits. Nevertheless, this model appears to be promising and should be further evaluated.

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Ivy Song Use of a Viral Dynamic Model to Evaluate Potential Dolutegravir Dosing Regimens in HIV-1 Patients with Resistance to Raltegravir and Elvitegravir

Ivy Song (1), Kimberly Adkison (2), Mark Lovern (3), Joannellyn Chiu (3), Jenny Huang (4), Cindy Vavro (1), Mounir Ait-Khaled (5), Brian Wynne (6), Sherene Min (1)
(1) GlaxoSmithKline, RTP, NC, US; (2) PAREXEL, RTP, NC, US; (3) Quantitative Solutions, Raleigh, NC, US; (4) GlaxoSmithKline, Mississauga, Canada; (5) GlaxoSmithKline, Stockley Park, UK;(6) GlaxoSmithKline, Collegeville, PA, US

Objectives: To develop a population PKPD model describing HIV-1 virologic response during the functional monotherapy phase in Phase 2b/3 studies of DTG in combination with background therapy in integrase inhibitor resistant (INIr) patients and apply the model to determine the viability of various DTG dosing regimens in treating HIV infection in INIr patients.

Methods: Short-term HIV-1 RNA(viral load) data from four Phase 2a/3 studies were described using a circular/proliferative(viral dynamic) system similar to that described by Jacqmin et al [1]. The model described the dynamics of healthy (target), actively infected, and latently infected CD4+ cell populations. Complementary models were developed in which minimum(Cmin) and average(Cavg) plasma concentration respectively served as the measure of drug

exposure. All covariates were tested on the IC50 parameter using a two-step (forward inclusion/backward elimination) procedure. Covariates evaluated included measures of baseline INI resistance, previous experience with elvitegravir or raltegravir, and viral susceptibility to background therapy. The impact of viral load observations below the quantitation limit(BLQ) was assessed through implementation of the M3 method [2]. The final model was evaluated using visual predictive checks. Simulations were performed to predict the response rates for various scenarios including 100mg BID vs the approved dose 50mg BID, and dosing with food (increasing DTG exposure), metal cation-containing dietary supplements (reducing DTG exposure), or enzyme-inducing drugs.

Results: A total of 751 viral load observations from 266 HIV-1 patients (247 INIr patients and 19 naïve to integrase inhibitors [INIn]), were included in the model building. The available data were well-described by the final population PKPD models, and the fits of Cmin and Cavg models were virtually identical. Of the covariates tested, only baseline INI resistance and Study Population (INIn vs INIr) were found to be significant. Simulations predicted that increasing the twice-daily DTG dose from 50mg to 100mg would yield small additional declines in Day 8 change from baseline in log10 viral load: -0.07 log, -0.05 log, -0.11 log, and -0.12 log for the overall population and the subpopulations with no Q148 mutation, with Q148+1 mutations, and with Q148+^{3}2 mutations, respectively. Dosing with food, metal cation-containing supplements, or enzyme inducers marginally affected Day 8 response..

Conclusions: This analysis supports the current dosing recommendation of DTG 50mg BID in INIr patients.

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Elena Soto Model informed drug discovery and development of novel treatments for hyperuricemia: from systems pharmacology to mechanistic PK/PD

E. Soto(1), B. Weatherley(1), M. Cella (2), P. Dua(2), S. Marshall (1)
(1) Pharmacometrics, Pfizer, UK; (2) Clinical Pharmacology, Neusentis, Pfizer, UK. Authors (except BW who is a Pfizer contractor) are employees and shareholders of Pfizer Inc

Objectives: The rising population prevalence of hyperuricemia (1) has renewed interest in the purine metabolic pathway (PMP). Dua et al (2) recently published a system pharmacology model which has determined sensitivity of the pathway to mono and dual inhibitory effects. This work highlighted the potential therapeutic value of simultaneous inhibition of XO (xanthine oxidase: enzyme responsible for oxidation of xanthine to uric acid (UA)) and URAT-1 (a transporter responsible for the reabsorption of UA). This therapeutic strategy is currently being explored via combination therapy (3) or as a target for a dual inhibitor (4). The aim of this work is to develop a mechanistic PKPD model to characterise the interaction between these points in the PMP in terms of impact on rate and extent of changes in serum and urinary concentrations of xanthine and UA.

Methods: A PKPD model was developed using NONMEM 7.2 starting from the systems model but simplified and calibrated based on healthy volunteer serum and urinary data from an internal

compound (URAT-1 inhibition) and from literature data (5). The model consisted of 4 compartments, where xanthine will be either renally cleared or converted into UA prior to elimination to the UA urinary compartment. Drug effects were tested in the UA formation, UA clearance and on the xanthine clearance. Simulations were undertaken to explore the relationship between both mechanisms.

Results: Simulations showed that a potent URAT-1 inhibitor would be characterised by a significant increase in the amount of urinary uric acid eliminated on day 1 of treatment, which would then return to baseline levels as steady state is rapidly achieved. It was demonstrated that titration could minimise the day 1 effects. A similarly effective XO inhibitor on the other hand would result in a decrease in the UA over time but an increase in circulating and urinary xanthine.

Conclusions: Simulations provided greater insight into the interaction between two key mechanisms in the PMP and how balancing those may help optimize treatment with existing and emerging mono therapies while providing targets for future dual inhibitor development.

This case study also illustrates how systems pharmacology can help define specific research questions which can be explored by focused mechanistic PK/PD modelling which can ultimately be fed back into the wider systems pharmacology model.

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Rujia Xie Relationship between the Dose of Urate Lowering Therapies and Serum Uric Acid in Healthy Volunteers and Gout Patients: A Model Based Meta-Analysis (MBMA)

Yi Sun1, Liang Li1, Scott Marshall2*, Wei Lu1, Rujia Xie3*
*1Peking University/Pfizer PMx Education center, 2Pfizer, Sandwich, UK, 3Pfizer (China) Research and Development Center, China,*Employees and shareholders of Pfizer Inc*

Objectives: The purpose of this model-based meta-analysis was to characterize the steady-state dose-response (DR) relationship for the reduction of sUA across compounds in different mechanism of action (Xanthine Oxidase Inhibitors (XOi), Urate transport (URAT1) inhibitors, and Purine nucleoside phosphorylase (PNP) inhibitor).

Methods: A comprehensive literature search was conducted for PNP inhibitor, XOi and URAT1 inhibitors administered alone or in combination to healthy volunteers (HV) or gout patients. Serum uric acid (sUA) data were extracted and the dose response relationship for sUA change from baseline (CFB) was analyzed using NONMEM v7.2. Summary level data of sUA CFB was available on 39 trials (153 unique arms) presenting 6946 gout patients and 395 healthy volunteers. The potential covariates (baseline sUA, population, race) were explored. Inter-trial and additive residual variability were estimated and the latter was weighted by sample size. The correlation among repeated measurements was investigated.

Results: The dose-response relationship for sUA CFB was adequately described by an E_{max} model and a floor effect was introduced that was set to 1mg/dL as the lowest boundary of sUA level. It was assumed that the compounds having the same mechanism of action had a common maximum effect (E_{max}) but different potency (ED_{50}). The different effect between HV and patients could be explained by the differences of baseline. E_{max} for Chinese population having Febuxostat was significantly lower from other races. At baseline 9.2mg/dL, derived E_{max} for XOi was -7.12mg/dL (-6.34mg/dL for Chinese) and the ED_{50} of Allopurinol and Febuxostat were 320.5mg and 41.3mg, respectively. For URAT1 inhibitors, derived E_{max} was -6.84mg/dL and ED_{50}s of Benzbromarone and Lesinurad were estimated to be 41.3mg and 492.7mg, respectively. Derived E_{max} of PNP inhibitor BCX4208 was -5.45mg/dL with ED_{50} of 68mg. The maximum effect of refractory population was about 66% of non-refractory population. The combination effect was less than additive among all the co-medication situations, suggesting it was less than the sum of their separate effect.

Conclusions: This model-based meta-analysis provided a broad overview and understanding of effect size of different classes of urate-lowering drugs in order to develop comparative product profiles, aid translation between different populations and predict potential combination effects in the drug development of novel Urate lowering agents.

Marios Spanakis Application of Simcyp® simulator platform for the assessment of the pharmacokinetic profile of Gd-DOTA regarding its disposition in brain tumors lesions with different vasculature

Marios Spanakis (1), Vangellis Sakkalis (1), Kostas Marias (1)
(1) Computational BioMedicine Laboratory, Institute of Computer Science, Foundation for Research and Technology - Hellas, Vassilika Vouton, GR-71110 Heraklion, Crete, Greece

Objectives: Gadolinium based contrast agents (GBCA) are used in dynamic –contrast enhanced magnetic resonance imaging (DCE-MRI) for diagnosis of lesions such as brain tumors with implementation of pharmacokinetic analysis for quantification of the vessel leakage of tumor's abnormal vasculature [1]. The aim of this work was to assess through physiologically-based pharmacokinetic modeling (PBPK) the impact of different fraction of vasculature of a brain tumor on the PK profile of Gd-DOTA (gadoteric acid, DOTAREM®).

Methods: The PK profiles were generated through whole body-PBPK models and in silico clinical trials with Simcyp® simulator platform [2]. The typically administered dose (i.v., 0.1 mmol/kg) was simulated for the estimation of tracer's concentration for up to 15 minutes post administration in order to be in line with the typical DCE-MRI clinical setting. The brain tumor lesion (BTL) compartment was introduced as an additional organ in the simulator with tissue

characteristics modified to fit those of brain and brain tumors. Keeping all parameters constant for BTL (size, composition) and the same virtual profile, simulations run modulating each time the proportion of capillary bed in the BTL (0.01-10% of the total tissue).

Results: The results from the simulations for Gd-DOTA estimate a mean systemic plasma concentration Cmax=2.3 mM, a mean AUC =163.16 μM.h and clearance CL= 5.6 L/h. The mean Cmax,int of intracranial blood was 1.6 mM with an AUC=159.73 μM.h. Regarding BTL, the maximum extravascular concentrations of Gd-DOTA ranged from 1.6-1.7 mM following the BTL's increased vasculature. Taken into consideration blood brain barrier permeability, Simcyp® predicted a zero concentration-time profile for the brain mass revealing the impact of BBB regarding tracer's limited disposition in the brain as it is observed in clinical settings of DCE-MRI.

Conclusions: The results of the PBPK approach through the application of Simcyp® reveal a suitable method to describe *in silico* the impact of different vasculature of a brain tumor on tracer's PK profile. The evaluation of tracer kinetics through *in silico* clinical trials and PBPK models represent novel approaches for DCE-MRI in population and/or individual level [3,4]. This methodology shows potentials on the possible coupling of the results with studies correlating image analysis with tumor growth models regarding the estimation of GBCA profiles in different population cohorts.

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Emmanouil G. Spanakis MyHealthAvatar platform: matching real life patients with the generated virtual profiles from in silico clinical trials

Marios Spanakis(1), Emmanouil G. Spanakis(1), Dimitris Kafetzopoulos(2), Vangelis Sakkalis(1), Manolis Tsiknakis(1,3), Kostas Marias(1), Feng Dong(4)
(1) Institute of Computer Science, Foundation for Research and Technology - Hellas, Heraklion, Crete, Greece; (2) Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology - Hellas, Heraklion, Crete, Greece; (3) Department of Informatics and Engineering, Technological Educational Institute of Crete, Heraklion, Crete, Greece; (4) Department of Computer Science and Technology, University of Bedforshire, Luton, Bedforshire UK

Objectives: MyHealthAvatar (MHA) platform aims towards a collaborative partnership among patients and healthcare providers [1]. Nowadays, in silico clinical trials (ISCTs), population pharmacokinetics, pharmacogenomics and information communication technologies have provided several tools towards stratified and personalized medicine approaches [2-4]. In this work a methodology of potential fitting of results generated through ISCTs with real life patients through virtual profiles of MHA is presented. To this respect, we use a simple example of discontinuation of warfarin administration during pre-operative period for a 55 year's old male patient with a MHA profile.

Methods: MHA's architecture is based on integration of multiscale data gained from several sources (i.e. demographic, biomedical, genomics, lifestyle) and transform them into a representation of health status as a "virtual twin" or avatar [1]. The integration of these information from different avatars can lead in a creation of a virtual population profile (i.e. patients follow anti-coagulating treatment). The population pharmacokinetics in this example are based on the results from simulation of S-warfarin administration in a virtual population through Simcyp® population based simulator [5].

Results: The results from the Simcyp® simulations generated a PK/PD profile of S-warfarin during and after the discontinuation of the treatment in a virtual population with different characteristics regarding demographic, physiology and genomic data. The data output from MHA platform allow also the generation of a virtual cohort with characteristics regarding demographic, physiology and pharmacogenomics (i.e. CYP2C9 polymorphism). To this respect, the best fit of data between these two virtual profiles, e.g. based on patient's demographics and genomic information, finally leads in generation of information regarding our real-life patient (in this example, the 55 years old male) serving as additional information tool regarding the schedule of the operation.

Conclusions: MHA aims to serve as an innovative representation of the health status for citizens whereas for clinicians MHA potentially could support clinical decisions by extrapolating and/or fitting profiles with simulation models (i.e. population pharmacokinetics) and visual analytics [6]. The potential interconnection with in silico tools can provide novel approaches towards implementation of stratified and/or personalized medicine [7].

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Claudia Stötzel A Markov Chain Monte Carlo Approach to Identify Pathological Situations in the Female Menstrual Cycle

Claudia Stötzel and Marcus Weber and Susanna Röblitz
Zuse Institute Berlin

Objectives: For the simulation of biological models, the identification of unknown parameter values such as growth and clearance rates of the involved substances is crucial. For a model of the female menstrual cycle, we use Bayesian methods to recover the joint probability distributions of the free parameters. We analyse the sampled marginal distributions and detect parameter regions which lead to pathological situations.

Methods: For a previously developed mechanistic model of the human menstrual cycle [1], which consists of 33 highly nonlinear ODEs and 113 parameters, we sample the joint posterior distribution of 82 free parameters. For this, a Metropolis-Hastings algorithm to generate a Markov chain that walks through the parameter space is implemented in Python. To account for the positivity of the parameters, a log-normal distribution is chosen for the transition probabilities. As the solution of the model has to be cyclic, only periodic solutions are accepted and, in every step, the data is shifted to match the periods. For the calculation of the likelihood, data were available for 40 individuals in courtesy of Dorothea Wunder, CHUV, Lausanne, and for 12 individuals from a

previous collaboration with Pfizer [1]. The sampled marginal parameter distributions are divided into intervals for which the transition probabilities are calculated and analysed.

Results: Several bimodal marginal parameter distributions are detected, which give a hint to a clustering of important parameter values. In particular, we found a set of parameter values that leads to the simulation of the polycystic ovary syndrome (PCOS).

Conclusions: The clustering of the marginal parameter distributions is a suitable approach to explore the parameter space and detect new dynamical characteristics of a given model. Our analysis is promising to lead to even more insights about unexplored simulation possibilities with an ODE model of biological processes.

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Ahmed Suleiman A Modeling and Simulation Framework Characterizing the Time Courses of Adverse Events in Non-Small Cell Lung Cancer Patients Treated with Erlotinib

Ahmed Abbas Suleiman (1); Sebastian Frechen (1); Matthias Scheffler (2); Thomas Zander (2); Lucia Nogova (2); Martin Kocher (3); Ulrich Jaehde (4); Jürgen Wolf (2); Uwe Fuhr (1)
(1) Department of Pharmacology, Clinical Pharmacology Unit, University Hospital of Cologne, Cologne, Germany; (2) Department I of Internal Medicine, Center for Integrated Oncology Cologne Bonn, University Hospital of Cologne, Cologne, Germany; (3) Department of Radiotherapy, University Hospital Cologne, Cologne, Germany; (4) Institute of Pharmacy, Clinical Pharmacy Department, University of Bonn, Bonn, Germany

Objectives: Based on a mathematical model [1,2], the use of pulsatile high doses of erlotinib together with a continuous-low dose was suggested as a dosing regimen instead of the standard regimen (150mg/day) to minimize the development of acquired resistance in non-small cell lung cancer (NSCLC) patients. Our aim was to build a modeling and simulation framework for adverse events (AE) commonly encountered during erlotinib treatment, namely rash and diarrhea, to provide insights into erlotinib toxicity.

Methods: AE data for model development were available from 39 advanced NSCLC patients first treated with erlotinib (150mg/day

oral; NCT00568841). Dates of AE incidence and resolution were recorded, and they were graded according to the National Cancer Institute-Common Toxicity Criteria (grade 1=mild, grade 2=moderate, grade 3=severe). Continuous-time Markov models [3] were developed to account for the transitioning of patients between different AE grades. Erlotinib exposure and covariates including the mutational status, radiotherapy and co-medications histories, laboratory findings and demographics were investigated for their influence on adverse events. A simulation study using the models built was conducted to compare the toxicities of different dosing regimens (standard and pulsatile regimens).

Results: Patients were more likely to experience an AE (rash or diarrhea) early during treatment, and erlotinib exposure was found to increase the risk of rash but not diarrhea. Interestingly, previous or concomitant radiotherapy decreased transitioning to higher rash grades by 81% ($p<0.01$). Simulations suggested the design of pulsatile regimens using the maximum tolerable weekly exposure.

Conclusions: The modeling and simulation framework developed demonstrated the tolerability of pulsatile erlotinib dosing regimens, and suggested that radiotherapy might mitigate erlotinib-induced rash.

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Elin Svensson Albumin concentrations and body weight in MDR-TB patients over time on treatment and the impact on bedaquiline pharmacokinetics

Elin M. Svensson (1), Mats O. Karlsson (1)
(1) Uppsala University, Uppsala, Sweden

Objectives: To characterize changes in albumin and body weight in patients treated for multidrug-resistant tuberculosis (MDR-TB) with bedaquiline (BDQ) and to investigate the potential impact of these changes on BDQ PK.

Methods: Data were obtained from two phase II studies of BDQ, a highly protein bound drug (unbound fraction fu<0.1% [1]), in MDR-TB patients [2-3]. Observations of albumin, body weight, BDQ and metabolite M2 plasma concentrations were available from the treatment period with BDQ plus optimized background therapy OBT (24 weeks) and following period with only OBT (up to week 120). Mechanistically plausible relationships of albumin, BDQ and its M2 metabolite, including effects of fu (inversely proportional to albumin concentration) were tested in population PK models. Clinical research was approved by institutional review boards and all subjects provided written informed consent.

Results: 4684 albumin observations and 5438 body weight observations from 335 patients were included. Albumin at screening was typically lower than the reference value for healthy individuals

and increased over time on treatment. A logistic growth model described the time-course of albumin best. Estimated parameters were A0 (albumin at start of treatment) 3.65 g/dl (RSE 0.9%), Ass (albumin at steady state [SS]) 4.05 g/dl (RSE 0.6%) and T½ (half-life to reach albumin SS) 22.3 weeks (RSE 13%). The IIV in A0, Ass and T½ were 16%, 10% and 118%, respectively. Body weight typically increased during treatment and could be described with a linear model; typical body weight at start of treatment (WT0) and end of follow up (WT120) were 56.7 (RSE 1.1%) and 62.5 (RSE 1.3%) kg, with IIVs of 21% and 22%. RSE in all IIVs were <10%. Correlations A0-WT0 and Ass-WT120 were 35% and 33%. Time varying albumin was used to predict changes in fu and hepatic capacity (i.e. clearance of BDQ and M2). The relationships improved the description of BDQ/M2 data significantly. Allometric scaling with time varying weight instead of weight at baseline improved the fit. The coefficients were 1 for volumes (fixed) and 0.18 for clearances (estimated, $p<0.05$).

Conclusions: Models describing typical and individual albumin concentrations and body weight were developed. Time-varying albumin and body weight were found to impact BDQ and M2 PK. Incorporating both effects simultaneously and accounting for changes over time aided the characterization of influence of body weight and albumin on BDQ patient PK which has not previously been described.

Acknowledgement
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Robin Svensson Application of the Multistate Tuberculosis Disease Model in Rifampicin Treated Pulmonary Tuberculosis Patients

Robin J Svensson and Ulrika SH Simonsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: To apply the Multistate Tuberculosis Disease Model [1], linked to rifampicin pharmacokinetics (PK), to clinical Phase IIa colony forming unit (CFU) data in drug-susceptible pulmonary tuberculosis (TB) patients. In addition, to perform clinical trial simulations using the developed final model in order to predict retrospective clinical data as an external validation of the disease template approach.

Methods: CFU data from 24 patients [2] receiving 0 (n=4, negative control group), 5 (n=3), 10 (n=8) or 20 (n=8) mg/kg rifampicin were analyzed using non-linear mixed effects modeling implemented in NONMEM 7.3 [3]. A previously developed rifampicin population PK model [4] was linked to the Multistate Tuberculosis Disease Model, including fast-, slow- and non-multiplying as well as dead bacterial states, earlier developed using *in vitro* data [1]. Drug effect was implemented as exposure-response relationships tested at several effect sites in the Multistate Tuberculosis Disease Model, including inhibition of growth of the fast-multiplying state and as stimulation of the death rate of all states, both alone and in all possible

combinations. External validation was performed by clinical trial simulation from the final model comparing the model predicted 95% prediction interval based on parameter uncertainty of the typical decline in CFU versus time to the mean±standard error of four datasets not used for model building.

Results: All system specific Multistate Tuberculosis Disease Model parameters were fixed to *in vitro* estimates except B_{max}. The parameter B_{max} described number of bacteria at stationary phase and was estimated throughout model building. All patients were assumed to have a stationary phase infection. Drug effect was best described by an on/off effect inhibiting growth of fast-multiplying bacteria in addition to slope models stimulating the death rate of slow- and non-multiplying bacteria. Stimulation of the death rate of the fast-multiplying state was not statistically significant. Clinical trial simulations predicted well four retrospective clinical trials using the final Multistate Tuberculosis Disease Model.

Conclusions: The Multistate Tuberculosis Disease Model was successfully applied to clinical data with rifampicin treated patients. Retrospective data was successfully predicted using clinical trial simulation with the final model which confirmed the utility of the approach in anti-tubercular drug development.

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Eva Sverrisdóttir Modelling drug-drug interactions between morphine and methylnaltrexone

Eva Sverrisdóttir (1) Mads Kreilgaard (2) Anne Brokjær (3) Anne Estrup Olesen (1,3) Lona Louring Christrup (1) Asbjørn Drewes (3,4)
(1) Department of Drug Design and Pharmacology, Faculty of Health Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark (2) Novo Nordisk, Måløv, Denmark (3) Mech-Sense, Department of Gastroenterology & Hepatology, Aalborg University Hospital, Mølleparkvej 4, DK-9000 Aalborg, Denmark (4) Department of Clinical Medicine, Aalborg University, Sdr. Skovvej 11, DK-9000 Aalborg, Denmark

Objectives: To establish the population PKPD relationship of morphine after rectal administration using pupillometry as a central biomarker. Furthermore, to evaluate if a peripheral opioid receptor antagonist, methylnaltrexone, can be assumed not to influence morphine's PKPD properties within the central nervous system.

Methods: Morphine hydrochloride (HCl) was administered to healthy male participants in a randomized, placebo controlled, double-blinded, four-way cross-over study, where 15 volunteers received placebo or 30 mg rectally administered morphine HCl in combination with either placebo or 12 mg methylnaltrexone administered subcutaneously. PK and PD assessment was carried out over 3 h. PK data from a previous study was included in the PK analysis [1]. Plasma concentrations and pupil diameter were fitted to PK and PD models using non-linear mixed-effects modelling

implemented in NONMEM V 7.3.0 [2]. The absorption of morphine after rectal administration was tested as first-order with or without absorption lag or as transit-compartment absorption with or without a first order absorption rate constant [3]. Pupil diameter was fitted to linear and E-max models. The influence of age, weight, height, and co-administration of methylnaltrexone was tested for PK and PD, as well as any interoccasion variability. Stepwise covariate modelling in Perl speaks NONMEM was used to search for categorical and continuous exponential, linear, hockey-stick, and power covariate relationships. The residual error models tested were proportional, additive, or a combination.

Results: Morphine distribution was best described with a two-compartment model and the absorption of morphine after rectal administration was described with two transit-compartment absorption with a first-order absorption between last absorption compartment and central compartment. Body weight correlated linearly to morphine clearance, and mean transit time varied between occasions. Preliminary results suggest that central effect evaluated by pupil constriction was best described with a linear model with effect delay, and that methylnaltrexone had no influence on morphine PK or PD.

Conclusions: Co-administration of methylneltrexone did not affect morphine PK or central PD effect.

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Maciej Swat Standardized Output: flexible and tool-independent storage format of typical M&S results

Nadia Terranova (1), Marc Lavielle (2), Mike K. Smith (3), Emmanuelle Comets (4,5), Kajsa Harling (6), Rikard Nordgren (6), Andrew C. Hooker (6), France Mentre (4,5), Maciej J. Swat (7)
(1) Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland, (2) Inria Saclay, France, (3) Global Clinical Pharmacology, Pfizer, Sandwich, UK, (4) INSERM, IAME, UMR 1137, Paris, France, (5) Univ Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, Paris, France, (6) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (7) EMBL-European Bioinformatics Institute, Hinxton, Cambridgeshire, UK

Objectives:

The definition and implementation of formats enabling a reliable exchange of pharmacometric models across software tools is one of the key goals for efficiently promoting collaborative drug and disease modeling and simulation (M&S) research.

PharmML, one of the DDMoRe interoperability platform elements, has been designed to play the role of the exchange medium for models [1]. Similarly, the Standardized Output (SO) has been developed as a complementary element, tool-independent format, for storing typical output produced in a pharmacometric workflow.

Methods:

Based on the requirements provided by the DDMoRe community, SO represents a flexible storage format for typical results and information coming from a pharmacometric step, performed in any DDMoRe target tool (e.g., NONMEM, MONOLIX, winBUGS).

The standard is developed as an XML schema definition, which reuses some structure elements of the PharmML schema [2] (e.g., for the specification of matrices and datasets) as well as some other existing standards (e.g., UncertML [3] is used to encode uncertainty).

Results:

In the current version the SO structure consists of the following seven main sections:

1. Tool settings: storing the reference to any file containing the tool settings of the performed task;
2. Raw results: storing the reference to original output files produced by the target tool;
3. Task Information: holding information about the modelling step execution (e.g., tool message, execution time);
4. Estimation: storing estimation results produced by different estimation techniques (e.g., MLE, Bayesian);
5. Model Diagnostic: storing information resulting from typical model diagnostic plots (e.g., individual fits, VPC);
6. Simulation: storing simulation results (e.g., individual time course, population and individual parameters, random effects, covariates, dosing records) for each replicate;
7. Optimal design: storing results (e.g., parameters values and precision, criteria, tests) obtained from an evaluation/optimization step.

A set of converters has been developed to allow for SO elements population directly from target tools.

Conclusions:

Beside capturing and storing various type of information, as a generic output model, SO aims at enabling effective data flow across tasks, thus, extending the workflow capabilities, and support the user in assessing, reviewing and reporting a modelling step.

This work is on behalf of the DDMoRe project (www.ddmore.eu).

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Amit Taneja Translational modelling of prolactin response following administration of D2 antagonists in rats

A. Taneja (1), A. Vermeulen (2), D. Huntjens (2), M. Danhof (3), E.C.M. De Lange (3), J.H. Proost (1)
(1) Division of Pharmacokinetics, Toxicology and Targeting, Groningen Research Institute of Pharmacy, University of Groningen, the Netherlands, (2) Model Based Drug Development, Janssen Research & Development, Beerse, Belgium, (3) Department of Pharmacology, Leiden Academic Center for Drug Research, Leiden University, the Netherlands

Objectives: Treatment with D_2 antagonists results in prolactin release, and thus prolactin is a biomarker of dopamine antagonism. We compare the model performance of two semi-mechanistic PKPD models, the pool model and the agonist-antagonist interaction model, to describe prolactin release following administration of risperidone (RI), paliperidone (PA) or remoxipride (REM) in rats. The hypothesis that potency differences exist for risperidone and paliperidone was evaluated and rat to human translations were conducted.

Methods: The models were fitted to single or multiple dose data on the 3 paradigm compounds. Different potencies (EC50 and KI) were estimated for RI and PA, as compared to a common potency. The pool model was modified to estimate RO_{50}, or the receptor

occupancy at half-maximal effect, a system specific parameter. This was done using model predicted and observed KI values. As peripheral D_2 antagonism is responsible for prolactin release, free population plasma concentrations of the D_2 antagonists were considered as the drivers of the pharmacodynamic (PD) response. Finally, we predicted the time course of plasma prolactin in humans following PA administration, using an inter-species scaling approach.

Results: Both models were able to describe the data and model performance was comparable. Potencies of RI and PA did not differ significantly. Estimated EC_{50} for RI and PA was 35.1(relative standard error 51%) and for REM it was 94.8 (31%) nM. KI values for these compounds were 14.6 (17%) and 165 (14%) nM respectively. RO_{50} was 28.7 (21%) %. System specific PD parameters were scaled using allometric principles, while RO_{50} was assumed to be species independent. Predicted human plasma prolactin profiles were comparable with observed and published findings. Tachyphylaxis due to depletion of the prolactin pool was predicted after the second dose.

Conclusions: The performance of both models was comparable in describing single and multiple dose data. Single dose typical human predictions with the pool model were in agreement with observed data.

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Sonya Tate Relative Bioavailability to Describe Variability in Exposure for an Oral Drug: A Population PK Model of Abemaciclib in Cancer Patients

Sonya C. Tate(1), Amanda K. Sykes(1), Palaniappan Kulanthaivel(2), Edward M. Chan(2), Donald E. Thornton(2), P. Kellie Turner(2), Damien M. Cronier(1)
(1) Eli Lilly and Company, Erl Wood, UK, (2) Eli Lilly and Company, Indianapolis, USA

Objectives: Describe the population pharmacokinetics (PK) of abemaciclib in cancer patients enrolled on a Phase I clinical trial.

Methods: PK data were collected in a multicentre, nonrandomized, open-label Phase 1 clinical trial of abemaciclib in the treatment of approximately 300 patients with advanced cancer. The study design consisted of a dose escalation phase (50, 100, 150 or 225 mg Q24H, or 75, 100, 150, 200 and 275 mg Q12H) and 6 tumour-specific expansion phases (150 or 200 mg Q12H). PK sampling was intensive, with samples collected for 72 hours after an initial single dose, and then on days 15, 22 and 28 of the continuous dosing regimen. The population PK parameters, inter-individual (IIV) and inter-occasion variability (IOV) were estimated using NONMEM 7.2 (FOCEi). Age, weight, gender, liver and renal function were tested via step-wise covariate modelling (forwards inclusion [ΔOFV > 3.84]; backwards exclusion [ΔOFV < 10.8 and ΔIIV < 5%]). Model performance was

evaluated by objective function mapping, visual predictive checks and bootstrap analysis.

Results: The popPK analysis dataset consisted of 224 patients with 4012 observations. The analysis population had a mean age of 60 (24 – 85) and mean body weight of 73.9kg (43.6 – 175); 67% were female and the majority were white (94%). The data were best described by a one compartment model with linear absorption (ka) of 0.197/h (IIV=77.6%), clearance (CL/F) of 35.9L/h (IIV=29.6%, IOV=52.1%) and volume of distribution (V/F) of 1050L; residual error was described with a combined model. Through model development, CL/F and V/F were found to be strongly correlated. Given the complex absorption observed in pre-clinical studies [1], this correlation was attributed to IIV in bioavailability. A relative bioavailability term (F_{rel}) was therefore implemented by fixing the mean population estimate to 1 and allowing IIV to be estimated. F_{rel} was also found to be time- and dose-dependent (initial F_{rel} IIV=73.4%, steady state F_{rel} IIV=123%) with 50% saturation occurring at 101 mg. Liver function markers (serum albumin and alkaline phosphatase) were found to significantly affect F_{rel}. However, there remained a high level of variability in exposure which could not be attributed to patient characteristics or laboratory parameters.

Conclusion: Explained variability [2] in abemaciclib exposure was far lower than unexplained variability, suggesting the impact of liver function on exposure is clinically negligible.

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Max Taubert Population pharmacokinetics of linezolid in intensive care patients

Max Taubert (1)*, Michael Zoller (2)*, Barbara Maier (3), Sebastian Frechen (1), Uwe Fuhr (1), Christina Scharf (2), Lorenz Frey (2), Michael Vogeser (3), Johannes Zander (3) * Both authors contributed equally to this work

(1) Department of Pharmacology, Hospital of the University of Cologne, Germany (2) Department of Anesthesiology, Hospital of the Ludwig-Maximilians-University of Munich, Germany (3) Institute of Laboratory Medicine, Hospital of the Ludwig-Maximilians-University of Munich, Germany

Objectives: Linezolid is an antimicrobial agent used in the treatment of severe infections including a set of multi-resistant pathogens. Although it takes on an important role in the treatment of infections in intensive care little is known about its pharmacokinetic properties and the sources of variability in this group of patients. The objective of our analysis was to develop a population pharmacokinetic model and to investigate the sources of variability in critically ill patients.

Methods: Data from a collective of 53 intensive care patients (19 women, 18 on Continuous Renal Replacement Therapy [CRRT], 16 with Acute Respiratory Distress Syndrome [ARDS], 15 with lung transplantation, 8 with liver transplantation, 16 with sepsis, median age 58 years, median weight 75 kg, median APACHE-II score 28, median SOFA score 12) with severe infections was used. Intravenous short-duration infusions of 600mg linezolid were

administered every 12 hours for 4 days. Multiple serum samples per day were taken and linezolid was quantified by a liquid chromatography/tandem mass spectrometry method. We developed a population pharmacokinetic model and investigated the influence of a set of covariates including laboratory values, intensive care scores and demographics using NONMEM.

Results: A two-compartment model with first-order elimination was found to be most suitable to describe the data. The central and peripheral volume of distribution were 19 (15, 26) L and 25 L respectively, the elimination clearance was 7.6 (4.4, 12) L/h (median and interquartile range [where applicable] of individual estimates). A complete bioavailability and an absorption constant of 1.7/h were found for oral administration. The body weight was linked to the central volume of distribution and to the elimination clearance. With increasing SOFA score the clearance decreased. The need for CRRT was linked to a central volume of distribution increased by 38% and patients suffering from ARDS had a 79% higher clearance. By including these covariate relationships the observed inter-individual variability could be reduced by 28% for the clearance and by 52% for the central volume of distribution.

Conclusions: The individual pharmacokinetic parameters of linezolid depend on the body weight and various parameters describing the severity of the disease. The individual concentrations required for the optimization of linezolid dosing may be predicted using our model.

Paulo Teixeira Population Pharmacokinetics of Phenobarbital in Children, Adolescents and Young Adults Patients.

Teixeira P (1), Pérez-Blanco JS (1), García García MP (2), García Sánchez MJ (1), Otero MJ (2), Santos Buelga D (1).
(1) Department of Pharmacy and Pharmaceutical Technology, University of Salamanca, Spain, (2) Service of Pharmacy, University Hospital of Salamanca, Spain.

Objectives: The main goal of this work was to develop an updated population pharmacokinetic model to identify and quantify the influence of demographics, clinical and treatment factors on the clearance (CL) of phenobarbital (PBT) in Children, Adolescents and Young Adults Patients.

Methods: Serum concentrations of PBT were taken from patients aged 0.08-25 years old, who had been treated with this drug. These patients were included in the TDM program, conducted in the University Hospital of Salamanca over the last 20 years. After applying the inclusion/exclusion criteria previously established, the final database included 304 serum concentrations from 118 patients. Pharmacokinetic analysis was performed with NONMEM V7.3 (FOCEI) considering a one-compartment model, fixing the absorption constant and volume of distribution at 1.33 h^{-1} and 0.9 L/kg, respectively [1-3]. Proportional error models were assumed to describe interindividual and residual variabilities. The analysed

covariates were: weight (WGT), age, gender (SEX), and concomitant treatment with carbamazepine (CBZ), clonazepam (CLO), phenytoin (PHT), lamotrigine (LTG), topiramate (TOP) and valproic (VLP) and another comedication with potential interaction (ACC). The predictive capacity was evaluated using a Bootstrap technique (n=1000).

Results: The covariates with significant influence on CL/F_{PBT} were: WGT (according to an allometric function [4]) and concomitant treatment with CBZ, PHT, VLP and ACC. ACC was excluded in the backward elimination process ($p<0.01$). The covariate CBZ was also eliminated in the final model because of the low clinical significance (PBT was as follows:

$$CL/F_{PBT}\ (L/h) = 0.26\times((WGT/70)^{0.58})\times(0.84\times PHT)\times(0.67\times VLP)$$

$w^2_{CL/F} = 0.026$ (*shrinkage*=9 %)

$s^2 = 0.012$ (*shrinkage*=17 %)
The standard estimation errors were lower than 15 % for all parameters.

The results obtained in the bootstrap show acceptable performance of the proposed model.

Conclusions:

The developed population pharmacokinetic model for PBT in children, adolescents and young adults patients includes WGT and the concomitant administration of PHT and VLP on CL/F_{PBT}. The inclusion of these covariates reduced interindividual and residual variabilities for 84 % y 43 %, respectively. This model appears to be adequate for clinical application in TDM. However, we consider necessary to carry out an external validation to confirm the results shown in this study.

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Donato Teutonico Development of a Cardio-Vascular Systems Pharmacology Platform

Katrin Coböken (1), Donato Teutonico (1), Thomas Gaub (1), Frank Kramer (2), Jörg Lippert (2), Michaela Meyer (1), Heiner Post (2), Walter Schmitt (2), Hubert Trübel (2), Rolf Burghaus (2), and Thomas Eissing (1)
(1) Bayer Technology Services, Leverkusen, Germany, (2) Bayer HealthCare, Wuppertal, Germany

Objectives: Mathematical modelling and simulation techniques provide an efficient approach in analyzing and predicting complex physiological systems and medical conditions. During the last decades, such tools have been applied to the modeling of the cardiovascular system with increasing model complexity. The objective of this project was to develop a computational framework integrating physiological knowledge as well as experimental data from all the different drug development stages capable of predicting cardiovascular parameters relevant in drug development.

Methods: We developed a Cardio Vascular Systems Pharmacology Platform that includes a detailed description of relevant hemodynamic processes along with their vegetative and hormonal regulation. The model was built in PK-Sim and MoBi[4)] by integrating different literature models[1),2),3)] and is parameterized for describing a healthy adult subject.

Results: The platform is able to predict physiological behaviors in a healthy subject and is validated in different perturbation scenarios including beta-blocker administration, tilt test and exercise. Model outputs are compared to the most relevant cardiac measurements including left ventricular pressure-volume relationship, mean arterial blood pressure, heart rate and cardiac output. The simulation of beta-blocker effects was used as proof-of-concept to simulate pharmacological intervention.

Conclusions: The cardiovascular model is able to describe the behavior of a healthy human cardiovascular system at rest, during exercise and after drug administration. The model structure is compatible with physiologically-based pharmacokinetic (PBPK) models allowing for the integrated dynamic description of concentration-dependent pharmacological effects on the cardiovascular system and, vice versa, pharmacodynamic effects influencing the pharmacokinetics. Further extensions of the platform will include the implementation of additional regulation mechanisms relevant for other drug classes as well as the parameterization of relevant disease populations.

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Hoai-Thu Thai Joint modeling of longitudinal tumor burden and time-to-event data to predict survival: application to aflibercept in second line metastatic colorectal cancer

Hoai-Thu Thai (1), Jean-Baptiste Fau (1), France Mentré (2), Emmanuelle Comets (2), Christine Veyrat-Follet (1)
(1) Drug Disposition, Department of Disposition, Safety and Animal Research (DSAR), Sanofi, Paris, France; (2) INSERM, IAME, UMR 1137, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

Objectives: Aflibercept (ziv-aflibercept in the US, ZALTRAP®) is a fusion protein of human vascular endothelial growth factor (VEGF) receptor domains that binds to VEGF-A, VEGF-B, and PlGF and inhibits tumor growth (1). In metastatic colorectal cancer, the VELOUR trial demonstrated significantly improved overall survival (OS) for aflibercept in combination with FOLFIRI, after failure of an oxaliplatin based regimen (2). The aim of this work was to analyze the treatment effect on tumor growth kinetics and the link to survival using a joint modeling framework accounting for informative dropouts.

Methods: Model building was conducted using 1069 evaluable patients from the VELOUR trial. Longitudinal data of tumor size (sum of target lesions) were first analyzed alone. Then, informative dropouts and OS data were both included for joint modeling using

hazard frailty models (3) with shared latent random effects. Parameters were estimated by maximizing the exact joint likelihood with the SAEM algorithm implemented in MONOLIX 4.3.2. Model selection was based on log-likelihood ratio tests and BIC. VPC and Kaplan-Meier plots were used to explore the impact of dropouts and to evaluate model performance.

Results: The best longitudinal PK/PD model involved a target-mediated drug disposition (TMDD) submodel for free and bound aflibercept (4), a kinetic-pharmacodynamic (K-PD) submodel for FOLFIRI dosing data and a tumor growth inhibition (TGI) model for the tumor size data with treatment effect driven by free aflibercept. In the joint model, the hazards of dropout and death depended on time and tumor size. The Weibull distribution best described informative dropouts while the log-logistic distribution best described the OS data. The simulated median OS were in agreement with those observed in both reference (FOLFIRI alone) and treatment (aflibercept + FOLFIRI) arms.

Conclusions: This present joint model well characterized the time course of tumor size, the treatment effect and the observed OS of patients in the VELOUR trial. By linking the full time-course of tumor size to survival and taking into account the informative dropouts, this model should provide a good prediction of clinical outcomes (e.g. survival in oncology) when performing model-based simulations of new clinical trials (e.g. new dose regimen, dose intensification in subpopulations of interest). A safety component should also be taken into account in this framework to ensure an adequate efficacy/safety balance.

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Mita Thapar Eltrombopag population pharmacokinetics-pharmacodynamics and effect on platelet counts following different regimens in Chinese adult patients with chronic primary immune thrombocytopenia

Kai Wu (1), Mita Thapar1 (2*), Colm Farrell2 (2), Siobhan Hayes3 (2), Haiyi Guo (3), Ming Hou (4), Jianping Zhang (5)
(1) Department of Clinical Pharmacology, Modeling & Simulation, GlaxoSmithKline, Shanghai, China, (2) ICON Early Phase Services, Marlow, Buckinghamshire, UK, (3) China Medicine Development, GlaxoSmithKline, Shanghai, China, (4) Department of Hematology, Qilu Hospital, Shandong University, Shandong, China, (5) Department of Clinical Pharmacology, Modeling & Simulation, GlaxoSmithKline, Research Triangle Park, NC, USA, (*) Presenting author

Objectives: The objectives were to characterize the population pharmacokinetics (Pop-PK) and pharmacokinetics/pharmacodynamics (Pop-PK/PD) of eltrombopag and to evaluate platelet count (PLTC) response following different eltrombopag regimens through simulations in Chinese adult patients with chronic primary immune thrombocytopenia (cITP).

Methods: NONMEM® program version VII level 3.0 was used for the Pop-PK and Pop-PK/PD analyses (ICON, Ellicott City, Maryland, USA). PDx-Pop® (Version 5.1) was used as a NONMEM interface. S-Plus

(TIBCO Spotfire S+® 8.2 for Windows) was used for plotting and analyzing NONMEM outputs. Model-based simulations were then performed to predict PLTC response.

Results: The Pop-PK of eltrombopag was described by a 2-compartment model with first-order absorption and elimination and absorption lag-time. The steady state exposure in Chinese patients was approximately 55% higher than the non-East Asian patients. The Pop-PK/PD of eltrombopag was described by a 4 transit compartments model where the increase in platelet production rate was linearly related to the plasma eltrombopag concentration. Only 11% of patients were identified as non-responders to eltrombopag. Simulations showed that about 70-80% steady state PLTC response was achieved at Week 2, and the proportion of patients achieving a PLTC of 50-150 x 10^9/L was comparable between Week 2 and 6 following 12.5, 25, 50, and 75 mg once daily (QD) dosing. 25 mg QD had a more balanced response than 12.5, 50, and 75 mg QD in efficacy (proportion of patients with a PLTC of 50-150 x 10^9/L, 27% vs 20, 30, and 30%) and the risk of thrombocytosis (proportion of patients with a PLTC >250 x 10^9/L, 4% vs 1, 10 and 16%). Simulations of PLTCs following the dose titration regimen showed that ≥ 42% of patients achieved a PLTC of 50-150 x 10^9/L at Week 6 or later, compared to ≤30% when 12.5, 25, 50, and 75 mg fixed QD doses were given. Only ≤5% of the patients had a PLTC >250 x 10^9/L throughout 24 weeks of treatment, compared to 3, 7, 16 and 24% when the fixed QD doses of eltrombopag were given, respectively.

Conclusion: The pop-PK and PK/PD of eltrombopag in Chinese cITP patients were adequately characterized in the current analyses and were consistent with the similar analysis done in other cITP populations. The modeling and simulation results support the eltrombopag dose titration regimen with 25 mg QD as a starting dose and a 2-week titration interval in Chinese cITP patients.

Yingying Tian Physiologically based pharmacokinetic model incorporating genetic polymorphism of CYP2D6 to predict the nonlinear kinetics of paroxetine

Yingying Tian, Sebastian Frechen, Ahmed Abbas Suleiman, Uwe Fuhr
Department of Pharmacology, Clinical Pharmacology Unit, University Hospital of Cologne, Cologne, Germany

Background: Paroxetine exposure increases more than linear with increasing doses and with decreasing number of active CYP2D6 alleles, which precludes individualized dosing by simple methods.

Objectives: To develop a physiological-based pharmacokinetic (PBPK) model for paroxetine able to describe its nonlinear kinetics among different genotypes.

Methods: PK data were obtained from an open, randomized, single-dose, 2-period, crossover pharmacokinetic study with two different formulations of paroxetine involving 40 healthy volunteers. CYP2D6 genotyping was carried out for all subjects. Data were analyzed using nonlinear mixed-effects modeling implemented in NONMEM V7.3.0. First step was to develop a single compartment model incorporating both inter-occasional variability and CYP2D6-mediated clearance. The structural model was then refined and transformed to a PBPK model by the introduction of physiological compartments and parameters and by incorporation of the mechanism-based inhibition process.

Results: A conventional one-compartment PK model with additional compartments for liver and enzyme and combined error model was developed. Among the covariate relationships tested, weight was identified as a significant covariate on volume of distribution of the central compartment. The model produces estimates pooled clearances according to the expected phenotype of CYP2D6*1, *2, *35 and CYP2D6 *9, *41.The model showed some underprediction for high concentrations. When temporarily removing subjects carrying the less frequent CYP2D6 alleles *9, *35 or *41 present in this study, the model was essentially unchanged.

Conclusions: The current model may serve as a promising base for further refinements. In particular, splitting of the pooled clearances into the respective clearances per underlying allele as well as a better description of the mechanism-based inhibition process need to be addressed.

Melanie Titze PK/PD modeling of biomarker modulation and tumor growth inhibition by BI 893923, a novel IGF-1 receptor inhibitor

M.I. Titze (1), O. Schaaf (2), M. H. Hofmann (2), M. Sanderson (2), S. Zahn, (2), J. Quant (2), T. Lehr (1)
(1) Clinical Pharmacy, Saarland University, Germany, (2) Boehringer Ingelheim RCV GmbH, Vienna, Austria

Objectives: The insulin-like growth factor 1 receptor (IGF-1R) plays an important role in tumor growth. BI 893923 is a novel and selective ATP-competitive IGF1R/INSR inhibitor. Aim of this work was to develop a population PK/PD model for human GEO colon carcinoma mice xenografts and to simulate the tumor growth inhibition (TGI) based on this model for different doses and schedules of BI 893923. The PK/PD model comprises the characterization of the relationship between BI 893923 plasma concentration and the biomarker phosphorylated IGF-1R (pIGF-1R) and further the evaluation of the association between pIGF-1R modulation and tumor growth.

Methods: Tumor bearing mice were treated with different doses (0-120 mg/kg p.o.) and dosing schedules (single dose (sd), multiple daily dosing (qd), or twice daily dosing (bid)) of BI 893923. Modeling was done in a sequential manner by first fitting plasma concentrations to a PK model using non-linear mixed-effects modeling implemented in NONMEM V7.3.0 [1]. The developed PK

model was linked to the pIGF-1R model and finally integrated in the tumor growth model. Model assessment was guided by common evaluation tools. Simulations of the final model with various dosing scenarios (sd, bid with intervals of 1, 4, 6, 12 hours) were done to determine the dosing regimen leading to the highest TGI.

Results: A three-compartment model with two absorption compartments for sequential fast/slow absorption and linear elimination from the central compartment best described BI 893923 PK. A turnover model was selected to describe pIGF-1R. The BI 893923 concentration in the effect compartment was linked to the inhibition of IGF-1R phosphorylation by an indirect response model. Control tumor growth was described by the Simeoni growth model [2] with an exponential growth rate of 0.0049 h^{-1} and linear growth rate of 1.24 mm^3/h. In contrast to the Simeoni model no cell death was induced but both growth rates were inhibited by the decreased pIGF-1R level as a combination of direct and time-delayed inhibition. Simulations revealed that with increasing interval for bid dosing the TGI increased.

Conclusions: The final PK/PD model described the relationship between BI 893923 plasma concentration, IGF-1R phosphorylation and tumor growth very good. Simulations suggest a bid dosing with an interval of 12 hours as the most effective one. The developed model is considered to be a predictive tool for the human therapeutic dose estimation.

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Huybrecht T'jollyn The effect of albumin redistribution on the PK of highly bound drugs: a simulation study using the Simcyp M&S platform

T'jollyn Huybrecht, Colin Pieter, Van Bocxlaer Jan, Vermeulen An
Ghent University

Objectives: : In drug therapy, the drug effect is assumed to be correlated with the unbound drug concentration circulating in the blood. In scientific literature, there's an ongoing discussion whether alterations in plasma protein levels affect a drug's unbound PK to a clinically significant effect and hence influence treatment efficacy (1, 2). In order to determine the effect of alterations in plasma albumin levels on the total and unbound PK of a drug, a simulation study in Simcyp was set up.

Methods: A virtual hypoalbuminaemic population was created in which half of the available plasma albumin was redistributed from plasma to the extracellular water surrounding the tissue cells (albumin leakage from intravascular to extravascular water) (1). A set of 4 compound files was created within Simcyp (high and low volume of distribution (Vd) and liver CLint). The change in total and unbound plasma and tissue concentrations of these compounds was assessed.

Results: Based on this simulation scenario, the effect of albumin leakage on the total and unbound PK of low/high clearance drugs

was independent from their distributional behavior. For low clearance drugs, Vtot, and CLtot increased in proportion to the change in fup (about two-fold) in hypoalbuminaemia, whereas AUC is decreased two-fold. AUCu, CLu, and unbound plasma concentration profiles are unchanged. For high clearance drugs, Vtot also increased proportionally with fup, whereas AUCtot and CLtot remained unchanged. CLu is decreased and AUCu is increased by a factor of 2, which is in line with the elevated unbound plasma concentration profiles.

Although the fup for low and high clearance drugs is doubled, the effective liver elimination is not increased. For low clearance drugs, the liver is provided with the same unbound drug input as in the normal situation, so unbound exposure is unaffected. However, since the total plasma concentration of high clearance drugs is lower in hypoalbuminaemia, non-restrictive elimination is much slower, increasing the unbound exposure to the drug.

Conclusions: In the case of 50% albumin redistribution to the extravascular space, dose reduction should only be considered for high clearance drugs for reasons of potential toxic side effects.

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Mira Tout The impact of initial metabolic tumor volume on rituximab pharmacokinetics and clinical response in patients with diffuse large B-cell lymphoma

Mira Tout (1), Guillaume Cartron (2), Olivier Casasnovas (3), Michel Meignan (4), Thierry Lamy (5), Gilles Paintaud (1,6), David Ternant (1,6)

(1) CNRS UMR 7292 GICC, Université François Rabelais, Tours, France, (2) Département d'Hématologie, CHRU de Montpellier, Montpellier, France, (3) Département d'Hématologie, CHU de Dijon, Dijon, France, (4) Département de Médecine Nucléaire, Hôpital Henri Mondor, Créteil, France, (5) Service d'Hématologie Clinique, CHU, Université de Rennes, UMR 917, Rennes, France, (6) Laboratoire de Pharmacologie-Toxicologie, CHRU de Tours, Tours, France

Objectives: Rituximab is a chimeric anti-CD20 monoclonal antibody that has profoundly improved the treatment of B-cell malignancies. High variability in clinical response to rituximab is partly explained by pharmacokinetic (PK) variability [1, 2]. An inverse correlation between rituximab concentrations and tumor burden was observed in the pivotal study [3]. Here we aimed to describe rituximab PK and concentration-effect relationship and to quantify the impact of metabolic tumor volume (MTV_0) [4] on rituximab PK parameters in patients with diffuse large B-cell lymphoma (DLBCL).

Methods: Data were available from 108 DLBCL patients who received rituximab 375 mg/m^2 IV infusions every 2 weeks for 4 cycles. PK analyses were performed using non-linear mixed-effects modeling implemented in Monolix® 4.3.2. MTV_0 was assessed with positron emission tomography (PET) at baseline. The tested covariates consisted of age, gender, body weight, height, BSA, MTV_0, and baseline leucocytes and lymphocytes levels. Logistic regression was applied to evaluate AUC, MTV_0 and other variables as predictors of response according to PET after cycle 4. Cut-off values associated with clinical response were determined by ROC curve analysis.

Results: A 2-compartment model with combined residual error was shown to adequately describe rituximab pharmacokinetics. The final PK model estimations of typical (interindividual standard deviation) clearance (CL), central (V1) and peripheral (V2) distribution volumes were 0.0232 L/h (48.2%), 3.96 L (28.7%) and 5.32 L (27.4%), respectively. V1 and V2 significantly increased by 2- and 9-fold between extreme MTV_0 values of 0.8 and 4340 cm^3, respectively. The increase in MTV_0 was associated with lower exposure ($R^2 = 0.51$, $p < 0.0001$) and a longer elimination half-life ($R^2 = 0.58$, $p < 0.0001$). A high AUC in cycle 1 ($AUC_1 > 9667.31$ mg.h/L) was significantly associated with a better clinical response ($p < 0.001$). Simulations suggest that patients with high MTV_0 values may benefit of higher rituximab doses.

Conclusions: This study is the first to describe the tumor volume effect on rituximab pharmacokinetics in DLBCL patients using a population approach. An increase in MTV_0 leaded to a decrease in rituximab exposure. A better clinical response was observed for higher exposure. This work may allow optimizing rituximab dose according to metabolic tumor volume.

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Mirjam Trame Integrated Data Mining and Systems Pharmacology to Explore the Comparative Safety of Brand-Name and Generic Drugs

Konstantinos Biliouris (1), Mirjam N. Trame (1), Stephan Schmidt (1), Lanyan (Lucy) Fang (2), Lawrence J. Lesko (1)
(1) Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, USA, (2) Food and Drug Administration, Office of Generic Drugs, Silver Spring, MD

Objectives: Antiepileptic drugs (AEDs) have recently been at the epicenter of the controversy over generic-brand drug substitution due to purported lack of seizure control or adverse events (AEs). The objective of this work was to interrogate the comparative safety of brand-name and generic AEDs using the FDA Adverse Event Reporting System (FAERS) [1].

Methods: We have undertaken a risk-based approach to examining how the AEs from brand-name AEDs compared with the AEs from their generic product counterparts throughout a 10-year time window (2004-2014). The focus was on three AEDs, phenytoin, levetiracetam and gabapentin. First, we conducted data mining in FAERS to identify the frequency, nature and corresponding patient outcome of AEs linked with these three brand-name and generic AEDs. Next, we exploited the *Molecular Analysis of Side Effects* (MASE) [2] integrated software platform to dissect the molecular

basis of the purported AEs, to assess causality and to generate hypotheses about the mechanism of observed differences in AEs.

Results: The difference in AEs frequency between brand-name and generic AEDs was not compelling. In some instances, however, the nature of the most commonly observed AEs differed between brand-name and generic drugs. Exploiting MASE, we identified the top 20 molecular targets (CYP enzymes, transporters and pharmacological receptors) of the active pharmaceutical ingredient in the products which allowed us to elucidate hypotheses about the mechanistic origin of purported AEs but not the reasons for differences in the nature of AEs between brand-name and generic products.

Conclusions: We used a versatile and mechanistic approach that combines data mining and systems pharmacology principles to compare the AEs from brand-name and generic AEDs and to explain the reasons for differences. Our approach, when coupled with physiologically based pharmacokinetic modelling and pharmacokinetic-pharmacodynamic modelling, could be implemented by regulatory agencies for identifying the AEs of a drug and for validating whether or not purported AEs are biologically plausible.

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Nikolaos Tsamandouras Application of the MCMC Bayesian estimation method in NONMEM in the context of physiologically-based pharmacokinetic modelling.

Nikolaos Tsamandouras (1), Amin Rostami-Hodjegan (1,2), Aleksandra Galetin (1) and Leon Aarons (1)
(1) Centre for Applied Pharmacokinetic Research, University of Manchester, UK, (2) Simcyp Ltd, Sheffield, UK

Objectives: Bayesian approaches are particularly useful for population data analyses with physiologically-based pharmacokinetic (PBPK) models, as often the fitted data are insufficient to inform the estimation of all model parameters and prior knowledge needs to be utilised. In NONMEM 7, an algorithm for MCMC Bayesian analysis is available and thus may serve as an alternative to WinBUGS in which implementation of complex models has always been a challenging task. The purpose of this work is to evaluate the performance of the Bayesian MCMC method in NONMEM in the specific context of PBPK modelling.

Methods: Diazepam population PK data that have been previously successfully analysed in WinBUGS with a whole-body PBPK model [1] were re-analysed with the Bayesian MCMC method in NONMEM and parameter estimates between the two platforms were compared. Specifically, diazepam plasma concentrations were available for 12 individuals after a 7mg IV infusion. Prior information

from pre-clinical species (rat) was utilised to facilitate the estimation of the tissue-to-plasma partition coefficients [1]. Additional practical issues regarding application of the MCMC algorithm in NONMEM for Bayesian PBPK modelling were also explored (e.g. selection of subroutine, assessment of chain convergence). Finally, the NONMEM generated posterior distributions were superimposed with the maximum *a posteriori* (MAP) point estimates (FOCE-I in conjunction to the prior functionality) [2] to assess the degree of agreement.

Results: Comparable results were obtained across the two platforms. As expected only the model parameters to which the plasma output is sensitive were substantially updated from the priors. It was also illustrated that in complex physiologically-based systems (often stiff), the selection of the differential equation solver (subroutine) is particularly critical for the computation time of the Bayesian analysis (ADVAN13 exhibited the best performance). In addition, it was evident that MCMC convergence in such complex models should be ideally assessed with multiple-chain diagnostics (e.g. Rubin-Gelman diagnostic). Finally, it was demonstrated that the modes of the NONMEM generated posterior densities can be very accurately captured by MAP estimation in the same platform with significant reductions in computation time.

Conclusions: The results of this work are providing further confidence for future use of NONMEM for Bayesian PBPK analyses of population data.

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Takayo Ueno Exposure-Response Analysis for Daclatasvir and Asunaprevir in Japanese Subjects with Hepatitis C Virus Infection

Takayo Ueno (1), Mayu Osawa (1), Tomoko Ueki (1), Yasuhiko Imai (1), Phyllis Chan (2), Tushar Garimella (2), Timothy Eley (2), Malaz AbuTarif (2), Richard Bertz (2)
(1) Bristol-Myers K.K., Research and Development, Tokyo, Japan (2) Bristol-Myers Squibb, Research and Development, NJ, USA

Objectives: The approval of the combination therapy of Daclatasvir (DCV), Hepatitis C Virus (HCV) NS5A inhibitor and Asunaprevir (ASV), HCV NS3 inhibitor in Japan, represented the world's first approval of an interferon (IFN) and ribavirin (RBV)-free HCV treatment. The current analysis characterized the relationship between exposures of DCV and ASV and sustained virological response (SVR) in Japanese subjects who are HCV genotype (GT) 1b non-responders to pegIFNa/RBV or IFNβ/RBV, and IFN based therapy ineligible naive/intolerant receiving DUAL (DCV+ASV) and provided insight into patient covariates that are most closely associated with efficacy.

Methods: The relationship between the probability of achieving SVR at 12 weeks post treatment (SVR12) and Cavgss estimated from PPK models for DCV and ASV, was described using a logistic regression (LR) model with data from two phase 2 and 3 studies in Japanese HCV GT-1b subjects (N=265). The functional form characterization,

which describes a relationship between DCV and ASV Cavgss and SVR12 and covariates identification (demographic, laboratory, prognostic and treatment covariates) were investigated during the model development steps. Non-parametric bootstrap and visual predictive check stratified by significant covariates were used for model evaluations.

Results:A linear LR model with slopes for DCV and ASV Cavgss, and interaction between DCV and ASV was identified as the base model for SVR12. In the final model, the slope for DCV Cavgss was statistically significant, but slope for ASV Cavgss and interaction between DCV and ASV were not. Among all the covariates screened, only the presence of NS5A baseline resistance mutation (BRM) Y93H was retained as a significant covariate in the final model. There was no evidence of a clinically meaningful effect of the following covariates on SVR rate: age >= 65 years, body weight, gender, creatinine clearance, ALT level, IL28B GT, baseline viral load, patient type, cirrhosis (yes/no), Study (phase 2/3), and OATP haplotype.

Conclusions: The ER model demonstrated a shallow relationship between DCV exposure and SVR12, and a flatter and non-statistically significant relationship between ASV exposure and SVR12. The presence of the NS5A BRM Y93H was a significant predictor of lower SVR12. Overall the ER model supported the high SVR12 rates for the DUAL combination in GT-1b HCV infected Japanese subjects and no dose adjustment is needed based on any of the covariates tested.

Moreno Ursino Incorporating pharmacokinetic information in phase I studies in small populations

Moreno Ursino (1), Emmanuelle Comets (2,3), Frederike Lentz (4), Corinne Alberti (5), Tim Friede (6), Nigel Stallard (7) and Sarah Zohar (1)

(1) INSERM, UMRS 1138, team 22, CRC, University Paris 5, University Paris 6, Paris, France, (2) INSERM, CIC 1414, University Rennes-1, Rennes, France, (3) INSERM, IAME, UMR 1137, University Paris Diderot, Paris, France, (4) Federal Institute for Drugs and Medical Devices, Bonn, Germany, (5) INSERM, UMR 1123, Hôpital Robert-Debré, APHP, University Paris 7, Paris, France, (6) Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany, (7) Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, The University of Warwick, UK

Objectives: To review and extend existing methods which take into account PK measurements in sequential adaptive designs for early dose-finding studies in small populations, and to evaluate the impact of PK measurements on the selection of the maximum tolerated dose (MTD).

Methods: This work is set in the context of phase I dose-finding studies in oncology, where the objective is to determine the MTD while limiting the number of patients exposed to high toxicity. We assume toxicity to be related to a PK measure of exposure, and consider 6 possible dose levels. Three Bayesian phase I methods from the literature were modified and compared to the standard

continual reassessment method (CRM) through simulations. In these methods PK measurement, more precisely the AUC, is present as covariate for a link function of probability of toxicity [1,3] and/or as dependent variable in linear regression versus dose [2,3].
We simulated trials based on a model for the TGF-β inhibitor LY2157299 in patients with glioma [4]. The PK model was reduced to a one-compartment model with first-order absorption as in [5], in order to achieve a closed solution for the probability of toxicity. Toxicity was assumed to occur when the value of a function of AUC was above a given threshold, either in the presence or absence of inter-individual variability (IIV). For each scenario, we simulated 1000 trials with 30, 36 and 42 patients.

Results: Methods which incorporate PK measurements had good performance when informative prior knowledge was available in term of Bayesian prior distribution on parameters. On the other hand, keeping fixed the priors information, methods that included PK values as covariate were less exible and led to trials with more toxicities than the same trials with CRM.

Conclusions: Incorporating PK values as covariate did not alter the efficiency of estimation of MTD when the prior was well specified. The next step will be to assess the impact on the estimation of the dose-concentration-toxicity curve for the different approaches and to explore the introduction of fully model-based PK/PD in dose allocation rules.

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Elodie Valade Plasma and seminal plasma population pharmacokinetics of emtricitabine and tenofovir

Elodie Valade(1)(2), Saïk Urien(1)(2), Silvia Martinez Illamola(1)(3), Maïlys De Sousa Mendes(1)(2), Naïm Bouazza(1)(2), Frantz Foissac(1)(2), Déborah Hirt(1)(2)(3), Jean-Marc Tréluyer(1)(2)(3)
(1)Université Paris Descartes, Sorbonne Paris Cité, EA 08, (2)Unité de Recherche Clinique Paris Centre, AP-HP, Paris, France, (3)Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, Paris, France

Objectives: The aims of this study were to describe the plasma and seminal plasma (SP) pharmacokinetics (PK) of emtricitabine (FTC) and tenofovir (TFV) in HIV-1-infected men, to assess the penetration of these drugs in the male genital tract and to evaluate their impact on the detectability of seminal plasma HIV load.

Methods: HIV-positive men from the EVARIST study (ANRS EP49) with undetectable plasma viral load for at least 6 months and receiving antiretroviral therapy with FTC and/or TFV were included. FTC and TFV plasma and SP concentrations were measured by LC-MS/MS. Data were analyzed using MONOLIX software version 4.1.4. Link between drugs seminal exposures and seminal plasma HIV load detectability was explored by ROC curves and multivariate logistic regressions.

Results: For FTC, 236 plasma concentrations (122 patients) and 209 SP concentrations (117 patients) were available. For TFV, 247

plasma concentrations (129 patients) and 217 SP concentrations (123 patients) were available. FTC and TFV plasma PK were best described by two-compartment models with linear elimination. Seminal plasma was modeled as an effect compartment with different input and output constants. FTC and TFV elimination clearances increased with creatinine clearance, and TFV elimination clearance decreased with lopinavir/ritonavir co-administration. No covariates were found to explain the PK variability in seminal plasma. Emtricitabine and tenofovir AUC_{0-24} in SP were higher than in plasma (median 38.14 vs 12.95 mg.h/L for FTC; 7.00 vs 2.99 mg.h/L for TFV). Median AUC_{0-24} ratios were 2.88 for FTC and 2.27 for TFV. Only 1 % of FTC AUC_{0-24} ratio were lower than 1 (CV = 54 %) for 12 % of TFV AUC_{0-24} ratio (CV = 125 %).

Conclusions: These are the first population-models describing FTC and TFV pharmacokinetics in plasma and SP. FTC and TFV concentrations in SP were higher than in plasma. TFV penetration in the male genital tract seems to be more variable than FTC penetration.

Pyry Välitalo Morphine efficacy in mechanically ventilated preterm neonates; an item response theory analysis

Pyry A.J. Välitalo(1), Monique van Dijk(2), Elke H.J. Krekels(1), Sinno H.P. Simons(3), Dick Tibboel(4), Catherijne A.J. Knibbe(1,5).
(1)Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands; (2)Department of Pediatric Surgery and Pediatrics, Erasmus MC-Sophia Children's hospital, Rotterdam; (3)Department of Neonatology, Erasmus MC-Sophia Children's hospital, Rotterdam; (4)Department of Intensive Care for Children, Erasmus MC-Sophia Children's hospital, Rotterdam; (5)Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands

Objectives: It has proven difficult to identify and quantify analgesic efficacy of morphine in newborns. This study aimed to assess the efficacy of morphine in preterm neonates undergoing endotracheal suctioning, using item-level data from multiple pain scales and item response theory (IRT) modelling.

Methods: The data included 140 preterm and term mechanically ventilated neonates, who were randomized to receive either placebo or morphine for analgesia in a double-blind study design[1]. Open-label morphine was allowed for rescue analgesia in both groups. Pain was quantified with items from COMFORT scale (CMT),

items from Premature Infant Pain Profile (PIPP), compound scores from Neonatal Infant Pain Scale (NIPS), and VAS scores.

A previously developed PK model [2] was used with sequential IPP estimation method[3] for PKPD modeling. Graded response models of the IRT framework were used to estimate pain as a latent variable[4] based on item-level data from CMT and PIPP, compound scores from NIPS and continuous scores of VAS. Uninformative items with discrimination values less than 1 were omitted from the PKPD analysis. The effect of morphine concentrations on the latent variable was tested with linear, power and (sigmoidal) EMAX models. Additionally, gestational age, postnatal age and bodyweight were tested as covariates on the latent variable.

Results: Only behavioural items of the CMT and PIPP scales had a discrimination value >1, and thus contextual and physiological items from these scales were omitted from the analysis. Morphine concentrations were found to reduce the latent variable pain before, during, and after endotracheal suctioning ($p<0.001$); the morphine concentration required to reduce pain by one between-subject standard deviation was 60 ng/mL. Moreover, a positive linear relationship was found between postnatal age and pain ($p<0.001$), but as patients were generally included on the first day of their life, it cannot be excluded that this relation was caused by for instance duration of mechanical ventilation.

Conclusions: As IRT based modeling weighs the information content of item scores dynamically, it is statistically more powerful than an analysis based on compound scores. Thereby the use of IRT reduces the risk of false negative findings. Based on these results, we conclude that there is a modest but definite analgesic effect of morphine in mechanically ventilated neonates.

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Sven van Dijkman Optimal dosing recommendations for combination therapy in epilepsy

Sven van Dijkman (1), Willem Rauwé (1), Meindert Danhof (1), Oscar Della Pasqua (1,2,3)
(1) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, The Netherlands; (2) Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Uxbridge, UK (3) Clinical Pharmacology and Therapeutics. University College London, 29-39 Brunswick Square London WC1N 1AX United Kingdom

Objectives: Despite numerous publications showing evidence of pharmacokinetic interaction between antiepileptic drugs (AED), this information has not been used to support the dose rationale for drug combinations.[1] In this study, we apply a model-based approach to assess the impact of drug-drug interactions on the pharmacokinetics of a variety of regimens and evaluate the need for paediatric dose adjustment when AEDs are used in combination.[2]

Methods: Population pharmacokinetic models from published literature for both children and adults were used as basis for the simulation of plasma concentrations of ten individual AEDs as well as commonly used therapeutic combinations. Pharmacokinetic profiles were simulated for a hypothetical population of adult and paediatric patients. Secondary pharmacokinetic parameters (AUC, Cmax and Cmin and their ratios in combination therapy) were subsequently used to evaluate the impact of the interaction on the resulting systemic exposure. Findings in children were compared to

the results in adults, with drug levels in literature being used as reference values. R v3.1.1 was used for simulation of the demographic data, data manipulation as well as for the preparation of graphical and statistical summaries. Pharmacokinetic profiles were simulated in R v3.1.1.

Results: Hierarchical models were implemented to describe the effect of body weight and age on clearance and volume of distribution. Where available, the influence of drug combinations on clearance was also taken into account. In contrast to current practice, simulated profiles clearly show that drug-drug interactions must be characterised to allow for the use of bridging concepts and extrapolation of data from adults to children. Significant differences were found for the ratio of AUC, Cmax and Cmin in adult and paediatric population between mono- and polytherapy. Our results suggest that currently recommended dosing algorithms and titration procedures in paediatric patients do not meet bridging criteria nor ensure that appropriate therapeutic levels are achieved.

Conclusions: The use of AED combination was shown to yield significantly different average plasma concentrations, as compared to the use of single drugs. Optimisation of dosing regimen and different titration algorithms are required to ensure appropriate benefit-risk balance of the treatment, especially in the sensitive paediatric population.

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Anne van Rongen Population pharmacokinetics of paracetamol and glucuronide, sulphate and CYP2E1 mediated metabolites in morbidly obese patients

A. van Rongen (1,2), M.Y. Peeters (1), D. Boerma (3), F.W. Huisman (4), B. van Ramshorst (3), H.PA. van Dongen (5), J.N. van den Anker (6,7,8), C.A.J. Knibbe (1, 2)

(1) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands. (2) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands. (3) Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands. (4) Department of Oral & Maxillofacial Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands. (5) Department of Anaesthesiology and Intensive Care, St. Antonius Hospital, Nieuwegein, The Netherlands. (6) Intensive Care, Erasmus MC Sophia Children's hospital, Rotterdam, The Netherlands. (7) Division of Clinical Pharmacology, Children's National Medical Center, Washington DC, USA. (8) Department of Paediatric Pharmacology, University Children's Hospital, Basel, Switzerland.

Objectives: Paracetamol is a widely used analgesic and is mainly metabolized via glucuronidation, sulphation and to a minor extent by CYP2E1, with the latter being responsible for hepatotoxicity. In obese patients, CYP2E1 activity is reported to be induced, thereby potentially changing the safety profile of paracetamol. The aim of this study was to determine the pharmacokinetics of paracetamol

and its metabolites (glucuronide, sulphate, cysteine and mercapturate) in morbidly obese patients.

Methods: Twenty morbidly obese patients (mean total body weight (TBW) of 142 kg (106-193.1 kg) and mean BMI of 46.2 kg/m^2 (40-55.2 kg/m^2)) participated in the study. All patients received 2 gram of intravenous paracetamol. Fifteen blood samples were collected per patient until 8 hours post dose and one sample was collected at 24 hours. Population pharmacokinetic modeling and covariate analysis was performed using NONMEM. Paracetamol cysteine and mercapturate metabolites were modeled in one compartment (1).

Results: A one compartment model for paracetamol, paracetamol glucuronide, paracetamol cysteine & mercapturate and a two compartment model for paracetamol sulphate best described the data. For the glucuronide and the cysteine & mercapturate metabolites, a transit compartment model was identified to capture the delay in formation. The formation clearance of the CYP2E1-mediated cysteine & mercapturate metabolites (population mean (RSE%) of 0.0185 L/min (15%)) and central volume of distribution of paracetamol (67.1 L (3%)) increased linearly with lean body weight ($p<0.001$) and body weight ($p<0.001$), respectively. While male patients were heavier than female patients, gender was identified as covariate for the formation clearance of the glucuronide metabolite (0.356 L/min (8%) vs 0.213 L/min (5%) for male vs female, $p < 0.001$) and for the elimination clearance of the cysteine & mercapturate metabolite (0.57 L/min (22%) vs 0.24 L/min (17%) for male vs female, $p< 0.001$). No other covariates were identified ($p>0.05$).

Conclusions: In morbidly obese patients, a substantial influence of (lean) body weight and gender was found on the formation clearance of the CYP2E1 mediated and glucuronide metabolites and central volume of distribution of paracetamol. As these findings may potentially influence the efficacy and safety of paracetamol in

morbidly obese patients, further study with inclusion of non obese individuals confirming these results, is required.

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Fiona Vanobberghen Population pharmacokinetics of tribendimidine metabolites in adults with Opisthorchis viverrini in Laos

Fiona Vanobberghen (1,2), Melissa Penny (1,2), Urs Duthaler (1,2), Peter Odermatt (1,2), Somphou Sayasone (3), Jennifer Keiser (1,2), Joel Tarning (4,5)

(1) Swiss Tropical & Public Health Institute, Basel, Switzerland; (2) University of Basel, Basel, Switzerland; (3) National Institute of Public Health, Vientiane, Lao PDR; (4) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; (5) Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK

Objectives: There is a pressing need for alternative treatments against the liver fluke *Opisthorchis viverrini* [1], as there is only one registered drug (praziquantel). Oral tribendimidine is a candidate drug with high efficacy against *O. viverrini* [2]; its pharmacokinetic (PK) properties are unknown yet essential to inform dosing and drivers of cure [3].

Methods: Two phase IIa trials were conducted in Laos in 68 *O. viverrini*-infected adults receiving single oral doses of 25-600 mg, with the same methodology but study 1 used 200 mg tablets and study 2 used 50 mg tablets (known different absorption properties). Venous whole-blood, plasma and capillary dried blood spot (DBS)

were sampled frequently, and concentrations of the two active tribendimidine metabolites p-(1-dimethylamino ethylimino)aniline (dADT) and acetylated dADT (adADT) were measured. *O. viverrini* egg burden in stool was assessed at enrolment and 21 days later, with cure being no eggs. The two studies were pooled and population PK were assessed using nonlinear mixed-effects modelling with NONMEM v7. We assumed fixed renal dADT clearance of 35%, with the remainder metabolising into adADT [3]. Values below the quantification limit were treated as missing data. We include body weight with allometric scaling and assessed other covariates by visual inspection and stepwise selection. We used univariable logistic regression to assess the relationship between PK and cure.

Results: A six-transit absorption model followed by a one-compartment disposition model for each metabolite described the data well. 10 year older age was associated with 10% lower dADT clearance. Study 1 had 84% higher mean transit time, 66% higher dADT volume of distribution (V_C/F) and 583% higher adADT V_C/F than study 2.

For a 200 mg dose, the median dADT maximum concentration (Cmax) was 2,460 nmol/L at median 6.83 hours; median half-life was 4.45 hours and median AUC 22,400 nmol/L. Highest cure rates (≥55% of participants) were observed with doses ≥100 mg. Higher dADT Cmax and AUC were associated with cure (both p=0.003).

Conclusion: We have for the first time described the population PK of tribendimidine. Known differences in the 200 mg versus 50 mg tablet formulations were captured by the covariate modelling. Further studies are needed to validate the structural model and confirm covariate relationships.

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Anders Viberg A Population PK Model for Simeprevir in Healthy Volunteers and Patients

Anders Viberg(1), Klas Petersson(1), Eef Hoeben(2) and Anne Brochot(2)
(1) qPharmetra LLC, Huddinge, Sweden, (2) Janssen Research & Development LLC, Beerse, Belgium

Objectives: Simeprevir (SMV) is a once-daily second-generation hepatitis C virus (HCV) NS3/4A protease inhibitor. Here we present a population PK (popPK) model describing the temporal course of SMV concentration and use it to investigate the relationship between pharmacokinetics (PK) and a selection of baseline demographics and disease characteristics.

Methods: PK data from 2183 non-Asian and Asian healthy volunteers and HCV-infected patients from 15 different SMV studies (doses of 25-200 mg) were used for the development of a popPK model in NONMEM® [1]. Data from 14 studies were used when developing the model and quantifying the inter-individual and inter-occasion variability (IIV and IOV). The linearized covariate search described by Khandelwal *et al.* [2] was used when testing potential covariate relationships. Following inclusion of covariates, the model was used to predict the SMV PK in the last study where genotype 4-infected patients were studied.

Results: The PK of SMV was described by a two-compartment model with non-linear elimination and 3 transit compartments for

absorption. The model chosen as the final covariate model included the impact of METAVIR score on relative bioavailability (F_{rel}) and peripheral volume of distribution (V2), gender, Asian origin and ALT on F_{rel}, age on maximum elimination capacity and mean transit time for absorption. The impacts of these covariates on exposure were all minor in relation to the large IIV. The model was able to accurately describe PK in the genotype 4-infected patients not included in the model development. $AUC_{0\text{-}24h}$ (median [5th to 95th percentile]) at steady-state following 150 mg once-daily dosing of SMV in non-Asian patients (n=1225) was estimated to be 46900 µg h/L (10900-285000), while C_{0h} was estimated to be 1030 µg /L (149-9500).

Conclusions: The time course of SMV PK was described by a two-compartment model with Michaelis-Menten elimination and transit compartments for absorption. The variability in SMV exposure was large and the model suggests that the majority of this variability is associated with V2 where IIV was estimated to be 188%. The largest covariate effect was found for Asian patients with F_{rel} predicted to be 70.4% higher as compared with non-Asian patients. However, the covariate effects on exposures were very small compared with the overall variability, indicating that the clinical relevance of the effect of Asian origin, METAVIR score, gender, age and ALT on SMV exposure is limited.

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Sandra Visser Translational modelling of regular human insulin pharmacokinetics and glucose dynamics in minipig and dog

Sandra A.G. Visser (1), Craig Fancourt (1), Chandni Valiathan (2), Ester Carballo-Jane (3), Margaret van Heek (3), Martin Bergstrand (4,5), Mats O. Karlsson (4,5), Maria C. Kjellsson (4,5), Carolyn Cho (1)
(1) Quantitative Pharmacology & Pharmacometrics, Merck & Co, US; (2) Applied Mathematics, Merck & Co, US; (3) Pharmacology, Merck & Co, US; (4) Pharmetheus, Uppsala, Sweden, (5) Dep Pharmaceutical Biosciences, Uppsala University, Sweden

Objectives: To develop a foundational framework for the extrapolation of insulin kinetics and glucose dynamics from preclinical animal models to human PKPD predictions for novel insulins in comparison to regular human insulin (RHI).

Methods: Time-course insulin and glucose data were available from both diabetic and non-diabetic minipigs administered a single bolus IV injection of RHI at 5 dose levels. The dog data were generated in glucose IV clamp studies in somatostatin-infused healthy dogs. The integrated glucose-insulin model [1] was used as the starting point to describe the minipig PKPD data. The final minipig model was allometrically scaled [2] to dog using individual body weights and baseline insulin and glucose to predict the data observed in dog, followed by re-estimation of parameters for which clamp studies were expected to provide information.

Results: For minipig**,** the two-compartment PK of RHI was independent of disease state. The data did not show saturable insulin-dependent elimination. Glucose elimination was described by both an insulin-independent and an insulin-dependent pathway, which was 5 times higher in non-diabetic than in diabetic minipigs. Also, the effect of glucose on its own production also differed between diabetic and non-diabetic minipigs. RHI PK in dog, using the allometrically scaled final minipig model was 50% over-predicted. When parameters were re-estimated from the dog data, the model provided a reasonable fit. Several glucose parameters changed compared to the minipig model, with insulin-independent glucose clearance estimated to be 3.7 times higher in dogs compared to minipigs. Also, RHI clearance was found to be 30% higher in dog than in minipig. In comparison to literature clinical RHI data, the dog model could predict PK and PD for RHI in healthy human subjects, up to therapeutic concentrations. Similarly, the diabetic minipig could predict RHI PD in T1DM patients albeit with a 30% under prediction of RHI CL.

Conclusions: In summary, an integrated PKPD model of glucose and insulin after administration of RHI was successfully developed from minipig data, applied to the dog clamp data, and extrapolated to human. This model builds a foundational framework for the extrapolation of insulin kinetics and glucose dynamics across species, and can be applied for human PKPD predictions for novel insulins in comparison to RHI.

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in rats, PAGE 21 (2012) Abstr 2540 [www.page-meeting.org/?abstract=2540]

Swantje Völler Comparison of current dose-reduction schemes for doxorubicin in young children using a recently developed population pharmacokinetic model

Völler, S.(1); Boddy, A.V.(2); Boos, J.(3); Krischke, M.(4); Würthwein, G. (4); Hempel G.(1)

(1) Westfälische Wilhelms-Universität, Institut für pharmazeutische und medizinische Chemie, Klinische Pharmazie, Corrensstraße 48, 48149 Münster, Germany, (2) Northern Institute for Cancer Research, Paul O'Gorman Building, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK; present address: Faculty of Pharmacy, University of Sydney, Sydney, NSW 2006, Australia, (3) Universitätsklinikum Münster, Klinik und Poliklinik für Kinderheilkunde, Pädiatrische Hämatologie und Onkologie, Funktionsbereich Pädiatrische Hämatologie und Onkologie, Albert-Schweitzer-Straße 33, 48149 Münster, Germany, (4) Universitätsklinikum Münster, Centre for Clinical Trials, ZKS Münster, Von-Esmarch-Straße 62, 48149 Münster, Germany

Objectives: Knowledge on the pharmacokinetics (PK) of doxorubicin, especially in very young children (<2 years), is extremely limited. As doxorubicin was featured on the European Medicines Agency priority list for studies on off-patent paediatric medicinal products, a phase II PK study investigating a possible age-dependency in the clearance (CL) of doxorubicin in children was conducted (EudraCT-Nr: 2009-011454-17). The population PK

(popPK) model built within the study was utilized in order to review current dosing concepts in children and to propose a model-based dose recommendation aiming at an equal exposure, calculated as area under the concentration-time-curve (AUC), in patients of all ages.

Methods: A three compartment model for doxorubicin, linearly scaled on BSA, with an additional power function for age on the CL, was developed in NONMEM 7.2®, based on samples from 2 administrations in 101 patients. Sets of 3 different hypothetic children of the same age were generated, one child on the 5th percentile of height (HT) and weight (WT), one child on the 50th percentile of HT and WT and one child on the 95th percentile of HT and WT [1]. The effects of five different currently applied dose adjustment schemes, based on age, WT or a combination thereof, were compared to the dose reduction scheme developed using the popPK model of our recent study. In order to study the effects of the developed scheme in the real-life patients, the empirical Bayesian estimates of the clearance of each study patient were used to calculate the resulting AUCs for the proposed dose reduction.

Results: The comparison of dose reduction schemes in hypothetical patients showed that the cut-off times for the termination of dose reduction were highly variable, e.g. between one year and slightly below three years in children on the 5th percentile of HT and WT. Furthermore, recommended doses in the same child differed up to 33% between schemes. When compared to the model-based recommendation, WT-based dose reductions performed slightly better than proportional reductions (i.e. 67 or 75%). However, our model proposes a continuous dose reduction that also affects children above three years. The application of the dose reduction scheme to our study population shows that AUC is adequately balanced in all age groups.

Conclusion: Current dose reduction schemes in the very young lead to inconsistent exposure. Our model might help to develop a general dose-reduction formula for this population.

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Johan Wallin Overall survival and change in tumor size in squamous NSCLC in relation to Necitumumab exposure

Johan Wallin, Amanda Long, Emmanuel Chigutsa
PKPD&Pharmacometrics, Eli Lilly

Objectives: This work aimed at defining the exposure-response of Necitumumab in the SQUIRE study, a 2nd generation human IgG1 monoclonal antibody that specifically blocks the ligand binding site of epidermal growth factor receptor (EGFR). Based on preclinical data, necitumumab potentially acts by inhibiting tumor growth, angiogenesis, and anti-apoptotic mechanisms.

Methods: To increase predictability and facilitate extrapolation, an integrated model for tumor size dynamics and OS was developed. Data from both necitumumab and control patients were utilized to create the model. Change in tumor size was determined from a summation of tumor growth and shrinkage. Various growth models were tested including linear, exponential and Gompertz growth; a first order process was used to describe tumor shrinkage. Development of resistance to therapy was tested by means of a time-dependent reduction in the first order process of tumor shrinkage. Tumor size at any time during treatment was then tested as a predictor of the hazard of death at the corresponding time in a model simultaneously describing OS and CTS. OS was described using a time to event modeling approach with the

Stochastic Approximation Expectation-Maximization (SAEM) estimation algorithm. Necitumumab drug effect was evaluated both as a direct inhibitory function on tumor growth, as well as directly on OS [1]. Various hazard models were tested including exponential, Weibull, Gompertz, combined Weibull and Gompertz, and log-logistic distributions of event times.

Results: The model that best described change in tumor size was comprised of linear growth and first order shrinkage [2]. The time to event model that best described the OS was a combination of Weibull and Gompertz functions for the hazard; tumor size was the most significant predictor. ECOG status at baseline was found influential. The drug effect was estimated as a fractional decrease in the baseline hazard for OS and as a fractional increase in the first order shrink rate of the tumor (separate Emax and EC50). Individuals with higher concentrations of necitumumab had improved efficacy; however, 99.6% patients had exposures above the EC50; population median exposure was close to Emax.

Conclusions: The model sufficiently describes the tumor growth dynamics and time of death in the population studied. Model estimates indicate patients treated with recommended dose of necitumumab obtain benefit.

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Chris Walsh Use of a physiologically-based pharmacokinetic modelling and simulation approach to rationalise actinomycin D dosing in paediatric oncology

Christopher Walsh (1), Jennifer Bonner (1), Alan Boddy (2), Trevor Johnson (3), Sibylle Neuhoff (3), Gareth Veal (1)
(1) Northern Institute for Cancer Research, Newcastle University, UK; (2) Faculty of Pharmacy, University of Sydney, Australia; (3) SimCyp Limited, UK.

Purpose: To use physiologically-based pharmacokinetic (PBPK) modelling and simulation in the prediction of the pharmacokinetics of actinomycin D in children, especially those less than one year of age who are at most risk of toxicity from the drug. Actinomycin D is an antibiotic used in the treatment of Wilms tumour and rhabdomyosarcoma in children. Despite being in use for over 40 years, very few studies have been conducted to characterise its pharmacokinetics. In particular the paucity of data available for very young children makes it hard to develop a sound rationale for dose selection in these patients.

Methods: The project is being carried out using the PBPK modelling and simulation software Simcyp version 13.1 (Simcyp Ltd., Sheffield, UK). Log P, pKa, blood to plasma ratio, cell monolayer permeability and p-glycoprotein transport data were determined in house and combined with data sourced from the available literature, including

information on renal and biliary clearance, to generate an actinomycin D compound file. For the simulation of clinical trial data, information was taken from previous work by Hill *et al*. (2014)[1] who studied 117 patients 2 actinomycin D intravenously. The population was split into three age categories: 1-6, 6-10 and 10-20 years. These age bins were further subdivided based on the dose received. Simulations were run for 26 hours following an IV bolus dose (relative to body surface area) over 3 minutes. A subset of the 10-20 year age group receiving 1.24 mg/kg actinomycin D was used to develop the model which was then tested against other age groups and adult data.

Results and conclusions: Simulations using p-glycoprotein transport information resulted in an over-prediction of drug clearance, potentially suggesting the involvement of additional transporters which were not accounted for in this model. The observed biliary and renal clearance values were not sufficient to account for total body clearance of actinomycin D and so an additional systemic clearance value was added based on fitting to observed data. Preliminary visual checks suggest a reasonable fit of the model to observed data, although the model fails to fully capture the plasma concentration variability seen at some early time points. The mean $AUC_{0\text{-}26}$ of simulated subjects is within 1.5-fold of the observed $AUC_{0\text{-}26}$ (84 ng/mL.h simulated vs. 93 ng/mL.h observed).

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Hechuan Wang A Pharmacokinetic/Viral Kinetic Model to Evaluate the Combination Treatment Effectiveness of Daclatasvir and Asunaprevir Against Genotype 1 Chronic Hepatitis C

Hechuan Wang (2), Liang Li (2), Yupeng Ren (2), Jenny Zheng (3), Gailing Li (3), Tianyan Zhou (1,2), Wei Lu (1,2)
(1) State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing 100191, China, (2) Department of Pharmaceutics, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China, (3) M&S Clinical Pharmacology, Janssen R&D, Beijing 100025, China

Objectives: To develop an integrated pharmacokinetic/viral kinetic (PK/VK) model to predict long-term virological response rates of daclatasvir (DCV) and asunaprevir (ASV) combination therapy in patients infected with genotype 1 (GT1) chronic hepatitis C virus (HCV).

Methods: A systematic publication search was conducted for DCV or ASV monotherapy or combination therapy in healthy volunteers or patients infected with GT1 HCV. A total of 635 study-level aggregate concentrations from 11 trials were used to build PK models for DCV and ASV separately. An integrated PK/VK model [1] was sequentially developed to characterize the effect of DCV and ASV on HCV viral RNA load based on 952 individual-level data from 71 patients in 4 single or multiple ascending dose studies. An Emax

function and a sigmoid Emax function were applied to describe the antiviral effect of DCV and ASV, respectively, depending on the drug concentrations at the effect compartment. The combined efficacy of DCV and ASV was based on the Bliss independence theory [2]. The PK/VK model was evaluated externally by comparing predicted virological response rates with observations.

Results: The developed PK/VK model could adequately describe both DCV and ASV PK profiles and viral load curves. EC_{50} of ASV was estimated to be 3.3 µg/L and 1.16 µg/L in GT 1a and 1b patients, respectively. DCV has a greater potency against GT 1 HCV with an estimated EC_{50} of 0.0323 µg/L and 0.0114 µg/L for GT 1a and 1b replicons, respectively. An empirical exponential function with a coefficient of 0.549 revealing EC_{50} of DCV changing over time could well describe the drug resistance in HCV GT 1a patients during DCV monotherapy. Baseline RNA was found to be a significant covariate on the loss rate of infected cells δ in a linear manner with a coefficient of -0.0514. The predicted virological response rates during- and post-treatment of combination therapy of DCV and ASV in HCV GT 1 patients are in general agreement with observed values in the external phase 3 clinical trial.

Conclusions: The proposed PK/VK model provides a useful platform for characterization of PK/PD relationships and predictions of long-term virological response rates to aid in future development of direct acting antiviral drugs.

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Estelle Watson The population pharmacokinetics of Compound X following single and multiple intravenous infusions, to healthy subjects and subjects following surgery.

Estelle Watson (1), Akash Khandelwal (1), Ronald Rosenburg (2) and Roberta Bursi (1)
(1) Pharmacometrics – Global Biometrics, Grünenthal GmbH, Aachen, Germany. (2) Global Clinical Development Strategy, Grünenthal GmbH, Aachen, Germany

Objectives: The aim of this study was to characterise the pharmacokinetics (PK) of Compound X in healthy subjects and subjects receiving Compound X following surgery, following single and multiple intravenous infusions (i.v.).

Methods: A population PK (Pop PK) model was developed using NONMEM (ICON plc v7.2) to characterise the time course of Compound X serum concentrations and its between-subject variability (BSV) derived from i.v. data, obtained from 9 clinical studies (5 healthy volunteer and 2 surgery patient studies) and in total comprised of 370 subjects from which 5764 serum samples were taken. The doses tested ranged from 1 to 80 mg. The stepwise covariate modelling (SCM) module in PsN was used to run the covariate analysis with an inclusion criteria of $p < 0.05$ and a backward exclusion criteria of $p < 0.01$. In total 13 continuous and 3 categorical demographic and physiological covariates were tested.

All 16 were tested on clearance (CL) and 4 on the central volume of distribution (Vd). Additionally the LASSO method was also used and compared with the SCM. Validations were performed on the base and final covariate models using goodness of fit, drop in objective function value (OFV) and visual prediction criteria (VPC).

Results: The PK of Compound X following i.v. administration was adequately described using a two compartment model with first order elimination, combined residual error model and a full omega block and was structurally consistent with previously published Pop PK models for oral formulations. Overall the addition of covariates caused minor (<7 %) change in the BSV of Population parameters estimates with eta shrinkage remaining < 15 % in all parameters. In the final model subject status (healthy with short or long infusion or surgery subject) and weight were incorporated in both CL and Vd, while CL additionally incorporated creatinine clearance as covariate.

Conclusions: A Pop PK model was developed using data from i.v. administered Compound X to healthy volunteers and subjects following surgery. The model described adequately the i.v. PK of Compound X. The model will be used in the future to simulate exposures for exposure-adverse event analysis.

Benjamin Weber New Insights in the Pulmonary Fate of Inhaled Drugs

Benjamin Weber (1) and Jens Markus Borghardt (2)
(1) Translational Medicine & Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany, (2) Department Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Berlin, Germany

Background/Objectives: Orally inhaled drug products are the preferred treatment options for pulmonary diseases [1, 2]. However, their pulmonary fate is often poorly understood. PBPK approaches may be an option for overcoming this knowledge gap. For inhaled drugs, however, PBPK approaches are often limited by missing *in vitro in vivo* correlation and an incomplete understanding of pulmonary PK processes, e.g. pulmonary deposition, dissolution and absorption[3-6]. Empirical modeling of PK data after intravenous (IV) and inhalational (INH) administration has recently been proposed as alternative for studying the pulmonary fate of inhaled drugs [7]. The objective of this work is to highlight how empirical modeling has recently helped to increase the understanding of the pulmonary fate of inhaled drugs [8-10].

Methods: Plasma and urine data after INH (in form of a solution via a soft mist inhaler) and IV administration of two inhaled drugs (olodaterol and tiotropium) from a total of 199 healthy volunteers obtained in six clinical studies were available. Model development was performed in a stepwise fashion for both drugs independently

(NONMEM 7.3.0). Systemic disposition parameters were fixed to estimates obtained from the data after IV administration. Oral bioavailability was assumed to be negligible for both drugs.

Results: Plasma and urine PK of both substances were adequately described by three parallel pulmonary depot compartments with associated first-order absorption processes on top of four or five compartment systemic disposition models. An extended pulmonary residence time (absorption half-lives of at least 21h) of a large fraction of the pulmonary available dose (~ 70% and 85% for olodaterol and tiotropium, respectively) was demonstrated.

Conclusions: Empirical modeling was successfully applied to increase the understanding of the pulmonary fate of two inhaled drugs. It was the first time that an extended pulmonary residence time for olodaterol and tiotropium was demonstrated in humans. This finding is particularly interesting as pulmonary absorption of dissolved drug is commonly assumed to be fast (expected absorption half-life ~ 5 – 60 min) [11] and certainly not in the range of one day. Thus, empirical modeling seems to be an attractive option for studying and improving the understanding of the pulmonary fate of inhaled drugs when adequately implemented. The additional knowledge might also be used to improve PBPK models for inhaled drugs.

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Franziska Weber Pharmacometric approach to characterize key metabolites of acetaminophen in preterm and term neonates

Franziska D. Weber (1), Henning Schmidt (2), Marc Pfister (1,3) John van den Anker (1,4)
(1) Department of Paediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel, Switzerland, (2) Novartis Pharma AG, Basel, Switzerland, (3) Quantitative Solutions LP, Menlo Park, CA, USA (4) Division of Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA

Objectives: Neonates of all gestational ages perceive pain [1]. Due to undesired side effects of opioids, acetaminophen (APAP) is used as an alternative [2]. Risk for hepatotoxicity associated with APAP [3,4]depends on its metabolism, which changes during the first weeks of life [5]. Preterm (< 37 gestational age (GA)) neonates may have less drug metabolism/elimination capacity than term (>= 37 GA) neonates. Characterizing population pharmacokinetics (PK) of APAP and its key metabolites is critical for establishing safe and effective IV dosing schemes for use of APAP in neonates.

Methods: A total of 2500 plasma samples for APAP and metabolites measurements were available from 35 neonates with gestational ages (GAs) between 23 and 41 weeks. The major metabolites, APAP-glucuronide (Mgluc) and APAP-sulfate (Msulf) were quantitated in

serum, as well as two surrogate markers of APAP-induced toxicity, (Mcys) and APAP-mercapturate (Mnac). Neonates with GAs <29 weeks were dosed 5x 15 mg/kg every 12h, whereas GAs >29 weeks were dosed 7x 15 mg/kg every 8h. Non-linear mixed effect models were applied to characterize population PK of APAP and its key metabolites.

Results: Population PK of APAP and its metabolites were described by linear metabolic formation rate constants (FRCs) and one-compartment models with linear elimination. Body weight (BW) at study beginning was found to be a statistically significant covariate on all model parameters in preterm and term neonates. Given available data, postnatal age (PNA) was a statistically significant covariate on several PK parameters in preterm but not term neonates: FRC of Msulf, Mnac, Mcys, CL of Mgluc and CLnac. In term neonates CL and volume of distribution (V) of parent drug were estimated to be 0.47 l/h and 2.98 l, respectively, and half-lives of investigated metabolites ranged from 4 to 8h. In preterm neonates CL and V of parent drug were estimated to be 0.14 l/h and 1.06 l, respectively, with half-lives of metabolites prolonged up to 30% as compared to values in term neonates.

Conclusions: For the first time the population PK of APAP and its key metabolites was characterized in preterm and term neonates. Model results suggest that PNA (in addition to BW) is affecting PK of APAP's metabolites in preterm neonates. This finding is consistent with the hypothesis that preterm neonates have less mature drug metabolism/elimination capacity than term neonates and may benefit most from organ maturation during the first weeks of life. The developed model will be applied to fine-tune APAP dosing strategies in neonates.

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Willi Weber PK of acetaminophen and its metabolites in preterm and term neonates using relevant external background information in a Bayesian approach with Stan

Sebastian Weber (2), Willi Weber (1), Franziska D. Weber (1), Henning Schmidt (2), Marc Pfister (1,3), Johannes N. van den Anker (1,4)

(1) Department of Paediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel, Switzerland, (2) Novartis Pharma AG, Basel, Switzerland, (3) Quantitative Solutions LP, Menlo Park, CA, USA (4) Division of Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA

Objectives: Drugs used in the adult population are urgently required in the treatment of pre- and term neonates. Acetaminophen (APAP) and its metabolites are well investigated in adults. In term and preterm neonates the PK information of APAP is still insufficient for choosing optimal dose regimens. Currently, iv administration of APAP is clinically investigated in neonates [1]. We obtained such study data, including concentrations of APAP and its glucuronide and sulfate metabolites in plasma. Without knowing the dose fraction formed to a specific metabolite, its volume of distribution remains unidentifiable in a NONMEM model. We employed a Bayesian approach to include extensive literature data from adults [2] into the model via the prior. This enabled calculation of all model

parameters, including formation rates and volumes. The main objective was to quantify development changes in the neonate metabolism on the PK of APAP and its metabolites.

Methods:

A one compartment model with linear elimination was used for APAP and its metabolites. Both metabolite compartments received their input as metabolized dose fraction from the parent compartment. Identified relevant external background information:

- in adults a dose fraction of 60% and 30% of APAP are renally excreted as APAP-glucuronide and -sulfate, respectively. Both of their clearances correspond to the GFR.
- '1/4' allometric scaling using body weight and maturation dependend on postmenstrual age (pma) were applied on all clearances and volumes [3].
- exponential increase with pma of glucuronide-formation, glucuronide & sulfat elimination clearance were incorporated into the model.
- exponential decrease with pma of the APAP volume of distribution

The study included in total of N=10 neonates with gestational age (GA) <=28 weeks who received 5x15mg/kg/12h and N=25 neonates with GA > 28, receiving 7x 15mg/kg/8h. Per subject on average 7.2 PK samples were obtained. We use the Bayesian software Stan for model parameter inference [4].

Results:

Full parameter sets for the parent drug and its metabolites were estimated for a reference neonate with a postmenstrual age of 34 weeks:

- elimination clearance CL[l/h/70kg]: APAP=17.1(15.7,18.7)95, APAPgluc=8.15(6.0,10.6)95, APAPsulf=7.0(5.9,8.24)95
- formation clearance CL[l/h/70kg]: APAPgluc=2.6(1.9,3.4)95, APAPsulf=12.9(11.1,14.7)95
- volume of distribution [l/70kg]: APAP=78.2(70.2,86.7)95 , APAPgluc=49.5(35.8,65.8)95, APAPsulf=28.5(24.8,32.3)95
- the maturation process of the glucuronide formation was about twice, 2.06(1.6,2.7)95, as fast as the GFR maturation process (11.9 weeks doubling time).
- the G/S formation ratio was found to increase rapidly from 1:10 for very early (pma=25) to about 1:2 for later (pma=45) neonates, drastically smaller than the adult 2:1 G/S ratio.

Conclusions: With a Bayesian approach we were able to interpret a sparse data set in the context of available background knowledge. This enabled us to obtain quantitatve results on the changing metabolism of neonates for APAP, APAPgluc & APAPsulf PK. The Stan model has been written to use NONMEM data sets, enabling rapid application in future analyses.

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Janak Wedagedera Towards more Realistic Clinical Trial Simulation: Establishing Inter-Correlations between Several Cytochrome P450 Enzyme Abundances in Human Liver

Janak R. Wedagedera (1), Khaled Abduljalil (1), Theresa Cain (1), Brahim Achour (2), Shriram Pathak (1), Mike Dunlave (3), Masoud Jamei (1) and Amin Rostami-Hodjegan (1,2)
(1) Simcyp Limited a Certara Company, Sheffield, United Kingdom; (2) Manchester Pharmacy School, University of Manchester, Manchester, United Kingdom; (3) Pharsight Corporation, 5625 Dillard Drive, Suite 205, Cary, North Carolina 27518.

Objectives: Success of clinical trial simulations greatly depends on identifying and incorporating true anatomical and physiological covariates when generating virtual populations. Recently, the inter-correlations between CYP450 (and UGT) metabolising enzymes in human liver microsomes have been reported [1, 2]. These data enable population-based PBPK models to more realistically assign CYP/UGT abundances when generating virtual subjects using Correlated Monte Carlo sampling.

This work aims at using reported data in [1, 2] to determine CYP450 enzymes covariance matrix of multivariate probability distribution function and compare the distributions against the currently generated data in Simcyp Simulator Version 14.

Methods: The marginal distributions of each CYP450 are assumed to be log-normal and are checked by obtaining normal plots for the log transformed abundance value. The correlation and covariance matrices for the whole dataset have been calculated using R Package (V 3.1.2). Eigenvalues of the covariance matrix have been tested for positivity and if negative eigenvalues occurred, then the nearest positive definite covariance matrix has been calculated. A new correlated sample has been obtained by calculating the Cholesky decomposition [3] of the nearest positive definite covariance matrix and this sample has been transformed into its original log-normal marginal distribution. A virtual population matching the real population demographics has been generated using the Simcyp Simulator V14 and the results were compared with Monte Carlo sampling data.

Results: Multivariate Cramer-Test shows the dissimilarity between the empirical distributions of the correlated and uncorrelated samples with 95% CI critical T-statistic of 141.565 vs observed: 9269.496. Kernel density estimate visually showed the differences between the two distributions.

Conclusions: Incorporation of the correlated CYP450 enzyme abundances when generating virtual subjects enables PBPK simulators to generate more realistic virtual population which can improve clinical study design and prediction of clinical outcome during drug development. Further research is needed to establish various transporters abundances inter-correlations which can have a significant impact on the drug concentration at the site of action and as a result on drug safety and efficacy.

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Thomas Wendl A whole-body physiologically-based pharmacokinetic (PBPK) Model for Itraconazole and its metabolite to predict dynamic drug-drug-interactions

Thomas Wendl, Donato Teutonico, Helen E. Hermes, Sabine Pilari, Thomas Eissing
Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, 51368 Leverkusen, Germany

Objectives: Regulatory authorities, e.g. the FDA, explicitly support PBPK model predictions for evaluating drug-drug interactions during drug development. Therefore, predefined PBPK interaction partner models are of great interest. In this study, a PBPK model for Itraconazole (ITZ), i.e. a potent competitive inhibitor of CYP3A4 is developed. Coadministration of ITZ with drugs mainly metabolized by CYP3A4 may result in increased plasma levels of these drugs. Thus, a dynamic whole-body PBPK model including both ITZ and its main metabolite hydroxy-itraconazole (OH-ITZ) was required to accurately predict drug pharmacokinetics under ITZ coadministration.

Methods: A whole-body PBPK model of ITZ and OH-ITZ in humans was established in PK-Sim® [1] using biometric data, physico-chemical and mass balance information about ITZ and OH-ITZ. The established model was adjusted to plasma concentration-time

profiles available in literature [2-4] and validated using independent data. The established model was then coupled to a previously established midazolam PBPK model in order to simulate the impact of ITZ coadministration on midazolam pharmacokinetics.

Results: The established model adequately describes published plasma concentration-time profiles for ITZ and OH-ITZ after i.v. and oral administration. Prediction of drug-ITZ-interactions is demonstrated by coupling the ITZ - OH-ITZ PBPK model to the midazolam whole-body PBPK model. Midazolam plasma concentration-time profiles under ITZ coadministration are adequately predicted by the model as competitive inhibition by both ITZ and OH-ITZ is taken into account.

Conclusions: The established ITZ - OH-ITZ whole-body PBPK model can be used to effectively predict the pharmacokinetics of drugs metabolized by CYP3A4 under ITZ coadministration.

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Paul Westwood Population pharmacokinetic meta-analysis of ramucirumab in cancer patients

Paul Westwood (1), Lisa O'Brien (2), Ling Gao (2), Michael Heathman (2)
(1) Eli Lilly, Windlesham, UK; (2) Eli lilly, Indianapolis, US

Objectives: Ramucirumab (RAM) is a monoclonal antibody (mAb) that binds vascular endothelial growth factor receptor 2. The aims of this analysis were to characterize the pharmacokinetics (PK) of RAM in cancer patients, characterize the inter-patient variability (IIV), and investigate patient factors that may influence RAM disposition.

Methods: The dataset consisted of 497 patients with 2782 observations from eight studies (Phase 1/1b, 2 and 3). A range of disease states were represented: gastric cancer (80.5%), non-small cell lung cancer (8.2%), colorectal cancer (1.6%), breast cancer (2.2%) and other tumour types (7.4%). RAM was administered as an IV infusion over approximately 1 hour, at either 8 mg/kg every 2 weeks or 10 mg/kg every 3 weeks. PK sampling varied between studies.
A pharmacostatistical model was first developed using the criteria of model plausibility, minimum objective function value (MOF), agreement between predicted and observed, magnitude and randomness of residuals, and precision of parameter estimates. Demographics, cancer indication, dose, renal function, hepatic status, and other laboratory values were assessed as covariates

using forward selection and backward elimination. Due to the nature of other mAbs, time and exposure dependency were also investigated. Covariates were considered significant if they decreased IIV in the relevant parameter by ≥5% and reduced the MOF by ≥6.635 ($p<0.01$) in forward selection and ≥10.828 ($p<0.001$) in backward elimination. The model was evaluated using objective function mapping and visual predictive check. All analyses were performed using NONMEM (Version 7.2).

Results: The PK of RAM were well characterized by a two-compartment model with IIV estimated on all parameters and covariance between CL and V1. A combined additive/proportional error model was used. No covariates were found to satisfy the predefined criteria, and no relationship was found between dose level or time and RAM PK. Mean (%CV) PK parameters derived from post-hoc parameter estimates were: CL 0.0140 L/hr (29.8%), Vss 5.5L (14.4%), and terminal half-life 15 days (24.1%).

Conclusions: The final model adequately described the time-concentration profile of RAM in patients with a range of cancer indications. The PK parameters were consistent with those obtained from non-compartmental analyses of Phase 1 and 2 studies, with the exception of half-life. Simulation using the model confirmed the appropriateness of weight-based dosing.

Sebastian Wicha Evaluation of the delta-method to efficiently compute probability of target attainment of antibiotics

Sebastian G. Wicha (1), Alexander Solms (2), Wilhelm Huisinga (2) and Charlotte Kloft (1)
(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) Institute of Mathematics, University of Potsdam, Germany

Objectives: To assess therapeutic success or failure of antibiotic treatments pharmacokinetic (PK)/pharmacodynamic (PD) breakpoints are frequently used in probability of target attainment (PTA) analyses. For this purpose, commonly time-consuming Monte-Carlo simulations (MCS) considering the interindividual variability in PK are performed. PTA is then calculated as the fraction of scenarios for which the PK/PD breakpoint is attained.
For an empiric probabilistic dosing module in the recently developed web-based dosing support software TDMx (www.tdmx.eu) [1], MCS was found too slow for convenient usage. Instead, interindividual variability bands around the typical PK profile and resulting PTAs were to be approximated by use of the delta-method (DM) and results were compared to conventional MCS.

Methods: A published population PK model of the beta-lactam antibiotic meropenem (MER) [2] was used for evaluation of MCS-

and DM-based PTAs. PK covariates were set to their typical values [2], serum creatinine to 0.7 mg/dL, minimal inhibitory concentration to 4 mg/L and the PK/PD breakpoint for MER to *f*T>MIC of 40% [2]. Short (1 h TID), prolonged (4 h TID) and continuous infusion (24 h) dosing regimens were assessed. Interindividual variability of the PK parameters was varied from 20% to 70% CV.
MCS-based PTAs were calculated based upon 1000 simulations each. For DM-based PTAs, the 'apparent' variance of the PK profile *var(f(ϑ,t))* was computed at each time point using the delta method with the Jacobian of the PK model *J* and the variance-covariance matrix *Ω* (*var(f(ϑ,t))=J*Ω*J^T*). With *var(f(ϑ,t))*, prediction intervals up to the 95th (in 1.25 steps) were derived for PTA calculation. Both methods were compared with respect to correlation and required CPU time.

Results: For MCS, the variability of PTA was 0.014 (SD) at n=1000 replicates. Differences between MCS-based and DM-based PTAs ranged from -0.05 and 0.03 (mean: -0.004) and were independent of the set interindividual PK variability. Both methods correlated well (R^2=0.995, DM=MCS×1.04-0.031). CPU time was ca. 1.3 sec. for DM and ca. 48 sec. for MCS for computation of a single dosing scenario.

Conclusion: DM-based computation of PTAs was in well agreement with the conventionally used MCS-based approach thereby reducing the required CPU time by > factor 35. The DM-based algorithm for PTA calculation was hence integrated in TDMx facilitating rapid empiric dosing decisions prior to initialising antibiotic treatment.

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Mélanie Wilbaux Semi-mechanistic model to characterize effects of gastric emptying on glucose absorption profiles in obese and non-obese adults

Mélanie Wilbaux (1), Bettina Woelnerhanssen (2), Christoph Beglinger (2), Anne Christin Meyer-Gerspach (2), Johannes N. Van Den Anker (1, 3), Marc Pfister (1, 4)
(1) Department of Paediatric Clinical Pharmacology, Paediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel (UKBB), Basel, Switzerland, (2) Division of Gastroenterology and Hepatology, University Hospital of Basel, Basel, Switzerland, (3) Division of Pediatric Clinical Pharmacology, Children's National Health System, Washington, DC, USA, (4) Quantitative Solutions LP, Menlo Park, CA, USA.

Objectives: Recent research indicates that dynamics of gastric emptying may be different in obese and non-obese adults and can affect both glucose absorption and glycemic control. Goal of this work was to develop a semi-mechanistic model that can be used to characterize effects of gastric emptying on glucose absorption and glycemic control in obese and non-obese healthy adults.

Methods: Data: Glucose, insulin, incretin (gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)) and gastric emptying data from 36 obese and 24 non-obese healthy adults were available. Oral glucose tolerance tests (OGTTs) were performed in each study subject with a solution containing 10g, 25g or 75g of

glucose. Blood samples and gastric emptying rates were collected at 0, 15, 30, 45, 60, 90, 120 and 180 min.
Model: A semi-mechanistic model was developed to characterize gastric emptying effects on glucose absorption and glycemic control. A population analysis was performed with non-linear mixed effects models using NONMEM 7.3.

Results: Glucose kinetics after administration of 10g, 25g or 75g glucose (OGTT) was characterized by a one-compartment model. The complex absorption profile of glucose was adequately described using individual gastric emptying profiles as time-varying covariate on glucose absorption rate. Observed insulin profiles affected both glucose production and clearance. Multiple differences between obese and non-obese subjects were identified, including: (1) a faster glucose absorption rate in obese subjects (Ka_{Obese}= 4 * $Ka_{Non\text{-}obese}$) and (2) a different insulin effect on clearance: linear insulin effect for non-obese and saturable (E_{max}) insulin effect for obese. There were no clear incretin effects on model parameters at the investigated dose levels. According to goodness-of-fit plots, glucose kinetics were properly fitted in obese and non-obese healthy adults, and visual predictive check demonstrated the good predictive performance of the model.

Conclusions: A semi-mechanistic model is useful to better understand interactions between gastric emptying, glucose absorption and glycemic control in obese and non-obese adults. Such model can be applied to investigate effects of bariatric surgery on glucose kinetics and characterize differences in glucose absorption between adults, children, infants and neonates.

Christian Woloch Development of a mechanistic PK/PD model to describe drug resistance using data from an in vitro dynamic PK/PD model.

Woloch C (1,2,3), Ba B (4), Benay S (1), Marouani H (1), Iliadis A (1)
(1) Laboratory of Pharmacokinetics, Faculty of Pharmacy, Aix-Marseille University, France (2) Laboratory of Pharmacology, Dupuytren Hospital, Limoges, France (3) Laboratory of Pharmacology, European George Pompidou Hospital, Paris, France (4) Laboratory of Pharmacokinetics, Faculty of Pharmacy, Bordeaux, France

Objectives: Multidrug resistant S.*maltipholia* (Sm) has emerged as an important global opportunistic pathogen associated with high mortality rate [1]. In vitro dynamic PK/PD models, commonly used to assess antibiotic efficacy, could provide valuable information on optimal dosing strategies allowing reducing the emergence of drug resistance [2]. The aim of this study is to develop a mechanistic PK/PD model to characterize Sm resistance against two fluoroquinolones (FQ), ciprofloxacin (CIP) and moxifloxacin (MOX). Performance of the PK/PD model will be compared to two already published semi-mechanistic models (SMM), SMM1 [3], SMM2 [4].

Methods: Human PK profiles of CIP (750mg/12h) and MOX (400mg/24h) were simulated in an in vitro dynamic PK/PD model during a 48h experience on three Sm strains [5]. For each experiment, the PK profile of drugs and the bacterial growth kinetics

with or without FQ were fitted simultaneously. PK/PD parameters were estimated using MATLAB (R2011b).

Results: Three bacterial subpopulations were considered in the PD model with sensitive, quiescent and resistant bacteria compartments to describe acquired or innate resistance. A Gompertz model was used for bacterial growth. FQ bactericidal effect was described by a derived Emax model which involves a Heaviside step function to link FQ bactericidal effect with a threshold FQ concentration. To account for the delay of the resistant mutant growth (innate resistance) or emergence (acquired resistance) and to link this delay with FQ concentration, a "time to resistance model" was developed.

Except SMM1 with RMSE up to 50% on the 6 experiments, SMM2 and the model here developed give acceptable bactericidal kinetics fitting (RMSE < 30%) respectively in 3 and 4 experiments. MOX effect delay is shorter and MOX is twice more effective than CIP on sensitive and resistant subpopulation. Moreover, the time to resistant model indicates that growth resistant subpopulation is delayed with MOX.

Conclusions: The PK/PD model here developed seems to be more informative on resistance characterization than previously published models. Flexibility of this model is oriented for pre-clinical phase development of antibiotics.

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Dan Wright Allopurinol dosing in patients with renal impairment

Daniel F.B. Wright (1), Stephen B. Duffull (1), Tony R. Merriman (2), Murray L. Barclay (3), Lisa K. Stamp (3)
(1) School of Pharmacy, (2) Department of Biochemistry, (3) Department of Medicine, University of Otago, Dunedin (1,2) and Christchurch (3), New Zealand.

Objectives:

1. To explore factors that predict allopurinol response in patients with gout.
2. To determine the probability of achieving the recommended plasma urate of ≤0.36mmol/L under the current renal dosing guideline [1]
3. To predict the maintenance doses required to achieve the target plasma urate.

Methods: The data were sourced from five studies (summarised in [2]). A population analysis was conducted using NONMEM® v.7.2. Covariates analysed included renal function, body size, sex, race, concomitant drugs, and renal transporter genotype. The final PKPD model was implemented in MATLAB (2014a). Stochastic simulations were performed under two scenarios; 1) using doses recommended by the current renal dosing guideline, and 2) using daily doses sufficient to achieve target plasma urate concentrations in >75% of simulates.

Results: A total of 1135 oxypurinol and 1178 urate plasma concentrations from 134 patients were available for analysis. A one compartment PK model with first order absorption and elimination was the best fit to the oxypurinol data. A simple direct effects (Emax) model provided an adequate description of the steady-state plasma urate data. A turnover model for urate did not provide a better description and was unstable. Renal function (CL), diuretic use (CL, Emax, baseline urate), and body size (CL, V) were found to be significant covariates. Under the maximum allopurinol doses currently recommended for renally impaired patients, the probability of achieving plasma urate concentrations ≤0.36 mmol/L for a 70kg patient not taking diuretics was 12%, 29%, 44%, 56% , and 64% for CLcr values of 20, 40, 60, 80, and 100 mL/min respectively. Diuretic use and increased body size were found to be primary determinants of maintenance dose requirements. Dose requirements were found to increase approximately 2-fold over a 3-fold range of weights and were 1.25-2 times higher in those taking diuretics. Renal function had only a relatively minor impact on allopurinol dosing. The model performed well when evaluated against external urate data.

Conclusions: A population PKPD model for allopurinol was developed. Simulations from the model support the contention that CLcr-based dosing for allopurinol will result in suboptimal treatment. The PKPD model provides a means of predicting allopurinol maintenance dose requirements for individual patients.

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Kehua Wu Genome-wide interrogation of FEV1 longitudinal model in asthmatic children

Kehua Wu (1,2), Eric R. Gamazon (1,3), George Clemmer (4), Scott T. Weiss (4), Kelan G. Tantisira (4), Nancy J. Cox (1,3), Wei Lu (2) and R. Stephanie Huang (1*)

(1) Department of Medicine, The University of Chicago, Chicago, IL 60637, USA; (2) State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, China; (3) Institue of Genome, Vanderbilt University, and (4) Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA.

Objectives: Most genomic studies of lung function have used phenotypic data derived from a single time-point (e.g., disease/not) ignoring the dynamic progression of a chronic disease. This study aimed to characterize lung function changes over time in asthmatics and identify genetic contributors to a longitudinal phenotype.

Methods: We present a population model that captures both natural growth of FEV_1 (forced expiratory volume in 1 second) in asthmatic children and airway responsiveness to the treatments, including three different long-term treatments (budesonide, nedocromil or placebo) and single inhalation of albuterol (a bronchodilator) at each of the clinical visit. Our model was built based on the data from 1041 asthmatic children who participated in the Childhood Asthma Management Program (CAMP) [1]. This longitudinal progression model was built using population-based

nonlinear mixed-effects modeling (NONMEM) with an exponential structure and the determinants of age and height.

Results: We found ethnicity was a key covariate for FEV_1 level. African-American asthmatic children have worse observed FEV1 than Caucasians and Mexican-Americans. Budesonide treated asthmatic children had a significant improvement in FEV_1 when compared to those treated with placebo or nedocromil ($p<0.001$).

FEV_1=exp(theta1*age+theta2*height+theta3+theta4)+theta5

Where, theta4 and theta5 refer to the drug effect of short-term albuterol and long-term budesonide treatment, respectively. Theta3 is a constant.

Upon evaluating those genetic variants that are located in the strong enhancer region in human lung fibroblasts, we found that a genetic variant (rs8106664; $p=1.1x10^{-5}$) strongly associated with airway responsiveness (theta4) in these CAMP subjects.

Conclusions: We developed an integrative method that combines mixed-effects longitudinal disease modeling and genome-wide association study. This study offers a strategy to explore the genetic determinants of disease progression and treatment effects, provide a comprehensive picture of disease pathophysiology and suggest potential treatment targets.

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Christine Xu Application of physiologically based pharmacokinetic (PBPK) modeling for prediction of complex drug-drug interactions involving induction and inhibition of CYP3A4 by fedratinib

Christine Xu, Vanaja Kanamaluru
Pharmacokinetics and Pharmacometrics, Drug Disposition, Safety and Animal Research, Sanofi Bridgewater, NJ, USA

Objectives: The objective of this analysis was to predict CYP3A based drug-drug interactions for fedratinib, a JAK2-selective inhibitor.

Methods: Fedratinib is a substrate of CYP3A4 with dose- and time-dependent nonlinear pharmacokinetics (PK). In vitro, fedratinib demonstrated time-dependent inhibition of CYP3A4 and a concentration-dependent increase in CYP3A4 gene expression (induction). A PBPK model was developed to predict complex drug-drug interactions involving induction and inhibition of CYP3A4[1]. SimCYP simulator was used with inputs of physico-chemical parameters and in vitro and in vivo PK data of fedratinib. After verification, the model was applied to predict fedratinib drug interactions that had not been assessed clinically, namely with ketoconazole at a different fedratinib dosing regimen or other perpetrators such as erythromycin or rifampicin.

Results: The PBPK model simulated PK profiles of fedratinib following a single 500 mg dose in healthy subjects or repeated 500 mg once daily (QD) doses in myelofibrosis patients were consistent with the observed profiles in vivo. The PBPK model predicted increase in fedratinib C_{max} and AUC following co-administration of 200 mg twice daily (BID) ketoconazole with a single 300 mg dose of fedratinib in healthy subjects was 2.07 fold and 3.02 fold, respectively. The corresponding observed increase in the clincal study was 1.93 and 3.06 for respectively. These results confirmed the performance of the PBPK model for subsequent application to untested clinical situations. Co-administration of 200 mg BID ketoconazole or 500 mg three times daily erythromicin with a single 400 mg dose of fedratinib predicted to an increase in AUC by 2.7-fold and 2.2-fold, respectively. However, repeated administration of 400 mg QD fedratinib with the CYP3A4 inhibitors predicted a smaller increase (1.7-fold and 1.2-fold, respectively). Co-administration of 600 mg QD doses of rifampin with a single 400 mg dose and repeated 400 mg QD doses of fedratinib predicted to a decrease in AUC by 5.6-fold and 1.8-fold respectively.

Conclusions: After a single dose of fedratinib, the PBPK model predicted up to a 3-fold increase or a 6-fold decrease in exposure of CYP3A4 inhibition or induction, respectively. The magnitude of effect was smaller after repeated doses and is likely due to an interplay of auto inhibition and induction of CYP3A4 by fedratinib. The PBPK model could be used to support dose recommendations when fedratinib is co-administered with CYP3A4 inhibitors or inducers[2].

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After the completion of this study, cases consistent with Wernicke's encephalopathy were reported in patients. All clinical trials involving fedratinib were halted.

Hadzliana Zainal Concentration-effect relationship of epidermal growth factor receptor inhibitor for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Hadzliana Zainal, Jill Norman, Joseph Standing, Patricia Wilson
UCL Centre for Nephrology, University College London, London

Objectives: Epidermal growth factor receptor (EGFR) upregulation has been implicated in ADPKD. Inhibition of EGFR will downregulate the downstream target activation of cell proliferation, indicated by the reduced expression of phosphorylated ERK expression. The aim of this project is to determine the concentration-effect relationship of the new generation EGFR inhibitor using PK/PD modelling.

Methods: The C57/BL6 Pkd null +/- mice were gavaged IC50 and IC10 doses on day 1 and subsequent daily dose through drinking water for 1, 2, and 4 weeks. Doses were calculated from previous in vitro proliferation assay. Plasma drug levels 1, 2, 4 and 6 hours post-gavage, terminal plasma and kidney drug concentrations were analysed for PK modelling. For the efficacy study, mice were given inhibitors at IC10 in drinking water for 3 months beginning 6- and 9-months. Kidneys were harvested for analysis of ERK expression through western blotting as PD end-point.

Results: The pharmacokinetic was best described by two-compartment distribution models with first order absorption and an

adaptation of enzyme turnover model. Estimated typical clearance (CL/F) value was 0.242 $L.h^{-1}$ and elimination rate constant (Ke) of $2.84h^{-1}$ and enzyme production rate (kENZ) of $0.043h^{-1}$. The stability of the model and predicted performance were confirmed by bootstrap method and numerical predictive check.

Conclusions: Based on experimental mice data and in vitro parameters, the model provides a useful tool to quantify the estimated antiproliferative effects and to propose an optimal dosing regimen in mice. Subsequently, biomarker of proliferation is used to relate the pharmacodynamics to the pharmacokinetic model for extrapolation into human use.

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Stefano Zamuner Modelling development for count data: NONMEM vs R

Stefano Zamuner, Tarjinder Sahota, Lia Liefaard
Clinical Pharmacology Modelling and Simulation, GSK, UK

Objectives: To explore key modeling development features for count data analysis using R and NONMEM including data exploration and model diagnostics.

Different models can be applied to count data; the simplest model assumes a Poisson distribution, where the mean is equal to the variance (equidispersion) [1]. If the variance is greater than the mean, the data is considered overdispersed, which can be modelled in multiple ways, e.g. inclusion of a between subject variability (BSV) term on lambda (mean of counts) when repeated observations are available, or with a Negative Binomial distribution [2, 3]. The current work provides recommendations for simulation and estimation of different count data distributions in R and NONMEM including model diagnostics.

Methods: Data were simulated using R (*rpois* function). Two different cases were explored: a) repeated observations with constant hazard and BSV in lambda (assuming CV of 30% or 100%) b) a dose response model where the hazard is a function of the dose (Emax model). Model fitting was performed with Poisson, Negative Binomial and Poisson with BSV (mixed-effects model) models, using the R functions, *glm*, *glm.nb* and *glmer* ("lme4" package)

respectively. The same models were fit in NONMEM 7.2.0 using the Laplacian estimation method [4]. Numerical stability, -2LL, AIC and bias in parameter estimates were compared. Bootstraps were performed to assess standard error estimates.

Results: For the first case study, the mixed effects model was consistently selected using AIC and likelihood ratio test (-2LL) as model selection criteria. This model was in line with the simulated model and suggests that model selection strategies based on log likelihood ratio tests or AIC criteria are sufficient to determine the underlying structural and random effects model.

Bias in parameter estimates was model dependent and consistent across software. In R, both *glm* and *glm.nb*, but not *glmer* appeared to significantly underestimate the standard errors of parameters as compared to bootstrap results.

Standard errors reported by NONMEM using the $COV routine provided more accurate standard errors for all models relative to R. NONMEM and R gave similar results with respect to OFV and parameter estimates.

Conclusions: The results of this analysis show that R and NONMEM are both adequate to describe longitudinal count data with constant hazard.

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Hinojal Zazo Gómez Dosage regimen evaluation of antiretroviral gold nanoparticles using Monte Carlo Simulation

H. Zazo (1, 2), A. Martín-Suárez (1, 2) and J.M. Lanao (1, 2)
(1) Department of Pharmacy and Pharmaceutical Technology. University of Salamanca, Spain. (2) Institute of Biomedical Research of Salamanca (IBSAL), Spain

Objectives: Evaluation of a dosage regimen of antiretroviral gold nanoparticles based on the PK/PD parameters estimated by Monte Carlo Simulation. An improved PK/PD model of antiretroviral gold nanoparticles previously developed has been used.

Methods: PK model describes serum nanoparticles and free stavudine released concentrations. PD model describes number of T cells (HIV target cells), number of macrophages (HIV reservoir) and virus load (from T cells, macrophages and total) . *A priori* information of PK and PD parameters were obtained from the literature . Both models are linked by Hill equation to predict the inhibition of virus replication by the antiretroviral drug inside the cell. The dosage regimens have been designed taking into account the toxic gold nanoparticles concentration (0.5 mM) and the serum stavudine concentrations achieve with the conventional drug formulations . The schedules evaluated have been: 1 mg/kg/day; 2 mg/kg/day; 2 mg/kg/2days; 4 mg/kg/2days and 3 mg/kg/3days. Monte Carlo simulations were performed to generate data of 1000

individuals during 10 years of treatment. The software package of probabilistic simulation GoldSim Pro version 10.1 (Goldsim Technology Group, Issaquah, WA, USA) has been used.

Results: PK model simulates multiple i.v administrations of antiretroviral gold nanoparticles. The nanoparticles serum concentration achieved is lower than the toxic in all dosage regimens evaluated. The serum stavudine levels achieved with the 6 mg/kg/3 days regimen are too high during more than 1 day. The others dosage regimens evaluated have therapeutic serum drug levels. According to this model, there is a high probability to have total viral load values lower than the target value (100 virions/µL) during a long time in all dosage regimens simulated. About the virus from the reservoir, the 3mg/kg/3 days regimen has the highest probability of exceeding the reservoir virus load target value (10 virions/µL). According to the number of T cells simulated, the 2 mg/kg/day regimen keeps healthy T cells/µL values (8 10^6cells/µL) with the highest probability.

Conclusions: According to the Monte Carlo simulation with the PK/PD antiretroviral gold nanoparticles model developed, the best dosage regimen evaluated is 2 mg/kg/day. This dosage regimen lets to control the viral load and the T cells number with a high probability (>70 %) during more than seven years with low drug and gold nanoparticles serum concentrations.

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Chiara Zecchin Modelling change in tumour size, survival and new lesions appearance in patients with ovarian cancer treated with carboplatin monotherapy or in combination with gemcitabine

Chiara Zecchin (1), Ivelina Gueorguieva (1), Nathan H. Enas (2), Lena E. Friberg (3)
(1) Lilly Research Laboratories, Sunninghill Road, Windlesham, Surrey, UK, (2) Lilly Research Laboratories, Indianapolis, Indiana, USA , (3) Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Objectives: Change in tumour size (CTS) is a marker of cytotoxic drug effects and there is growing interest in using this metric as primary endpoint [1], allowing earlier evaluation of treatment outcome compared to conventional metrics such as overall survival (OS). The objective of this study is to develop a model to quantify CTS during therapy and to investigate the predictive value of CTS, lesions location on trial enrolment and time of new lesion appearance on OS in metastatic ovarian cancer (MOC).

Methods: Data from a Phase III randomized study, comparing the efficacy of gemcitabine plus carboplatin versus carboplatin monotherapy in patients with recurrent MOC, was available for analysis [2]. The database included 336 patients, (173 followed up until death, 163 censored). A modelling approach was applied to characterise the CTS time course, evaluating several exposure

measures to describe drug effects. Parametric time-to-event (TTE) models were investigated to predict appearance of metastasis, OS and dropout probability as functions of CTS and other covariates.

Results: The CTS model [3,4,5] successfully described the data. Resistance to treatment was however not statistically significant and the two drugs promoted tumour shrinkage with independent additive effects. Drug exposure was incorporated as the per-cycle AUC predicted from the doses and literature PK models [6,7]. Metastasis appearance, OS and dropout probabilities were described using parametric TTE models, with a Weibull hazard increasing with time. Two time-varying covariates, describing tumour evolution during treatment, were included in the OS model: the predicted relative CTS up to week 12 (and thereafter rCTS at week12), and the appearance of new lesions. Other included (time-constant) covariates were tumour size and ECOG status at baseline. The rCTS at the end of the first treatment cycle was a significant predictor in the metastasis appearance model.

Conclusions: Metrics from the developed CTS model, quantifying the effect of carboplatin monotherapy and when combined with gemcitabine, could successfully predict metastasis appearance and OS probability in MOC. In addition to appearance of new lesions, predicted rCTS(t) up to week 12 was a significant predictor of OS probability and better than rCTS at fixed time points such as week 6 or 8. Predicted rCTS after first treatment cycle was the best predictor for appearance of new metastasis.

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Fan Zhang Application of a mixture model to lamotrigine XR bioequivalence study

Jiansong Yang, Fan Zhang
Department of Clinical Pharmacology Modeling and Simulation, GSK, China

Objectives: A single-dose, randomized, parallel-group, open-label study in 126 healthy subjects was conducted to investigate BE of 250 mg lamotrigine XR relative to the combination of 200 and 50 mg lamotrigine XR. The 90% CIs for geometric mean ratio of $AUC_{0-\infty}$ and C_{max} were (0.735, 0.956) and (0.894, 1.045), respectively. Although $AUC_{0-\infty}$ failed to meet the BE criterion (0.80, 1.25), the cause of $AUC_{0-\infty}$ difference between two groups seemed to stem from clearance (CL) rather than absorption. The aim of this study was to perform *post hoc* analyses using population pharmacokinetic (PK) modeling approach.

Methods: Pop PK model for lamotrigine XR was developed using nonlinear mixed-effect models in Monolix (version 4.3.3) by the SAEM algorithm combined with a MCMC procedure. Prior data indicated a polymorphic metabolism of lamotrigine, and a bimodal distribution of CL was also observed in this study. Thus, the Pop PK model incorporated a mixture variable on CL with two populations. Formulation (250 mg lamotrigine XR & 200+50mg lamotrigine XR) was tested as a covariate for PK parameters.

Results: The PK of lamotrigine XR was best described using a one-compartment model with 0-order oral absorption and an absorption lag time. The final mixture model separating subpopulation with different CL was able to significantly reduce the between subject variability and objective function value. CL values for subjects with slow and quick clearance were 0.573L/h and 1.96 L/h, respectively. Formulation wasn't a significant covariate for PK parameters, suggesting the two formulations were bioequivalent. Bayesian post-hoc subpopulation classification indicated there were 9 and 3 subjects with slow clearance in (200 mg + 50 mg) and 250 mg treatment groups, respectively. This uneven numbers of subjects with slow clearance between the two BE groups might explain why $AUC_{0-\infty}$ failed to meet BE criterion. Excluding the subjects with slow CL (11% of overall subjects) resulted in meeting BE criterion for both $AUC_{0-\infty}$ and C_{max}, with 90% CIs for geometric mean ratios of (0.832, 1.062) and (0.915, 1.076), respectively.

Conclusions: The AUC difference between two BE groups was a result of elimination difference, instead of absorption difference. Uneven ratios of high:low clearance subjects between the two BE groups were the main cause of failure to demonstrate BE for $AUC_{0-\infty}$. Population approach, although not commonly used in BE analysis, proved a valuable tool for *post hoc* analyses.

Jenny zheng Could we rely on p values only for characterizing exposure response (ER) relationship by a Cox model for oncology trials?

Jenny Zheng, Michael Amantea
Pfizer Inc, San Diego, CA

Objectives: The ER relationship for oncology drug is often examined using the Cox model under an assumed linear relationship between log hazard and drug exposure. When data from control (C) and experimental (E) arms are used and patient's exposure is assigned a 0 in C, a false ER relationship driven by the efficacy difference between E and C may be developed even the true ER relationship is flat. The simulations evaluated 1) the rate of a false ER relationship, 2) how to identify a false ER relationship, 3) two sensitivity analyses, and 4) the bias on effect estimates.

Methods: Simulations assumed an exponential distribution for event time and a log-normal distribution for exposures. Two scenarios were simulated: 1) a treatment effect is present but ER relationship is flat, or 2) the treatment effect is a linear function of drug exposure. The simulated event times and the status under various sample sizes and treatment effects were fitted using a Cox model. An ER relationship was considered significant if the p value for the coefficient of exposure was < 0.05 and the estimated HR was less than 1.

Results: In scenario 1, N=80, the rate of obtaining a false ER relationship was 18.9%, 45.1%, 74.4%, and 92.0%, when hazard ratios (HR) were 0.8, 0.7, 0.6, and 0.5, respectively. The rate of a false ER relationship was reduced to < 5% by the sensitivity analyses. An upward trend between martingale residual and exposure was observed when an ER relationship was false. A larger sample size resulted in a higher rate of a false ER relationship. In scenario 2, N=80, the power of deriving an ER relationship was 49.9%, 92.8%, 99.8%, and 100%, respectively, when HRs at the median concentration of E to C (HRMC) were 0.76, 0.56, 0.44, and 0.33; sensitivity analyses reduced the power of deriving an ER relationship to 15.1%, 35.1%, 61.5%, and 79.3%, respectively. When N=250, applying the sensitivity analyses, the power of deriving an ER relationship was 26.2%, 77.5%, 96.0%, and 99.4%, respectively, when HRMC were 0.76, 0.56, 0.44, and 0.33. The corresponding bias was 9.5%, 2.8%, 0.6%, and 1.0%.

Conclusions: The power of characterizing an ER relationship is reasonable when a hazard ratio was < 0.56. However, the rate of having a false ER relationship was high. Sensitivity analyses can effectively reduce the rate of a false ER relationship but also the power of charactering an ER relationship. In addition to p values, diagnostic plot and sensitivity analyses are needed for model assessment in ER analysis.

Xuan Zhou A Systems Pharmacology Model for Predicting Anticoagulant Effects of Rivaroxaban in Healthy Subjects: Assessment of Drug Pharmacokinetic and Binding Kinetic Properties

Xuan Zhou (1), Dymphy R.H. Huntjens (2), Ron AHJ. Gilissen (1)
(1) Department of Pharmacokinetics, Metabolism and Dynamics, Discovery Sciences, Janssen, Belgium, (2) Model-Based Drug Development, Janssen, Belgium.

Objectives: To investigate the application of an integrated pharmacokinetics (PK), drug-target binding kinetic (BK) and systems biology model to predict the anticoagulation effects of a factor Xa (FXa) inhibitor--rivaroxaban in healthy subjects, and to use this model to compare the effects of FXa inhibitors with different binding properties.

Methods: The systems model consists of 55 ordinary differential equations (55 species, 89 reactions, 139 kinetic parameters) that are based on the chemical kinetic theory. The simulation of drug concentration after multiple oral doses (5, 10, 20 and 30 mg twice daily) was conducted based on the reported two-compartment PK model with 1st order absorption for rivaroxaban [1]. The predictions of prothrombin time (PT) and activated partial thromboplastin time (aPTT) were based on the connection of free drug concentration, target binding kinetics and systems biology model. A sensitivity analysis was performed to evaluate the impact of individual

parameter and species on the interested state variables. To verify these results, several simulations for rivaroxaban were conducted whereby binding kinetic parameters were varied.

Results: From the simulations, rivaroxaban prolonged PT and aPTT in concentration-dependent, incremental manner through its inhibition of free and bound FXa. The predictions were in agreement with observed published data [2]. The sensitivity analysis indicated that both target binding kinetics (k_{on} and k_{off} for drug-FXa interaction) and drug concentration have high sensitivity on the response of PT and aPTT. Remarkable changes were observed in the simulated time profiles of PT and aPTT when k_{on} and k_{off} were varied 100-fold separately. This indicates the importance of binding kinetics on the pharmacodynamics effects.

Conclusions: The current model predicts the clotting time reasonably well and the role of pharmacokinetics and binding kinetics was further highlighted by sensitivity analysis and simulations. We believe that this model represents a good starting point and has potential to serve as a tool for new compound and or target selection for the management of coagulation.

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Simon Zhou Complex absorption affecting terminal half-lives leading to pseudo "flip-flop" pharmacokinetics

Simon Zhou (1), Yan Li (1), Maria Palmisano (1) and Duxin Sun (2)
(1) Celgene Cooperation, Summit, NJ, USA, (2)College of Pharmacy, Univ. of Michigan, Ann Arbor, MI, USA

Objectives: Traditional PK model with first order absorption slower than elimination generates flip-flop plasma PK-time profile in which the terminal half-lives reflects slower rate of absorption. PK studies with IV and extravascular administration of drugs rarely produce pharmacokinetic profiles that can be entirely explained and accurately modeled by a slower first order absorption. The goal is to develop a mechanistic model to describe non-first order drug release and its impact on characterization of PK properties.

Methods: A new PK model with Weibull function for absorption and saturable elimination affected by slower drug input to portal vein was adopted to capture time varying drug releases/absorption in vivo and slower drug clearance caused by slower absorption. The new and traditional PK models were coded in NONMEM and applied to human PK data of oxycodone and two Celgene drug candidates following IV and PO administration including modified release formulations[1]. Sensitivity analyses was conducted to address the relationship between modes of drug release/absorption and PK profiles plus terminal half-lives.

Results: When drug release is varying with time and hepatic drug extraction ratio is high, traditional PK model could not be applied consistently to describe drug absorption and elimination. Errors were forced on absorption or elimination parameters or both parameters when IV and PO profiles were fitted separately or simultaneously. The new PK model with Weibull function on absorption and slower clearance with slower absorption adequately describes the complex interplay between absorption and elimination in vivo. The mode and distribution of Ka over time accounted for the slow drug release and absorption components following PO administration of oxycodone and two Celgene drugs. Terminal phase of PK profile was shown to reflect slower drug clearance due to slower drug absorption, resulting in a pseudo "flip-flop" that the terminal half-life is predominately driven by slower elimination with NO actual drug absorption.

Conclusions: PK models with Weibull absorption functions and release rate-dependent clearance capture the absorption and elimination kinetics for drug with high extraction ratios . It showed no actual drug absorption during the terminal phase but slower drug clearance caused by slower release/absorption producing the appearance of flip-flop and incorrect fraction of dose absorbed estimation by traditional PK model.

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Rui Zhu Assessment of correlations between early and late efficacy endpoints to identify potential surrogacy relationships in non-Hodgkin lymphoma: a literature-based meta-analysis of 108 Phase II and Phase III studies

Rui Zhu (1), Dan Lu (1), Yu-Waye Chu (1), Akiko Chai (1), Michelle Green (2), Nancy Zhang (2), Jin Yan Jin (1)
(1) Genentech, Inc., California, USA; (2) Quantitative Solutions, Inc., California, USA.

Objectives: Demonstration of clinically meaningful improvements in progression-free survival (PFS) and/or overall survival (OS) in clinical trials of novel therapeutic agents for the treatment of non-Hodgkin lymphoma (NHL) are necessary for their regulatory approval. However, NHL trials with OS or PFS as primary endpoint require large sample sizes and long follow-up durations. In this study, correlations between early and late efficacy endpoints were assessed with published clinical trial-level data to identify potential surrogate endpoints for OS or PFS in each of the three major NHL subtypes: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL).

Methods: Phase II and phase III studies in patients with DLBCL, FL, or MCL, published from 1993 to 2013, encompassing 108 unique trials with 129 trial arms, were identified and used in the analysis. Approximately 71%, 52%, and 48% of trials in DLBCL, FL, and MCL

included rituximab-containing therapies, respectively. Correlations between efficacy endpoints were analyzed using weighted linear regression and Pearson's correlation.

Results: In trials of newly-diagnosed DLBCL, six-month PFS was strongly correlated with 2-year OS (R^2=0.81, 95% confidence interval [CI] 0.51-0.96). Six-month PFS was strongly correlated with 3-year PFS (R^2=0.89, 95% CI 0.62-0.96) in FL and was moderately correlated with 2-year OS (R^2=0.69, 95% CI 0.40-0.91) in MCL trials. Linear regression determined that a 10% increase in 6-month PFS would predict for a 22.6% +/- 1.1% increase in 3-year PFS in FL. In addition, both 6-month PFS and complete response (CR) rate showed moderate correlations with median PFS in FL trials with R^2=0.66 (95% CI 0.52-0.98) and R^2=0.69 (95% CI 0.22-0.89), respectively. However, correlations between CR rate and median OS were not evaluable due to limited data in all three NHL subtypes.

Conclusions: Six-month PFS may be a potential surrogate endpoint for 2-year OS in newly-diagnosed DLBCL and MCL and for 3-year PFS in FL, and both 6-month PFS and CR rate may be potential surrogate endpoints for median PFS in FL patients. Confirmation and validation of these correlations may facilitate early interpretation of NHL trials.

Simbarashe Peter Zvada Population Pharmacokinetics of Efavirenz Among HIV infected South Africans Across Different Age Groups Including Pregnant Women

Simbarashe Peter Zvada [1], Sherwin Sy [2], Nikolaus Bauer [3], Mirjam von Bibra [3], Daniel Clemens [3], Hartwig Klinker [3], Hartmut Derendorf [2], Bernd Rosenkranz [1]
[1] Division of Clinical Pharmacology, Stellenbosch University, South Africa, [2] Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, USA, [3] Department of Internal Medicine II, Center of Infectious Diseases, University of Würzburg Medical Center, Würzburg, Germany

Background and objectives: Efavirenz is widely used for the treatment of HIV in children and adults, including pregnant women. The existing population pharmacokinetic models of efavirenz in the literature do not include clinical data from children, adults and pregnant women. The aim of this study was to develop a model that describes the population pharmacokinetics of efavirenz in children and adults including pregnant women, and to investigate factors which may alter the pharmacokinetics of efavirenz.

Methods: Clinical data and efavirenz concentration-time data were obtained from a prospective, open label, uncontrolled study which comprised of HIV-positive adults (N=271), children (N=48) and pregnant women (N=63) in South Africa. Sparse blood sampling, consisting of one sample per patient, was conducted in patients

who are already at steady state. A validated high performance liquid chromatography method was used to determine efavirenz serum levels. NONMEM 7.3 was used for the population pharmacokinetic modelling of efavirenz. Previously published efavirenz model supplied the prior pharmacokinetic information [1] required for a full Markov Chain Monte Carlo Bayesian (MCMCB) analysis; FOCE-I algorithm also utilized prior information. Body weight was included through allometric scaling on clearance and volume parameters. A mixture model with 3 subpopulations was used to group the drug-metabolism phenotypes of these patients.

Results: The population pharmacokinetics of efavirenz was best described by a one compartment model with first-order absorption and elimination. Interindividual variability was incorporated in the oral clearance and volume of distribution. The estimates of FOCE-I were almost identical to MCMCB; the former was preferred due to shorter computational time. The clearances were 6.3, 10.1 and 16.0 L/hr for the slow, intermediate and fast metabolisers with approximately 50% of the adults grouped as rapid metaboliser and the majority from this group being females. No other covariates were identified.

Conclusions: Our model adequately described the population pharmacokinetics of efavirenz in children and adults, including pregnant women. Adults are at risk of low levels of efavirenz with females being at a higher risk. The model developed in this study could be used to simulate relevant doses of efavirenz and can potentially be used in therapeutic drug monitoring scenarios.

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Kristin Dickschen PBPK modeling to guide experimental design in preclinical and clinical development

Kristin Dickschen (1), Juergen Jaeger (1), Meike Hutt (2), Nadine Pollak (2), Martin Siegemund (2), Oliver Seifert (2), Roland Kontermann (2), Klaus Pfizenmaier (2), Michael Block (1)
(1) Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, Leverkusen, Germany; (2) Institute of Cell Biology and Immunology, University of Stuttgart, Stuttgart, Germany

Objectives: One of the hallmarks of cancer that can potentially be addressed by oncological substances is resisting cell death [1]. Here, targeting the death receptors (DR) DR4 and DR5 with tumor necrosis factor (TNF)-related apoptosis inducing ligands (TRAIL) represents a promising approach [2, 3]. Physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) modelling provides a powerful tool to give guidance at the preclinical stage for further experiments and to assess expectations and risks for clinical development. We here present a detailed approach on how such an assessment might work in reality.

Methods: A PBPK/PD model of cetuximab targeting human epidermal growth factor receptor (EGFR) was established in mice and patients. A second PBPK model for an EGFR-targeted TRAIL fusion protein in non-tumor bearing mice was built. The PBPK

models were developed by use of the systems biology software suite including PK-Sim® and MoBi®. Specific processes included in the models are target expression, target binding, FcRn binding, target receptor availability, and receptor internalization [4]. In addition, a PD model was integrated in order to represent tumor growth dynamics. By using cetuximab as a benchmark a rationale for further development of a TRAIL fusion protein in tumor-bearing mice was developed and analyzed.

Results: The developed cetuximab PBPK model adequately describes observed plasma PK in mice, tumor-bearing mice, and patients. Moreover, tumor PK and impact on tumor growth are well reflected by the model. The EGFR-targeted TRAIL fusion protein model also describes observed plasma PK in non-tumor bearing mice adequately. For both PBPK models the impact of changes in PK on tumor growth dynamics is investigated by a detailed analysis of similarities and differences of the compounds, e.g. binding to EGFR, binding to DR4/5, and FcRn binding. These results will be used to inform future experiments of the TRAIL fusion protein, e.g. inform sampling in experiments with tumor-bearing mice.

Conclusions: PBPK/PD model-guided development of a compound has the potential to analyze potential and risks of a compound very early. By means of the presented example it was shown how such modelling approaches could provide first a consistent picture of the available biological knowledge of a new compound and second a rationale for the next steps in the development with guidance from simulations, e.g. by optimizing sampling times in experiments.

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Irene-Ariadne Kechagia A simulation study to investigate the identifiability of parameters in a minimal PBPK model structure with target binding

Irene-Ariadne Kechagia, John M. Harrold, Juan Jose Perez-Ruixo, Aris Dokoumetzidis
School of Pharmacy, University of Athens, Greece; Amgen Inc, Thousand Oaks, CA USA

Objectives: To use simulations for investigating the ability to estimate the parameters of a minimal physiologically based pharmacokinetic (PBPK) model structure with target binding.

Methods: A minimal PBPK model of target engagement was constructed to represent localized inflammation. Most organs were lumped into either tight or leaky compartments, while a third compartment was constructed to understand target binding in a diseased tissue. Target was assumed to be primarily synthesized in the interstitial space (ISF) of the diseased tissue, but also, at a lesser extent in plasma and the ISF of other tissues, eliminated systemically from the plasma space, and distribute in the tissues through lymphatics, both uptake and recycling. Drug distributes into the compartments and binds to target in all compartments, while it is eliminated from plasma. The drug-target complex can distribute among the compartments and is eliminated from plasma. The parameters to be estimated were: Drug and complex plasma clearance; target plasma clearance and initial plasma concentration;

and binding parameters. Two scenarios about the target half-life were considered, a short half-life (30 minutes, scenario A) and a longer half-life (6 hours, scenario B). The identifiability of the parameters was examined by two methods: (a) By simulating concentration time profiles with the model and attempting to estimate the desired parameters. The relative bias (RBIAS) and the standard errors (RSE) of the estimates were calculated in order to assess the accuracy and the precision of the estimation (method EST). (b) By evaluating the Fisher Information Matrix (FIM) for the true parameter values and calculating the RSEs of the parameters (method FIM). Two datasets were used: (a) with two outputs, i.e. total drug and total target in plasma, (b) with three outputs, i.e. same as in (a) plus the complex in plasma.

Results: The two methods EST and FIM produced similar conclusions, i.e. low RBIAS of EST corresponded to low RSEs in FIM and vice versa. For Scenario A, drug clearance was estimated with high precision (RSE<2%, RBIAS <1%), target parameters (RSE<20%, RBIAS <5%) and complex clearance (RSE<23%, RBIAS < 17%) were reasonably estimated but binding parameters were not (RSE>48%, RBIAS <130%). Three outputs gave better results than two, especially for target parameters and complex clearance. Similar results were drawn for scenario B (long target half-life).

Conclusions: In a minimal PBPK model structure including target binding, most parameters except the binding parameters can be estimated reasonably.

Thomas Dorlo Population pharmacokinetics and pharmacodynamics of miltefosine in mono- and combination therapy regimens for visceral leishmaniasis in East Africa

Thomas P.C. Dorlo (1,2), Anke E. Kip (2,3), Fabiana Alves (4), Jorge Alvar (4), Ahmed Musa (5), Eltahir Khalil (5), Monique Wasunna (4,6), Mats O. Karlsson (1)

(1) Uppsala University, Uppsala, Sweden, (2) Utrecht University, Utrecht, The Netherlands, (3) Netherlands Cancer Institute, Amsterdam, The Netherlands, (4) Drugs for Neglected Diseases initiative, Geneva, Switzerland, (5) Institute of Endemic Diseases, Khartoum, Sudan, (6) Kenya Medical Research Institute, Nairobi, Kenya

Objectives: Miltefosine is the only oral drug available to treat the neglected tropical parasitic disease visceral leishmaniasis, with established efficacy of a miltefosine monotherapy regimen (28 days) on the Indian subcontinent. A recent trial investigated efficacy of this 28-day regimen (2.5 mg/kg/day) in an East African population (Sudan and Kenya) and compared to a shorter combination regimen of 10 days miltefosine following a single infusion of liposomal amphotericin B. The objective of the current analysis was to establish a PK-PD relationship for miltefosine in East African visceral leishmaniasis patients in Sudan and Kenya, focusing on the effect of miltefosine exposure on the time to recrudescent infection (i.e. relapse) using a time-to-event approach.

Methods: Plasma concentrations from 95 patients (48 monotherapy, 47 combination therapy) were included in the population PK modeling using NONMEM v7.3. Various structural, variability, covariate and error models were assessed using FOCE-I. BLOQ data were handled using the M3 likelihood-based method. Laplacian estimation was used to estimate parametric survival functions on the time to relapse data. Various summary PK parameters ($AUC_{0\text{-}EOT}$, Time>EC50, Time>EC90), normalized within each treatment arm to allow simultaneous analysis, were evaluated as hazard-changing covariates.

Results: A two-compartment population model with first-order absorption fitted the miltefosine PK data adequately. Relative bioavailability was found to be decreased (-73%, RSE 3.1%) during the whole first week of treatment for the monotherapy arm but only on the first day of the shorter combination regimen. Time to relapse of infection could be described using a constant baseline hazard. A Weibull function did not improve the fit. Only normalized Time>EC90 improved the model significantly ($p<0.05$) when added in a sigmoidal maximum effect function on the baseline hazard (baseline 1.7 relapses/year, RSE 69.5%). The additional inhibiting effect of liposomal amphotericin B on the relapse hazard was estimated at 58% (RSE 19.2%).

Conclusions: The here established PK-PD relationship for miltefosine will be useful in informing the PK target-to-attain to further select new miltefosine dosing strategies in combination regimens for visceral leishmaniasis in East Africa.

Anne-Gaelle Dosne Determination of Appropriate Settings in the Assessment of Parameter Uncertainty Distributions using Sampling Importance Resampling (SIR)

Anne-Gaëlle Dosne (1), Martin Bergstrand (1), Mats O. Karlsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Sampling Importance Resampling (SIR) [1] has been proposed as a method for assessment of parameter uncertainty without the need for repeated parameter estimation and making no assumptions regarding the uncertainty distribution [2]. A number of questions are likely to arise when performing SIR. The objectives of this work were to develop criteria to select appropriate settings for the SIR method in terms of number of initial samples and proposal uncertainty distribution, as well as to investigate the impact of replacement on SIR results.

Methods: SIR was performed using NONMEM 7.3 on three real data examples [3-5] with 2000, 4000, 6000, 8000 and 10,000 initial vectors, i.e. 2, 4, 6, 8 and 10-fold the number of resampled parameters (1000 in this case). Initial parameter vectors were sampled on inflations or deflations of the asymptotic covariance matrix, for which all variances were multiplied by factors of 0.5, 0.75, 1, 1.5, and 2 while correlations between them remained unchanged. Parameter vectors were allowed to be resampled with

no, limited (to 5 times) or unlimited replacement. dOFV quantile distribution curves of the resampled parameters, the value of the integration of these curves between the 2.5th and 97.5th quantiles ($dOFV_{int}$) and the value of importance ratios (IR) over parameter value of the initial samples were investigated as criteria potentially qualified to judge the appropriateness of SIR settings.

Results: The convergence of dOFV quantile distributions and their location in relationship to the reference chi-squared distribution was used as a graphical indicator of when a sufficient number of initial samples was reached and whether the proposal uncertainty was appropriate. $dOFV_{int}$ was used to confirm this quantitatively. Trends in IR over parameter plots enabled to assess potential needs for inflation on the parameter level. Limited replacement was shown to increase SIR efficiency.

Conclusions: Quantitative and qualitative criteria to determine whether the number of initial samples and the proposal uncertainty distribution are appropriate when using SIR were developed. These criteria are easy to use and will facilitate reliable use of the SIR method. SIR is readily implemented in PsN [6] and automation of the choice of initial settings based on the developed criteria will be considered.

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Stephen Duffull An approximation to the solution of systems of nonlinear ordinary differential equations in pharmacokinetics-pharmacodynamics

Stephen Duffull (1), Gareth Hegarty (1,2)
(1) School of Pharmacy, University of Otago; (2) Department of Mathematics and Statistics, University of Otago, New Zealand

Objectives: PK and PKPD models are often formulated as systems of ordinary differential equations (ODE). The most common nonlinearity in PK is due to Michaelis-Menten processes but other nonlinear structures are common in PKPD. Due to the nonlinearity it is not possible to solve these systems, except in the simplest cases, in closed algebraic form and iterative time-stepping algorithms are employed. These algorithms, e.g. the Runge-Kutta methods, although very effective general solutions may be slow, are prone to imprecision, provide solutions at discrete time points and require knowledge of the stiffness of the system. In this work we propose a rapid iterative solution that is exact to any arbitrary level of accuracy and is continuously differentiable over time.

Methods: If we have an ODE of the general form dy/dt=f(t,y)+A(t,y)y with defined initial conditions, then this system can be linearised to a time-varying linear system by plugging in our previous value of y{n-1} as the predictor of our updated value of y{n}, such that:

dy{n}/dt = f(t,y{n-1}) + A(t,y{n-1})y{n}.

Here we can see that the system is no longer nonlinear as the functions f and A do not depend on the current iteration of y{n}. The time-varying linear solution can now be solved using standard procedures such as integrating factors and (if needed) Gauss-Legendre quadrature.

This general method is applied to a first-order input Michaelis-Menten output model.

Results: The starting values of y for the times of interest were set to that provided by a linear first-order input-output system (i.e. when n=1, y{n-1} was given by the linear system). The solution is provided for 5 Gaussian quadrature steps with 7 iterations of the iterative linearization. It was shown that the relative error for successive linear approximations decayed exponentially indicating the solution was convergent and at these settings the relative error was 1e-5.

Discussion: A method for solving nonlinear ODEs is presented and illustrated with a simple example. Because the solution depends continuously on time and analytical derivatives available the method is particularly amenable to estimation and optimisation problems.

Sulav Duwal Systematic in silico analysis of the efficacy of NRTIs for pre-exposure prophylaxis (PrEP) against HIV-1

Sulav Duwal(1), Max von Kleist(1)
(1) Dep. of Mathematics and Computer Science, Freie Universität Berlin, Germany

Objectives: Nucleoside reverse transcriptase inhibitors (NRTIs) are backbone compounds for modern HIV-1 treatment. They are pro-drugs, which, after intracellular phosphorylation, compete with endogenous nucleotides for incorporation into nascent viral DNA and thus prevent polymerization. Plasma- and effect-site PK are usually asynchronous and cell-specific for NRTIs, which is also true for the PD, due to their mechanism of action [1]. While the NRTIs tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) have recently been approved as PrEP compounds, we aim to assess the prophylactic utility of approved NRTIs and those that were never tested for this purpose *in silico*, when taken continuously, sporadically and on-demand [2].

Methods: We developed PK-PD models for FTC, TDF and lamivudine (3TC) and explored their efficacy in PrEP, based on stochastic simulation & analysis. Data was collected from various PK studies to link dosing, plasma- and intracellular PK for each drug. Depending on the data sources, we used different methods for parameters estimation, including non-linear mixed effect modelling. We

coupled the intracellular PK to a HIV-1 model (PD) [3,4] using the Emax equation. The latter was mechanistically confirmed for NRTIs [1]. Using PD data, we estimated the IC50 value for each drug. These values were then compared to a mechanistic approach [1] that relies on *in vitro* (enzymatic) data. An analytical formula [4] was used to compute the prophylactic efficacy based on intracellular NRTIs levels, while drug administration schemes were assessed using hybrid stochastic-deterministic simulation.

Results: For all drugs, a two compartment model with a first order absorption best described the plasma PK. The intracellular PK was captured in terms of saturable uptake & anabolism and first order elimination. IC50 values estimated from PD profiles showed remarkable agreement with mechanistically derived IC50s [1] and suggest strong potency against wild type HIV at clinically achieved concentrations. The protection level provided by 3TC, FTC and TDF relative to the absence of drug was computed.

Conclusions: The PK-PD models for all drugs adequately characterized their clinical profiles. Our approach suggests strong potency of FTC and 3TC against HIV-1 in PrEP. The mechanistic IC50 [1] may be used to assess drug potency in various target cells. In the future, co-administration and synergistic effects of NRTIs, e.g. with respect to PrEP, will be explored.

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Helena Edlund Covariate analysis of infliximab in Crohn's disease using available PK models as prior

Helena Edlund (1,2,3), Casper Steenholdt (3), Mark A Ainsworth (3), Jørn Brynskov (3), Ole Ø Thomsen (3), Wilhelm Huisinga (4), Charlotte Kloft (1)
1. Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, 2. and Graduate Research Training Program PharMetrX, Germany, 3. Dept. of Gastroenterology, Herlev Hospital, Denmark, 4. Institute of Mathematics, Universitaet Potsdam, Germany

Objectives: A substantial proportion of patients with Crohn's disease (CD) lose response to the monoclonal antibody infliximab (IFX) [1]. The pharmacokinetic/pharmacodynamic (PK/PD) relationship of IFX in CD has primarily been assessed using minimal IFX concentrations (Cmin), limiting the predictive performance [Edlund et al. submitted]. Currently, two population PK models for IFX in CD are available implementing different, non-overlapping covariates [2,3]. This study aimed to explore the PK/PD relationship, starting by assessing covariates affecting IFX clearance (CL) exploiting the prior knowledge in [2,3].

Methods: PK/PD data originated from a 20-week investigator-initiated clinical study including 69 CD patients with treatment failure to IFX maintenance therapy [4]. As dose intervention the patients received either (i) IFX with shortened dosing interval, or (ii) were treated according to an algorithm based on IFX and anti-drug

antibody (ADA) concentrations. IFX and ADA samples were drawn at weeks 0, 12 and 20 (all Cmin). Crohn's disease activity index, C-reactive protein and patient demographics were measured at weeks 0, 4, 8, 12 and 20. The two available PK models were re-parameterised and compared with respect to predictive performance, plausibility (e.g. structural model and covariate implementation). Based on structure and estimated parameter values of the priormodel, further covariate analysis were performed on CL using NONMEM 7.3.

Results: The available PK models showed good agreement of estimated parameters values of volumes of distribution and CL, both when compared internally as well as with PK traits of the monoclonal antibodies drug class [5]. The resulting prior-model was a 2-compartment model with body weight implemented according to allometric principles on volumes of distribution and CL. Due to the sparse data situation the population estimates of V1, V2 and Q as well as their covariate relationships to body weight were fixed. The estimate of CL and the IIV parameters were implemented using the PRIOR functionality. The covariate analysis confirmed characteristics earlier identified to predict differences in CL.

Conclusions: Based on data from an investigator-initiated clinical study and two published PK models we confirmed covariates identified to affect IFX CL. The resulting PK model will be used to investigate the PK/PD relationship of IFX in CD, aiming to identify the effective therapeutic range.

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Miro Eigenmann Modeling of acquired resistance under TKI treatment

Miro Eigenmann (1), Nicolas Frances (2) and Antje Walz (3)
Roche Innovation Centre Basel, Hoffmann-La Roche Ltd., Basel

Objectives: It is reported that most patients under tyrosine kinase inhibitor (TKI) treatment will eventually develop resistance versus TKI drugs [1-3]. The aim of this work is to develop a semi-mechanistic PK/PD model including a resistance mechanism under TKI treatment (Erlotinib and Gefitinib) in tumor xenograft mice.

Methods: Tumor growth inhibition (TGI) experiments were conducted in primary patient tumor (LXF A677) bearing mice receiving Erlotinib or Gefitinib treatment. The mice were randomized into treatment groups, control, 6.25mg/kg, 25mg/kg or 100mg/kg for each drug and treatment was daily orally administered for 14 days. Tumor volume was monitored over 30 days and sparse plasma PK data were collected.
A semi-mechanistic PK/PD model involving adaptive resistance mechanism was developed based on published evidence on resistance emergence after TKI administration [3]. The performance of the resistance model was compared to a simple direct effect model [4]. The model development and parameter estimation was done in Monolix v4.3.2. The models were evaluated in terms of parameter estimation precision, residual error, Akaike information criterion and visual predictive checks. Simulation analyses were performed in Berkeley Madonna v8.3.18.

Results: Pre-clinical data upon TKI treatment were better described by a model involving a resistance mechanism as compared to a simple direct effect TGI model. The resistance model suggests selection of resistant cells upon TKI treatment (acquired resistance).The initial fraction of resistant cells is assumed to be zero in treatment naïve mice. Growth rate of the resistant cell population was estimated to be 1.18 times slower than in the parental cell population. Simulations show the impact of the dosing regimen on total tumor and the emergence of the resistant cell population.

Conclusions: This modeling exercise supports and describes the dynamic of previously reported resistance upon TKI treatment. Adding a mechanism for adaptive resistance to a TGI model allows for a more precise estimation of potency parameters and to better support compound development. Estimated resistance related parameters and simulation studies are in line with findings by Chmielecki et al. [3]. This model could also be used in optimizing the administration protocol [5, 6].

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Rena Eudy Sclerostin-Mediated Osteocyte Control in Bone Remodeling: Extension of a Multiscale Systems Model to Consider New Therapies for Osteoporosis

Rena J. Eudy (1), Marc R. Gastonguay (1,2), Kyle T. Baron (2), Matthew M. Riggs (2)
(1) Department of Biomedical Engineering, University of Connecticut, USA, (2) Metrum Research Group, LLC, Tariffville, Connecticut, USA

Objectives: To extend a mathematical, multiscale systems model of bone metabolism [1], in order to 1) describe kinetics of sclerostin mAbs that are currently in clinical development, and the changes these elicit on serum sclerostin, bone turnover markers, and bone mineral density (BMD) within typical osteoporotic patients, 2) validate the model extension in an external clinical data set [2] and 3) further our knowledge of the role of the osteocyte in bone remodeling.

Methods: A target-mediated drug disposition (TMDD) model was developed to describe kinetics of single and multiple doses of sclerostin mAbs, blosozumab and romosozumab, and total sclerostin in NONMEM (v7.2) using summary level public data from five clinical trials. The sclerostin PK model and parameter estimates were inserted into the larger bone model, with sclerostin PD modeled to affect osteocyte-mediated resorption and formation through inhibition of Wnt signaling. Sclerostin PD parameters were

initially tuned to relevant subsets of clinical data and then refined using a quadratic approximation method optimizing an ordinary least squares (OLS) objective function in R. Simulations were performed in R (v.3.1.2).

Results: The bone model predicted changes in turnover markers and changes in lumbar spine (ls) and total hip (th) BMD consistent with clinical data. These results were validated using an external dataset from a recent blosozumab clinical trial [2]. The predicted mean change from baseline at 52 weeks (180mg dosed Q2W) for lsBMD was 16.5% (observed; 95%CI: 14.9; 12.6-17.1%) and for thBMD was 6.8% (4.5; 3.2-5.8%), respectively.

Conclusions: This mechanistic model of bone metabolism adequately predicted clinical outcomes resulting from sclerostin mAb administration in a typical osteoporotic population. The model also proposes relative contributions of the osteocyte to feedback signaling elicited through changes in sclerostin and upregulation of the Wnt pathway, a finding that has not been elucidated by laboratory experimentation.

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Marc-Antoine Fabre Using a Model-Based approach to support the design of the first in-man study of a 2.5 generation Antisense Oligonucleotides (ASO) compound targeting the androgen receptor (AR).

Marc-Antoine Fabre (1), Tanya Coleman (2), Keith Parry (2), Paul Elvin (2)
(1) AstraZeneca, Alderley Park/Cambridge UK; (2) Sarah Cannon Research Institute UK.

Objectives: Using Pharmacometrics techniques to provide a mechanism for capturing the current knowledge and associated uncertainty about a new compound relative to its competition, and provide a framework for enhancing strategic decision-making.

Methods: Building a Modeling and Simulation framework for a new drug using scientific literature data from similar ASO pharmacology compounds and also competitors' data to generate knowledge for efficacious dose in FTIM. Plasma pharmacokinetic (PK) concentrations of Mipomersen, a second generation ASO compound were generated by Monte Carlo technique (SAS) and in-house 2.5 generation ASO data was used to validate the PK model. PKPD modeling analysis was performed by non-linear mixed effect modeling techniques (NONMEM 7.2).

Results: Twenty-one subjects in 3 cohorts (100 mg, 200 mg and 300 mg) and 600 plasma concentrations of Mipomersen data were

generated to develop the PK model; 21 subjects and 343 plasma concentrations of in-house data were used to validate the model. The pharmacometric activities confirmed the consistency and the predictability of PK properties across the class of second-generation of ASO drugs. ASO concentrations were found to decline in a bi-phasic manner with rapid and almost complete distribution of each drug from plasma to tissues within the first 48 hours after dosing. The population estimates of the 2.5 generation ASO for clearance, inter-compartmental clearance, central and peripheral volume were 3.03 L/h, 0.256 L/h, 6.28 L and 135 L, respectively, with inter-individual variability (IIV) of 21% and 28% for clearance and central volume.

Conclusions: Model-based approach helps to convert data into knowledge to inform the clinical team on the ASO PK characteristics and to select the optimal starting dose.

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Gregory Ferl Mechanistic model of amyloid beta and anti-amyloid beta mAb dynamics

Gregory Z. Ferl, Angelica Quartino, Lee Honigberg, Saroja Ramanujan
Genentech, Inc.

Objectives: Our goal was to develop a mechanistic mathematical model capable of predicting neutralization of soluble monomeric Aβ in the brain, cerebrospinal fluid (CSF) and plasma during the course of Alzheimer's disease therapy with anti-Aβ monoclonal antibodies (mAbs) that possess varying PK/PD properties.

Methods: We utilized physiologic information from the literature to develop a model structure and assign values to model parameters. Within the model structure and parameter space we address mechanisms related to nonsoluble Aβ species, transport rates of Aβ and the mAb-Aβ complex from brain to CSF, degradation rates of Aβ and the mAb-Aβ complex in brain, transport of Aβ across the blood brain barrier and steady state mAb concentration in brain.

Results: Our model is able to simulate steady-state, on-treatment mAb, Aβ and mAb-Aβ complex concentration-time profiles in brain, CSF and plasma, allowing us to explore the impact of antibody pharmacokinetics, Aβ binding affinity and other physiologic model parameters on percent neutralization of soluble monomeric Aβ in brain.

Conclusions: Based on our model, we were able to generate predictions regarding neutralization of soluble monomeric Aβ in brain during anti-Aβ mAb therapy and develop hypotheses regarding mechanisms that drive increased total Aβ concentrations which have been observed in CSF and plasma during treatment.

Sylvain Fouliard Interpretability is coming: using a minimal PBPK model in a population analysis

Sylvain Fouliard, Tanguy Jamier, and Marylore Chenel
Department of Clinical Pharmacokinetics and Pharmacometrics, Servier, France

Introduction: The classical mammillary compartmental models in population analyses are becoming more and more complex, integrating physiological or pharmacological features (enterohepatic recycling, multiple absorption sites…). Yet, the interpretation of peripheral compartments parameters is not straightforward. In parallel, minimal PBPK models [1-3] are proposed as a simplification of full PBPK models, allowing the estimation of interpretable parameters.

Objectives: To evaluate a minimal PBPK model in a population analysis framework, and to investigate the relationship between the parameters of an empirical 3-compartment PK model, and that of a minimal PBPK model.

Methods: Blood concentration-time profiles of drug S (an anticancer drug in development) were simulated in 1000 individuals, after a single 1-h infusion intravenous administration using a population mammillary 3-compartment model and an extensive measurement design. The model structure proposed in [1] (composed of a blood compartment and 2 distribution compartments) was implemented in NONMEM, then used to fit the data, with some parameters

(cardiac output, blood volume, total body volume…) constrained to physiological values. The model was parameterized in terms of partition coefficients (Kp), tissue volumes, and fractions of blood flow. The constraints on parameters were implemented using logit-normally distributed random effects.

Results: The minimal PBPK model was successful in describing the data, and inter-individual variability was estimated on every parameter but one. As expected, blood clearance value was similar between the two models. The two distribution compartments' volumes were 20 L and 61 L respectively, and with different Kp (65 and 1 respectively) and perfusion (19% and 28% of cardiac blood flow respectively). This shows a distribution of drug S in both extensively and poorly vascularized tissues, consistently with the large volume of distribution of the drug. A Kp of 65 in poorly vascularized tissues can be explained by a high affinity for adipose tissues (lipophilic compound). Distribution of the drug in extensively vascularized tissues is consistent with drug S anticancer activity (distribution in tumour).

Conclusions: This works illustrates how pharmacometricians can make good use of a minimal PBPK model in population PK analyses of rich data. These should be promoted in a general framework, as it allows better parameter interpretation, hypotheses generation, and assumption testing, than classical mammillary distribution models.

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Linda Franken Pharmacokinetics of morphine, morphine-3-glucuronide and morphine-6-glucuronide in terminally ill patients.

L.G.W. Franken (1), A.D. Masman (1), B.C.M de Winter (1), B.C.P. Koch (1), F.P.M. Baar (2), D. Tibboel (1), T. van Gelder (1) and R.A.A. Mathot (3)

(1) Erasmus Medical Centre, Rotterdam, Netherlands, (2) Laurens Cadenza, Rotterdam, Netherlands, (3) Academic Medical Centre, Amsterdam, Netherlands

Objectives: To develop a population pharmacokinetic (PK) model for morphine and its two major metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in terminally ill patients, to determine covariates that can be used for dose individualisation.

Methods: A population pharmacokinetic analysis was conducted with 199 randomly collected samples obtained from 47 terminally ill patients, using non-linear mixed effects modelling NONMEM 7.2.0 [1]. In the covariate analysis blood chemistry levels (e.g. albumin and creatinine), patient characteristics (e.g. age, diagnosis) and time to death were analysed by forward inclusion followed by, backward elimination. For the evaluation of the final model a normalised prediction distribution error (NPDE) analysis was performed.

Results: The data were best described by a two-compartment model for morphine, a one-compartment model for both M3G and

M6G and proportional residual error models for all the compounds. Between-subject variability (BSV) could be estimated for the bioavailability of oral morphine, morphine clearance, metabolite clearance and the volumes of distribution of the metabolites. Typical clearance values were 49.4 l/h (morphine, BSV 53%), 1.56l/h (M3G, BSV 31%) and 1.94 l/h (M6G, BSV 31%). Serum creatinine was negatively correlated with metabolite clearance and serum albumin was positively correlated, together explaining 78% of the between-subject variability in metabolite clearance. Furthermore we showed that morphine clearance decreased from 49.4 L/h to 31.4 L/h in the last three weeks before death. Evaluating the final model by NPDE analysis showed accurate predictive ability (global adjusted P value > 0.05).

Conclusion: The population pharmacokinetics of morphine, M3G and M6G in terminally ill patients were accurately quantified. Serum creatinine and albumin levels together were a better predictor of metabolite clearance than creatinine alone. This may be caused by the presence of cachexia and loss of muscle mass in terminally ill patients, in whom serum creatinine may overestimate renal function. Lower albumin levels may be an indicator of cachexia, and for overestimation of GFR based on creatinine levels. Our results show that morphine clearance declines as death approached and that M3G and M6G can accumulate in patients with decreased renal function. Dose adjustment might therefore be required in these patients, however the clinical effect of this requires further study.

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Achim Fritsch PK/PD Modeling of Sunitinib in Patients with Metastatic Colorectal and Renal Cell Cancer

Achim Fritsch (1), Friederike Kanefendt (1), Andreas Lindauer (1), Martina Kinzig (2), Fritz Sörgel (2), , Ulrich Jaehde (1)
(1) Institute of Pharmacy, Clinical Pharmacy, University of Bonn, Germany, (2) IBMP - Institute of Biomedical and Pharmaceutical Research, Nürnberg-Heroldsberg, Germany

Objectives: Oral multi-tyrosinekinase inhibitors are widely used and established treatment options in numerous tumour entities. Yet, response rates are often low and valuable surrogate endpoints which indicate therapy response are lacking. However, there is increasing evidence that several circulating proteins may serve as predictive biomarkers in pharmacokinetic/pharmacodynamic (PK/PD) models.
The aim of this investigation was the development of PK/PD models to describe the anti-angiogenic response to sunitinib and to identify potential predictors for efficacy in patients with metastatic colorectal cancer and renal cell cancer.

Methods: 21 patients with CRC and liver metastases receiving a daily dose of 37.5 mg sunitinib on a 4 weeks on/2 weeks off treatment schedule in addition to FOLFIRI participated in this prospective, open label, single arm, multicentric study. Concentrations of sunitinib, its active metabolite SU12662, measured using LC-MS/MS. VEGF-A, VEGFR-2 and 3 were quantified using commercially available ELISA kits and validated

immunoassays, respectively. PK/PD models were developed using NONMEM (v 7.1.2). Potential predictors for time to progression (TTP) were analyzed using Cox regression and a model-based approach.
As part of the non-interventional EuroTARGET project, which aims at identifying and characterizing host and tumour-related biomarkers in metastatic renal cell cancer (mRCC), these models will be further extended.

Results: Biomarker concentration-time courses could be well described by an indirect response model. Minimum concentrations relative to baseline were estimated as 0.63 and 0.59 for sVEGFR 2 and sVEGFR 3, respectively. Concentrations of both biomarkers were highly correlated, however did not predict TTP. Instead, higher exposure to the unbound active drug (sum of sunitinib and SU12662) was identified as predictor for TTP (HR: 0.49 (95% CI: 0.27-0.88), p=0.013). Within the EuroTARGET project, recruitment of mRCC patients receiving sunitinib is still ongoing.

Conclusions: Concentration-time profiles of drug, metabolite, and biomarkers could be well described by PK/PD models. The extent of biomarker response was comparable with healthy volunteers but did not predict tumour response in patients with mCRC. In contrast, TTP was correlated with active drug pharmacokinetics. The developed PK/PD models will be extended using drug and biomarker concentrations from mRCC patients in order to analyze differences between the two tumor entities

Aline Fuchs Population pharmacokinetic study to evaluate dosing strategies of imipenem in neonates and infants

(1) Aline Fuchs, (2) Eric Giannoni, (1,3) Monia Guidi, (4) Laurent A. Decosterd, (5) Oscar Marchetti, (6) Marc Pfister, (1,7) Nicolas Widmer, (1) Thierry Buclin, (1,3) Chantal Csajka
(1) Division of Clinical Pharmacology, Service of Biomedicine, Department of Laboratory, Lausanne University Hospital, Lausanne, Switzerland, (2) Service of Neonatology, Department of Paediatrics, Lausanne University, Lausanne, Switzerland, (3) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland, (4) Innovation and Development Laboratory, Service of Biomedicine, Lausanne University Hospital, Lausanne, Switzerland, (5) Service of Infectious Disease, Lausanne University Hospital, Lausanne, Switzerland, (6) Department of Paediatric Clinical Pharmacology, University Children's Hospital Basel, Basel, Switzerland, (7) Pharmacy of Eastern Vaud Hospitals, Vevey, Switzerland

Objective: Imipenem is a broad spectrum antibiotic used to treat severe infections in critically ill patients. Imipenem pharmacokinetics (PK) was evaluated in a cohort of neonates treated in the Neonatal Intensive Care Unit of the Lausanne University Hospital. The objective of our study was to identify key demographic and clinical factors influencing imipenem exposure in this population.

Method: PK data from neonates and infants with at least one imipenem concentration measured between 2002 and 2013 were analyzed applying population PK modeling methods. Measurement of plasma concentrations were performed upon the decision of the physician within the frame of a therapeutic drug monitoring (TDM) programme. Effects of demographic (sex, body weight, gestational age, postnatal age) and clinical factors (serum creatinine as a measure of kidney function; co-administration of furosemide, spironolactone, hydrochlorothiazide, vancomycin, metronidazole and erythromycin) on imipenem PK were explored. Model-based simulations were performed (with a median creatinine value of 46 µmol/l) to compare various dosing regimens with respect to their ability to maintain drug levels above predefined minimum inhibitory concentrations (MIC) for at least 40 % of the dosing interval.

Results: A total of 144 plasma samples was collected in 68 neonates and infants, predominantly preterm newborns, with median gestational age of 27 weeks (24 – 41 weeks) and postnatal age of 21 days (2 – 153 days). A two-compartment model best characterized imipenem disposition. Actual body weight exhibited the greatest impact on PK parameters, followed by age (gestational age and postnatal age) and serum creatinine on clearance. They explain 19%, 9%, 14% and 9% of the interindividual variability in clearance respectively. Model-based simulations suggested that 20 mg/kg every 12 hours maintain drug concentrations over a MIC of 4 mg/l for at least 40 % of the dosing interval during the first days of life, whereas neonates older than 14 days of life required a dose of 20 mg/kg every 8 hours. Infants (ie. >28 days of life) required a dose of 25 mg/kg every 6 hours.

Conclusion: Dosing strategies based on body weight and post-natal age are recommended for imipenem in all critically ill neonates and infants. Most current guidelines seem adequate for newborns and TDM should be restricted to some particular clinical situations.

Saskia Fuhrmann Effect of mouse model immunity on antibody biodistribution

Saskia Fuhrmann (1,4), Charlotte Kloft (3) and Wilhelm Huisinga (2)
(1) Institute of Biochemistry, Universitaet Potsdam, Germany; (2) Institute of Mathematics, Universitaet Potsdam, Germany; (3) Institute of Pharmacy, Dept. Clinical Pharmacy & Biochemistry, Freie Universitaet Berlin; (4) Graduate Research Training Program PharMetrX: Pharmacometrics & Computational Disease Modelling, Freie Universitaet Berlin and Universitaet Potsdam, Germany

Objectives: Wild-type mice and xenograft mice are frequently used to study the PK and PD of monoclonal antibodies (mAbs). Protection from elimination by binding to the FcRn receptor is known to be a major process influencing the kinetics of mAbs as well as endogenous IgG (IgGendo). Since the therapeutic mAb concentrations following clinically relevant doses are typically manifold below the IgGendo concentrations [1], the clearance of mAb by this pathway appears to be linear. The levels of IgGendo in xenograft mice, however, are reduced, and this effect on mAb disposition has not yet been studied. The objective was to investigate the impact of FcRn expression and IgGendo level on mAb PK in the context of the simplified PBPK model [1] within two different scenarios, i.e. (i) FcRn wild-type (WT) mice following intravenous immunoglobulin (IVIG) therapy and (ii) immunodeficient i.e. SCID mice.

Methods: Physiological parameters were taken from [2]. The experimental plasma and tissue data of mAb (7E3), administered intravenously at 8 mg/kg following 3 different doses of IVIG, were extracted from [3] for FcRn WT mice. For SCID mice, the experimental plasma and tissue data of mAb (8C2), administered at 1 mg/kg and 25 mg/kg, were extracted from [4]. The steady-state plasma concentration of IgGendo was reported for FcRn wild-type mice [5] and for SCID mice [6]. The extraction ratios and FcRn expression levels were estimated for two groups of tissues (tight and leaky), based on tissue properties. We assumed no FcRn expression in plasma. MATLAB R2013a was used for modelling and simulations.

Results: The extended PBPK model accurately characterized the impact of IVIG on 7E3 PK, based on competition between IgG for binding to the FcRn receptor. Interestingly, we observed higher extraction ratios for tight tissues than in the leaky tissues. The estimated FcRn expression levels for WT mice would result in lower fraction unbound of mAb to FcRn and faster elimination kinetics in SCID mice, than observed experimentally. This suggests that also the FcRn expression levels are lower in immunodeficient mice compared to wild-type mice.

Conclusions: The concentration of total IgG and the elimination from tight tissues have a relevant impact on the PK of mAbs. This is important when investigating the influence of xenograft host models on tumour disposition.

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María García-Cremades Modelling tumour growth and survival of patients with pancreatic cancer receiving Gemcitabine

Maria Garcia-Cremades (1), Celine Pitou (2), Philip W Iversen (3), Iñaki F Troconiz (1)

(1)Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona, Spain, (2) Global PK/PD & Pharmacometrics, Eli Lilly and Company, Windlesham, Surrey, UK, (3) Lilly Research laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, USA.

Background: Gemcitabine is a nucleoside antimetabolite anticancer pro-drug that shows activity against several solid tumours. Its main indication given as a single agent is to treat pancreatic cancer. Gemcitabine has been chosen as model drug to build a translational approach from early to advanced (clinical) stages in drug development as a part of pillar 3 of working package I (models in oncology) within the IMI7 founded project, Drug Disease Models Resource (DDMoRe).

Objective: The aim of this evaluation was to build a joint tumour size and survival pharmacokinetic-pharmacodynamic model of Gemcitabine in patients with advanced pancreatic cancer.

Methods: Information related to tumour size and survival was obtained from a clinical phase II and a phase III studies where

Gemcitabine was given on standard treatment (1500 mg/kg over 30 min i.v infusion) to patients (n=287) with unresectable pancreatic cancer (locally advanced or metastic). Drug exposure was calculated for each patient using a pharmacokinetic model previously developed. Tumour size and Survival versus time data were linked and described using the population approach with NONMEM 7.2. Model evaluation was performed through predictive checks.

Results: The model used to describe the tumour mass over time incorporates a disease progression component modelled as an exponential growth, a drug efficacy part dependent of drug exposure represented by the metabolite AUC, together with resistance development. Predicted tumour changes over time were linked to probability of survival as an argument for the hazard, which is described using a Weibull model.

Conclusion: The modelling exercise, which is currently ongoing, predicts the efficacy of Gemcitabine in terms of tumour growth inhibition and survival of patients with pancreatic cancer. It is expected to have a potential impact on the development of new anticancer drugs as well as optimizing the standard treatment of patients receiving Gemcitabine, predicting the likelihood of the treatment success and assisting with the dosing regimen selection.

Acknowledgements: This work was supported by the DDMoRe project.

Charkoftaki Georgia Population pharmacokinetics of cyclophosphamide and its 4-OH metabolite in patients with glomerulonephritis

Georgia Charkoftaki, Aris Dokoumetzidis, Melanie Joy
University of Colorado, Skaggs School of Pharmacy, University of Athens, School of Pharmacy, University of Colorado, Skaggs School of Pharmacyand School of Medicine, Division of Renal Diseases and Hypertension

Objectives: The purpose of this study was to develop a population pharmacokinetic (PK) model for cyclophosphamide (CY) and its 4-hydroxy cyclophosphamide (4-OH CY) metabolite in patients with glomerulonephritis secondary to lupus and small vessel vasculitis and to identify patient characteristics that may influence the drug's absorption and disposition.

Methods: The study consisted of patients with glomerulonephritis (n=23) who participated in pharmacokinetic evaluations of CY and 4-OH CY. All patients had received monthly i.v. cyclophosphamide prior to study participation. The i.v. cyclophosphamide dosages were dependent on body surface area; mean dose was (i) 1.5±0.5 g/m^2 or (ii) 0.8±0.2 g/m^2. Blood samples for CY and 4-OH CY determination were collected at the beginning of the infusion and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18 and 24 h after commencement and were assayed by LC/MS/MS method. Kidney function, serum albumin and polymorphisms in drug metabolism and transport genes were

evaluated. Plasma concentration-time data of CY and 4-OH CY (metabolite) were analyzed in two stages with a population approach using NONMEM®. 4-OH CY was analyzed conditional to the results of CY.

Results: The parent drug (CY) model was found to be one compartment with linear elimination with apparent volume of distribution $V=154*(WT/95)^{0.373}$ L, IIV= 21.2% and with apparent clearance $CL=14.4*(WT/95)^{0.471}$ L/h, IIV= 20.4%. The metabolite (4-OH CY) was modeled as one compartment with linear elimination and the production rate was proportional to the elimination of the parent drug. The typical V_m/F_m was 17.3 L with IIV= 33% and the fraction converted from parent to metabolite was $F_m=0.441$. Elimination rate constant of the 4-OH CY was $K_{met}=8\ h^{-1}$. The production rate constant of 4-OH CY was $F_m*CL_P/V_P=0.041\ h^{-1}$ and was found to be lower than the K_{met}, therefore half-life of 4-OH CY is determined by its production rate rather than its elimination (flip-flop pharmacokinetics). The final PK model was validated using nonparametric bootstrapping and a visual predictive check.

Conclusions: The population PK data described here suggest that only 44% of CY gets metabolized to the 4-OH CY metabolite in patients with glomerulonephritis, while this percentage is around 75% for patients receiving CY as an anti-cancer therapeutics.

Eva Germovsek An Argument for Standardised Scaling: Comparison of Methods for Scaling Clearance in Children

Eva Germovsek (1), Charlotte IS Barker (1, 2), Joseph F Standing (1)
(1) Institute of Child Heath, University College London, London, UK; (2) Institute for Infection and Immunity, St George's, University of London, London, UK

Objectives: Clearance changes with both body size (usually measured by weight) and age due to maturation of processes such as glomerular filtration and drug metabolising enzymes [1]. As George Box famously said: "All models are wrong, some are useful". Hence different modellers use different methods for parameterising clearance-related covariates for age and size. Different parameterisation leads to difficulties in comparing estimates between studies of similar drugs, and limits the possibility to learn about clinical maturation and size-related clearance (CL) changes. Arguments in favour of one parameterisation or another are usually based on fitting a single model to a distinct dataset [2, 3, 4]. We aimed to compare different parameterisations of maturation and size fitted to the same dataset, hence providing a clear way to compare distinct methods.

Methods: We conducted a systematic literature review of PubMed (search updated in April 2015) for publications containing information about CL of intravenous gentamicin (mainly renally

cleared) and midazolam (mainly hepatically cleared) in three different subpopulations (neonates/infants, children, adults). We then searched for models for size and maturation, through systematic literature review and by writing to email discussion groups. The identified models were then fitted to CL data. Visual comparison of the fit of the models was undertaken and the mean prediction errors (MPE) and root mean square errors (RMSE) were compared.

Results: We identified 44 and 38 clearance reports for gentamicin and midazolam CL, respectively, and 18 distinct CL covariate models. Visual examination showed that models with fixed allometric exponent and no function describing organ maturation overpredicted the neonatal CL for both drugs. The best fit according to the Akaike information criterion and the MPEs provided CL models where allometric weight scaling was combined with a sigmoidal maturation function or the allometric exponent changed with age in a sigmoidal fashion.

Conclusions: Most models that included size and age described the CL of both drugs well, and were able to capture the neonatal and adult CL. Thus, we suggest using a combination of allometric weight scaling with a sigmoid maturation function, as exemplified here by gentamicin and midazolam, two drugs representing different elimination routes.

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Leonid Gibiansky Approximations of Target-Mediated Drug Disposition (TMDD) Equations for Systems with 1:2 and 2:1 Drug-Target Binding Stoichiometry

Leonid Gibiansky, Ekaterina Gibiansky
QuantPharm LLC, North Potomac, MD, USA

Background: TMDD equations were initially written and are used assuming 1:1 stoichiometry of drug-target binding even though many biological systems do not conform to this assumption. Specifically, this assumption is violated for monoclonal antibodies that have two identical binding sites. Although standard TMDD equations provide excellent fit of the observed data, it is of interest to derive correct equations and approximations that assume true binding stoichiometry between the drug and the target.

Objectives: To derive the TMDD model and its approximations for biological systems with 2:1 and 1:2 stoichiometry of drug-target binding.

Methods: TMDD equations for systems with 2:1 and 1:2 drug-target binding were formulated. Equations for total drug and total target concentrations were then derived. Quasi-steady-state (QSS) conditions for two drug-target complexes were used to derive explicit relations that express concentrations of the free drug, the free target, and drug-target complexes via total drug and total target concentrations. These expressions together with differential

equations for the total drug and total target concentrations constitute the QSS approximations of the corresponding TMDD systems. QSS systems with zero internalization rate or zero dissociation rate correspond to quasi-equilibrium (QE) or irreversible binding (IB) approximations of the TMDD equations. Michaelis-Menten (MM) approximations were derived assuming that concentrations of the drug-target complexes are much lower than concentrations of the free drug. To check the validity of the derived equations, concentration-time profiles from the full TMDD models and the corresponding QSS approximations were simulated for several dosing regimens.

Results: Simulations demonstrated a good agreement between exact and approximate equations, with some deviations at low concentrations. Additional investigations are planned to investigate applicability of these approximations across the range of system parameters. In addition to predictions of free and total, drug and target concentrations, new approximations also predicted concentrations of two drug-target complexes with different stoichiometry.

Conclusions: QSS, QE, IB, and MM approximations of the TMDD models with 1:2 and 2:1 binding were derived. They can be used to provide a more detailed and precise description of the TMDD systems with 1:2 and 2:1 binding stoichiometry than those of the standard TMDD model.

Ekaterina Gibiansky Comparison of Population Pharmacokinetics and Exposure-Response Relationships of Intravenous Rituximab and Subcutaneous Rituxumab in Patients with Chronic Lymphocytic Leukemia

Ekaterina Gibiansky (1), Michael Brewster (2), Clarisse Chavanne (3), Nicolas Frey (3), and Candice Jamois (3)
(1) QuantPharm LLC, North Potomac, MD, USA; (2) Clinical Pharmacology, Roche Pharma Research & Early Development (pRED), Roche Innovation Center Welwyn, UK, F. Hoffmann-La Roche Ltd; (3) pRED, Clinical Pharmacology, Roche Innovation Center Basel, Switzerland, F. Hoffmann-La Roche Ltd.

Objectives: To compare safety and efficacy responses in patients receiving intravenous or subcutaneous Rituximab (RTX IV/SC) using a population pharmacokinetic (PPK) model.

Methods: 1777 SC and 2962 IV concentrations in 255 patients from two phase 3 studies were analyzed. A PPK model was built with NONMEM software; several covariates were investigated. Diagnostics plots and various predictive check procedures were used for model evaluation.

Exposure-Response relationships (E-RR) were explored graphically in the largest phase 3 study in previously untreated CLL patients using data respectively from 87 and 86 patients in the IV

and SC arms (Cycle 1: 375 mg/m^2 IV, Cycles 2-6: 500 mg/m^2 IV or 1600 mg SC). The analyzed endpoints were: occurrence of SAEs, Grade 3+ AEs, occurrence and grades of neutropenia, time course of neutrophil and B-cell counts, and best overall response (BOR).

Results: A linear two-compartment PPK model with time-dependent clearance ($CL=CL_{inf}+CL_T.exp(-k_{des}t)$) described RTX concentrations. Estimates of CL_{inf} (207 mL/day), inter-compartment clearance (420 mL/day), central volume (4.99 L), peripheral volume (V_P, 3.7 L), terminal half-life at Cycle 6 (32 days), absorption rate constant (0.372 1/day), and SC bioavailability (F_{SC}, 63.3%) were typical for monoclonal antibodies. High CL_T (1550 mL/day), possibly attributable to target-mediated elimination, decreased with a half-life of 17.4 days. Steady-state was achieved after six 28-day cycles.Clearances and volumes increased with BSA; V_P was 9% lower in females; F_{SC} decreased with increasing BMI. While fixed SC dosing lead to larger differences in exposure ($C_{trough,ss}$ and $AUC_{\tau,ss}$) between light and heavy patients compared to BSA-adjusted IV dosing, exposures for all body-size groups were not lower than exposures attained by IV dosing.Consistent with target-mediated elimination, CL_T was higher in patients with higher WBC and tumor size at baseline, leading to lower initial exposure in patients with higher disease burden.There were no differences between IV and SC arms in safety E-RR and in B-cell response. Patients in all categories of BOR in the IV arm and patients with PR in the SC arm had the same exposures, while patients with CR in the SC arm had higher exposures.

Conclusions: The tested SC regimen provides equal or higher RTX exposure compared to the reference IV regimen across the whole range of body sizes. There are no differences between IV and SC treatments in E-RR. Thus, the switch to SC administration does not impair the anti-B-cell activity of RTX.

Bojana Golubovic Population pharmacokinetic analysis of tacrolimus TDM data in stable kidney transplant patients

Golubović B (1), Vučićević K (1), Jovanović M (1), Radivojević D (2) , Kovačević Vezmar S (1), Prostran M (3), Miljković B (1)
(1)Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy, Belgrade, Serbia (2) Nephrology Clinic, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia (3) Department of Pharmacology, Clinical Pharmacology and Toxicology, University of Belgrade - School of Medicine, Belgrade, Serbia

Objectives: The aim of the study was to explore pharmacokinetic characteristics of tacrolimus and potential factors that significantly contribute to its variability in stable kidney transplant patients.

Methods: TDM data for period about one year after transplantation of 45 stable adult kidney transplant patients were collected from patients' records. All measured concentrations were trough. Pharmacokinetic analysis was performed using NONMEM® software (version 7 level 2) and Perl speaks NONMEM (version 3.5.3). A one-compartment model with first-order absorption and elimination was used as a structural model. Influences of demographic characteristics, biochemical variables and co-therapy on clearance (CL/F) were analyzed. FOCEI was used for parameters estimation and internal validation was performed.

Results: Interindividual variability of tacrolimus CL/F was best characterised by the exponential error model. Residual variability in tacrolimus concentrations was most adequately described by proportional model. Estimated typical clearance (CL/F) value was 4.27L/h. Among tested covariates significantly influences on CL/F were recorded for weight (WT) and daily dose of tacrolimus (DTAC). In the forward modelling building step inclusion of DTAC decreased OFV by 24.283, while inclusion of WT in the submodel with DTAC decreased OFV by 13.999. Omissions of these factors in backward step induced increment in OFV by 34.432 and 13.999. The mean interindividual coefficient of variability for CL/F in the final model was 14.2 %, while residual variability was 0.302. Internal validation indicated acceptable stability of the final model and precision and predictive performance.

Conclusions: In the present study tacrolimus CL/F was found to increase with WT and DTAC. Relationship between CL/F and DTAC may be due to so-called TDM effect. Other analyzed covariates did not influence tacrolimus CL/F significantly.

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Ignacio Gonzalez Development of a Systems Pharmacology Model for Inflammatory Bowel Disease (IBD)

Ignacio Gonzalez-Garcia (1) (2), Itziar Irurzun-Arana (1), Leire Ruiz-Cerdá (1), Chuanpu Hu (3), Honghui Zhou (3), An Vermeulen (4), Iñaki F. Trocóniz (1), José David Gómez-Mantilla (1)
(1) Pharmacometrics and Systems Pharmacology. Pharmacy and Pharmaceutical Technology Department. University of Navarra, Pamplona 31080, Spain. (2) Pharmacy and Pharmaceutical Technology Department. University of Valencia. Valencia, Spain. (3) Janssen Research and Development, LLC, Spring House, PA 19477, USA (4) Janssen Research and Development, a division of Janssen Pharmaceutica NV, Beerse B-2340, Belgium

Objectives: Inflammatory Bowel Disease (IBD) is a gastrointestinal tract (GIT) disorder characterized by processes of remission and relapse producing a functional impairment[HZ1] [VA[2] of the gut wall. It includes Crohn Disease (CD) and Ulcerative Colitis (UC) [1, 2]. The objective of the current work was to develop a systems pharmacology model for CD and UC integrating the main known components and reactions.

Material and Methods: The development of the theoretical disease network is based on the information obtained from the literature. Once the most relevant relationships were identified, the network was built using Boolean functions. Network validation was carried

out by comparing the results reported in literature for selected nodes and the corresponding relative expression simulated profiles obtained by 10,000 simulations.

Results: The network contains information about 5 kinds of immune cells, different membrane and cytosol receptors, and several cytokines, resulting in 45 nodes and more than 100 interactions. The network model was able to simulate the GIT state in healthy subjects and patients with active disease condition. The simulation exercise allowed identification of model elements, which, once their status with respect to the healthy condition was modified, allowed recreation of disease conditions.

Conclusions: A systems pharmacology model integrating the main known pathways in IBD, and discrimination between CD and UC was constructed and validated. The model has shown its applicability in identifying altered pathways, which resembled different statuses of the disease, opening up the potential to identify therapeutic targets.

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Mario Gonzalez Sales inVentR: a new flexible, powerful and efficient R package for model drug development using NONMEM®.

Mario González-Sales (1,2), Olivier Barrière (2), Pierre Olivier Tremblay (2), Fahima Nekka (1), Mario Tanguay (1,2).
(1) Université de Montréal, Montréal, Canada, (2) Inventiv Health Clinical, Montréal, Canada.

Objectives: The pharmacometrician workflow can be summarized in five common steps: 1) build the dataset, 2) explore the data, 3) model the data, 4) validate the model and 5) communicate the findings. The automatization of these steps saves time, money and avoids errors. The objective of this work was to create a flexible and user-friendly tool to help the pharmacometrician in his daily tasks.

Methods: The inVentR package consists of a series of functions developed in R [1], for data assembling, input and output visualization, and model development. An important focus has been put on user friendliness, documentation, training examples, and extensibility.

Results: A function to build a dataset in the specific format required for the NONMEM® analysis from basic tabulated files is provided. This function can handle PK and PD data, multiple analytes and responses, and also different types of administration routes including: bolus, infusion, and first and/or zero order absorption processes. An exhaustive list of functions is made available for

plotting purposes. These functions use a friendly syntax with a high level of abstraction that allows vectorized input, such as multiple thetas or covariates, and return *ggplot* [2, 3] objects. This way, we take advantage of the modularity of *ggplot* to allow different layers to be combined or the plot to be faceted later. Moreover, there are specific functions dedicated to increase the efficacy and reproducibility during the modeling process. These functions can, among others, provide reasonable initial estimates, summarize model parameters, duplicate a model updating the value of the parameters, and run NONMEM® from R. inVentR package can be used to easily generate professional reports and informative outputs.

Conclusions: The inVentR package is a very flexible, powerful and efficient tool that helps the pharmacometrician through the complex model building process. inVentR will be available as an open source package from the Comprehensive R Archive Network (CRAN).

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Isabel Gonzalez-Alvarez Modelling of intestinal degradation and absorption of Clavulanic acid from In Vitro and In Situ data.

Frances-Fernandez, E., Mangas-Sanjuan,V., Piqueras M., Gonzalez-Alvarez, M, Gonzalez-Alvarez, I, Bermejo, M.
Pharmacokinetics and Pharmaceutical Technology Area, Department of Engineering, Miguel Hernandez University (Spain)

Introduction: Clavulanic acid is a beta-lactamase inhibitor and it has been coadministered orally with amoxicillin since 1981 for different infections treatment. It is metabolized extensively in the liver, 1 hour half-life and it shows around 30-40% renal excretion. It is ionized through the gastrointestinal tract (pKa 2.7).

Objective: The aim of this work is to establish the absorption mechanisms involved in the absorption of clavulanic acid in the small intestine after *in situ* experiments.

Materials and Methods: An *in situ* perfusion method without recirculation described by Doluisio [1] and adapted to our experimental conditions was used to determine the absorption mechanism involved using male Wistar rats (270-300g). *In situ* experiments were performed at 0.25, 0.625, 1.25 and 2.5 M of clavulanic acid in duodenum, jejunum and ileum. Permeability rate coefficients were estimated by non-linear regression of decreasing concentrations in lumen. The fitting procedures were performed

using NONMEM 7.2 with FOCE+I for objective function estimation and ADVAN13 subroutine [2]. For graphical and statistical analysis, the R software was used. Pc-VPC [3] and bootstrap analysis were performed using PsN and Xpose version 4.5.3.

Results: The analysis of *in situ* data were well modeled using a common compartment for all intestinal segments. The best model able to describe the observations obtained was a passive diffusion in all three segments of the small intestine with an active absorption transporter in the duodenum. All parameters in the model were estimated with good precision based on the values of the results from the bootstrap analysis. The population model provides a proper description of the drug concentration data, based on GOF and pc-VPC.

Conclusions: Clavulanic acid shows a passive diffusion absorption combined with an active absorption transporter in the duodenum segment of the small intestine. Based on pharmacokinetic parameters obtained, the absorption is mainly involved in the first segment (duodenum) of the small intestine. The higly variable absorption related to clavulanic acid might be caused because of the gastric emptying frequence, due to duodenum is the most relevant segment involved in the absorption of clavulanic acid.Further studies incorporating the degradation process involved through the gastrointestinal tract may contribute to explain differences observed in the in vivo absorption.

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Verena Gotta A PK/PD meta-analysis to assess inter-study variability and translational value of preclinical exposure-QTc predictions

V Gotta (1), F Cools(2), K van Ammel(2), D J Gallacher(2), S A G Visser(3), F Sannajust(4), P Morissette(4), M Danhof(1), P H van der Graaf(1)

(1) Systems Pharmacology, Leiden Academic Center of Drug Research (LACDR), Leiden University, Leiden, The Netherlands. (2) Global Safety Pharmacology, Janssen Research & Development, Janssen Pharmaceutica NV, Beerse, Belgium. (3) Quantitative Pharmacology and Pharmacometrics / Merck Research Laboratories, Merck & Co., Inc., Upper Gwynedd, PA, USA (4) SALAR-Safety and Exploratory Pharmacology Department / Merck Research Laboratories, Merck & Co., Inc., Westpoint, PA, USA

Objectives: Drug-induced QTc-interval prolongation (?QTc) is assessed in preclinical cardiovascular safety studies as a surrogate for pro-arrhythmic risk in human. These studies in conscious telemetered dogs (4-8 animals) can be based on varying designs (e.g. dose range, number of doses, route of administration, study duration, PK/PD sampling in same animals or a satellite group, no PK). We aimed to assess the quantitative consistency of pharmacodynamic (PD) relationships derived from such studies (inter-study variability, ISV), and the preclinical-clinical correlation of PD effects.

Methods: A total of 14 studies (moxifloxacin: N=6 studies/n=32 dogs, dofetilide: N=6/n=27, and sotalol: N=2/n=10) were analyzed using population PK/PD modeling – first separately, then in a meta-analysis by pooling data from each compound. Typical PD relationships were derived with 95%CIs from each model. Preclinical PD meta-predictions were used as a reference to evaluate ISV and translational relationships with clinical effects (derived from a systematic literature review). For moxifloxacin, ISV was additionally assessed in a hierarchical random-effects model[1].

Results: The PDs of all 3 drugs was best characterized by sigmoidal E_{max}-models (meta-models, all with ?QTc$_{max}$≈50ms or 20% from baseline). The 95%CIs of 13/14 (93%) study-derived PD predictions comprised the meta-prediction, despite varying structural PK/PD models. ISV of ?QTc-predictions at upper therapeutic exposure was ±30% (range: ±1-69%). Predicted ?QTc increase within unbound therapeutic range was 4–12 ms (moxifloxacin, 2.9–5.6 µM, EC_{50}=11.6 µM), 4–18 ms (dofetilide, 0.4–2 nM, EC_{50}=4.2 nM), and 14-19 ms (sotalol, 3.7–11 µM, EC_{50}=10.1 µM), and was overlapping with clinical %?QTc from baseline. Including an ISV-level in the moxifloxacin meta-model decreased PD BSV by 10-26%, BSV on the hill coefficient decreased most. Resulting ISV (24-39%, RSE>100%) did not exceed BSV (28-37%).

Conclusions: This study provides a first quantitative assessment of ISV in preclinical ?QTc evaluations. Results suggest that consistent predictions can be obtained from highly varying studies by systematic PK/PD analysis, i.e. suitable for translational purpose. Furthermore, a 10% ?QTc-effect[2] seems to correspond already to a half-maximal effect in dog (and to a ≥35ms effect in human), suggesting that this is an unsatisfying study sensitivity target. Utilizing PK/PD analysis can improve the detection of small preclinical ?QTc [3].

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Thaddeus Grasela Toward Progressive Reporting of Modeling and Simulation Results – Part 1: Analysis of KIWI™ Metadata

Thaddeus H Grasela (1), Sébastien Bihorel (1), Cynthia A Walawander (1), Jill Fiedler-Kelly (1), David Fox (1), and Andrew Rokitka (1)
Cognigen Corporation, a subsidiary of Simulations Plus, Inc, Buffalo, New York

Background: Technical reports for pharmacometric modeling provide comprehensive documentation, typically including data assembly methods and disposition, modeling strategy, and analysis results, but are costly and time consuming and do not necessarily serve the dynamic R&D lifecycle which requires an ongoing accretion of data from Phase 1, 2, and 3 trials. Cognigen implemented KIWI™ in 2011, a secure internet-based service providing high throughput NONMEM® processing. KIWI is the basis for a progressive reporting process that facilitates the capture of critical information during model development, enables team access to evolving, interim results, and facilitates rapid assembly of technical reports.

Objective: Perform an analysis of KIWI metadata to assess system performance and evaluate its use in facilitating progressive reporting.

Methods: NONMEM runs are submitted via KIWI and maintained, along with the analysis datasets, on a secure server. Processing is done by a dedicated cluster of Linux servers. KIWI metadata is stored using a relational database management system, broadly grouped into categories of project management and NONMEM run-specific information. KIWI connection flags denote the use of a specific run for other activities, such as performing a visual predictive check, and can be used for critical path identification.

Results: Modeling efforts for 32 drugs were performed using KIWI over 3.5 years. The mean (SD) duration of a modeling effort was 367 (313) days with 1.75 (1.16) modeling projects per effort and a duration of 214 (227) days per project. About 30 (16) runs per project were labeled as critical path, representing ~2% of the runs per project. Generally, ≥ 10 plots of various types were produced per critical path run and sometimes considerably more. Approximately 80% of covariate analyses required ≤ 3 forward selection steps and 77% required ≤ 3 backward elimination steps. Final models included 15 (16) thetas, 5 (6) etas, 1 (1) off-diagonal eta, and 2 (2) epsilons. Graphs and pre-formatted, report-quality tables of results were easily exported, saving upwards of 2 hours per run.

Conclusions: KIWI provides ready access to analysis metadata that can be used to monitor system requirements and analysis status, as well as forecast resource needs for subsequent modeling efforts. Ongoing efforts are directed at leveraging metadata and run connections to automate progressive reporting and further facilitate the preparation of technical reports.

Bruce Green Impact of Concomitant Antiretrovirals, and CYP2C9 and CYP2C19 Polymorphisms on the Pharmacokinetics of Etravirine

Bruce Green (1), Herta Crauwels (2), Thomas N. Kakuda (3), Simon Vanveggel (2), Magda Opsomer (2), Anne Brochot (2)
(1) Model Answers Pty Ltd, Brisbane, Australia, (2) Janssen R&D, Mechelen, Belgium, (3) Janssen R&D, Titusville, USA

Background: HIV type-1 infected patients are routinely treated with multiple drugs. Etravirine is a non-nucleoside reverse transcriptase inhibitor indicated in combination with other antiretrovirals (ARV) for treatment-experienced patients >=6 years of age. The purpose of this analysis was to determine if any covariates, including concomitant ARVs, could explain any of the variability in the PK of etravirine.

Methods: 4728 plasma concentrations from 817 adult subjects across 4 clinical studies were used to develop a population PK model for etravirine. Covariates evaluated were baseline age, total bodyweight (WT), creatinine clearance (CRCL), sex, race, CYP2C9 and CYP2C19 phenotypes, and the presence of the following concomitant medications: atazanavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir, tenofovir disoproxil fumarate or enfuvirtide. A mixture model was used to assign CYP2C9 or CYP2C19 phenotype for subjects where this was unknown (UNK).

Results: 0.2%, 3.2%, 10.8% and 85.5% of subjects were poor (PM), intermediate (IM), extensive (EM) and UNK CYP2C9 metabolisers, respectively. 0.4%, 2.6%, 6.7%, 3.2%, 0.6%, and 86.5% were PM, IM, EM, rapid, ultra-rapid, and UNK CYP2C19 metabolisers, respectively. WT ranged from 34.5-160kg. A 1-compartment model with first-order input and a lag-time best described the data. Estimates of CL/F, Vc/F, Ka and ALAG1 were 41.7 L/hr, 972 L, 1.16 /hr, and 1.32 hr, respectively. Estimates of between-subject variability on CL/F, Vc/F and relative bioavailability (F) were 39.4 %CV, 35.9 %CV and 35.5 %CV, respectively. Between-occasion variability on F was estimated to be 30.0 %CV. There were no apparent effects of age, sex, race or concomitant ARVs. CL/F increased non-linearly with increasing WT and CRCL where:

$$CL/F = 41.7 \times (WT(kg)/71)^{0.291} \times (CRCL(L/hr)/6)^{0.246}$$

and the exponent of 0.291 on WT aligns with allometric theory by approximating a value of 0.75 on lean bodyweight.[1,2] CL/F for known PM was 15.2 L/hr, with CL/F for subjects of UNK CYP2C9 or CYP2C19 phenotype either the same as the population value (41.7 L/hr) or 9.42 L/hr, depending upon the mixture model allocation.

Conclusions: WT, CRCL, and CYP2C9 or CYP2C19 phenotype were found to describe some of the variability in etravirine CL/F, although the effects were not considered clinically relevant. Also, there were no apparent clinically relevant differences in the effect of concomitant ARVs on the PK of etravirine for adult subjects predominantly taking co-administered boosted protease inhibitors (PIs) as a background ARV regimen.

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Jinju Gug Model-based assessment of risks and benefits of tissue plasminogen activator treatment in acute ischemic stroke

Jinju Guk (1,2) Dongwoo Chae (1,2) Hankil Son (1,2), Kyungsoo Park (1)

(1) Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea. (2) Brain Korea 21 plus Project for Medical Science, Yonsei University, Seoul, Korea

Objectives: Although thrombolysis with recombinant tissue plasminogen activator (t-PA) is licensed for treatment of stroke, it has been an important issue to manage the increased risk of treatment-related intra-cerebral hemorrhage. With this background, this work aimed to develop a quantitative tool to assess benefit and risks of t-PA treatment in ischemic stroke.

Methods: Longitudinal NIHSS score changes for 337 acute stroke patients treated with t-PA at Severance hospital were collected from electronic medical record. Patients' age, weight, underlying diseases, medications, laboratory test results, stroke territory were collected also. Using item response theory (IRT)-based disease progression model, NIHSS scores for the period of 24h after treatment begins were analyzed, where, for IRT model, graded response and generalized partial credit response (GPCR) models were examined [1,2]. Model building proceeded sequentially using NONMEM 7.3 with Laplacian method, by first obtaining an item characteristic curve (ICC), consisting of slope, difficulty and baseline

severity parameters then obtaining a disease progression model for time-varying severity by fixing ICC parameters at estimates from the first step. Model evaluation was performed using VPC, with equal-size binning due to inhomogeneity and heteroscedacity in data clustering [3].

Results: A set of 13 test scores, with each test having the score of 0, 1 or 2 (3 categories), 0, 1, 2 or 3 (4 categories), or 0, 1, 2, 3 or 4 (5 categories), composed the aggregate NIHSS scores ranging from 0 to 42 [4]. Most observations occurred within 2 h post-treatment. 7 bins were chosen, with more bins located at early times. With GPCR model being selected and standard normal distribution for baseline severity, time-varying severity was modeled to be decreased exponentially with time, with half-life of 1.44 h and maximum decrease of 1.5 on the logit scale. VPC showed estimated ICC and disease progression models predicted data adequately.

Conclusion: This preliminary result showed the feasibility of applying IRT model to assess t-PA treatment outcome. Observation mostly occurring within 2h post-treatment reflects the importance of model's predictability at early times and incorporating dropout model along with covariate model for prognosis factors, which is under development. Predicting the probability of having hemorrhagic event will be also incorporated in the model for assessing risks of t-PA treatment.

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Beatriz Guglieri-Lopez A tumour growth inhibition model based on serum M-protein levels in patients with multiple myeloma treated by lenalidomide.

Beatriz Guglieri-López (1), Alejandro Pérez-Pitarch (1), Mónica Climente-Martí (2), Matilde Merino-Sanjuán (1).
(1) Department of Pharmacy and Pharmaceutical technology, Faculty of Pharmacy, University of Valencia. Valencia. Spain. (2) Pharmacy Department. Doctor Peset University Hospital. Valencia. Spain. (3) Pharmacy Department . University Clinical Hospital of Valencia. Spain.

Objective: To model the pharmacodynamic M-protein response induced by lenalidomide given in patients with multiple myeloma (MM).

Methods: Data were available from 39 MM patients with measurable M-protein levels who started treatment with lenalidomide between March 2009 and October 2014 in two Spanish Hospitals. A simplified tumour growth inhibition (TGI) model based on a previous published model [1] was used to estimate response metrics based on time profiles of M-protein (taken as a marker of tumour size) after lenalidomide administration. A parameter representing non-monoclonal component (NMC) was added to the model in order to restrict the tumour growth and the effect of lenalidomide to myeloma cells.

$dMprot/dt = KL \cdot (Mprot(t)-NMC) – KD(t) \cdot (Mprot(t)-NMC);$

$KD(t)=KD_0 \cdot e^{-\lambda \cdot t}$

KL: tumour growth rate; KD: drug effect; λ: drug resistance.

Model parameters were estimated using non-linear mixed-effects modelling implemented in NONMEM V7.3.0 [2]. Relationship between these TGI metrics and covariates was assessed using Stepwise Covariate Model building tool of PsN v4.2.0. The performance of the model was evaluated using a visual predictive check (VPC) based on 1000 simulated replicates of the development dataset (30 patients) from week 8 onwards. The bootstrap resampling technique was also used for internal validation. External validation was conducted by assessing the ability of the population model to predict M-protein levels from week 8 onwards in a separate group of 9 patients using the normalized prediction discrepancy distribution error (NPDE) add-on package for R [3].

Results: The model was composed of sub-models for tumour growth dynamics, drug effect and drug resistance. The decrease of M-protein levels to normal range at the end of cycle 2 (week 8) was linearly correlated to drug effect and drug resistance. The M-protein level at week 8 was correlated to NMC. The model indicated good prediction and a lack of bias in goodness-of-fit plots and VPC. The external validation showed that NPDE were not different from a normal distribution (global adjusted p-value=0.987).

Conclusion: Internal and external validation techniques demonstrate that this model can be used to predict M-protein profile from week 8 onwards in multiple myeloma patients treated by lenalidomide. The described model could be part of a PK/PD model framework to simulate expected survival taking into account drug exposure.

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Benjamin Guiastrennec In vitro-in vivo modeling of erosion profiles for HPMC/DCP gel matrix tablets

Benjamin Guiastrennec (1), Erik Söderlind (2), Sara Richardson (2), Martin Bergstrand (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (2) Pharmaceutical Development, AstraZeneca R&D, Mölndal, Sweden

Objectives: To predict *in vitro* and *in vivo* erosion rate for several of hydroxypropyl methylcellulose (HPMC) and dicalcium phosphate (DCP) based gel matrix tablets, under fasting and fed conditions and to integrate findings in an interactive simulation tool.

Methods: Data were available from a previously published study where *in vitro* erosion profiles of 4 tablet formulation with various amount of HPMC and DCP were assessed under a range of pH and mechanical stress (rpm) [1]. A study was also conducted in healthy volunteers (n=5) to simultaneously measure the *in vivo* erosion rate and the gastrointestinal (GI) location of the tablets under fasting and fed conditions. A previously published tablet volume model and a Michaelis-Menten like model were evaluated on the *in vitro* data [2]. Stepwise covariate modeling (SCM) was used to investigate the effect of tablet formulation and experimental conditions (pH, rpm) on the model parameters. The *in vitro* model and its final estimates were used to predict *in vivo* erosion profiles. The pH in the different GI locations was fixed to literature values while the mechanical

stress was estimated for each GI segment [3,4]. R and the package Shiny were used to create the interactive simulation tool [5].

Results: The Michaelis-Menten like model was selected over the tablet volume model. The final estimates were 22.79 mg/h for V_{MAX} and 29.42 mg for K_M. The SCM identified significant (α = 5 %) effect of pH and DCP on K_M and pH, DCP, HPMC and rpm on V_{MAX}. The *in vivo* mechanical stress was estimated to 26.3 rpm in fasting stomach, 90.8 rpm in fed stomach, 44.6 rpm in small intestine and 25.1 rpm in colon. *In vivo* predictions were in good agreement with the observed erosion rates, except the formulation with the lowest amount of HPMC under fasting condition, which was overpredicted.

Conclusions: The *in vitro* erosion model successfully predicted the erosion *in vivo* under fed and fasting conditions. Model misspecification for one of the formulation was suspected, as HPMC concentrations were too low to form a proper gel matrix. Significantly lower estimates for *in vivo* mechanical stress in comparison with previous publication may indicate that some factors in the *in vitro-in vivo* translation are yet to be characterized [2]. The integration of the model in a simulation tool will ease future *in vitro-in vivo* translation.

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Gustaf Wellhagen Quantifying drug effects in phase 2a anti-diabetic studies: Power and accuracy of four HbA1c models

Gustaf J. Wellhagen, Mats O. Karlsson, Maria C. Kjellsson
Department of Pharmaceutical Biosciences, Uppsala University

Background and Objectives: Several dynamic models of HbA1c have been suggested for the analysis of anti-diabetic study data: FPG-FSI-HbA1c (FFH) [1], FPG-Hb-HbA1c (FHH) [2], Integrated Glucose-RBC-HbA1c (IGRH) [3] and ADOPT [4]. HbA1c formation is in these models driven by fasting plasma glucose (FPG) or mean plasma glucose (MPG), with or without fasting serum insulin (FSI). The aim with this project was to investigate the power to detect a drug effect and the accuracy of the estimated drug effect on HbA1c for the four models.

Methods: Data was simulated to mimic a 12-week parallel group phase 2a clinical trial with type 2 diabetic patients. Glucose and insulin were simulated using the Integrated Glucose-Insulin (IGI) model [5] with one of 5 drug effects acting on: basal insulin secretion (BASI), incretin response (INCR), insulin dependent glucose elimination (CLGI), insulin independent glucose elimination (CLG) or endogenous glucose production (EGP). The IGRH model was used to simulate HbA1c as a mechanistic function of MPG. The simulated data was analyzed with and without the drug effects using each of the four models. The power to detect a drug effect

was assessed using Monte Carlo Mapped Power (MCMP) calculations. Using the difference in Objective Function Value (OFV) between full and reduced runs gave rise to the ΔOFV displayed in Table 1. Accuracy was assessed by calculating the Relative Estimation Error (REE) of the ΔΔHbA1c for each model.

Results: 1. As seen in Table 1, the FFH model needed the least number of individuals to identify a drug effect compared to other models except in one case. The FHH and ADOPT models were the most quick and stable to run. The accuracy of the parameter estimates was better for the MPG driven models (IGRH and ADOPT), with lower REE.

Table 1. Ratio of ΔOFV

	BASI	**CLG**	**CLGI**	**EGP**	**INCR**
IGRH/FFH	0.87	0.62	0.88	0.71	1.07
IGRH/FHH	1.00	0.87	1.02	0.84	1.26
IGRH/ADOPT	0.98	0.98	0.98	0.98	0.98

Conclusions: The FFH model displayed a higher power compared to the other models except for one drug effect where the ADOPT model needed the fewest number of individuals. This is probably due to additional information given by the FSI records. The IGRH and ADOPT models produce the most accurate predictions of HbA1c at the end of the study. The relative merit of models depends on which mechanism of action the studied drug has.

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K. Melissa Hallow Interactive evaluation of dosing regimens for a novel anti-diabetic agent: a case-study in the application of RxODE

K. Melissa Hallow[1], David A James[2], Wenping Wang[2]
[1] University of Georgia, Athens, GA, USA, [2] Novartis Pharmaceuticals, East Hanover, NJ

Objective: RxODE is a new R package that facilitates straightforward PKPD simulation within R, providing an efficient and versatile way to specify dosing scenarios and sampling schedules and to perform simulation with variability with minimal custom coding. Because simulations are performed entirely within R, it also takes advantage of the R ecosystem, including powerful graphics packages and the Shiny package for developing user interfaces. Here we show how we have used RxODE to develop an interactive tool for exploring different dose regimens and expected efficacy for a novel anti-diabetic agent.

Dual sodium glucose cotransporter (SGLT) 1/2 inhibitors reduce glucose levels by inhibiting both gut absorption and renal reabsorption of glucose. However, EC50s for these two mechanisms can be quite different, and drug concentrations in the gut decline much faster than in plasma. In this complex pharmacodynamic setting, PKPD simulation provides a means for determining an appropriate dosing regimen and for evaluating efficacy potential.

Methods: An existing model of glucose-insulin dynamics[1] was adapted to incorporate the dual mechanism of action of an SGLT 1/2 inhibitor, and K-PD parameters were estimated in NONMEM using phase II biomarker data. The model was then implemented in R using RxODE. RxODE compiles the model in C, and thus run times are extremely fast. It also provides a function for generating R shiny apps to interface with the model, which can then be further customized, shared online with clinical teams, and used to facilitate interactive simulation.

Results: The generated shiny app utilizes RxODE to allow users to vary simulation parameters, including dose, regimen (QD, BID, TID), and dose timing relative to meals, and to visualize in real time the effects on glucose profiles and HbA1c. It also allows real-time evaluation of the impact of parameters for which there is large uncertainty, such as the time constant for gut drug concentrations.

Conclusions: RxODE provides a tool for straightforward specification and simulation of a wide range of dosing scenarios. It takes advantage of the R ecosystem, including powerful graphics packages and Shiny. Thus, it can facilitate real-time, interactive engagement with clinical teams, reducing collaboration lag time. We are currently developing functionality to facilitate parameter estimation of RxODE models using the nlme package[2].

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Kelong Han Tumor Growth Inhibition Modeling of Onartuzumab in Combination with Erlotinib Does Not Suggest Dose Intensification Would Improve Outcome in Patients with 2nd and 3rd Line Non-small Cell Lung Cancer

Kelong Han, Pascal Chanu, Fredrik Jonsson, Helen Winter, Rene Bruno, Jin Jin, Mark Stroh
Clinical Pharmacology, Genentech Inc., South San Francisco, CA; Pharsight Consulting Services, Lyon, France; Pharsight Consulting Services, Stockholm, Sweden; Pharsight Consulting Services, Marseille, France

Objectives: The phase III trial OAM4971g comparing onartuzumab (ONT) plus erlotinib vs erlotinib in MET-positive patients with 2nd and 3rd line NSCLC did not meet the primary endpoint of overall survival (OS). An exposure-response analysis was performed to assess whether a higher ONT dose may yield better efficacy without significantly changing the safety profile.

Methods: Data of 636 patients from the phase II study OAM4558g and phase III study OAM4971g were pooled. Tumor growth inhibition (TGI) models were fit to longitudinal tumor size data to estimate individual TGI metrics including time to tumor re-growth (TTG), growth rate constant and tumor size ratio to baseline at week 8. Cox regression models were developed for time-to-event endpoints (progression-free survival [PFS], OS and TTG) and

investigated relationships with baseline prognostic (Px) factors and ONT exposure. Incidence of adverse events was modeled by logistic regression.

Results: An exposure-response analysis of MET-positive patients in OAM4558g and OAM4971g suggested longer PFS and OS for patients whose ONT steady-state trough concentration is above the upper quartile. However, exposure-response relationship with these clinical endpoints may be confounded by unobserved Px factors that may impact both OS and exposure. One way to address the confounding issue is to incorporate an explanatory variable, e.g. TGI metrics. After TGI metrics were included while building the OS model, ONT exposure was no longer significant. TTG is the only TGI metric remaining in the final OS model. The final OS model indicated that longer OS is associated with higher albumin, longer TTG, fewer metastatic sites, female gender, ECOG performance score equal to 0, and higher age. On the other hand, ONT exposure was not significantly associated with TTG after adjusting for Px factors. Longer TTG is associated with the presence of EGFR mutation and higher albumin. Finally, higher ONT exposure is associated with increased incidence of infusion reactions and peripheral edema. However, the clinical significance of this exposure-safety relationship has not been determined.

Conclusions: Higher ONT exposure is not significantly associated with improved OS after adjusting for Px factors and TTG, but there was a trend of unknown clinical significance toward increased incidence of infusion reactions and peripheral edema. These results do not support testing a higher ONT dose in this population.

Jacqueline Hannam A model for the respiratory effects of remifentanil and propofol during sedation and analgesia

Jacqueline A Hannam (1, 2), Iñaki F Trocóniz (1), Xavier Borrat (3), Pedro L Gambús (3)
(1) Pharmacometrics and Systems Pharmacology, School of Pharmacy, Universidad de Navarra, Pamplona, Spain, (2) Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand, (3) Systems Pharmacology Effect Control and Modeling Research Group, Department of Anesthesia, Hospital CLINIC de Barcelona, Barcelona, Spain.

Objectives: Propofol and remifentanil are commonly combined for sedation and may act synergistically on the respiratory system. Most models describing respiratory effects for anesthetic drugs are developed in controlled study conditions or health volunteers. We aimed to develop a model for propofol-remifentanil effects on respiratory depression in patients undergoing noxious procedures, in a clinical setting.

Methods: Data were available for 136 patients undergoing endoscopy with sedation using propofol with remifentanil. Participants were randomized to receive a fixed, targeted controlled infusion (TCI) of propofol 2.0 μg/ml, propofol 3.0 μg/ml, remifentanil 1.0 ng/ml or remifentanil 2.0 ng/ml. TCI targets of the second drug (remifentanil or propofol) were determined for each participant using the Dixon up-down method.[1] Predicted plasma

concentrations were related to measured transcutaneous arterial pressure of carbon dioxide ($PaCO_2$) using an indirect model with rebound mechanism.[2] Data were analyzed using NONMEM 7.2. Covariate relationships were investigated for age, noxious stimuli (endoscopy tube insertion) and A118G genotype for the μ-opioid receptor (OPRM1).

Results: Participants had a median (range) age of 64.0 (25.0-88.0) years, weight of 70.0 (35.0-98.0) kg and height of 164.0 (147.0-190.0) cm. Seven percent were recessive homozygous for OPRM1 polymorphism. Remifentanil inhibited arterial pressure of carbon dioxide ($PaCO_2$) removal with an IC_{50} of 1.13 ng/ml and k_{e0} of 0.28 min^{-1}. Propofol affected system modulation with an IC_{50} of 4.97 μg/ml (no effect-site compartment). Propofol IC_{50} and remifentanil k_{e0} were reduced with increasing age. Noxious stimuli and genotype were not significant covariates. Iso-effect concentration pairs at steady state conditions, identified using simulation, suggested synergistic drug effects.

Conclusions: An indirect effect model with rebound mechanism can describe remifentanil and propofol induced changes in $PaCO_2$ in patients undergoing noxious procedures. The model may be useful for identifying optimal dosing schedules for these drugs in combination that provide adequate sedation but avoid respiratory depression.

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Michael Heathman A Joint Concentration-Response Model for ABPM Measurements of Systolic and Diastolic Blood Pressure

Michael Heathman (1), Mary Jane Geiger (2), Amparo de la Peña (1)
(1) Eli Lilly and Company, Indianapolis, Indiana, USA; (2) Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA

Objectives: To characterize the relationship between the concentration of an experimental drug, LY, and ambulatory blood pressure monitoring (ABPM) measurements of systolic (SBP) and diastolic (DBP) blood pressure.

Methods: A multicenter, randomized, double-blind, parallel-arm, placebo-controlled study was conducted to evaluate the effects of LY on blood pressure using ABPM. ABPM was measured at approximately the maximum LY concentration. Patients (755) were randomized to placebo or 1 of 2 LY treatment arms. ABPM was performed prior to randomization, and at 3 other visits over 26 weeks. Five plasma samples were collected from each patient for determination of LY concentrations.
Separate circadian rhythm (CR) models were developed for SBP and DBP, using data from placebo treated patients. A combination of cosine functions was used to model CR, parameterized in terms of amplitude and phase. Inter-patient and inter-occasion variability were assessed on each parameter. NONMEM 7.2 was used for all analyses.

A 2-compartment model was used to describe the pharmacokinetics (PK) of LY. The CR models for SBP and DBP were each combined with the PK model; exposure-response relationships were evaluated using data from all 3 treatment arms. Demographics, smoking status, hypertensive status, and concomitant medications were evaluated as covariates.
Finally, a linked model for SBP and DBP was developed, incorporating covariance in both inter-patient and inter-occasion variability. This model was qualified using bootstrap and visual predictive checks (VPC). The VPC included SBP and DBP, and the derived variables mean arterial pressure (MAP) and pulse pressure (PP).

Results: The final linked model described the CR of SBP and DBP using 2 cosine functions, with periods of 24 and 12 hours. While separate amplitude parameters were used for SBP and DBP, phase parameters were shared.
SBP decreased with increasing LY concentration, while no relationship was found for DBP. Consistent with physiology, baseline SBP was found to increase with age. Gender influenced baseline DBP, with males having 7% higher values.

Conclusions: The combined concentration-response model described SBP and DBP response to LY very well, based on the VPC. The relationship between SBP and DBP was also well characterized, based on the VPC of MAP and PP. The final model provided an understanding of blood pressure response to LY therapy, and allowed prediction of responses to LY in alternative dosing regimens.

Andrea Henrich External evaluation of a PK/PD model describing the time course of paclitaxel and neutropenia in patients with advanced non-small cell lung cancer

Andrea Henrich (1,2) , Markus Joerger (3), Wilhelm Huisinga (4), Charlotte Kloft (1), Zinnia P. Parra-Guillen (1)
(1) Dept. Clinical Pharmacy & Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) Graduate Research Training program PharMetrX, Germany, (3) Dept. of Oncology & Haematology, Cantonal Hospital, St Gallen, Switzerland and (4) Institute of Mathematics, Universitaet Potsdam, Germany

Objectives: Paclitaxel (PTX) exhibits complex pharmacokinetics (PK) with high interindividual variability and also severe toxicity, namely neutropenia, which makes PTX an appealing drug for dose individualisation. The concentration time-course of PTX and the resulting neutropenia was previously described by a PK/pharmacodynamic (PD) model, and a dose individualisation algorithm was built considering sex and age as covariates [1]. Subsequently, a clinical trial (CEPAC-TDM) was initiated to evaluate whether the proposed dosing algorithm was able to reduce grade 4 neutropenia without reducing treatment efficacy. The aim of the work here presented is to externally validate the previously described PK/PD model using the data collected from the CEPAC-TDM study.

Methods: Data from the CEPAC-TDM study was obtained for the analysis. Briefly, patients were randomised into 2 arms, each comprising 183 patients. In Arm A, standard PTX dose (200 mg/m2) in combination with a platinum-based drug was administered 3-weekly for up to 6 cycles, while in Arm B the previously published algorithm was used to select initial and subsequent doses. PTX plasma concentrations 24 h after PTX administration were available only for Arm B. Shortly before and 15 days after the drug administration, neutrophil concentrations for both arms were obtained. PTX and neutrophil concentrations were visually explored and the performance of the previously published model was evaluated using basic goodness of fit plots and visual predictive checks (NONMEM 7.2, PsN 4.2 and Xpsose4 4.5.3).

Results: Patients in Arm A were exposed to higher PTX doses overall. In this arm, females exhibited more profound neutropenia than men. While in Arm B, in which dose was individualised from the beginning based on sex and age, comparable exposure and neutrophil time course were observed. The results from the performed evaluation showed a model misspecification at the pharmacodynamics level. In addition, bone marrow exhaustion was identified which could partly explain the less predictive performance of the model in the later cycles.

Conclusions: Based on the external evaluation results, the proposed PK/PD model needs to be refined to take into account bone marrow exhaustion. In a next step, the refined model will be used to re-evaluated the dosing algorithm.

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Young-A Heo Modeling of blood pressure lowering effect for co-administration of valsartan and amlodipine

Young-A Heo 1,2 Yukyung Kim1,2, Mijeong Son1,2, Jinju Gug1,2 DongWoo Chae1,2, Hankil Son1,2, Nick Holford3, Kyungsoo Park1
1 Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea 2 Brain Korea 21 Plus Project for Medical Science, Yonsei University, Seoul, Korea 3 Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

Objectives: The objective of this study was to develop population pharmacokinetic (PK) and pharmacodynamic (PD) model for antihypertensive effect of amlodipine and valsartan combined therapy.

Methods: Pharmacokinetic (PK) modeling was first carried out for both drugs using data collected from 48 healthy volunteers receiving a combined formulation of 10mg amlodipine and 160mg valsartan as a single dose. Systolic (SBP) and diastolic blood pressure (DBP) data were also collected from combination therapy. SBP and DBP data for monotherapies were gathered from literature search. Using constructed PK models, PD models for monotherapy of each drug and combination therapy were built with NONMEM 7.2 using the data collected from literature search and clinical trial

respectively. Visual predictive check (VPC) was performed for model evaluation.

Results: Two-compartment model with zero order absorption best described the PK data of both drugs. For BP, monotherapy data for amlodipine was best fitted into a linear model and that for valsartan into linear (SBP) and E_{max} model (DBP). Combined therapy was best described with proportional interaction term, (ADDR(1+ALPHA)) where ADDR refers to the sum of BP lowering effects from amlodipine and valsartan monotherapies and ALPHA being the interaction term of combined therapy. Estimated ALPHA for SBP and DBP were -0.707 and -0.380 respectively, indicating the infra-additive interaction for both SBP and DBP, which was consistent with literature result about combination therapy of ARBs and CCBs.

Conclusions: The population PK model adequately described the observed concentrations and developed BP models successfully described the efficacy of combination treatment of amlodipine and valsartan in comparison to monotherapy of each drug.

Christoph Hethey Mechanism-based pharmacodynamic modelling of bacterial growth inhibition by antibiotics

Christoph Hethey (1,2), Charlotte Kloft (2,3), Wilhelm Huisinga (2,4)
(1) Institut für Biochemie und Biologie, Universität Potsdam; (2) Graduate Research Training Program PharMetrX: Pharmacometrics & Computational Disease Modelling; (3) Institute of Pharmacy, Dept. Clinical Pharmacy & Biochemistry, Freie Universität Berlin and (4) Institut für Mathematik, Universität Potsdam

Objectives: Typical drug-effect models directly link bacterial population growth and exposure to antibiotics. They rarely account for known mechanisms of action of the drug - which are particularly relevant for the analysis of synergistic or antagonistic effects of drug combinations[1]. Our aim was to develop a generic pharmacodynamic model which allows for mechanistic integration of antimicrobial drug effects on the cellular level to predict the impact on bacterial growth.

Methods: Control bacterial growth experiments without drug resulted in baseline values for population growth. An established single cell model was extended to predict cell-level parameters from this growth rate[2]. Instantaneous drug effects were integrated on the cellular level and exemplified for protein synthesis inhibitors. Time dependent cellular responses to this inhibition were predicted by a transit compartment cell-cycle model. Parameter estimation

and model assessment for time-kill curves (TKC) were based on training and validation data sets.

Results: The model successfully predicts data for diverse experimental observations: (i) TKC data (*E. coli*, tetracycline) for constant drug exposure; (ii) septation dynamics during shift from exponential into stationary phase (*B. subtilis*, no drug); (iii) impact of drug and growth medium on cellular RNA concentrations (*E. coli*, chloramphenicol) and (iv) lag times between increase of cell number and population mass after change of growth medium (*E. coli*, no drug). The peptide chain elongation rate turns out to be a crucial predictor for bacterial cell composition during drug exposure. Since all scenarios show good agreement between predicted and experimental data, these promising results are a first step to mechanistically model bacterial growth during exposure to multiple antibiotics.

Conclusions: Our model allows to quantify the impact of strain, growth media and pre-experiment history on TKC and other readouts of antibiotic in vitro assays. Typically, a direct comparison between different experiments is not possible. Mechanistic models, as presented here, can fill this gap - they explicitly consider parameters like control growth rate or persister fractions and extract relevant information. This is critical when comparing the in vitro effects of different antibiotics, for example to ensure optimal combination therapy.

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Jules Heuberger Population Pharmacokinetic/Pharmacodynamic Modeling of a next generation recombinant human Factor VIIa (LR769) to Derive the Dose to be Studied in Phase 3.

Jules Heuberger
Centre for Human Drug Research

Objectives: To develop a population PK-PD model to characterize the Factor VIIa concentration-effect relationship for Thrombin Generation Assay with platelets (AUC of peak, TGTp_AUC), activated partial thromboplastin time (aPTT), thromboelastography (MCF: maximum clot firmness) and Prothrombin fragments 1+2 (F1+2). This model was then used to optimize a treatment regimen that is expected to be effective in treating and preventing bleedings in hemophilia A/B patients with inhibitors.

Methods: Data on the administration of 25, 75 and 225 µg/kg LR769 to 15 hemophilia A/B patients from a randomized, open label multiple dose cross-over study were used to develop a PK/PD model. FVIIa activity was assessed by modified STACLOT rTF assay. The identified population PK-PD models were used to simulate the response curves as a function of Factor VIIa activity with different dosing regimens.

Results: A two-compartment model for bolus IV administration was selected for the pharmacokinetics of FVIIa, with lean body mass

(LBM) as a covariate on Vd and inter-individual variability on the elimination rate constant. Using the PK model as a driving factor, four PD models were developed for the different PD measurements. A sigmoidal maximal effect model was identified for TGTp_AUC, MCF, F1+2 (increasing with increasing FVIIa) and aPTT (decreasing with increasing FVIIa) with the latter two having a gamma fixed at 1. Also, the effect in F1+2 showed a delayed effect, which was modelled using an effect compartment. Several dose regimens were simulated and evaluated for desired effect levels.

Conclusions: Based on these results, LR769 showed dose responsiveness and two dosing regimens were chosen to be studied in the Phase 3 study: 75µg/kg every 3hrs and 225µg/kg, if needed followed 9 hrs later by 75µg/kg were deemed to have the most optimal effect-profile. Preliminary results of the ongoing Phase 3 study indicate these doses may be effective and safe.

Rollo Hoare Modelling CD4 T cell reconstitution in HIV-infected children starting antiretroviral therapy

Rollo L Hoare (1,2), Robin Callard (1,2), Joseph F Standing (1,2,3)
(1) Institute of Child Health, University College London, 30 Guilford St, London, UK; (2) Centre for Mathematics and Physics in the Life Sciences and Experimental Biology, University College London, Gower St, London, UK; (3) Great Ormond Street Hospital NHS Foundation Trust, Great Ormond St, London, UK

Objectives: Antiretroviral therapy (ART) is the standard treatment for adults and children infected with human immunodeficiency virus (HIV). HIV mainly infects CD4 T cells, causing a decline in CD4 T cell concentration. This decline leaves patients immunocompromised and hence vulnerable to opportunistic infections. ART suppresses HIV replication, reducing viral load, allowing CD4 T cells to reconstitute. This reconstitution is slow, taking between one a two years. Studying immune reconstitution in children is challenging because the rapidly developing immune system results in a three-fold decrease in expected CD4 T cell concentrations for age [1].

Methods: This work combines an adapted version of a mechanistic model previously constructed for paediatric HSCT reconstitution [2] with a model for virus dynamics [3]. The resulting model has two compartments: a CD4 concentration compartment and a viral load compartment. The thymus produces new CD4 cells, which once they enter the periphery can proliferate or die. The underlying biology of the system is then taken into account by using mathematical

functions on these rates to model age dependence due to the effects of development on thymic output, loss and proliferation, and concentration dependence due to competition for resources such as cytokines and sp-MHC. Virus is produced in CD4 cells, so production depends on their concentration. Furthermore, the HIV-induced increase in loss of CD4 cells is included, proportional to viral load. We apply this model to paired longitudinal data for both CD4 concentration and viral load collected in two different studies.

Results: The final model has good descriptive and simulation properties, giving sensible biological parameters for the reconstitution. Mean CD4 concentrations are found to be much below those expected of a healthy child.

Conclusions: A mechanistic model has been successfully applied to data for the reconstitution of CD4 T cells in HIV-infected children starting ART. The model has the potential to give insight into the effects of a range of covariates, such as socio-economic factors, the ART drugs used, or the age of the patient at the start of ART.

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Richard Höglund Artemether-lumefantrine coadministration with antiretrovirals; population pharmacokinetics and dosing implications

Richard M. Hoglund (1,2), Pauline Byakika-Kibwika (3,4), Mohammed Lamorde (4), Concepta Merry (4), Michael Ashton (5), Warunee Hanpithakpong (1), Nicholas P. J. Day (1,2), Nicholas J. White (1,2), Angela Äbelö (5), Joel Tarning (1,2)
(1) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand,(2) Centre for Tropical Medicine & Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK, (3) Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda, (4) Infectious Diseases Institute, Makerere University College of Health Sciences, Kampala, Uganda, (5) Unit for Pharmacokinetics and Drug Metabolism, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Objectives: Drug-drug interactions between antimalarial and antiretroviral drugs may influence antimalarial treatment outcomes. The aim of this study was to investigate the potential drug-drug interactions between the anti-malarial drugs; lumefantrine, artemether and their respective metabolites desbutyl-lumefantrine and dihydroartemisinin, and the HIV-drugs efavirenz, nevirapine and lopinavir/ritonavir.

Methods: Data from two clinical studies, investigating the influence of the HIV-drugs efavirenz, nevirapine and lopinavir/ritonavir on the pharmacokinetics of the antimalarial drugs lumefantrine, artemether and their respective metabolites, in HIV infected patients were pooled and analysed using a nonlinear mixed-effects modelling approach.

Results: Efavirenz and nevirapine significantly decreased the terminal exposure to lumefantrine (decrease of 70% and 25%, respectively) while ritonavir/lopinavir substantially increased the exposure with 440%. All antiretroviral drugs decreased the total exposure to dihydroartemisinin (decrease of 72%, 41% and 60% for efavirenz, nevirapine and ritonavir/lopinavir, respectively). Simulations suggest that a substantially increased artemether-lumefantrine dose is required to achieve equivalent exposures when co-administered with efavirenz (250% dose increase) and nevirapine (75% dose increase). When co-administered with ritonavir/lopinavir it is unclear if the increased lumefantrine exposure compensates adequately for the reduced dihydroartemisinin exposure and thus whether dose adjustment is required. The pharmacokinetics of efavirenz were not affected by concomitant administration of artemether-lumefantrine while the elimination clearance of nevirapine was increased by 65%.

Conclusions: There are substantial drug interactions between artemether-lumefantrine and efavirenz, nevirapine and ritonavir/lopinavir. Especially the antimalarial drugs are affected. Given the readily saturable absorption of lumefantrine, the dose adjustments predicted to be necessary will need to be evaluated prospectively in malaria-HIV coinfected patients.

Nick Holford The Influence of Body Composition on Ethanol Pharmacokinetics using a Rate Dependent Extraction Model

Nick Holford (1), Yu Jiang (2), Daryl J. Murry (2), Timothy L. Brown(3), Gary Milavetz (2)
(1) Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand (2) College of Pharmacy, University of Iowa, USA (3) National Advanced Driving Simulator, Center for Computer Aided Design, University of Iowa, USA

Objectives: 1) to apply a model capable of linking first pass hepatic extraction with ethanol absorption rate in order to identify hepatic mixed-order, first-order and non-hepatic first order elimination processes for ethanol.
2) to explore the effect of body composition on ethanol disposition parameters.

Methods: 108 subjects were dosed orally to achieve a target peak blood ethanol concentration of 650 mg/L and 1150 mg/L using a randomized, crossover design. A total of 6025 breath samples were measured using an Alco-Sensor IV breathalyzer. Breath ethanol was converted to equivalent blood concentrations for pharmacokinetic analysis. A semi-mechanistic rate dependent extraction model [1] with zero-order input to the gut with subsequent first order absorption was used to describe the data. Between subject variability (BSV) and between occasion variability (BOV) were tested

on all parameters. Portal blood flow (Qpv) [2] was predicted from fat free mass (FFM) which was used to predict hepatic vein concentration (Chv) and hepatic intrinsic clearance (CLI). Portal vein concentration (Cpv) was predicted from Qpv and ethanol absorption rate into the portal vein.

$$Chv=Cpv*Qpv/(Qpv+CLI)$$

$$CLI=Vmax/(Km+Chv) + CLFO$$

Allometric scaling using different size metrics was used for volume of distribution (V), the maximum metabolizing capacity (Vmax), hepatic first order clearance (CLFO), and non-hepatic first order clearance (CLNH). The size metrics were total body weight (TBW), FFM [3] and normal fat mass (NFM) [4].

$$NFM=FFM+Ffat*(TBW-FFM)$$

Censored observations were included by using Beal's M3 method [5]. Data were analyzed using NONMEM 7.3.0.

Results: The bootstrap average values for the population parameters are shown in the table. Model selection guided by objective function value (OFV) suggested the existence of CLNH but the 95% bootstrap confidence interval included zero for both CLFO and CLNH when they were both included in the model.

Parameter	Units	Population Estimate	BSV	BOV
Volume	L/70kg NFM	38.6	0.091	0.149
Vmax	g/h/70kg TBW	15.8	0.258	0.309
Km	mg/L blood	62.5	1.22	0.438
CL non-hepatic	L/h/70kg	0.13	0.166	-

	TBW			
First-order from gut	1/h	8.83	-	1.21
Zero-order input to gut	h	0.301	-	0.492
Ffat for volume	-	0.458	-	-

BSV and BOV calculated from sqrt(NONMEM omega)

Conclusions: A rate dependent extraction model improves model fitting compared with a simple mixed order model. Normal fat mass was determined to be the best size descriptor for V and total body weight for Vmax.

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Xiao Hu Exposure-Response Analysis of Peginterferon Beta-1a in Subjects with Relapsing Remitting Multiple Sclerosis

Xiao Hu (1), Yaming Hang (1), Yue Cui (1), Shifang Liu (1), Jie Zhang (1), Ivan Nestorov (1)
(1) Biogen Idec Inc

Objectives: To establish a population pharmacokinetic (PK) model of peginterferon beta-1a (PEG-IFN) in relapsing remitting multiple sclerosis (RRMS) patients and develop the relationship between PEG-IFN exposure and annualized relapse rate (ARR).

Methods: PK and ARR data were obtained from a double-blind placebo-controlled Phase 3 study in RRMS patients (n=1512), in which 125 mcg subcutaneous PEG-IFN every 2 (Q2W) or 4 (Q4W) weeks reduced ARR (primary endpoint) significantly [1]. Using post-hoc PK parameters derived from a population PK model developed using NONMEM [2], PEG-IFN exposure was represented by monthly cumulative AUC for each subject. Four models were tested to describe the distribution of relapse counts, including Poisson, zero-inflated Poisson, log-normal Poisson, and Poisson gamma (equivalent to negative binomial) models. Covariates screened for the exposure-response model included baseline relapse rate in the past 3 years, age, Expanded Disability Status Scale, sex, McDonald Criteria, T2 lesions at Week 24, gadolinium-enhanced (Gd+) lesions at Week 24. Parameters were estimated using Bayesian analysis

with Gibbs sampling in WinBUGS v1.4.3 [3]. Non-informative priors were used for parameter estimates.

Results: The relapse count was best described by a Poisson gamma model. The relationship between monthly cumulative AUC and ARR was well described using a log-linear model. In general, the ARR decreased as cumulative AUC increased. The slope for ARR reduction was steep in the Q4W AUC range, especially at below median AUC. In contrast, the slope started to level off in the Q2W AUC range. The model demonstrated that the better efficacy of the Q2W dosing regimen as compared with the Q4W dosing regimen was driven by its greater PEG-IFN exposure. Among all covariates tested, both T2 lesion volume and Gd+ lesion volume at 24 week improved model prediction, indicating the efficacy observed in MRI lesion at Week 24 was related to the ARR at Year 2. Inclusion of Gd+ lesions improved the model prediction better than the T2 lesion.

Conclusions: The model suggested that greater PEG-IFN exposure in the Q2W group explain the enhanced efficacy, as accounted by ARR, observed for the Q2W group, as compared to the Q4W group.

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Moustafa Ibrahim Design of Phase I Studies based on Mechanism of Action of Anti-Diabetic Drugs; Assessing power, precision and accuracy in a simulation study of glucose tolerance tests

Moustafa M. A. Ibrahim, Siti M. Sheikh Ghadzi, , Maria C. Kjellsson, Mats O. Karlsson
Department of Pharmaceutical Bioscience, Uppsala university

Background and Objectives: In anti-diabetic drug development, phase I studies usually involve short-term glucose provocations, e.g. meal tolerance test (MTT) and graded glucose infusion (GGI). With a highly nonlinear, complex system as the glucose homeostasis, the various provocations will contribute with somewhat different information. The aim with this project was to investigate the most appropriate study design in phase I, for several hypothetical mechanisms of action (MoA) of a study drug. Power to detect drug effect and accuracy of quantification of drug effect was assessed using simulations.

Methods: Five drug effects in diabetes therapeutic area were investigated using six study design models. The MoA of drug effects were stimulation of basal insulin (BINS), glucose clearance, both insulin dependent (CLGI) and independent (CLG), as well as inhibition of endogenous glucose production (EGP) and absorption of oral glucose (GABS). The study design were oral glucose tolerance test (OGTT), intravenous glucose tolerance test (IVGTT) single meal tolerance test (sMTT), 24-hours meal tolerance test (MTT-24),

graded glucose infusion (GGI) and repeated fasting glucose sampling, i.e. no provocation (NO). The models used for simulations and estimations were different versions of the integrated glucose-insulin model (IGI) [1-3]. Monte carlo mapped power (MCMP) [4] was used to calculate, for each study design, the power to detect each of the above mentioned drug effects. Stochastic simulation and estimation (SSE) was used for determination of the most precise study design model in computing the size of a particular drug effect The power and precision of models, were determined by using the MCMP and SSE tools implemented in PsN version 3.5 (PsN, Uppsala University, Uppsala, Sweden) [5] and NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD) [6]. Graphs and Data set creation for NONMEM were performed using R [7].

Results: The power of IVGTT and GGI was similar for all MoAs, always higher than sMTT if the drug effect was not on GABS. The 24-MTT was more powerful than sMTT for all MoAs except CLG. Using repeated fasting measurements were surprisingly powerful, and was for many MoAs similar to sMTT. The study design with the highest drug parameter precision was not always the most powerful to detect the drug effect.

Conclusion: Pharmacometric model-based simulations can be a valuable tool in the design of phase I studies in phase I anti-diabetic drug studies as the power and precision of various study designs is highly dependent on MoA of study drug.

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Itziar Irurzun-Arana Methodology for Boolean Modeling of Biological Networks Applied to Systems Pharmacology

Itziar Irurzun-Arana (1), Jose Martín Pastor (1), Leire Ruiz-Cerdá (1), Ignacio Gonzalez-Garcia (2), Iñaki F. Trocóniz (1), José David Gómez-Mantilla (1).

(1) Pharmacometrics & Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona 31080, Spain. (2) Pharmacy and Pharmaceutical Technology Department, University of Valencia. Valencia, Spain.

Objectives: To provide an overview of the methodology to perform Boolean modeling in Systems Pharmacology, describing the required tools and steps for its implementation.

Methods: Boolean network models are the simplest discrete dynamic models in which the components of a system are represented by nodes and the interactions among them by edges. This type of networks only assumes two states for each component (ON or OFF). The state of each node is determined by its regulator nodes in the network based on Boolean Functions (BFs), which are a combination of AND, OR and NOT operations [1-3]. We describe a method to write BFs in the R environment in order to study the evolution of the constructed network as a function of time. As there is no explicit notion of time in a logic model, each round a network

is updated can be considered a time step. The result of the simulations may differ depending on the updating method chosen for the model, which can be synchronous or asynchronous [1-3]. In addition, several tools were developed for the exploratory and quantitative analysis of the network output to evaluate the level of activation of the nodes in all time steps or to cluster the nodes that lead to similar alterations within the network.

Results: Our approach for Boolean modeling of Systems Pharmacology networks entails the following steps: 1) development of the model structure (nodes, edges, and BFs) based on evidence from literature or experimental data, 2) R programming of the corresponding BFs, establishing the stochastic procedure to update the nodes of the network, 3) development of a parallelized simulation algorithm, and 4) analysis of the system output. Moreover, a system perturbation analysis can be performed in order to see which node knockouts or persistent activations lead to significant changes of the network dynamics [1].

Conclusions: Since Boolean models are parameter free, they serve as a starting point for modeling complex pharmacological systems for which a detailed kinetic characterization is not available [1,3]. Applying the proposed tools, simulations of the dynamics of a biological system can be performed, studying the effect of perturbations. The resulting models can be used to analyze signaling networks associated with diseases in order to predict the pathogenesis mechanisms and design potential therapeutic targets.

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Esther Janssen Population pharmacokinetic analysis of lamivudine in children aged 5 months – 18 years

Esther J.H. Janssen* (1), Diane E.T. Bastiaans* (2), Pyry A.J. Välitalo (1), Annemarie MC van Rossum (3), Diana M Gibb (4,5), Evelyne Jacqz-Agrain (6,7), Hermione Lyall (8), Catherijne A.J. Knibbe (1,9), David M. Burger (2)

(1) Division of Pharmacology, LACDR, Leiden University, Leiden, the Netherlands, (2) Department of Pharmacy, Radboud University Medical Center, , Nijmegen, the Netherlands, (3) Division of Pediatric Infectious Diseases and Immunology, Erasmus MC/Sophia, Rotterdam, the Netherlands, (4) Medical Research Council/Clinical Trials Unit, London UK, (5) Department of Pediatrics, Great Ormond Street Hospital, London, UK, (6) Department of Pediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, Université Paris VII, Paris, France, (7) Clinical Investigation Center CIC9202, INSERM, Paris, France, (8) Department of Pediatrics, St Mary's hospital, London, UK, (9) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands

Objectives: Lamivudine is a nucleoside reverse transcriptase inhibitor and used as part of antiretroviral therapy in HIV-infected children. A population pharmacokinetic analysis was performed to explore the impact of covariates on lamivudine pharmacokinetics.

Methods: Population pharmacokinetic modelling was performed in NONMEM 7.3 using data from four different studies[1-5], of which two were used for model building[1] and two for model

validation[2-5]. Children (n=180) were aged 0.4-18 years (median age 6.6 years) and received a daily oral lamivudine dose of 60-300 mg. A median of 12 samples per individual was available. Different absorption models and different covariates were investigated. For the covariate analysis, different functions (e.g. power function, exponent function, maturation function) were evaluated. The model was validated internally and externally[6].

Results: A two-compartment model with sequential zero order and first order absorption best described the data. Apparent clearance and central volume of distribution was 13.2 L/h and 39.0 L for a median individual of 16.6 kg, respectively. Bodyweight was identified as the most significant covariate on both apparent clearance and the apparent volume of distribution, which was implemented with a power function for both parameters. The external validation confirmed the predictive ability of the final model.

Conclusions: In this study, bodyweight alone was able to explain 19% of variation in apparent clearance and 14% of variation in apparent volume of distribution. As these covariate functions may reflect not only the development of clearance and distribution volume, but also age-dependent changes in bioavailability, further analysis, which includes intravenously administered lamivudine, is warranted in order to get insight in these age-dependent changes in parameters.

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Nerea Jauregizar Pharmacokinetic/Pharmacodynamic modeling of dynamic time-kill curves for anidulafungin against Candida

Nerea Jauregizar (1), Sandra Gil-Alonso (1), Ignacio Ortega (2), Elena Eraso (3) and Guillermo Quindós (3)

(1) Department of Pharmacology, Faculty of Medicine, University of the Basque Country (UPV/EHU), Spain. UFI11/25 "Microbios y Salud". (2) Research Development and Innovation Department, Faes Farma S.A. Leioa. Spain. (3) Department of Immunology, Microbiology and Parasitology, Faculty of Medicine, University of the Basque Country (UPV/EHU), Spain. UFI11/25 "Microbios y Salud"

Objectives: In vitro time-kill curves are attractive tools for studying the pharmacodynamics of antimicrobial agents as they provide detailed information of antimicrobial efficacy as a function of both time and concentration [1]. The aim of this study was to apply a mathematical model that is appropriate for characterizing pharmacodynamics of anidulafungin, from dynamic time-kill experiments with changing anidulafungin concentrations, against *Candida.*

Methods: A one-compartment in vitro infection model was developed to simulate exponentially changing drug concentrations of anidulafungin in the presence of viable *Candida* cells, at C_{max}=5.47 μg/ml. The culture broth from the central compartment was continuously supplied and removed at a flow rate adjusted to

simulate a half-life equal to 25.6 h. Samples for viable counts were taken at time points 0, 2, 4, 6, 24 and 48 h after start of experiments. Data was modeled using NONMEM V7.2.0 [2] with first order conditional estimation method. Diagnostic plots and precision of parameter estimates were evaluated to assess model performance. Additionally, human PK data for anidulafungin were used to simulate expected time-kill curves for anidulafungin under typical dosing regimens.

Results: Time-kill data were best fit by using an adapted sigmoidal E_{max} model that corrected for delay in the growth of *Candida* and the onset of the anidulafungin activity, steepness of the concentration-response curve, and saturation of the cell number of *Candida*. Dynamic time-kill curves of assayed strains were well predicted by the model. Moreover, the mathematical model can be used to simulate expected kill curves for anidulafungin dosing regimens.

Conclusions: We have shown that it is feasible to fit dynamic time-kill data of anidulafungin against *Candida* by using an adapted E_{max} mathematical model. Our approach of combining in vitro time-kill data with existing in vivo PK data might serve as a model for future studies to define optimal antifungal regimens.

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Shuangmin Ji Model-based Meta-analysis to Determine the Efficacy of Entecavir and Adefovir in the Treatment of Chronic Hepatitis B

Shuangmin Ji (1), Chenhui Deng (2), Kehua Wu (1), Liang Li (1), Tianyan Zhou (1), Mats Karlsson (2), Wei Lu (1)
(1) School of Pharmaceutical Sciences, Peking University, Beijing, China; (2) Pharmacometrics Research Group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: The objectives of this study were to (1) develop a semi-mechanistic model to characterize the dynamics of viral DNA load in hepatitis B virus (HBV) infected patients who had received treatment of entrcavir (ETV) or adefovir (ADV), (2) to describe the life cycle of HBV for efficacy comparison of two drugs, and (3) to identify potential covariates of virus kinetics.

Methods: Publications were retrieved from PubMed database according to the pre-defined inclusion and exclusion criteria. Mean and individual data of HBV DNA after start of treatment were analyzed using a nonlinear mixed-effects modeling (NONMEM) approach and first-order conditional estimation with interaction (FOCE-I) laplacian method. The significance of potential covariates was evaluated. Variance of estimates and model robustness were assessed using sampling importance resampling (SIR) and individual visual predictive check (VPC) approaches.

Results: A three-compartment model, including target hepatocytes compartment, infected hepatocytes compartment and virus load compartment, was built to describe HBV DNA kinetics after administration of ETV or ADV, which is first and second line treatment, respectively. A density-dependent proliferation of hepatocytes is assumed in this model, and part of the healthy hepatocytes is assumed not to be infected . The death rate of infected hepatocytes for ETV and ADV is 0.0428 and 0.0311 per day respectively, almost 10 times of the healthy hepatocytes (0.004 per day). HBV DNA was significantly decreased by both treatments. ED50 of ETV in patients with or without prior treatments was 0.0055 mg and 0.0015 mg, respectively.

Conclusions: Model-based meta-analysis is useful to compare different drugs in the same class or identify significant covariates by pooling literature data and building pharmacological models. Further development of this viral kinetic model may provide information about drug resistance and therefore improve understanding of this disease.

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We thank Gailing Li, Jia Ji and ShanShan Bi for their support and contributions to this project.

Feng Jin Population Pharmacokinetic Modeling of Sofosbuvir, a NS5B Polymerase Inhibitor, and Its Metabolites, in Patients with Hepatitis C Virus Infection

Feng Jin, Brian Kirby, Yuying Gao, Brian Kearney, and Anita Mathias
Gilead Sciences, Foster City, CA 94404

Objectives: Sofosbuvir (SOF), a potent NS5B polymerase inhibitor with broad HCV genotype coverage, is approved for the treatment of genotype 1, 2, 3, and 4 chronic HCV infection in treatment-naïve and -experienced patients and HIV/HCV co-infected patients. As a prodrug, SOF undergoes extensive sequential metabolism to form its major metabolites GS-566500 and GS-331007. The objective of this analysis was to develop a mechanistic integrated population pharmacokinetic model for SOF, GS-566500 and GS-331007, and to evaluate the impact of covariates on their PK.

Methods: Data from 8 clinical studies conducted in HCV-infected patients (n=1288) were included in this analysis. Data were analyzed using NONMEM 7.3 with first order (FO) method. Stepwise forward addition followed by backward elimination was implemented in the covariate (age, gender, race, body weight, ethnicity, creatinine clearance (CLCR) or estimated glomerular filtration rate (EGFR), cirrhosis status, IL28B status, Ribavirin usage, food, and concomitant medications) model building process to develop final

PopPK model. Various model assessment methods were used to evaluate the model performance.

Results: Plasma PK of SOF and its metabolites was well described by the integrated model. The PK model was parameterized in clearances (CL), volumes (V), absorption rate constants (ka), lag times, and relative fraction absorbed of each analyte. Between-subject random effects were tested on clearances, volumes, and absorption rate constants. The following statistically significant parameter-covariate relationships were identified: gender on SOF and GS-331007 CL; food on SOF ka, GS-331007 V and ka; and CLCR on GS-566500 and GS-331007 CL. The population median estimated clearances were 78.26 L/hr, 81.45 L/hr, and 27.66 L/hr for SOF, GS-566500, and GS-331007, respectively, with the relative molar % of dose absorbed at 13.2%, 23.6%, and 63.2% respectively. The covariates tested did not have a clinically meaningful impact on SOF and its metabolites exposures. PK/PD results utilizing exposures from this integrated model were consistent with those from individual models previously established for SOF and GS-331007.

Conclusions: SOF, GS-566500, and GS-331007 PK were adequately described by an mechanistic integrated model. Relative to the individual model, this integrated model provided further insight on the conversation of SOF to its metabolites.

Mats Jirstrand Sensitivity Equations Provide More Robust Gradients and Faster Computation of the FOCE Approximation to the Population Likelihood

Joachim Almquist (1,2), Jacob Leander (1,3), Mats Jirstrand (1)
(1) Fraunhofer-Chalmers Centre, Gothenburg, Sweden (2) Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden (3) Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden

Objectives: The first order conditional estimation (FOCE) method [1] is still one of the parameter estimation workhorses for nonlinear mixed effects (NLME) modeling used in population pharmacokinetics and pharmacodynamics [2]. However, because this method involves two nested levels of optimizations, with respect to the empirical Bayes estimates and the population parameters, FOCE may be numerically unstable and have long run times, issues which are most apparent for models requiring numerical integration of differential equations.

Methods: We propose an alternative implementation of the FOCE method, and the related FOCEI, for parameter estimation in NLME models [3]. Instead of obtaining the gradients needed for the two levels of quasi-Newton optimizations from the standard finite difference approximation, gradients are computed using so called sensitivity equations.

Results: The advantages of the approach are demonstrated using different versions of a pharmacokinetic model defined by nonlinear differential equations. We show that both the accuracy and precision of gradients can be improved extensively, which will increase the chances of a successfully converging parameter estimation [4]. We also show that the proposed approach can lead to markedly reduced computational times. The accumulated effect of the novel gradient computations ranged from a 10-fold decrease in run times for the least complex model when comparing to forward finite differences, to a substantial 100-fold decrease for the most complex model when comparing to central finite differences.

Conclusions: Considering the use of finite differences in for instance NONMEM and Phoenix NLME, our results suggests that signicant improvements in the execution of FOCE are possible and that the approach of sensitivity equations should be carefully considered for both levels of optimization.

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Åsa Johansson Application of an Item Response Theory model to describe Amyotrophic Lateral Sclerosis Functional Rating Scale data

Åsa M. Johansson (1), Inez de Greef (2), Bernard Muller (2), and Piet H. van der Graaf (1)
(1) Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands, (2) Treeway B.V., Rotterdam, The Netherlands.

Objectives: To develop an Item Response Theory (IRT) model which describes Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) data. The IRT model will, in a later stage, be used in a disease progression model for Amyotrophic Lateral Sclerosis (ALS).

Methods: The severity of ALS is assessed through the ALSFRS, consisting of 10-12 tasks with 5 levels of fulfilment (0-4). IRT can be applied to ALSFRS data to link the probabilities to complete the different tasks (to certain extents), to the patient's disability level (disease stage) [1]. The disease stage is a latent trait, which is only assessable through the evaluation of the data. The latent trait is assumed to be normally distributed in the population. The IRT model can be combined with a pharmacometric model to describe how the disease progresses over time [2].

ALSFRS data from 4,838 ALS patients were accessed through the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database. A total of 42,775 evaluations of ALSFRS were available,

and each evaluation was regarded as a separate individual in the fitting of the IRT model. The individuals were divided into three groups, based on the location of their first symptoms: limb onset, bulbar onset, and combined limb and bulbar onset. Separate sets of parameters (probability curves) were estimated for the three onset groups. A homogeneous graded response model [3], and different versions of a heterogeneous graded response model [4], were fitted to the data. The models were evaluated based on objective function values (OFV), distribution of the latent trait variable (should be approximately normally distributed), and visual comparisons between predicted and observed probability curves.

Results: The homogeneous graded response model resulted in a skewed distribution of the latent trait variable, and the visual comparison of predicted and observed probability curves revealed a model misspecification at later stages of the disease. The final heterogeneous graded response model resulted in a significantly lower OFV, and a normally distributed latent trait variable.

Conclusions: An IRT model describing ALSFRS data was developed. The IRT model will be used in a disease progression model for ALS, to evaluate the effect of new therapies.

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Francine Johansson Azeredo Comparing the fungicidal effect of free amphotericin B with to a novel miccele system against Candida albicans by a PK/PD modeling approach

Francine Johansson Azeredo (1), Miguel Adelino da Silva Filho (1), Christian Assunção da Silva (1), Hartmut Derendorf (2), Eryvaldo Sócrates Tabosa do Egito (1)
(1) Programa de Pós Graduação em Ciências da Saúde, UFRN, Natal-RN, 59012-570, Brazil; (2) Department of Pharmaceutics, University of Florida, Gainesville-FL, 32603, United States of America;

Objectives: The aim of this study was to model the time-kill curves of static concentrations of a novel formulation containing Amphotericin B (AmB) against *Candida albicans* in order to better analyze its pharmacological effect and to compare this effect to the free AmB one by PK-PD model approach [1].

Methods: The super-aggregated formulation containing AmB was prepared by heating the AmB micelle system as previously described [2]. The prepared formulation (AmB-DOC-H) activity against *C. albicans* ATCC 90027 was analyzed in an in vitro PD study. In vitro time-kill curves were obtained by counting the number of colony forming units (CFU) as a function of time after yeast exposition to AmB concentrations multiple of MIC (0.25, 0.5, 1 and 2 times MIC). Experiments were followed in triplicate for 24 h. We adapted a published E_{max} model to describe the time course of the

fungicidal activity of AmB and its resistance [3] using the software NONMEM v. 7.0 (ICON®, USA).

Results: Both free AmB and AmB- DOC-H MICs against *C. albicans* were 0.25 µg/mL. The PK/PD model that better described the AmB-DOC-H fungicidal effect has compartments for drug-susceptible fungus (S), susceptible fungus that need a growing lag time (Slag) and insusceptible fungus (R) with first order rate constants for growth (knet) and one that stimulates the transfer from the proliferating stage into the resting stage (kSR). All the population Pk-PD parameters obtained from the modeling were estimated with acceptable precision, showing values of 1.58 h-1 (9%) and 1.22 h-1 (7%) for Emax of free AmB and AmB-DOC-H, respectively. The values of EC50 were 0.0326 µg/mL (18%) and 0.0801 µg/mL (17%) of free AmB and AmB-DOC-H.

Conclusions: A PK/PD model that incorporates both the *C. albicans* lag time of growth and rate of transfer to resting stage was used so it could well characterize the observed time courses of fungicidal killing over a wide range of concentration-time profiles, indicating that these factors needs to be considered when proposing dosing regimen for this drug. Moreover, AmB- DOC-H showed a promising potency against *C.albicans* according to the estimated EC50 value which was higher than the estimated for the free AmB.

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Niclas Jonsson Population Pharmacokinetic Simulations of Two Paliperidone Palmitate Formulations

Mats O. Magnusson (1)*; Mahesh N. Samtani (2)*; Elodie L. Plan (1); E. Niclas Jonsson (1); Stefaan Rossenu (3); An Vermeulen (3) (*equal contribution)

(1) Pharmetheus, Uppsala, Sweden; (2) Johnson & Johnson Pharmaceutical Research & Development, L.L.C., NJ, USA; (3) Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutical N.V., Beerse, Belgium.

Background: Population pharmacokinetic (PK) models have been developed for paliperidone palmitate 1 and 3-month formulations (PP1M and PP3M).

Objective: To investigate dosing strategies for PP3M and to explore the impact of selected covariates using the final models, including significant subject covariates, as simulation tools.

Methods: A 1-compartment model with parallel zero and first-order absorption describing the PK of PP1M [1] and a 1-compartment model with 2 saturable absorption processes describing the PK of PP3M [2] were used for simulations in R 3.0.2 [3]. Covariates of interest [2] were obtained by resampling subject covariates available in the PK database for PP1M and PP3M in order to keep realistic correlations across the covariates. Simulation scenarios with varying dosing times and covariate values were generated. The

population median and 90% prediction interval of the simulated concentration-time profiles were plotted for simulation outcomes evaluation.

Results: PP3M administered every 12 weeks, at doses that are a 3.5-fold multiple of the corresponding PP1M dose, appears to result in paliperidone exposures similar to those obtained with doses of PP1M every 4 weeks. Paliperidone PK, when administered as PP3M, was not significantly altered in subjects of different sex or using the deltoid or the gluteal injection site. Once stabilized on treatment with PP3M, trough paliperidone plasma concentrations were similar in subjects with different BMI. Furthermore simulations showed that subjects with mild renal impairment were expected to have higher exposures, however dose adjustment is not required for PP3M since it is done when initiating PP1M. Peak plasma concentrations for a typical patient were achieved within 30-33 days after a single PP3M injection over the dose range of 175-525 mg eq. The PK of paliperidone palmitate was dose-proportional for overall exposure and appeared to be dose-proportional for Cmax over a dose range of 175-525 mg eq. At steady-state the PP3M peak-to-trough ratio was 1.6-1.7 following gluteal and deltoid administrations, which is similar to the peak-to-trough ratios following deltoid PP1M injections. The apparent half-life of the PP3M formulation was in the range of 84-95 days following a deltoid injection and 118-139 days following a gluteal injection.

Conclusion: The explored PK simulation scenarios provided important guidance on PP3M dosing in schizophrenic patients and supported a once every 3 months injection cycle.

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Amita Joshi Survey of methodologies for exposure-response analysis of oncology drugs approved in FDA from 2010 to 2013

Tong Lu, Dan Lu, Bert L. Lum, Mark Stroh, Priya Agarwal , Nalin Tikoo , Jin Y. Jin, Amita Joshi
Genentech, Inc.

Objectives: Exposure-response (E-R) analysis is extensively used in drug development and regulatory decision-making, and is still a developing field in oncology given many unique challenges. The survey will provide an overview of methodologies for E-R analysis in FDA oncology review and other E-R methodologies, and discuss pros and cons.

Methods: 28 New Molecular Entity (NME) in oncology approved by FDA from 2010 to 2013 were surveyed based on "clinical pharmacology and biopharmaceutics review" that publicly available [1]. Both exposure-efficacy (E-E) and exposure-safety (E-S) analyses were reviewed. FDA's approach was chosen when different from sponsor. Results are summarized as pie charts and table with pros and cons as well as case examples.

Results: In total, there were 37 E-E and 32 E-S analyses performed for the 28 NMEs. Typical E-E analysis included Kaplan-Meier (K-M) plots & Cox proportional hazard (Cox PH) model of survival data (19 cases), and logistic plot & regression model for binary data (11 cases). Compared to K-M plots stratified by exposure, which can be

influenced by confounding factors, Cox PH model assess the E-E relationship by adjusting for those factors, and has been combined with K-M plots in majority of cases (15/19). For E-S analysis, logistic plot & regression model played a central role (21 cases) given most safety data were treated as binary endpoints. Box plots can be used to visualize E-R relationship for categorical data; but it might fail to identify one that is not sufficiently steep; logistic plot is more sensitive to detect E-R relationship, but both plots can be influenced by confounding factors, which has been considered by logistic regression model. Additional methodologies that were not in the review include longitudinal PK/PD model for biomarker or tumor response data, longitudinal and repeat time-to-event model for categorical data, parametric model and case-matching analysis for survival data, etc. These methodologies may be more robust to refine E-R relationship by integrating data in longitudinal fashion; however, comparisons of these methodologies for E-R assessment in oncology need further evaluation.

Conclusions: The survey reviewed and summarized the E-R analysis for recently approved oncology drugs by FDA, together with other E-R methodologies. It provides a framework for appropriate application and further advancement of E-R methodology to support dose justification and optimization especially in oncology.

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Marija Jovanovic Nonlinear mixed effects modelling approach in investigating amitriptyline pharmacokinetics

Jovanović M (1), Vučićević K (1), Golubović B (1), Ćulafić M (1), Timotijević I (2), Pokrajac M (1), Miljković B (1)
(1) Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy, Belgrade, Serbia; (2) Institute of Mental Health, University of Belgrade - School of Medicine, Belgrade, Serbia

Objectives: The aim of the study was to investigate pharmacokinetic characteristics of amitriptyline (AMT) and influence of different variability factors in patients with depression.

Methods: A total of 280 AMT concentrations were obtained from depressive patients after administration of single dose. An average dose of AMT was 91.07 ± 31.34 mg. Pharmacokinetic analysis was performed by nonlinear mixed effects modelling using NONMEM® software (version 7 level 2) and Perl speaks NONMEM® (version 3.5.3). Parameters estimation was performed by FOCE with interaction. Influence of AMT dose, demographic characteristic and co-therapy on AMT CL/F was investigated.

Results: Structural model was developed as a one-compartment model with first-order absorption and elimination implemented in ADVAN2/TRANS2 subroutine. The interindividual variability was evaluated by an exponential model while residual variability was

best described by proportional model. The estimated CL/F was 70.4 (66.36 - 74.44) l/h, V/F was 1300 (1216 - 1384) l and k_a was 0.633 (0.497 - 0.769) h^{-1}, for a typical patient. Among tested covariates, only influence of weight on CL/F was significant (p<0.01). Inclusion of covariate into the base model decreased interindividual coefficient of variability for CL/F, and in the final model it was 8%. There were no significant impact of gender, AMT dose and co-therapy with lithium and fluvoxamine on AMT elimination. Residual variability in the final model was 0.29 (0.266 - 0.315). Acceptable model performances were confirmed by adequate diagnostic plots and internal validation.

Conclusions: The final population AMT model describes and quantifies influence of weight on AMT elimination in patients with depression. The results can be used for estimation of CL/F and individualization of dosing regimen.

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Vincent Jullien Population pharmacokinetics of bumetanide in term newborn infants with seizures

Vincent Jullien (1),Ronit Pressler (2), Geraldine Boylan (3), Mats Blennow (4), Neil Marlow (2), Catherine Chiron (1), Gerard Pons (1)
(1) INSERM U1129, Paris, France, (2) University College London, UK, (3) University College Cork, Ireland, (4) Karolinska Institutet and University Hospital, Stockholm, Sweden

Objectives: Experimental data supported the use of bumetanide for the treatment of neonatal seizures due to hypoxic-ischaemic encephalopathy (HIE). The objectives of the study were to develop a population PK model of bumetanide in this population and to evaluate the possible relationship between the exposure to the drug and its efficacy/safety.

Methods: Infants with HIE and seizures not responding to a loading dose of 20 mg/kg IV phenobarbitone were included in the study. Bumetanide was administered by IV route every 12 hours for 48 hours. Four different unitary dose levels (0.05, 0.1, 0.2, and 0.3 mg/kg) were evaluated. Primary end point for efficacy was the reduction of electrographic seizure burden by ≥80% within hours 3 and 4 after the first bumetanide administration compared to the baseline without need for rescue AED over the next 48h. Screening for hearing impairment was performed for toxicity evaluation. Four blood samples of 500 µL were drawn per infant. The infants were randomly assigned to one of 2 sampling groups. Population PK analysis was performed using MONOLIX software (version 4.2). For

each newborn, AUC after the first dose (AUC1) and the total cumulative AUC (AUC2) were calculated using individual estimates of clearance, and possible relationship between AUC1, AUC2 and efficacy or the occurrence of hearing loss was investigated.

Results: Fourteen newborn infants (4 girls) were included in the study. Four infants were allocated to dose level 0.05mg/kg, three to 0.1mg/kg, six to 0.2mg/kg and one to 0.3mg/kg. Only 2 infants met all criteria for a positive seizure outcome. Three infants died (due to the severity of HIE and/or comorbidities) and among the 11 survivors three were subsequently found to have hearing loss. Forty-nine blood samples were available for PK evaluation. The best structural PK model was a 2-compartment model with first-order elimination from the central compartment. BW was found to explain the IIV of the elimination clearance of bumetanide. Mean population parameters (% IIV) were: CL (L/h) = 0.063 x (BW/3.4)1.69(22 %), Vc (L) = 0.285, Vp (L) = 0.443 (42 %), Q (L/h) = 0.594. Eta shrinkage was 21 % for CL and 23 % for Vp. No trend was observed between AUC1 or AUC2 and efficacy/toxicity.

Conclusions: This is the first population PK model for bumetanide in newborn infants. Bumetanide was associated to an unfavorable efficacy/safety ratio for the treatment of neonatal seizure.

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Rasmus Juul Exploring the relationship between analgesic event rate and pain intensity in kidney stone surgery: A Repeated Time to Event Pilot Study

RV Juul(1), KV Pedersen(2, 4), LL Christrup(1), AE Olesen(1, 3), AM Drewes(3), PJS Osther(4), TM Lund(1)
1) Department of Drug Design and Pharmacology, University of Copenhagen, Denmark. 2) Department of Clinical Genetics, Vejle Hospital, Denmark. 3) Mech-Sense, Aalborg University Hospital, Denmark, 4) Urological Research Center, Lillebaelt Hospital, University of Southern Denmark, Fredericia, Denmark

Objectives: Opioid consumption has often been reported as an indirect measure of pain in postoperative pain trials. The rate of consecutive analgesic events can be described by repeated time-to-event (RTTE) modelling in order to analyse the dynamical changes and concentration-effect-relationships with analgesic consumption. However a relationship with pain intensity has not yet been established. The aim of this pilot study was to discuss how best to investigate the relationship between RTTE hazard of analgesic events and pain intensity in postoperative pain.

Methods: Data was available from 44 patients undergoing kidney stone surgery (percutaneous nephrolithotomy), who were randomized to morphine or oxycodone administered upon request (1). Pain intensity was recorded on Numerical Rating Scale (NRS) every 15 min until 4 hours after admission to recovery ward. RTTE modelling of analgesic events was performed in NONMEM 7.2 and

PsN (2). Gompertz and exponential distribution models were evaluated. Post-hoc linear mixed effect modelling was performed between estimated RTTE hazard and observed NRS using the lme4 package in R (3).

Results: A Gompertz distribution model adequately described data, with a baseline event rate of $0.64h^{-1}$ (RSE 25%) and a decline in event rate with a half-life of $1.2h^{-1}$ (RSE 22%). No significant differences were found between morphine and oxycodone. Post-hoc linear mixed effects modelling of the estimated RTTE hazard and NRS is demonstrated, but do not optimally describe the categorical nature of NRS.

Conclusions: An RTTE model well described both morphine and oxycodone consumption data. RTTE modelling is a promising tool to investigate correlations between opioid consumption and pain intensity in time, but appropriate methods needs to be applied to study this relationship.

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Matts Kågedal Binning of exposures in survival analysis for oncology – A simulation study

Matts Kagedal (1) , Russ Wada (2), Shang-Chiung Chen (1), Jin Jin (1)
1. Genentech 2. Quantitative Solutions

Objectives: The aims of an exposure-response (E-R) analysis in oncology includes 1) to describe the relationship between drug exposure and survival and 2) to assess the risk of loosing efficacy in low exposure patients by comparing efficacy in patients with low exposure to control. The analysis is often performed as a time-to-event analysis where patients are binned into equally sized groups based on exposure. Few bins may result in a low probability in picking up an E-R trend since a wide range of exposures with different efficacy will be pooled into one group, while many bins will result in few patients per bin and large variability/uncertainty in the hazard ratio (HR) estimation. This simulation study was performed to assess the impact of binning by quartiles, tertiles or twotiles on the ability to 1) detecting an E-R trend; and 2) compare efficacy in the low exposure treatment bin over control.

Methods: A simulation study was performed assuming a 2-arm oncology trial with n=100 per arm. Two E-R scenarios were assumed: one with no E-R trend and a hazard ratio (HR) of 0.67 across all exposure levels, and one with an E-R trend where the HR ranged from 1 to 0.4 from low to high exposure. The simulated trials were evaluated after binning exposure by quartiles, tertiles and twotiles.

Results: In the first scenario of no E-R trend (True HR=0.67), it was concluded that efficacy was similar to or better than control (HR point estimate<1, CI<1.25) in 79% (quartiles), 87% (tertiles) and 94% (two-tiles) of the simulated studies, suggesting a quartile based analysis would fail to fulfill this criterion in 21% of the cases, while a two-tile based analysis would fail in only 4% of the cases. “No substantial E-R trend” was correctly concluded in 82% (quartiles), 85% (tertiles) and 89% (twotiles) of the simulated studies. In the second scenario with an E-R trend, there was no indication of worse efficacy (HR point estimate<1.25) than control in the low-exposure bin in 84% (quartiles), 91% (tertiles) and 98% (two-tiles) of the simulated studies. A “Substantial E-R trend” was correctly concluded in 92% (quartiles), 88% (tertiles) and 77% (twotiles) of the simulated studies.

Conclusions: The proposed clinical trials simulations approach enabled a quantitative evaluation of a key component of the E-R analysis plan. Binning by tertiles appears to provide the best ability to draw correct exposure-response conclusions in the tested oncology trial design.

Vangelis Karalis A computational methodology for the validation of the terminal slope estimate

Vangelis Karalis, Aristides Dokoumetzidis, Panos Macheras
Laboratory of Biopharmaceutics & Pharmacokinetics, National & Kapodistrian University of Athens, Athens, Greece

Objectives: To develop a criterion using the dC/dt *versus* C plot for testing whether the slope of the terminal (logC vs. t) data points, represents the real exponential terminal phase of the data points.

Methods: For classical first-order elimination kinetics in one or a multi-compartment system, the relationship between dC/dt and C for the terminal phase data points is: dC/dt = - Kz*C (Eq.1) where Kz refers either to the elimination rate constant for the one-compartment system or to the smallest of the rate constants associated with the multi-compartment system. According to Eq.1, the dC/dt *versus* C plot of the terminal segment data points is a straight line with slope matching Kz and zero y-intercept. Due to the errors associated with the variables dC/dt, C, simulation studies were performed using errorless and contaminated with error C, t data. Several scenarios were investigated such as pharmacokinetic scenarios (e.g., one- and two-compartment models), sampling schemes, approximation method for the dC/dt estimate etc. In all cases, the slope and the intercept of the regression lines were calculated using Eq.1.

Results: For errorless data and sampling schemes ensuring real terminal phase data points following exponential elimination, the intercept values were found to be very close (non statistically significant) to zero. This small deviation is associated with the calculation errors of dC/dt. Negative y-intercepts statistically significant than zero were calculated for experimental data reported in the literature obeying power law elimination. For C, t error data generated from linear one and two compartment models, the y-intercept estimate is related to the sampling scheme and the standard error of the Kz estimate. In this case, a relationship between the y-intercept estimate, the standard error of the Kz estimate and the relative ratio of AUC of the area up to the last quantifiable concentration over area extrapolated to infinity was developed.

Conclusions: A computational method was explored for the validation of the terminal slope estimate relying on the analysis of terminal data points. Significant components for this criterion were found to be the relative ratio of AUC and the standard error of the Kz estimate.

Mats Karlsson Influence of clinical trial design to detect drug effect in systems with within subject variability

Chenhui Deng, Elodie L. Plan and Mats O. Karlsson
Pharmacometrics Research Group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: In many clinical development programs, identification of drug effect is attempted through hypothesis test based on data from a cross-over (XO) or, more commonly, a parallel (PA) group trial. One question relating to the absolute and relative merits of the two trial types concerns the capability of detecting drug effects in systems with within-subject variability (WSV). In a previous study, systems with WSV were analyzed using dynamic parameter IOV (*d*IOV) or stochastic differential equations (SDE) [1]. The aim of this study is to investigate type I error calibration and power to detect drug effects in PA and XO trials with WSV.

Methods: Stochastic simulations and estimations (SSE) were applied with a model including an exponential decay placebo effect and a linear dose effect. A *d*IOV was introduced on the maximum placebo effect for simulations. Models with or without drug effect, and with or without *d*IOV, SDE for system noise (SDEs) and SDE for parameter variability (SDEp), were fitted to the simulated datasets. Randomization tests were performed to investigate the type I error and power was determined following type I error control. A novel

mixture model approach was proposed to investigate the drug effect in XO studies.

Results: Uncalibrated type I errors were high for XO, but not PA, trials. The power to detect existing drug effects was much higher for XO than PA trials even after type I error calibration. Among models with or without WSV misspecification, similar results were obtained for PA trials, whereas they varied for XO trials, with increased power when WSV was more adequately described (true model>SDEs>SDEp>no WSV). The randomization test-derived test statistics for decrease in OFV were stable and close to the χ^2-distribution value in PA trials, but dissimilar and large among explored structural models with different drug effects in XO trials. When applying the proposed mixture model approach in XO trials, cutoffs, similar for different drug effects among different models, were considerably lower than with the above method and in agreement with χ^2-distribution.

Conclusions: XO trials are more powerful than PA trials; however assessment of drug effects in XO trials is made more complex in the presence of WSV. We have presented alternatives to handle this in terms of (i) extended models for WSV, (ii) randomization test for XO trials, and (iii) a mixture model approach for appropriately contrasting models with or without drug effects.

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Evgenia Kartsaki Translating Pharmacogenomics for Personalised Medicine

K. Lakiotaki (1), E. Kartsaki (1), A. Kanterakis (1), T. Katsila (2), G. P. Patrinos (2), G. Potamias (1)
(1) Institute of Computer Science, Foundation for Research & Technology – Hellas, Heraklion, Crete (2) Department of Pharmacy, University of Patras, Hellas

Objectives: To develop an integrated electronic Pharmacogenomics (PGx) web service that provides personalized genotype-to-phenotype translation services, linked to drug recommendations.

Methods: Genomic information repositories are mainly developed and maintained by stable governmental funded efforts, along with data sharing services (e.g., NCBI's dbSNP, dbGaP, dbVar and ClinVar). In contrast, the curation of genes related to the absorption, distribution, metabolism, and excretion - toxicity (ADMET) of drugs are usually handled by locus-specific databases such as, the Human Cytochrome P450 (CYP) Allele Nomenclature (www.cypalleles.ki.se), or databases focusing on transporters, receptors, and kinases [1]. Other online resources offer documented frequencies of pathogenic genetic variations that lead to inherited disorders in various populations worldwide, e.g., FINDbase (www.findbase.org) [2]. We developed automatic tools that combine data from heterogeneous sources (PharmGKB, dbSNP, Ensemble) and link them to available, up to date, pharmacogenomics information [3]. These tools are integrated into

a single web portal, where users can query for combinations of genes, drugs and alleles, and browse related clinical guidelines. Moreover, users may upload genotypes in Variant Call Format (VCF) and receive personalized drug recommendations, when available.

Results: To demontrate the integrated electronic Pharmacogenomics web service, we explored genome data from phase3 1000 Genomes Project (1kG). Statistical analysis shows a wide population differentiation in ADMET variants among 1kG populations. In general, individuals of African ancestry exhibit greater pharmacogenomics profile differentiation in most ADMET genes, which can be attributed to increased genetic heterogeneity of African population.

Conclusions: We developed an integrated electronic PGx assistant that offers personalized diagnostics based on genomic evidence. The novelty of its approach rests in its ability to infer an individual's phenotype (metabolizer status) based on a corresponding genotype profile and PGx data that are open and free. Based on this connection, the system acts as a "one stop shop" web portal for clinicians - by supporting them in making informed decisions, and for researchers - by providing a single place with information to understand, document and assess individuals' differences in drug efficacy.

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Ron Keizer New open source R libraries for simulation and visualization: "PKPDsim" and "vpc"

Ron Keizer (1,2,3), Devin Pastoor (4), Rada Savic (1,2)
(1) UCSF, San Francisco, CA (2) InsightRX, San Francisco, CA (3) Pirana Software & Consulting, the Netherlands (4) University of Maryland, Baltimore, MD

PKPDsim library

In pharmacometrics, many models are defined as systems of ordinary differential equations (ODEs). Although solving ODEs numerically in R is relatively straightforward using the deSolve library, the implementation of e.g. infusions and complex dosing regimens as well as the incorporation of random effects is cumbersome. Therefore, modelers commonly resort to Berkeley Madonna (BM) for exploratory simulations and teaching purposes instead of relying on R. BM does provide excellent interactivity features and is fast[1], but is inferior to R regarding plotting functionality, cumbersome regarding implementation of dose regimens and multi-level variability, and not open source/free.

The PKPDsim R library aims to offer similar features to Berkeley Madonna but within the R environment, so that the user can take advantage of R's powerful statistics and visualization tools. The library facilitates simulation of dosing regimens for PKPD mixed-effects models, leveraging either the fast Boost C++ library or R::deSolve for numerical integration. The PKPDsim library can be used from the R command line, but can also dynamically generate

Shiny frontends to allow interactive use for model exploration and teaching purposes.

vpc library:
Model simulations and simulation-based diagnostics such as the Visual Predictive Check are essential parts of the modeling workflow. Most modelers will be familiar with the functionality offered by e.g. PsN[4]/Xpose[5] or Monolix[6]. These tools are somewhat inflexible, however, as they are limited to one specific software and produce plots that are not easily tweakable and/or extendible.
The new 'vpc' library is written completely in R, and includes all plots also available in PsN/Xpose/Monolix: continuous, prediction-corrected, categorical, censored, survival, Kaplan-Meier Mean Covariate plots[7], as well as NPDE plots with uncertainty[8]. In comparison with the aforementioned tools, the “vpc” R library has the following strengths:

- use input data from any simulation tool (e.g. R, Matlab, ADAPT, Monolix, Phoenix, or the PKPDsim library introduced above)
- parsing and visualization steps in same environment (R)
- more binning strategies, easier to change binning
- output is ggplot2 object: easier customizable and extendable
- flexible plot options to e.g. optionally plot only observed data, or only simulated percentiles
- fast, by leveraging dplyr for main calculations

Both libraries will soon be released on CRAN, but are currently already available from http://www.github.com/ronkeizer.

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Lena Klopp-Schulze In silico simulation study: A comparison of two population pharmacokinetic models of tamoxifen and its major metabolite endoxifen

Lena Klopp-Schulze (1), Markus Joerger (2), Zinnia Parra-Guillen (1), Charlotte Kloft (1)
(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) Medical Oncology and Clinical Pharmacology, Dept. of Internal Medicine, Cantonal Hospital St. Gallen, Switzerland

Objectives: A high variability in the pharmacokinetics (PK) of tamoxifen and its metabolite endoxifen in estrogen receptor-positive breast cancer patients has been associated with differences in clinical efficacy and treatment-related toxicity. Therefore, optimising tamoxifen therapy by a personalised approach has been proposed [1]. The aim of this study was to compare the characteristics of two recently published PK models of tamoxifen and endoxifen and its ability to reflect observed data [3].

Methods: Concentration-time profiles of tamoxifen and endoxifen were simulated in Berkeley Madonna using the published PK models "Ter Heine model" [1] and "Dahmane model" [2]. Deterministic and stochastic simulations (each N=1000) of 20 mg QD p.o. tamoxifen for 6 month were performed using typical population PK estimates and clinically relevant covariates (CYP2D6, CYP3A4/5) on PK. The

results were compared to steady-state concentrations reported in [3] and to a proposed threshold concentration associated with therapeutic success ($C_{Endoxifen}$ of 5.97 ng/mL) [4]. The percentage of virtual patients with endoxifen steady-state plasma concentrations above the therapeutic threshold was calculated for each population.

Results: The two evaluated models used different approaches to describe drug-metabolite concentrations. While Ter Heine et al. implemented a hypothetical liver compartment to describe the formation of endoxifen, Dahmane included two additional metabolite compartments accounting for two routes of endoxifen formation. When comparing the simulations of the virtual populations using typical covariates, the Dahmane model showed considerably higher steady-state concentrations of tamoxifen and endoxifen compared to the Ter Heine model. Hence, the probability of target attainment, i.e. as percentage of patients above the proposed threshold, was higher for the simulated typical patient profiles using the Dahmane model compared to the Ter Heine model. Additionally, the Dahmane model described the observed data better.

Conclusion: This simulation study of tamoxifen and endoxifen displayed substantial differences between the investigated PK models. Also for anticipated exposure-response, as indicated by the proposed threshold concentration, the two population PK models resulted in a profoundly different probability of target attainment. External validation with respect to the predictiveness of the PK models is currently ongoing and will eventually contribute to a more comprehensive understanding of the PK of tamoxifen and endoxifen.

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Jane Knöchel Impact of randomness of mutation dynamics on the development of drug resistance under antiviral therapy

Jane Knöchel (1,2), Sathej Gopalakrishnan (2,4), Charlotte Kloft (3), Wilhelm Huisinga (1)
(1) Computational Physiology Group, Institute of Mathematics, Universitaet Potsdam, Germany (2) PharMetrX Graduate Research Training Program, Freie Universitaet Berlin and Universitaet Potsdam, Germany (3) Department of Clinical Pharmacy and Biochemistry, Freie Universitaet Berlin, Germany (4) Current address: AbbVie, Ludwigshafen, Germany

Objectives: The emergence of resistant mutants within treated HIV patients has been studied intensively by deterministic mathematical models. These models, however, are not able to predict the observed probability of treatment success/failure in a treated patient population, which hinders comparison to clinical data. For realistic mutational landscapes, the relevance of randomness of mutation dynamics on the appearance of drug resistance has not been studied. Our objectives were therefore to quantify the impact of random effects on the development of resistance and treatment outcome.

Methods: We used a two-stage mechanistic HIV infection model [1] to describe in vivo viral and mutational dynamics. The model includes drug-specific mutation pathways and resistance factors

estimated from clinical data. The stochastic model was implemented based on a hybrid model approach [2] to stochastically model the appearance of new mutations. The accumulation of mutations for two drugs: zidovudine (ZDV) and indinavir (IDV) was studied. Simulations were performed in Matlab (R 2014a).

Results: We observed a delayed appearance of mutations in the stochastic model compared to the deterministic model. Whereas the extent of the delay was low for preexisting drug-resistant genotypes, for non-preexisting genotypes that developed under therapy, we found a more pronounced delay (up to twofold). A main reason for the observed difference is the way the viral numbers are represented in the two modelling approaches. While the stochastic model correctly accounts for the discreteness of viral numbers, the deterministic model approximates viral numbers continuously. As a consequence, all mutations are instantaneously present in the deterministic model. Further we observed different dynamics of accumulation of drug-resistant mutants. In the stochastic model some mutants have a transient rise after which they decline again, while this was not observed in the deterministic model.

Conclusions: Randomness and discreteness of viral load impact the emergence of mutations. This finding is expected to have a major impact on the mutation dynamics under antiviral combination therapy.

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Gilbert Koch Model for characterizing copeptin kinetics and response in healthy volunteers

Gilbert Koch (1), Ingeborg Schnyder (2), Mirjam Christ-Crain (2), Konrad Strauss (3), Wiebke Fenske (3), Marc Pfister (1,4)
(1) Paediatric Pharmacology and Pharmacometrics Research Center, University of Basel, Children's Hospital (UKBB) , Basel, Switzerland (2) Division of Endocrinology, University Hospitals, Basel, Switzerland (3) Endocrinology, University Hospital of Würzburg, Germany (4) Quantitative Solutions, Menlo Park, CA, USA

Objectives: Vasopressin, a neurohypophysal hormone, is used in clinic to diagnose diabetes insipidus. Copeptin is evaluated as a new biomarker because it is a more stable in-vitro and an easier to measure peptide than vasopressin. A semi-mechanistic model to characterize kinetics of copeptin and sodium related increase in central copeptin release in heathy subjects was developed.

Methods: Serum sodium and copeptin data were collected in a study in healthy subjects. The study consisted of two consecutive phases: (i) administration of hypertonic saline infusion to increase serum sodium for 180 min or until the target sodium concentration of 150 mmol/l was reached, (ii) administration of 5% glucose infusion to decrease serum sodium for 40-60 min. Data was fitted with a non-linear mixed-effect model.

Results: A total of 1019 sodium and 1017 copeptin measurements from 93 healthy subjects were available for model-based analysis.

Infusion models with zero order input rates were applied to describe administered sodium and glucose infusions. Time varying sodium concentrations were modeled to quantify the stimulating effect of serum sodium on copeptin release. The developed semi-mechanistic model adequately characterized kinetics of copeptin and indicated that central copeptin release instantaneously increases with increasing serum sodium to a maximum rate of ~0.5 pmol/min. Estimated elimination rate of copeptin was 0.017/min resulting in a plasma half-life of 40 min, which is ~2 fold longer than reported for vasopressin.

Conclusions: A semi-mechanistic model can be useful to characterize both kinetics and response of the new biomarker copeptin in healthy subjects. This model will be applied to investigate the diagnostic value of copeptin in adult and pediatric subjects with diabetes insipidus.

Stephan Koehne-Voss The impact of unmodelled interoccasion variability in bioavailability and absorption on parameter estimates in population pharmacokinetic analysis

S. Koehne-Voss (1), A. Gautier (1), G. Graham (1)
(1) Novartis Pharma AG Basel

Objectives: In their landmark paper Karlsson and Sheiner [1] showed that ignoring interoccasion variability in pharmacokinetic data can lead to biased population pharmacokinetic parameter estimates. They considered intravenous administration models in their simulations. We study the effect of unaccounted interoccasion variability in drug bioavailability and absorption on parameter estimates.

Methods: Simulations were performed in which data were generated from a one-compartment model with first-order absorption. The model included independent random effects for absorption (ka), apparent clearance and volume (CL/F, V/F), and bioavailability (F). Interoccasion variability between two occasions was present either in relative bioavailability (F) or absorption rate (ka). Two study designs were considered. In the first design single dose data were generated for occasion 1 and steady state data for occasion 2. In the second design steady state data were simulated on both occasions. Dense and sparse sampling strategies were considered. Simulated datasets were analysed with NONMEM V7.3

using the FOCEI method and an analysis model that matched the data generating model or an analysis model that matched the data generating model but with interoccasion variability not accounted for.

Results: Our simulations show that in the one-compartment model with first-order absorption not modelling interoccasion variability in ka leads to overestimation of ka and V/F. Estimated intersubject variability for ka is inflated. Estimates of CL/F seem to be less affected by unaccounted interoccasion variability in ka.

Unaccounted interoccasion variability in F can lead to biased estimates of apparent clearance and volume, although the bias was mostly small in our examples. Estimated intersubject variability can be seriously overestimated for CL/F, V/F, and F, with the bias for CL/F and V/F being more pronounced in designs that combine single dose and steady state dosing compared to designs with steady state dosing only. Intersubject variability for ka can be seriously underestimated.

Conclusions: When sampling pharmacokinetic data on several occasions interoccasion variability in absorption and bioavailability should be included in the model to avoid potential bias in population pharmacokinetic parameter estimates. In this simulation example bias was more pronounced in random effect parameters compared to fixed effect parameters.

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Julia Korell A population pharmacokinetic model for aripiprazole and dehydro-aripiprazole

Julia Korell (1), Bruce Green (1), An Vermeulen (2)
(1) Model Answers Pty Ltd, Brisbane, Australia; (2) Janssen Research & Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium

Objectives: The aim of this work was to develop a population pharmacokinetic (PK) model for aripiprazole and its metabolite, dehydro-aripiprazole.

Methods: Steady-state plasma concentration–time data for aripiprazole and dehydro-aripiprazole were available from an open-label PK study in 86 subjects. Model development was performed in two steps: 1) a population PK model for the parent drug was developed on the aripiprazole data alone, then 2) sequential modeling using the PPP+D method [1] was applied to obtain a parent-metabolite PK model using the combined aripiprazole and dehydro-aripiprazole data. Covariates tested for the parent and parent-metabolite model included weight, lean body weight (LBW), age, sex, race, and CYP2D6 phenotype. Model development was performed in NONMEM v7.2, using FOCE with interaction. The final parent-metabolite model was evaluated using visual predictive checks (VPCs).

Results: A one-compartment model with first-order absorption and elimination together with a proportional error best described the aripiprazole data. Between-subject variability (BSV) was included on

all structural parameters. LBW and CYP2D6 phenotype were found to be significant covariates on aripiprazole plasma clearance. The typical clearance (CL/F) of aripiprazole in extensive metabolizers was found to be 3.44 L/hr (BSV = 32.6%). Ultra-rapid metabolizers showed an increase in CL/F of 49%, while CL/F decreased by 53% in poor and intermediate metabolizers. Typical estimates for the volume of distribution (V/F) and absorption rate constant of aripiprazole were 243 L (BSV = 38.3%) and 1.54 hr^{-1} (BSV = 73.1%), respectively.

The PK of dehydro-aripiprazole in the final parent-metabolite model was also best described by a one-compartment model with first-order elimination. The typical clearance of dehydro-aripiprazole (CLm/fm) was 10.9 L/hr (BSV = 42.7%). The fraction of aripiprazole metabolized (fm) to dehydro-aripiprazole was fixed at 1, while the volume of distribution of the metabolite was fixed to the estimate of the parent drug. LBW was also a significant covariate on CLm/fm.

VPCs for the final parent-metabolite model showed adequate predictive performance of the model to describe both aripiprazole and dehydro-aripiprazole data.

Conclusions: A sequential parent-metabolite PK model for aripiprazole and dehydro- aripiprazole with adequate predictive performance was developed.

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Wojciech Krzyzanski Physiologically structured population model (PSP) of heterogeneity of target binding to describe resistance of Gram-negative bacteria to polymyxin B (PB)

Wojciech Krzyzanski (1), Alan Forrest (1), Gauri Rao (1)
(1) University at Buffalo

Objectives: To set up a framework for application of PSP models [1] for studying resistance of cell populations to cytotoxic drugs based on heterogeneity of distribution of target binding properties among cells and to apply it to explain resistance of Gram-negative bacteria to PB.

Methods: The drug binding parameter K_D (dissociation equilibrium constant) is assumed to vary between cells and is considered as individual cell state characteristics (structure). A theory of PSP offers a p-state equation describing the time course of the density distribution of K_D upon exposure to cytotoxic drug concentration (environment). The drug increases the hazard of cell death as a sigmoidal function of receptor occupancy (RO). The initial distribution of K_D is described by the Weibull function. *In vitro* time-kill studies were performed [2] to describe the pharmacodynamic effect of PB (0, 1, 2, and 4 mg/L) against an initial inoculum of 10^6 CFU (colony forming units)/mL of *Klebsiella pneumoniae* strain, BAA1705. Serial cultures obtained at 0, 1, 2, 4, 6, 8, 24, 28, 32, and

48 h were quantified. The PSP model was used to describe the PB action against the bacteria using the nlinfit function in MATLAB.

Results: Based on the balance between the cell growth and death hazard functions, the PSP model provides a criterion for eradication or survival of cells exposed to the drug depending on their K_D values. For cell populations with the first-order (population size independent) growth rate there exists a critical K_{Dcrit} such that cells with $K_D < K_{Dcrit}$ become extinct over time whereas cells with $K_D > K_{Dcrit}$ continue growing. Consequently, only a fraction of the initial population grows to form a new (resistant) population. The K_{Dcrit} increases with increased drug concentrations. The PSP model with saturable (population size dependent) growth rate [3] was applied to the time-kill data. PB exposure resulted in a maximal increase in the death hazard by 22.9-fold with $RO_{50} = 2.3$. The K_D distribution in the inoculated bacteria was right skewed with a median of 32.9 nM. The PSP model predicts that the bacteria regrow to reach a steady state. However, as time passes, cells with specific binding affinity to PB are eradicated and cells with weaker affinity are able to transiently persist.

Conclusions: Heterogeneous distribution of K_D among cells results in emergence of a resistant population. The PSP models can adequately quantify the time course of K_D distribution.

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Anne Kuemmel Calculation of confidence and prediction intervals for pharmacokinetic and pharmacodynamic models

Anne Kümmel (1), Jasper Dingemanse (1), Andreas Krause (1)
(1) Actelion Pharmaceuticals Ltd, Department of Clinical Pharmacology, Modeling and Simulation, Allschwil, Switzerland

Objectives: The variability of pharmacokinetic (PK) and pharmacodynamic (PD) models can drive the decision-making processes, e.g., for defining safety margins or selecting doses. Therefore, confidence of model predictions is an important aspect of their utility. Available fitting tools typically provide information about the confidence for the estimated model parameters, but information about the confidence around the primary result, e.g., the predicted concentration-time or exposure-response curve, is not available directly. The objective of this project was to develop a single-interface framework for data fitting, confidence and prediction interval derivation for any user-specified function with visualization of the results.

Methods: The methodological framework was implemented in R using available estimation methods for nonlinear closed-form models. Either nonlinear least squares or maximum-likelihood estimation is used for the estimation. Confidence intervals are calculated using either the delta method, by bootstrapping, or

Monte-Carlo-simulations [Bonate 2011, Lavielle 2014]. Prediction intervals are assessed with Monte-Carlo simulations.

Results: Using two case studies, a dose-response and a PK profile, the different algorithms for confidence interval calculation are discussed with respect to implementation and results. The case studies show how the framework can be used in the study-design or analysis phase. The impact of different error models on the estimation and prediction results is demonstrated.

The utility of the framework is compared to other software typically used in PK/PD modeling that partially overlap with the presented workflow: PFIM for study design optimization, Monolix, and NONMEM/Xpose for parameter estimation and model diagnostics, and Berkeley Madonna and MLXPlore/Simulx for model simulations and visualization. These tools evaluate study designs or models based on diagnostics regarding model parameter estimates and agreement of observations and predictions or visualize simulations, but typically lack information about the confidence of the model predictions.

Conclusions: A general approach to data fitting, confidence and prediction interval calculation as well as result visualization can be implemented in an R framework, handling any user-defined closed-form function for PK/PD modeling. Different methods for estimation or confidence calculation besides different error structures are implemented, suitable for teaching and model exploration purposes.

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Brigitte Lacroix A time-to-event model for the immunogenicity of certolizumab pegol in rheumatoid arthritis subjects

Lacroix BD (1,2), Kirby H(3), Oliver R(3), Parker G(3), Friberg LE(1), Karlsson MO(1)
(1)Uppsala University, dept of pharmaceutical Sciences, Uppsala, Sweden (2)UCB, Braine, Belgium (3)UCB, Slough, UK

Objectives: The advent of biologic therapies improved greatly the treatment of chronic inflammatory diseases. However, these drugs may induce an unwanted specific immune response directed against them. The immunogenicity of biologic drugs is of concern for all healthcare stakeholders and methods for better characterization are needed, as well as means to minimize the occurrence of anti-drug antibodies (ADA). The objective of this analysis was to develop a time-to-event model for characterizing the immunogenicity of certolizumab pegol in subjects suffering from rheumatoid arthritis included in phase II and phase III clinical trials.

Methods: The time to event model was analyzed based on previously estimated individual certolizumab pegol concentration-time profiles. A model describing the time to appearance of ADA was developed. The probability of an individual not to develop ADA to time t was described by a parametric survival function. Various functions for describing the shape if the hazard function were tested during the model building. In the addition to the drug

exposure other covariates were tested, such as the dose of concomitant methotrexate, the frequency of dosing, the formulation and the concomitant use of other medications.

Results: The hazard of developing ADAs was predicted to depend on time since start of treatment, trough drug concentration in the preceding dosing interval and the concomitant use of methotrexate. Specific study effects were added into the model in order to capture the trends in two studies that remained non-explained after the covariates had been tested.

Conclusions: The proposed model characterized the time to initiation of ADA formation. The immunogenicity was predicted to appear mainly during the first three months following the start of the treatment and to be reduced at higher trough concentrations of CZP, as well as with concomitant administration of methotrexate. The model may be used to test strategies for minimizing the immunogenicity, such as the use of a loading dose or the reduction of the intervals between dosing.

Silvia Maria Lavezzi Toxicity assessment via drug-drug interaction modeling for trabectedin in patients with advanced malignancies

Lavezzi Silvia Maria, Mezzalana Enrica, De Nicolao Giuseppe
Laboratory of Bioinformatics, Mathematical Modelling and Synthetic Biology, Department of Electrical, Computer and Biomedical Engineering, University of Pavia, via Ferrata 5, Pavia, I-27100, Italy

Objectives: Trabectedin is a DNA minor groove binder, marketed in Europe for treating soft tissue sarcomas and, in combination with liposomal doxorubicin, ovarian cancer[1]. Trabectedin is metabolized mainly by cytochrome P450 3A4 (CYP3A4)[1]. A PK study describing the interaction of trabectedin with agents modulating CYP3A4 activity indicates an increased exposure of trabectedin when given with ketoconazole[2]. Our aim is to simulate the effects of CYP3A4 inhibitors of different strengths on the incidence and severity of neutropenia following the administration of trabectedin and establish possible dose reductions of trabectedin given concurrently with CYP3A4 inhibitors.

Methods: A previous approach[3] was reverse-engineered to define the proportion of the CYP3A4 contribution to the metabolization of trabectedin based on the available PK study[2]. The same approach was used – based on available population PK and PK-myelosuppression nonlinear mixed effect models[4,5] – to simulate the effect of CYP3A4 inhibitors of different strengths: ranitidine

(mild), diltiazem (moderate), and itraconazole (strong). For each scenario, 900 virtual patients were simulated with the aid of R, SimulX and Shiny, investigating also possible dose reductions.

Results: The simulations indicated that mild or moderate CYP3A4 inhibitors provided a lower increase of the systemic exposure to trabectedin compared to itraconazole (+15% and 38% versus + 52% in terms of median AUC). As a consequence, the predicted incidence and severity of neutropenia increased compared to the administration of trabectedin alone (e.g., grade 4 neutropenia episodes increased by 2%, 8% and 11%, respectively). The dose reduction necessary in order to avoid the increase in exposure and adverse events depends on whether dexamethasone is administered together with trabectedin or not. With dexamethasone, the dose needs to be reduced by 175, 379 and 464 mcg/m^2, respectively for ranitidine, diltiazem and itraconazole coadministration, while, without dexamethasone, reductions are of 222, 479 and 587 mcg/m^2.

Conclusions: This work exploits a previously published framework[2] in a population PK context to predict the expected PK and PK-PD changes when trabectedin, a CYP3A4 substrate, is given with CYP3A4 inhibitors of different strength, studying trabectedin dose alterations. An analogous approach[6] could be applied to the coadministration of CYP3A4 inducers.

Work supported by the DDMoRe project (www.ddmore.eu).

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Olivia le Saux Development and validation of a model of PSA kinetics predicting prostate cancer aggressiveness during screening

Le Saux O. (1, 2), You B. (1, 2), Henin E. (1), Pierrillas P. (1), Perrin P. (3), Ruffion A. (3), Boniol M. (4), Freyer G. (1, 2), Tod M. (1), Colomban O. (1)

(1) EMR 3738 CTO, UCBL - HCL Faculté de Médecine Lyon-Sud, Université Lyon 1, Oullins, France. (2) Medical Oncology Unit, Centre Hospitalier Lyon Sud, Pierre-Bénite, France. (3) Urology Department, Centre Hospitalier Lyon Sud, Pierre-Bénite, France. (4) Strathclyde Institute of Global Public Health, Biostatistics, International Prevention Research, Lyon, France.

Objectives: Prostate cancer (PC) is the most common cancer among men [1]. A growing number of cancers is detected by screening. Tools to distinguish aggressive and indolent tumors are necessary to avoid over-diagnosis and overtreatment. We developed a kinetic model of PSA (Prostate-Specific Antigen), a protein produced by the prostate gland, to differentiate the aggressive PCs among screened PCs.

Methods: We used the data from the American PLCO trial [2], developed to evaluate PC screening. Between 1993 and 2011, 76693 men, enrolled at 10 study centers across the United States, were randomized to annual PSA screening for 6 years (n=38343) or to usual care. Patients, aged 55-74, were excluded in the context of

prior PC or current cancer treatment. Individual pre-operative PSA data were analyzed with a semi-mechanistic non-linear mixed effect model, using NONMEM 7.3. Selection and evaluation of the best model were achieved using likelihood, goodness-of-fit plots and simulation-based diagnostics. Data from the screening group was randomly split in a learning (2/3) and a validation set (1/3). Aggressiveness of PC was defined as: biopsy Gleason score ≥7, and/or clinical stage ≥III, and/or fatal.

Results: On the 38343 screened men, 4250 developed a PC, 1643 developed an aggressive PC and 152 died from this cancer. Various models were evaluated. PSA kinetics was best described by a non-steady-state one compartment model with first and zero orders production by malignant and non-malignant prostate cells respectively and first order elimination. According to goodness-of-fit plots, PSA kinetics in healthy and cancer patients were properly fit over the 6-year period, and Visual Predictive Check showed good agreement between observed and simulated values. Relative Standard Errors of typical mean parameters and inter-individual variability were all less than 5%. Over the study period, median PSA production by cancer cells was 2 times more important than non-malignant cells' production.

Agreement of the proposed model in the validation set, along with the relationships between kinetic parameters and PC aggressiveness will be presented.

Conclusions: Our semi-mechanistic model describes PSA kinetics in healthy and cancer patients. If relationships between kinetic parameters and PC aggressiveness were demonstrated, it would provide an interesting tool for distinguishing the most aggressive tumors among screened PC and for adjusting treatment delivered to patients.

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SeungHwan Lee A population pharmacokinetic analysis of CKD-516 in patients with advanced solid tumor

SeungHwan Lee, Seonghae Yoon, Jangsoo Yoon, Jaeseong Oh, Kyung-Sang Yu, In-Jin Jang
Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea

Objectives: CKD-516 is a newly developed vascular disrupting agent and its active metabolite, S-516 has a potent cytotoxicity against cancer cells. The aim of this study was to develop a population pharmacokinetic model of intravenous CKD-516 in patients with advanced solid tumor.

Methods: CKD-516 concentration-time data were obtained from two independent phase I studies. Subjects of the first study received CKD-516 intravenously once-weekly for 3 weeks and plasma samples for pharmacokinetic analysis were taken for 24 hours after the first dose. Subjects of the second study received twice-weekly for 3 weeks and plasma samples were taken for 24 hours after the first and last doses. Population pharmacokinetic model was developed using NONMEM®, version 7.2.

Results: A total of 205 concentrations of CKD-516 and 346 concentrations of S-516 from 44 subjects were included in

population analysis. Pharmacokinetics of CKD-516 and S-516 was best described using a two-compartment model with an additional metabolite compartment. In covariate analysis, dose group and body surface area (BSA) had a significant effect on rate constant of formation (k13) and clearance (CLM) of S-516, respectively. The population mean estimate of central volume (V1), peripheral volume (V2), clearance (CL) and inter-compartmental clearance (Q) of CKD-516 was 11.8 L, 146 L, 61.1 L/h and 25.8 L/h, respectively. The value of k13, CLM and BSA effect on CLM of S-516 was 0.0775 /h or 0.122 /h (only in subjects with 5.0mg/m2/day dose once-weekly), 0.294 and -1.18, respectively. Most of the data were within 5th and 9th percentile in visual predictive check (VPC), which indicated that the model had acceptable predictive performance for CKD-516 and S-516 pharmacokinetics.

Conclusions: A two-compartment model an additional metabolite compartment adequately characterized the pharmacokinetics of CKD-516 and S-516. Application of the population pharmacokinetic model may help decision makings in clinical development of CKD-516.

Donghwan Lee Population pharmacokinetic analysis of Doripenem in Korean patients with acute infections

Dong-Hwan Lee1,2, Jong-Lyul Ghim1,2, Jae-Gook Shin1,2, Sung-min Kim3

1Department of Clinical Pharmacology, Inje University Busan Paik Hospital, Busan, Korea 2Department of Pharmacology and Pharmacogenomics Research Center, Inje University College of Medicine, 3Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan, Korea

Objectives: The aim of this study is to investigate the population pharmacokinetic (PK) profiles of Doripenem in Korean patients with acute infections.

Methods: Four consecutive 250-mg or 500-mg doses of Doripenem were intravenously infused over 1 hour every 8 hour for patients with creatinine clearance of ≤ 50 ml/min or > 50 ml/min, respectively. Blood samples from 38 patients at steady-state were taken pre-dose and at 0 min, 30 min and 4-6 hours after the 4^{th} infusion. The population PK analysis was conducted using a nonlinear mixed effect modeling software, NONMEM. Covariate screening was conducted applying general additive models for PK parameters. Likelihood ratio test was used to select significant covariates, with the significance levels of $p < 0.05$ for selection and $p < 0.01$ for elimination. The final model was evaluated by the visual predictive check. The probability of patients with T>MIC (the percentage of a dosing interval during which the concentration of

drug exceeds the minimal inhibitory concentration) of ≥40% [1, 2] for MIC of 1, 2, 4, and 8 μg/mL was calculated in each dataset with 38 patients for 100 simulation datasets.

Results: The Doripenem PK was well described by a one-compartment model. The typical values (relative standard error) were 7.114 L/h (9.197%) and 17.18 L (8.516%) for clearance and volume of distribution, respectively. The coefficient of variations of the inter-individual variability (relative standard error) for these parameters were 50.66% (14.31%) and 36.25% (24.69%), respectively. The correlation coefficient between clearance and volume of distribution was 0.5053. Residual variability was best explained by a combined error model with 28.17% proportional and 0.2012 μg/mL additive error. Doripenem clearance increased by 0.8144% with creatinine clearance increasing by 1 ml/min and the inter-individual variability for clearance was decreased from 60% to 50%. Most of the observed data were within the 90% prediction interval in the visual predictive check. The median (range) percentage of patients with T>MIC of 40% were 97% (87-100%), 92% (79-100%), 76% (58-92%) and 39% (21-55%) for MIC of 1, 2, 4, and 8 μg/mL.

Conclusions: The PK profiles of Doripenem at steady-state in Korean patients with acute infections were well described by a one-compartment model. Doripenem clearance was significantly influenced by the creatinine clearance. The dose of Doripenem should be adjusted according to MIC.

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Joomi Lee Population pharmacokinetic modeling and simulation of moxifloxacin in human aqueous humor after topical ocular application

Joomi Lee, Boram Ohk, Sook-Jin Seong, Mi-Ri Gwon, Hae Won Lee, Seunghoon Han, Young-Ran Yoon
Clinical Trial Center, Department of Biomedical Science and BK21 plus program, Kyungpook National University Hospital and School, Daegu, Korea

Background: The fourth-generation fluoroquinolone moxifloxacin is currently one of the antibiotic agents of choice for cataract surgery in most countries. Because it is difficult to obtain the concentration of moxifloxacin in human aqueous humor, the pharmacokinetic (PK) modeling of moxifloxacin has been rarely reported. The purpose of this study was to develop a population PK model to facilitate the understanding of the pharmacokinetics of moxifloxacin in human aqueous humor of patients undergoing cataract surgery after topical ocular administration of moxifloxacin hydrochloride ophthalmic solution 0.5%.

Methods: In 37 patients scheduled for cataract surgery, one drop of 0.5% moxifloxacin hydrochloride was topically administered 4 times a day on the preceding day and 4 times (q15min) for one hour right before surgery. Aqueous sample was collected 0.25 hour after the final dose. The concentration was determined using a validated liquid chromatography with tandem mass spectrometry method. A population PK analysis was performed using nonlinear mixed-effects

modeling (NONMEM, Ver.7.1). Because of the insufficient data from our study, the dataset were generated for PK modeling from those presented in a published reference, using a statistical software package R (Ver. 2.11.1). The aqueous maximum concentration (Cmax): minimum inhibitory concentration for 50% of isolates (MIC50) values were calculated to predict successful bacteriologic response to moxifloxacin and the resultant clinical efficacy.

Results: A one-compartment disposition model with first-order absorption described the best fit to a total of 1000 generated dataset. The population parameter estimates for clearance, central volume, and absorption rate constant were 0.57 L h-1, 0.66 L, and 0.51 h-1, respectively. Through this PK model developed, the predicted PK parameters from 37 patients were obtained, and compared with the reference values. The mean Cmax/MIC50 value in our study was 26, which was consistent with that reported in the reference.

Conclusions: The population PK model developed adequately described the data observed in human aqueous humor after topical ocular administration of moxifloxacin. The developed model could be useful to optimize dosing regimen for topical prophylaxis before intraocular surgery.

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Diao Lei CD25 Occupancy by Daclizumab HYP in Patients with Relapsing Forms of Multiple Sclerosis

Lei Diao (1), Yaming Hang (1), Ahmed A. Othman (2), Devangi Mehta (1), Lakshmi Amaravadi (1), Ivan Nestorov (1), Jonathan Tran (1)
(1) Biogen Idec, Cambridge, MA, (2) AbbVie, North Chicago, IL

Objectives: Daclizumab high-yield process (HYP) is a humanized IgG1 monoclonal antibody specific for CD25, the alpha subunit of the high-affinity interleukin 2 receptor. In registration enabling studies in patients with relapsing forms of multiple sclerosis (RMS), daclizumab HYP demonstrated robust efficacy on clinical endpoints and radiological measures of the disease. This analysis characterized the quantitative relationships between daclizumab HYP exposure and CD25 occupancy on target T cells in blood of RMS patients.

Methods: Population analysis using NONMEM 7.2 was applied to ≥ 7000 observations obtained from 1400 RMS patients participating in the Phase 2 and 3 studies. CD25 saturation was determined using flow cytometry. Saturation was defined as ≤ 1% antigen rich $CD4^+$ T cells staining positive with daclizumab HYP competing antibody. A sequential approach was implemented in which the PK part was fixed utilizing a developed population PK model. Briefly, a two-compartment model adequately described the PK of daclizumab HYP in RMS patients. Clearance was 0.212 L/day and central volume of distribution (Vc) was 3.92 L, scaled by body weight, with exponents of 0.87 and 1.12, respectively. Peripheral volume of distribution was 2.42 L. Absolute bioavailability (100–300 mg) for

subcutaneous administration was 88%. Terminal half-life was 21 days. Sampling scheme for CD25 occupancy is sparse mostly once every month except for 19 patients in the intensive PK subgroup in one study (OBSERVE) where the early sampling points included 8h and 24h.

Results: CD25 receptor occupancy by daclizumab HYP in RMS patients was characterized by a sigmoidal inhibitory E_{max} model. Separate parameters including gamma and IC50 were needed to characterize the saturation following the first dose and the desaturation after treatment cessation. CD25 occupancy upon daclizumab HYP administration is rapid with complete saturation within approximately 7 h post 150 mg SC dose. Maintenance of saturation of CD25 is predicted when daclizumab HYP serum concentration ≥ 5 mg/L while the unoccupied CD25 levels are predicted to return to baseline values when daclizumab HYP serum concentration decreases to approximately ≤ 1 mg/L.

Conclusions: The model described the relationship between daclizumab HYP exposure and the kinetics of CD25 occupancy. At daclizumab HYP exposures determined to be efficacious in clinical trials, the occupancy of CD25 on target T cells was rapid, complete and reversible in parallel with daclizumab HYP clearance from the body.

Giulia Lestini Optimal design for informative protocols in xenograft tumor growth inhibition models

Giulia Lestini (1,2), France Mentré (1), Paolo Magni (2)
(1) IAME, UMR 1137, INSERM, University Paris Diderot, Paris, France, (2) Dipartimento di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Pavia, Italy

Objectives: The in vivo evaluation of antitumor effect is an important step of the preclinical drug development. Xenograft experiments are performed, but tumor size measurements are usually taken only during treatment [1], preventing a correct identification of certain parameters of Tumor Growth Inhibition (TGI) models. Our aim was to use optimal design approach in TGI models to evaluate the importance of including measurements during the tumor regrowth phase in those studies.

Methods: We considered the Simeoni TGI model [2]. Optimal design was performed for several examples of xenograft experiments in treated and control arms, reported in [2,3], involving different drugs, schedules and cell lines. Various scenarios were studied. Basic scenarios are those with same real settings as in [2,3]. In other scenarios, the parameter related to the cells death rate (k_1), was set larger than the reported value to assess the effect on the experimental design. Finally sampling design was optimized, for each selected experiment, with or without the constraint of not sampling during tumor regrowth, that we defined as "short" and "long" studies, respectively. In the long study, measurements could be taken up to six grams of tumor weight, for ethical reasons,

whereas in the short study the experiment was stopped two or three days after the end of the period of treatment. Design optimization was performed using the determinant of the Fisher Information Matrix in PFIM 4.0 [4]. Predicted Relative Standard Errors (RSE) and D-optimal criterion were used to compare those scenarios.

Results: As expected, predicted RSE and D-optimal criterion obtained in long studies were better compared to those obtained in the short study of the corresponding experiments. Indeed, some optimal times were located in the regrowth phase, highlighting the importance of continuing the experiment also after the end of the treatment.

Conclusions: Based on results obtained here, making measurements during tumor regrowth should become a general rule for more informative preclinical studies in oncology.

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Yan Li Characterization of the Oral Absorption Profiles of Sustained or Extended Release Formulations of Losartan, Dexibuprofen, Methylphenidate, and Tramadol Using Weibull Drug Release Functions

Yan Li (1), Maria Palmisano (1), Duxin Sun (2) and Simon Zhou (1)
(1) Celgene Cooperation, Summit, NJ, USA; (2) College of Pharmacy, University of Michigan, Ann Arbor, MI, USA

Objectives: In traditional pharmacology and modeling, oral absorption is approximated by a constant rate constant. It provides a reasonable description of overall PK profile, but rarely captures the kinetic oral absorption phase with particular problems for sustained or extended (Controlled CR) release formulations. Weibull functions have been successfully applied to characterize the in vitro drug dissolution from various IR and CR dosage forms. The aim of this analysis is to characterize the in vivo oral absorption profiles of IR and CR formulations of Losartan, Dexibuprofen, Methylphenidate and Tramadol using Weibull absorption function.

Methods: Human plasma concentration-time profiles of IR and CR formulations of Losartan, Dexibuporfen, Methylphenidate, and Tramadol were digitized from published manuscripts. The PK data were fitted by 1 or 2 compartment structural models with constant rate of absorption or time-varying Weibull absorption functions. The Weibull absorption functions was adopted to represent physiologic

processes of drug release and absorption in vivo. The modeling and simulation were conducted using NONMEM 7.2.

Results: Data fitting with constant rate of absorption rate did not yield consistent PK parameters for IR and CR formulation of lorsartan, dexibuporfen, methylphenidate and tramadol, requiring separate sets of PK parameters of Ka, CL and V for IR and CR formulations and poor data fit of absorption phase of PK profiles. The models with single or dual Weibull absorption functions well-characterized the overall PK profile with consistent CL and V parameters and the early absorption phases for both IR and CR formulations. The analysis also provided a mechanistic link between the values of Weibull distribution parameters (λ and κ) and the diffusion mechanisms of the drug release in vivo. For all 4 drugs, oral absorption stopped between 6 and 8 hours, providing a new insight into the physiological limit of stretching oral absorption with modified release. Simulations further demonstrated the numerical stability and statistical rigor of Weibull absorption models to describe complex drug absorption.

Conclusions: Drug release from IR and CR formulations have mode and distribution that could not be adequately described with a first order process. Weibull functions with versatile time varying release/absorption rates are proper models to characterize drug absorption, and useful to compare and qualify CR formulations.

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Andreas Lindauer A two-part mixed-effects model for semi-continuous data to describe the effect of transdermal rotigotine on restless legs symptoms in adults

Lindauer, A (1), Elshoff, J-P (2), Wilkins, J (1), Olsson Gisleskog, P (1)
(1) SGS Exprimo NV, Mechelen, Belgium, (2) UCB, Monheim, Germany

Objectives: To quantify the dose-exposure-response relationship of rotigotine in adult patients suffering from restless legs syndrome (RLS) and to assess the expected efficacy response to daily administration of rotigotine transdermal patches at different dose levels via simulations.

Methods: Pharmacokinetic (PK) and efficacy data from 3 large placebo-controlled clinical trials in adult RLS patients were used. The dataset included all verum patients that had at least 1 PK sample and all patients receiving placebo (N=709). Data from the remaining patients (N=582) were retained for external validation of the model. A simple PK model was developed to describe the average concentration at steady state (Cav,ss).
Subsequently, a two-part mixed-effects model for semi-continuous data [1] was employed, linking Cav,ss to International Restless Legs Syndrome Rating Scale (IRLS) score (range: 0; no symptoms – 40; most severe). IRLS scores >0 were treated as continuous data applying a longitudinal placebo sub-model and an Emax function for the concentration-response relationship; for IRLS scores equal to

zero the likelihood of such observations was modeled with a logistic regression function. The F_FLAG functionality in NONMEM 7.2 was used for the simultaneous modeling of categorical and continuous data. The response at different dose levels was then simulated using Simulo 6.2 [2].

Results: An allometric relationship between body weight and apparent clearance with a fixed exponent of 0.75 significantly improved the fit of the PK model.
The two-part model successfully accounted for the disproportionately large number of IRLS scores of 0 in the dataset. A visual predictive check on the validation dataset demonstrated close correspondence between observed and simulated IRLS scores.
The likelihood of IRLS scores of 0, increased with time, up to a plateau of 13.5%, and with concentration. EC50 of 0.218 ng/mL was well-estimated (90%CI: 0.154-0.225) and corresponded to a dose of about 1.5 mg/24h in a typical adult patient.

Conclusion: A clear exposure-response relationship between rotigotine Cav,ss and the IRLS score could be established. The two-part mixed-effect model previously described by Olsen et al.[1] was successfully implemented in NONMEM and proved useful in modeling data with observations at the boundary of the measurement scale. The concentration-IRLS model provides a framework to simulate the expected response to rotigotine administration in other populations in order to aid in designing future clinical studies.

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Jos Lommerse Raltegravir dosing in neonates (IMPAACT P1110) – Use of allometry and maturation in PK modeling to develop a daily dosing regimen for investigation during the first weeks of life.

Jos Lommerse (1), Diana F Clarke (3), Anne Chain (2), Han Witjes (1), Hedy Teppler (2), Edmund Capparelli (4), Edward P Acosta (5), Matthew Rizk (2), Larissa Wenning (2), Thomas Kerbusch (1), Stephen A Spector (7), Betsy Smith (8), Mark Mirochnick (6)
(1) Quantitative Solutions, Oss, The Netherlands (2) Merck Research Laboratories, Rahway, USA (3) Boston Medical Center, Boston, MA, USA (4) University of California at San Diego, San Diego, CA, USA (5) University of Alabama at Birmingham, Birmingham, AL, USA (6) Boston University School of Medicine, Boston, MA, USA (7) San Diego and Rady Children's Hospital, San Diego, CA, US (8) National Institute of Health, NIAID, Division of AIDS, Bethesda. MD, USA.

Objectives: To determine a raltegravir (RAL) daily dosing regimen for prevention or treatment of HIV infection in 0-6 week old infants for use in IMPAACT P1110 using a two cohort adaptive design where PK data from Cohort 1 are included in PK modeling to guide daily dosing in Cohort 2.

Methods: IMPAACT P1110 is an open label, non-comparative dose-finding study of raltegravir in HIV exposed neonates at high risk of acquiring HIV-1 infection. An initial cohort of 6 full-term infants (2.9-3.8 kg, 3/3 M/F) received two 3 mg/kg doses of raltegravir – one

within 48 hours after birth and a second at 7-10 days of life. Plasma samples for RAL assay were collected around each dose. RAL concentrations were measured by a validated LCMS assay.
A population PK model was developed based on the P1110-cohort 1 data and RAL concentrations from a phase 1 study in 24 HIV infected infants and children (IMPAACT P1066, cohorts 4-5, 4 wks to

Results: A 2-compartment model with first order absorption provided best fit. Apparent clearance changed dramatically from very low at birth to fully matured at 6 months. The absorption rate also changed rapidly, from 16% at birth to 90% of the maximum rate within 2 weeks. Despite the considerable maturation and body-size changes, the model described the observed RAL concentration data well. Subsequently, the model was used to simulate typical individual RAL exposures receiving various dosing regimens and evaluate their ability to meet the defined exposure criteria.

Conclusions: There are few antiretrovirals with an appropriate formulation and adequate PK data for use in neonates. RAL is metabolized via UGT-1A1, whose activity is known to be extremely low immediately after a birth followed by a dramatic increase over the first weeks and months of life [3,4]. Using simulations from our model, we have selected a daily dosing regimen for evaluation in Cohort 2 of P1110.

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Dominik Lott Population pharmacokinetics of the selective S1P1 receptor modulator ponesimod and its primary metabolites in healthy and organ-impaired subjects

Dominik Lott (1,2), Jasper Dingemanse (1), Matthias Hoch (1), Thorsten Lehr (2), Andreas Krause (1)
(1) Actelion Pharmaceuticals Ltd, Department of Clinical Pharmacology, Modeling and Simulation, Allschwil, Switzerland, (2) Saarland University, Department of Clinical Pharmacy, Saarbrücken, Germany

Objectives: Development of a population pharmacokinetic (PK) model for the characterization of ponesimod and its two metabolites M12 and M13 in healthy and hepatically/renally impaired subjects.

Methods: Plasma concentration-time data from 153 individuals in 5 Phase 1 studies were available; data from single and multiple doses as well as an up-titration regimen, an intravenous (i.v.) and an oral (p.o.) formulation in the dose range from 5 to 100 mg were pooled. In total, 3735, 3548, and 3427 concentrations were available for ponesimod, M12, and M13, respectively.

A semi-mechanistic population PK model for parent and metabolites with metabolite formation in the gut/first liver passage and in the systemic circulation with incorporation of hepatic and renal function

was implemented in Monolix version 4.3.1. After modeling the parent compound, metabolites were sequentially added to the model. Covariates, i.e., hepatic and renal function, were tested on the model parameters (clearance and metabolite formation) and added if statistically significant ($p < 0.05$). The adequacy of the model was evaluated based on visual predictive checks, goodness-of-fit plots, and parameter variability.

Results: The PK characteristics of ponesimod were accurately described by a two-compartment model with first-order rate constants for absorption, metabolism, and elimination. Model diagnostics showed a good fit. Hepatic function was found to have a significant effect on the clearance of ponesimod and its metabolites.

Comparison of the PK profiles following i.v. and p.o. administration of ponesimod suggested metabolite formation in the gut/first liver passage prior to reaching the systemic circulation, described by rate constants characterizing metabolite formation and absorption. The combination of i.v. and p.o. data allowed estimation of bioavailability as well as the separation of metabolite formation at two sites.

Conclusions: The population PK model suggested relevant ponesimod metabolism prior to reaching the systemic circulation, e.g. , in the gut/first liver passage.

Hepatic function has a strong impact on the clearance of ponesimod as well as its primary metabolites. The model may serve as a valuable tool for the future drug development process and dose adaptation of ponesimod in hepatically impaired patients.

Gaohua Lu Challenges in predicting the drug-drug interaction between dextromethorphan and rifampicin using a physiologically based pharmacokinetic (PBPK) model that includes three metabolites of dextromethorphan

Lu Gaohua, Kim Crewe, Rachel Rose, Amin Rostami-Hodjegan, Karen Rowland Yeo, Masoud Jamei
Simcyp Limited (a Certara company)

Objectives: Dextromethorphan (DEX) is an *in vitro* and *in vivo* probe substrate for CYP2D6 that undergoes O-demethylation to dextrorphan (DOR) and N-demethylation to 3-mthoxymethorphinan (3MM). Both metabolites are then further metabolised to 3-hydroxymorphinan (3HM). In addition to CYP2D6, CYP3A4 and UGT2B7 are also involved in the elimination of DEX and its metabolites. In this study a PBPK model was developed for DEX and its 3 metabolites to explore the complex mechanism of drug-drug interaction (DDI) between DEX and rifampicin (RIF).

Methods: The Simcyp Simulator (V14R1) was used to build the PBPK model for each of the moieties. In particular, the elimination kinetics of the currently available DEX compound model in the Simulator were revised based on *in vivo* data for the major contributing enzyme CYP2D6 and *in vitro* data for the relative contributions of minor metabolic enzymes (including CYP2B6, 2C9, 2C18, 2C19 and 3A4). The DOR PBPK model was developed based

on the clinical PK profiles after IV and oral dosing of DOR. Where relevant data were lacking, parameters relating to the parent were used for the PBPK models for 3MM and 3HM. The DEX model is linked to the 3 metabolite models via its elimination pathways. The performance of the PBPK model as a whole was verified using independent clinical data sets that had not been used in the model development. Sensitivity analysis was used to explore the potential for 2D6 induction by RIF.

Results: The whole PBPK model including DEX and its 3 metabolites was verified using various clinical studies in CYP2D6 EM and PM subjects, as well as DDI between DEX and quinidine. The observed DEX-RIF DDI could not be fully explained by induction of CYP3A4 alone (AUC Ratio=0.67 simulated vs. 0.27 observed [1]) and sensitivity analysis indicated that induction of CYP2D6 by RIF was required in order to recover the extent of clinical DDI.

Conclusions: The developed PBPK model was able to describe the complex kinetics of DEX and its 3 metabolites, as well as elucidate the mechanism of interaction between DEX and RIF. Although it is generally accepted that CYP2D6 is non-inducible the findings of the current study indicate that this may not be the case. Further studies are warranted to support this finding.

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Tong Lu Clinical Trial Simulations to Assess the Probability of Revealing Biomarker Dose-Response in Ph1 Trials

Tong Lu (1), Yuying Gao (2), Lichuan Liu (1), Alex Huang (1), Amita Joshi (1), Jin Yan Jin (1)
(1) Genentech, Inc.; (2) Quantitative Solutions, Inc.

Objectives: For rational dose selection of targeted anticancer agents, it is critical to obtain early assessment of clinical activity and target modulation. However, in Phase 1 dose escalation, biomarker dose-response (D-R) assessment based on tumor biopsy data is challenging, considering the uncertainty around efficacious dose, small sample size, high inter-subject variability, and high biopsy failure rate. The objective of this work is to assess the power of detecting biomarker D-R relationship by clinical trial simulations.

Methods: 1) Simulation: Based on available biomarker D-R relationship (inhibitory Emax model), 3 scenarios were simulated with ED50 within, below, or above Phase 1 dose range. 1000 sets of parameters were generated per scenario, incorporating typical value and uncertainty for E0 (baseline) and ED50, inter-trial variability for ED50 (assume 75%), and residual error variability for E0. Two biopsy data (pre- and post-treatment) per subject were simulated, with 1000 subjects per dose for 6 dose levels in each scenario. 2) Bootstrapping: 1000 Ph1 trials with 6 dose levels and typical 3x3 design (n=3/dose) for each scenario were generated by resampling from the virtual subjects. 50% failure rate was applied

independent of dose (n=9/trial). Biopsy data for each trial was fitted by Emax model to get 1000 sets of bootstrapped parameters per scenario. 3) Power evaluation: a) Power of estimating D-R relationship was assessed by % of bootstrapped parameters falling into predefined interval ([0.7-1.3]) of true value; b) Power of detecting D-R was assessed by % of subject achieving target inhibition at given dose (ie. success rate).

Results: For base scenario where ED50 was in the middle of the dose range, 52% of the bootstrapped ED50 fall into desired range of true value, indicating a decent power of detecting true D-R relationship in spite of small sample size and high failure rate. In scenarios where ED50 was below or above the dose range, the values were down to 43% or 28%. Simulation also suggested strong likelihood of ED50 underestimation when ED50 was above the dose range. The success rate of detecting D-R was high if ED50 was below or within the dose range, and was <50% if above the dose range.

Conclusions: Theoretical simulations of biomarker D-R were used to inform oncology biomarker strategy. Under different scenarios, simulation can be conducted with varying assumptions to assess the probability to reveal the biomarker D-R in Ph1 trial.

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Paolo Magni Evaluation of software tools for Bayesian estimation on population models with count and continuous data

E. Borella, L. Carrara, S.M. Lavezzi, E. Mezzalana, L. Pasotti, G. De Nicolao, P. Magni
Laboratory of Bioinformatics, Mathematical Modelling and Synthetic Biology, Department of Electrical, Computer and Biomedical Engineering, University of Pavia, via Ferrata 5, Pavia, I-27100, Italy

Objectives: In recent years, Bayesian modelling techniques have received increasing attention. Different tools have been developed to perform Bayesian estimation using Markov Chain Monte Carlo (MCMC) methods. The aim of this work is to compare five tools in order to evaluate their performances and limitations on both algebraic and ordinary differential equation (ODE) population models..

Methods: WinBUGS 1.4.3 (with BlackBox Component Builder 1.5 and WBDiff interface), Stan 2.5.0 (with RStan 2.5.0 interface), OpenBUGS 3.2.3, NONMEM 7.3.0 and JAGS 3.4.0 were compared. Two models were selected for this purpose: a Poisson count model concerning a randomized clinical trial of an anticonvulsant for epilepsy treatment [1], and a two-compartment PK ODE model with linear and non-linear elimination, already used for a Phase I dose escalation study of a monoclonal antibody for epilepsy [2,3]. For the first model, data and uninformative priors from a published study were used to perform the estimates [1]. For the second model, PK

data were simulated using the Simulx function of the R package mlxR and informative priors were defined using literature data [2]. The tools were tested on a single platform and the Effective Sample Size (ESS, computed via R coda package) per execution time (T) was used as a performance index for comparison.

Results: Similar posterior distributions were obtained with all the tools for the Poisson count model. OpenBUGS and Stan showed superior performance in terms of ESS/T. In NONMEM, the implementation of the model requires the objective function to be written explicitly, resulting in a less user-friendly model encoding than the other tools. NONMEM also has a limited distribution choice (Normal and InverseWishart), hence parameter transformations were required to encode the chosen models. The ODE model could be implemented only with NONMEM and WinBUGS, since JAGS does not include an ODE solver, OpenBUGS gives errors solving population models with ODEs and Stan could not finish the estimation process. NONMEM and WinBUGS with BlackBox showed comparable performance for the ODE model, while WinBUGS alone showed, on average, a considerably lower ESS/T.

Conclusions: The performed tests highlighted tool-specific limitations and performance differences. The evaluation on models with different features, like the ones used in this work, will support the choice of the most suitable tool for Bayesian estimation tasks in several contexts.

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Mats Magnusson Population Pharmacokinetic Modeling of Paliperidone Palmitate 3-Month Formulation

Mats O. Magnusson (1)*; Mahesh N. Samtani (2)*; Elodie L. Plan (1); E. Niclas Jonsson (1); Stefaan Rossenu (3); An Vermeulen (3) (*equal contribution)

(1) Pharmetheus, Uppsala, Sweden; (2) Johnson & Johnson Pharmaceutical Research & Development, L.L.C., NJ, USA (3) Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutical N.V., Beerse, Belgium

Background: A new paliperidone palmitate 3-month formulation (PP3M) has been developed aiming at retained efficacy compared to the marketed paliperidone 1-month formulation (PP1M).

Objectives: To characterize the dose-concentration-time relationship of paliperidone following administration of PP3M.

Methods: Pharmacokinetic (PK) data were obtained from 1 single-dose Phase 1 study (R092670-PSY-1005) and 1 repeated-dose Phase 3 study (R092670-PSY-3012). Plasma concentrations were analyzed using non-linear mixed-effects PK modeling implemented in NONMEM 7.3.0 [1]. A previously developed PK model for PP1M was used to describe the PK of paliperidone after PP1M administration [2] for patients in Study R092670-PSY-3012 who were treated with PP1M for 4 months before PP3M treatment commenced. The final model for PP3M was based on 8990 PK samples from 651 subjects.

Results: The PP1M PK model provided an adequate description of the PP1M data when the model parameters were associated with uncertainty [3] (10%). A 1-compartment model with 2 saturable absorption processes (slow and fast) was developed to characterize the PK of paliperidone after PP3M administration. The covariates in the PP3M model were creatinine clearance on clearance, BMI on volume of distribution, injection volume on the absorption rate, and injection site and sex on the maximal absorption rate for the slow saturable absorption process.

Conclusions: The PK characteristics of paliperidone when administered as a single and multiple injections of PP3M were well captured in a population PK model for PP3M.

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Adedeji Majekodunmi Impact of Hepatitis C coinfection on Immune reconstitution in HIV-infected children undergoing therapy

Adedeji Majekodunmi
University College London

Objectives: The effect of HCV co-infection on CD4 T cell recovery in treated HIV-infected children is poorly understood. The main aim of this study is to investigate the significance of Hepatitis C virus (HCV) co-infection on CD4 T cell reconstitution of HIV-infected children undergoing anti-retroviral therapy. Secondly, to investigate the importance of other covariates on this relationship.

Methods: 78 age-matched European children selected from an observational study conducted by the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) were included into this study. The children were aged between 1month and 25 yrs and were all receiving antiretroviral therapy. There were a total of 39 Hepatitis C co-infected and 39 HIV mono-infected children who had CD4 counts measured over a 5 yr period. The CD4 counts were transformed into z scores to accommodate for age fluctuations in CD4 counts [3]. We fitted this longitudinal data using a recently developed exponential model containing three parameters and within the frame work of non-linear mixed effects modelling [1]. Estimates were obtained for pre-antiretroviral therapy z scores (intercept), long term antiretroviral therapy z scores (asymptote)

and rate of increase in CD4 z scores (c). Covariates investigated include age at start of therapy, gender, aids status, hepatitis C status and country of origin.

Results: The analysis revealed that hepatitis C did not have a significant effect on immune reconstitution in these HIV-infected children undergoing therapy. This was confirmed using both univariate and multivariate analysis. In our HCV status-inclusive univariate model, the impact of HCV co-infection on either intercept or asymptote was not statistically different from zero ($p = 0.3935$ and $p = 0.0951$ respectively). As expected, younger children had a higher rate of CD4 T cell recovery ($p = 0.0329$) and higher pre-ART age-adjusted CD4 counts ($p = 0.0021$) compared to older children.

Conclusions: Our results are in agreement with a study published in 2007 looking at the impact of HCV on immune reconstitution in 44 Spanish children [2]. Although this Spanish study did not use a modelling based approach, they established that hepatitis C did not have a significant impact on CD4 T cell recovery in HIV-infected children receiving treatment.

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Victor Mangas-Sanjuan Population PK Model of Lithium and Drug Compliance Assessment

Perez-Castello, I(1); Mangas-Sanjuan, V(2); González-García, I.(2,3); Gonzalez-Alvarez, I(2); Marco-Garbayo, JL(1); Troconiz, I(4); Bermejo, M (2).
(1) Hospital of Gandia; (2) Pharmacokinetics and Pharmaceutical Technology Area, Miguel Hernandez University; (3) Pharmacokinetics and Pharmaceutical Technology Department, University of Valencia; (4) Pharmacometrics and Systems Pharmacology. University of Navarra.

Introduction: Lithium is an antidepressant used as primary treatment for the prevention of episode recurrences in bipolar disorder, acute treatment of mania and to a lesser extent depression. Due to its relatively narrow therapeutic range and high inter-individual (IIV) and residual (RSV) variability, routine therapeutic drug monitoring (TDM) of lithium is therefore necessary to ensure dosing schedules with satisfactory result and without severe side effects and toxicity.

Methods: 96 psychiatric patients were enrolled in this. Lithium carbonate was administrated to all patients at different dose levels (200, 300, 400, 600 and 800 mg) and administration intervals (8, 12 and 24 h). Different demographic, biochemical and anthropometric covariates were selected. Patients received several treatment cycles and one plasma concentration measurement for each patient was obtained always before starting next cycle (pre-dose) at steady

state. Experimental data were fitted using non-linear mixed-effects modelling implemented in NONMEM 7.2. Different approaches were implemented in order to capture the concentration profiles observed: (1) addition of IIV on CL, (2) use of Prior information and (3) IOV on bioavailability dose fraction (F1). Model selection was based on the lowest and significant OFV and goodness-of-fit (GOF) plots. Covariate analysis was performed manually, adding the covariates into the final base model. Final model evaluation was carried out using prediction corrected-visual predictive check (pc-VPC) (n=1000) and Bootstrap (n=1000) analysis.

Results: Plasma observations were described using a two-compartment model. Creatinine clearance (CrCl) was selected as significant covariate on typical clearance parameter with a power relationship. Individual concentration-time course profiles from selected individuals were represented.

Conclusions: The addition of inter-occasion variability on the bioavailability dose fraction (F1) allowed for a better characterization of the individual profiles and to assess drug compliance. Nearly half of the F1 estimated (46%) were different from 1±10%, representing that patients did not meet the prescribed dose regimen along all monitored cycles. The final model was able to characterize the number of individuals/observations out of the therapeutic interval with more precision compared to the other approaches proposed.

Alison Margolskee You can't always get what you want: The (mis)use of deconvolution in IVIVC

Alison Margolskee (1), Adam S. Darwich (1), Aleksandra Galetin (1), Amin Rostami-Hodjegan (1,2), and Leon Aarons (1)
(1) University of Manchester, Manchester, UK, (2) Simcyp Ltd., Sheffield, UK

Objectives: It is generally believed that IVIVC should be possible for high permeability, dissolution rate limited formulations [1]. The aim of this research was to determine the impact of different rate limiting conditions on the applicability of traditional deconvolution methods to IVIVC.

Methods: Plasma concentration profiles following IV, oral solution, and IR formulation administration were simulated using a simplified absorption and transit model. Intestinal transit, dissolution, and absorption rate constants were varied across a range of values approximately covering those observed in the literature [2,3]. Two traditional deconvolution methods, Wagner-Nelson and numerical deconvolution, were applied to the simulated profiles. IVIVC plots and their corresponding correlation coefficients were analyzed for each combination of parameters to determine the applicability of the deconvolution methods to IVIVC under a range of rate-limiting conditions.

Results: For highly absorbed formulations, the correlation coefficients obtained during IVIVC were comparable for both

methods, and steadily declined with decreasing dissolution rate and increasing transit rate. The applicability of numerical deconvolution to IVIVC was not greatly affected by absorption rate, whereas the applicability of Wagner-Nelson fell when dissolution rate overcame absorption rate and absorption became the rate limiting step.

Conclusions: The discrepancy between the expected and deconvolved input arises from the violation of a key assumption of deconvolution, that the unknown input and unit impulse enter the system in the same location. Traditional methods of deconvolution may need to be replaced by more physiologically meaningful models to expand the application of IVIVC to low solubility/permeability compounds and nontraditional formulations.

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Eleonora Marostica Population PK/PD modelling of QT-interval prolongation in awake dogs and humans

Eleonora Marostica (1), Karel Van Ammel (2), Ard Teisman (2), Jan Van Bocxlaer (1), Koen Boussery (1), Filip De Ridder (3), An Vermeulen (1,3) and David J. Gallacher (2)
(1) Laboratory of Medical Biochemistry and Clinical Analysis, Ghent University, Belgium; (2) Global Safety Pharmacology and (3) Model Based Drug Development, Janssen R&D, Beerse, Belgium

Objectives: Drug-induced Torsades de Pointes (TdP) and consequent sudden cardiac death are positively correlated with QT-interval prolongation. Conversely, not all "QT-prolonging drugs" induce TdP. Irrespective of this inconsistency, the early risk biomarker QT-interval prolongation is frequently used to deselect drugs. Hence, the need for an improved understanding of it is obvious. The work's aims were: to develop a pharmacokinetic/pharmacodynamic (PK/PD) model to describe "QT data" in awake dogs and humans receiving drugs that are known to affect the QT interval (i.e. moxifloxacin, C1, C2, and C3); to determine the unbound concentration needed to reach 50% probability (CP_{50}) of QT-interval prolongation/shortening; to assess the approach's translational opportunities between species.

Methods: A population PK model was developed for each compound and species using NONMEM 7.1. The QT interval was then modelled as a sum of individual heart-rate correction, circadian rhythm, and drug effect [1]. Different model structures

were assessed. The final PK/PD models were then implemented in WinBUGS 1.4.3 according to a fully Bayesian approach. The probability of QT-interval prolongation/shortening greater than 10 ms was assessed for all the compounds. Based on the posterior distributions of the parameter estimates, the probability curves of the typical and the new subject/dog were calculated.

Results: For each compound and species, the QT profiles were well described by the PK/PD models. Similar CP_{50} of moxifloxacin, C1, and C2 are needed in dogs and humans to reach the same effect. Dogs were less sensitive than humans to QT-interval prolongation when receiving C3 (CP_{50} dogs > CP_{50} humans). However, in all cases, when looking at the typical subject/dog, the probability curve for humans was steeper than the one for dogs. This finding is in agreement with [1], where moxifloxacin and two other drugs were analyzed. The drug-effect parameter estimates provided a translational scaling factor of 2.3.

Conclusions: The proposed model was able to describe both QT-interval prolongation and shortening. The knowledge of the translational scaling factor can provide an insight into the possible effect that a new compound may have on the QT interval in humans, based on the drug effect observed in dogs. The inclusion of more compounds could improve the estimate of the translational scaling factor as well as our understanding of the relationship between dogs and humans.

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Lisa Martial Dose reduction of caspofungin in ICU patients with Child Pugh B will result in suboptimal exposure.

Martial LC(1,2) Brüggemann RJ(1,2) Schouten JA(3) van Leeuwen HJ(4) van Zanten AR(5) de Lange DW(6) Verweij PE(7,2) Pickkers P(8) Muilwijk EW(1,2) Dorlo TPC(9,10).

(1)Department of Pharmacy, Radboud university medical center, Nijmegen, The Netherlands (2)The Netherlands Radboud Institute for Health Sciences, Nijmegen, The Netherlands (3)Department of Intensive Care, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands (4)Department of Intensive Care, Rijnstate Hospital, Arnhem, The Netherlands (5)Department of Intensive Care, Gelderse Vallei Hospital, Ede, The Netherlands (6)Department of Intensive Care and National Poison Information Center, University Medical Center Utrecht, Utrecht, The Netherlands (7) Department of Medical Microbiology, Radboud university medical center, Nijmegen, The Netherlands (8)Department of Intensive Care, Radboud university medical center, Nijmegen, The Netherlands (9)Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (10) Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, the Netherlands.

Objectives: Caspofungin (CAS) is an echinocandin antifungal agent and is used as first-line therapy for the treatment of invasive candidiasis. CAS is administered intravenous at a loading dose of

70mg on day 1, followed by 50mg QD. Maintenance dose should be increased to 70mg for bodyweight (BW) ≥80kg and decreased to 35mg for patients with Child-Pugh score B (CPB).[1] AUC/MIC is used as PK-PD target parameter.[2] CPB is only valid for patients with cirrhotic livers. Using CPB in non-cirrhotic patients may result in suboptimal exposure. We aimed to confirm this using a population PK approach, evaluating the target attainment.

Methods: CAS PK data from a study in ICU patients (21 patients; median(range) age and BW were 71(45-80) years and 75(50-99)kg; N=419 observations) were available.[3] A POP-PK model was built (NONMEM 7.2, Pirana, PsN, R). The following dosing regimens were simulated in a cohort of 1706 hematological patients, (assumed to be representative for ICU patients) median(range) BW 76(39-145)kg: licensed regimens (I) 70/50 for BW<80kg; 70/70 (for BW>80kg); (II)70/35 for CPB; adapted regimens (III) 100/50 (for CPB); (IV) 100/70; (V) 100/100. Target attainment based on a preclinical PK target (AUC/MIC≥865) for *C.albicans* was assessed on day 14 for three relevant MICs (0.03, 0.06, 0.125), as PK targets for CAS are lacking.[2]

Results: A 2-compartment PK model best fitted the CAS data. BW was scaled linear on V1 and allometric on CL. IIV on all parameters was estimated and a full omega-block was used. CPB could not be confirmed as a covariate on any parameter. Median AUC(95%CI) were for (a) BW≤80kg 106(37-316), BW>80kg 116(39-348); (b) BW≤Median AUC(range) were for (I) BW≤80kg 102(39-386), BW>80kg 113(44-459); (II) BW≤80kg 71(26-270), BW>80kg 56(22-230); (III) BW≤80kg 102(39-387), BW>80kg 80(32-328); (IV) BW≤80kg 142(55-541), BW>80kg 113(44-459) and (V) BW≤80kg 203(78-772), BW>80kg 160(64-656). PK target attainment was the for whole cohort for MIC0.03 (I) 100% (ii) >99% (III-V) 100%; for MIC0.06 (I) 99% (II) 73% (III) 95% (IV) >99% and (V) 100% and for MIC0.125 (I) 47% (II) 14% (III) 36% (IV) 69% (V) 97%.

Conclusions: CAS maintenance dose should not be reduced in non-cirrhotic (i.e. ICU) patients based on CPB as it results in 17-39% lower target attainment (MIC0.06 µg/mL), increasing the risk of therapeutic failure. Given the favorable safety of CAS, maintenance dose of 70 mg should be considered.

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Emma Martin Design of preclinical experiments: an example in chemotherapy-induced myelosupression

Emma C. Martin (1), Leon Aarons (1) and James W. Yates (2)
(1) Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, The University of Manchester, United Kingdom, (2) AstraZeneca, Innovative Medicines, Oncology, Modelling and Simulation, Alderley Park UK

Objectives: To investigate a new preclinical study design (referred to as a compact design) that removes the need for satellite animals for the collection of pharmacokinetic (PK) data, by characterising the PK in the main study animals, taking no more than one sample in 24 hours to build up a full profile over the course of the study.

Methods: The design's performance was tested through a simulation study, based on drug concentration and neutrophil count data following administration of chemotherapy in rats. One hundred datasets were simulated from a model based on available data, using both the compact design and a traditional design using satellite animals. The effect of the compact design on parameter and variance estimates following the fitting of a PKPD model was investigated, as well as the potential effect of inter-occasion variability (IOV).

Results: The compact design performed equally well, and had little impact on parameter estimates, or variation estimates, indicating that it may be a preferable alternative to traditional satellite designs whilst using fewer animals. When IOV was ignored during analysis

the PK model parameters remained well estimated, however the inter-individual variation (IIV) and residual errors were inflated. Ignoring IOV in the neutrophil model caused some bias in parameter estimates, as well as inflating the inter-individual variation and residual error. Estimating IOV improved parameter estimates, but IIV and IOV could not be well estimated simultaneously using the compact design.

Conclusions: Using the proposed compact design removes the need for a satellite group, reducing the number of animals, without impacting the ability to model the data. If IOV is suspected, caution should be used, as the variation in the PK model can be inflated.

David Mawdsley Model Based Network Meta-Analysis for Pharmacometrics and Drug-Development: a 3 year Research Collaboration between Pfizer and the University of Bristol.

David Mawdsley (1), Meg Bennetts (2), Sofia Dias (1), Martin Boucher (2), Tony Ades (1), and Nicky J. Welton (1)
(1) School of Social and Community Medicine, University of Bristol
(2) Pharmacometrics, Global Clinical Pharmacology, Pfizer Ltd

Objectives: Meta-analysis is a well-established methodology for combining the results of randomised controlled trials (RCTs) that compare the same treatments and outcomes. However, in drug-development, early-phase studies explore the action of compounds over dose and time. Model-based meta-analysis (MBMA) has been developed to use non-linear pharmacokinetic-pharmacodynamic type models that allow dose-response and time-course effects within meta-analysis [1-3]. Network Meta-Analysis (NMA) allows simultaneous comparison of multiple treatments [4,5], and provides a framework for model comparison and assessment of evidence consistency [6]. Although multiple doses can be compared, this is done by either "lumping" similar doses, or by regarding them as separate treatments. "Lumping" introduces the potential for inconsistency between comparisons, which can invalidate the results of NMA. Regarding them as separate treatments can lead to sparse or unconnected networks. MBMA has recently been used to assess multiple treatment comparisons, however little attention has

been given to assessment of model fit and consistency. This project aims to integrate the two approaches in a Model Based Network Meta-Analysis (MBNMA), to model multiple treatments, dose and time-course that incorporates assessment of model fit [6] and consistency [7].

Methods: We illustrate the importance of assessing model fit using a MBMA comparing Naproxen vs placebo for treating pain. The fit and model predictions are compared for different time-course models. We indicate how the methods can be extended to multiple treatments, using a network of trials of multiple treatments, doses and time-points for osteoarthritis.

Results: We show that parameter estimates are sensitive to choice of model and that "lumping" in a NMA can lead to inconsistent treatment effects, motivating a model-based analysis.

Conclusions: Results can be sensitive to model choice, and ignoring dose can lead to inconsistency. It is therefore essential to assess fit and consistency. In January 2015 Pfizer Ltd & the University of Bristol started work on a 3 year Medical Research Council (MRC) Industry Collaboration Agreement project to develop MBNMA methods. This offers the potential to combine all the available dose-response and time-course evidence in a MBNMA to compare the relative efficacy of multiple treatments, while allowing model fit [6] and evidence consistency [7] of the whole network to be assessed.

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Poster: Drug/Disease modeling - Infection | IV-19 | Thursday 15:20-16:40

Osawa Mayu Population Pharmacokinetic Analysis of Daclatasvir and Asunaprevir in Japanese Subjects with Hepatitis C Virus infection

Mayu Osawa (1), Takayo Ueno (1), Tomoko Ueki (1), Yasuhiko Imai (1), Phyllis Chan (2), Tushar Garimella (2), Timothy Eley (2), Malaz AbuTarif (2), Richard Bertz (2)
(1) Bristol-Myers K.K., Research and Development, Tokyo, Japan (2) Bristol-Myers Squibb, Research and Development, NJ, USA

Objectives: The approval of the combination therapy of Daclatasvir (DCV) and Asunaprevir (ASV) in Japan represented the world's first approval of an interferon and rebavirin-free Hepatitis C Virus (HCV) treatment. The objectives of these analyses were to develop the DCV and ASV population pharmacokinetic (popPK) models for estimating the effects of demographic, pathopysiologic, and disease-related covariates for Japanese HCV patients and providing individual patient PK parameter estimates for subsequent exposure-response analysis.

Methods: These popPK models were developed with FOCE-I in NONMEM V7.2.0 from four (DCV) and two (ASV) Phase 2/Phase 3 studies in Japanese subjects with HCV infection. The ASV tablet formulation was used for Phase2 study. To improve the oral bioavailability and mitigate food effect, the ASV softgel capsule formulation was developed for Phase 3 study. Total individuals included in the analysis for DCV and ASV were 336 and 265,

respectively. A one-compartment model was selected as the structural model based on model development work. The full-covariate model was developed by incorporating the effects of all pre-specified covariates on structural model parameters. Highly correlated covariates were screened and the one showing the largest decrease in OFV compared to base model was retained in full model. The final model was developed by backward elimination from the full model. Model evaluation was conducted using visual predictive check and bootstrap.

Results: Significant covariates for DCV included gender, treatment description and creatinine clearance on CL/F and body weight on V/F, and for ASV included baseline and time-varying aspartate aminotransferase (AST) and cirrhosis on CL/F, formulation on CL/F and V/F. The final model indicated that worsening of hepatic status (presence of cirrhosis and increase in AST) led to decrease in ASV CL/F. The bioavailability of the softgel capsule formulation of ASV was higher than the tablet formulation. The effects of all covariate effects for DCV PK in the final model were within or overlapped the 80-125% difference from typical value.

Conclusions: The popPK models adequately described the PK profiles of DCV and ASV in Japanese subjects with HCV infection.The magnitude of estimated covariate effects on DCV PK were small and not clinically meaningful. ASV CL/F decreased with cirrhosis and increasing baseline and time-varying AST indicating an association between hepatic markers and ASV CL/F.

Lynn McFadyen The Population Pharmacokinetics of Active Metabolites of a prodrug PF-0417132, (Dissociated Agonist of Glucocorticoid Receptor), in Rheumatoid Arthritis subjects

Barry Weatherley (1), Lynn McFadyen (1), Daniela Conrado (2), Brinda Tammara (3)
(1) Pharmacometrics, Pfizer, Sandwich, UK (2) Clinical Pharmacology, Pfizer, Groton, USA (3) Clinical Pharmacology, Pfizer, Collegeville, USA

Objectives: Develop a PK model for PF-00251802 (parent) and its active metabolite PF-04015475 after oral administration of the prodrug PF-0417132.

Methods: PK data were obtained from a phase 2, randomized, double-blind efficacy and safety study of PF-04171327 (1, 5, 10, 15 mg dose daily) compared to 5 and 10 mg of prednisone and placebo over an 8 week period with a 4 week tapering period thereafter. PK trough samples were obtained at weeks 2, 4, 6, 10, 12 and at week 8 at 0, 1, 2, 3, 4 hours after dose.

179 patients had 1607 parent and metabolite concentrations (including samples below the quantitation limit (BLQ) and taper concentrations). 43 subjects were males (24.0%) and 136 were females (76.0%).

NONMEM 7.2 was used for a simultaneous fit to all parent and metabolite data in ordinary space. Inter-individual variability (IIV) (CL, V2 and Ka for parent; CLm and metabolite central volume V3 for metabolite) were modeled exponentially. Visual predictive checks were performed for parent and metabolite with and without taper and BLQ values to select the final model.

Results: A 2-compartment model for parent, with assumed 100% conversion to metabolite (1-compartment) was acceptable on VPC and concentration profiles, after removal of BLQ and taper concentrations. Inter-occasion variability on F1 reduced from 51% to 23.8% with BLQ and taper concentrations removed. IIV on CL (33%) and CLm (44%) were moderate but high on KA (249%). Residual variability for parent was 19.9 % and 0.305 ng/mL and for metabolite 7.8% and 0.10 ng/mL, for proportional and additive components. Important covariate effects, after allometric scaling of parent drug, were age and sex on parent clearance (CL) and sex and weight on metabolite clearance (CLm). Compared to a reference male of age 40 y and weight 70 kg with CL=7.29 and CLm =17.2 L/h, the reference female had a 27% drop in parent CL (5.4 L/h) and a 34% drop in CLm (11.4 L/h). Age effect on CL was a 6% decrease for every 10 years above 40 years. The weight effect on parent CL was fixed at 0.75 (allometric) with the power weight effect on CLm estimated at 0.45 (SE 30%).

Conclusions: Covariates age, weight and sex, in combination, predict AUC differences > 2- fold at their extremes. Post hoc graphical analysis showed that the sex covariate on PK did not translate to efficacy differences.

Authors are contractors to (BW) or employees and shareholders of Pfizer Inc (LM, BT, DC).

Johanna Melin Population pharmacokinetic analysis of AZD4818 in healthy volunteers following three different routes of administration.

Johanna Melin (1)(2)(3), Bo L Olsson (3), Carl Johansson (3), Charlotte Kloft (1), Ulrika Wählby Hamrén (3)
(1) Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) Graduate Research Training Program PharMetrX, Germany, (3) AstraZeneca R&D, Mölndal, Sweden.

Background: The pharmacokinetics (PK) of drugs administered via inhalation may be different in comparison to when administered intravenously. Several factors such as solubility, mucociliary clearance, pulmonary disposition patterns, lung anatomy and disease status may affect the PK and thereby also the pharmacodynamics (PD) of inhaled drugs [1]. Population PK analyses have previously been performed to quantify the different lung absorption processes, thereby increasing the mechanistic understanding of inhaled drugs [2, 3]. To this end, an in-house compound (AZD4818) previously in development for COPD was selected as model drug. AZD4818 is a water soluble base with expected limited mucociliary clearance.

Objectives: This analysis aims to use a population PK approach to characterize the pharmacokinetics of AZD4818 after intravenous

(iv), oral (po) and pulmonary (pi) administration and to evaluate the impact of the lung PK on the apparent systemic PK.

Methods: Data from a single-dose 4-way cross over study in healthy volunteers (N=12) following iv, po and pi (with two devices: one dry powder inhaler, and one nebuliser) administration of AZD4818 were used for model development. Plasma and urine concentration-time data were included in the analysis using NONMEM 7.3 and PsN 4.2.0 [4,5]. The PK disposition model was developed on data after iv administration and data following pi and po administration were sequentially included to estimate absorption specific parameters. Similar approaches have previously been used [2,3]. GOF plots, model convergence, precision of parameter estimates and visual predictive checks were used to evaluate model performance.

Results: A three compartment disposition model with renal and non-renal clearance described the data after all administration routes adequately. Absorption processes were described separately for pi and po administration, and the pulmonary administration included three rate constants. A major proportion of the inhaled dose was absorbed with the slowest absorption rate, potentially explaining the absorption-rate limited elimination (flip-flop kinetics) observed after inhalation. Small differences in absorption pattern between the two devices were observed.

Conclusions: The proposed model, separating and quantifying the different absorption processes for inhaled AZ4818, may be applied on future inhalation compounds to evaluate the effect of drug- and inhalation device-specific factors on absorption-related parameters.

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Zhaoling Meng PK/PD modeling of recurrent events and clinical trial simulation in optimizing Phase 3 dose selection

Zhaoling Meng, Tao Sheng, Lei Ma, Qiang Lu, Dimple Patel and Hui Quan
sanofi

Objectives: Dose selection for confirmative Phase 3 studies is always considered as one of the most difficult tasks in drug development. When the endpoint is of event type, the difficulty for dose selection could increase due to the relatively small Phase 2 study sample size and lack of sufficient data to appropriately quantify the dose-response relationship. We explored the utilization of plasma concentration data for a more informative dose justification through the exposure-response relationship modeling.

Methods: A negative binomial PK/PD model for accounting over-dispersion is applied to establish the relationship between exposure and a recurrent event endpoint. Baseline covariates which potentially can impact treatment effect are included. Through the PK/PD model, treatment effects of different doses can be predicted for dose justification. Clinical trial simulations (CTS) were utilized to incorporate the PK/PD modeling results and Phase 2 knowledge, assist the selection of Phase 3 patient population and trial design options, assess the impact of the design assumption uncertainty and predict Phase 3 probability of success.

Results: The annualized exacerbation event rate in asthma was fitted with the above models. The approach provided satisfactory results for dose justification. Also, trial simulation provided further useful information for dose selection in achieving the desired probability of success.

Conclusions: PK/PD modeling on a recurrent event endpoint combined with CTS can ensue in a more informative decision making for the Phase 3 dose selection.

Enrica Mezzalana Integrating Target Mediated Drug Disposition (TMDD) into a minimal physiologically based modelling framework: evaluation of different quasi-steady-state approximations

Mezzalana Enrica (1), Lavezzi Silvia Maria (1), Zamuner Stefano (2), De Nicolao Giuseppe (1), Ma Peiming (3), Simeoni Monica (2)
(1) Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy, (2) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, UK, (3) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, China

Objectives: Target-mediated drug disposition (TMDD) often occurs with monoclonal antibodies (mAbs); hence various models were developed to describe this phenomenon [1]. Cao and Jusko [2] incorporated a quasi-steady-state (QSS) TMDD component into the minimal physiologically-based PK (mPBPK) model [3]. Assuming peripheral target binding, we explored the mPBPK model combined with the full TMDD model, denoted model I, and three approximated models [4], denoted model II, III and IV, to assess the feasibility of these approximations with respect to identifiability issues. The aim is to understand how informative is plasma PK about binding processes occurring in periphery.

Methods: With the PK parameters estimated in [2] for romosozumab (a mAb for the cure of osteoporosis), models I, II, III, IV were simulated using R and SimulX and sensitivity analysis

performed. In particular, mAb PK data were simulated according to model I. Then, the full and approximated models were fitted with NONMEM 7.3 in different situations (without binding, with binding only in leaky tissues, and only in tight tissues) and with different types of data (drug concentration in plasma alone, with the addition of total drug concentration in the binding site, with the addition of total receptor concentration in the binding site). Drug related parameters were estimated while volumes and flow rate parameters were fixed to typical physiological values.

Results: For all models (I-IV), the contribution of elimination through internalization of the complex can be evaluated from drug concentration profiles in plasma: when binding is simulated in tight tissues, this contribution results negligible if compared to the situation without binding. Instead, if binding is simulated in leaky tissues, or both leaky and tight, the nonlinear elimination due to TMDD prevails. Identifiability issues arose almost under any condition, especially when attempting to partition the plasma and the non-linear peripheral clearance. In simulation, model I and II are almost equivalent, while model II yields different profiles primarily for receptor concentration in binding sites, while model IV exhibits a substantially different behavior.

Conclusions: : The full TMDD model and three QSS approximations [4] were plugged into a mPBPK model developed for mAbs [3]. Simulated profiles were compared and identification issues evaluated in the most significant contexts relative to binding site and measurements availability.

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Robin Michelet Bioequivalence of desmopressin in children: a population pharmacokinetic study

Robin Michelet (1), Pauline De Bruyne (2), Lien Dossche (2), Johan Vande Walle (3), Jan Van Bocxlaer (1), An Vermeulen (1)
(1): Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Belgium, (2): Department of Pediatrics and Medical Genetics, Faculty of Medicine and Health Sciences, Ghent University, Belgium, (3): Department of Pediatric Nephrology, Ghent University Hospital, Belgium

Introduction: Off-label use of drugs in the pediatric population is widespread: 50-90% of drugs are not tested in children [1]. The project SAFE-PEDRUG aims to provide new medical and ethical guidelines for conducting clinical trials in children, based on a rational combination of bottom-up and top-down investigations. Desmopressin (DDAVP), one of the drugs under study, is a synthetic vasopressin analogue used in nocturnal enuresis treatment. Two formulations, a tablet (TAB) and a lyophilisate (MELT), exist of which the bio-equivalence has been established in adults but not in children. This pilot study investigates how the drug product influences the pharmacokinetics and provides suggestions for subsequent studies.

Methods: Earlier published data on 22 children (mean age 12.7 y and mean weight 50.1 kg) were included in the study. Blood samples were taken 1h, 2h and 6h after both TAB and MELT dosing at 200 and 120 µg, respectively. Dosing events were 2 weeks apart

and patients received a standardized meal before administration [2]. In addition, an available part of historical data (28 patients, 1-3 samples per patient) from Osterberg et al. [3] were also included in the analysis.

A 1-compartment model with first order absorption was fitted to the data using NONMEM (v. 7.3, [4]). Covariates were selected through one-by-one screening to construct a full model, followed by backward deletion. The final model goodness-of-fit (GOF) was evaluated by means of diagnostic tools and a sensitivity analysis (SA) was performed to evaluate the sampling design.

Results: The popPK model was able to describe DDAVP plasma concentrations adequately as is shown by the different diagnostics. The NPDE distribution did not significantly differ from the normal distribution and the basis GOF plots only showed a slight bias at low concentrations. In this model, formulation and fasted/fed state were included as significant covariates on F1 and body weight on distribution volume. MELT was found to be 1.321 times more available as TAB, while being fasted increased the bioavailability 2.01 times. SA showed optimal sampling times to be between 0.5 and 1.5, and at 5 hours.

Conclusions: For the first time in children, the difference in relative bioavailability between the two DDAVP drug products has been proven to be significant. Furthermore, sampling times for a further study were suggested which should result in more informative data and consequently generate a more reliable model.

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Iris Minichmayr Pharmacokinetic-pharmacodynamic target attainment of intravenous linezolid regimens in plasma and peripheral tissue fluids of four distinct populations

I.K. Minichmayr (1,2), M. Zeitlinger (3), A. Schaeftlein (4), C. Kloft (1)
(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) and Graduate Research Training program PharMetrX, Germany, (3) Dept. of Clinical Pharmacology, Medical University Vienna, Austria, (4) Dept. of Clinical Pharmacy, Saarland University, Saarbruecken, Germany

Objectives: Linezolid (LZD) is an oxazolidinone antibiotic used for the treatment of gram-positive infections. It is approved in a fixed dosing regimen of 600 mg twice daily, irrespective of individual patient characteristics. The objective of the present work was to explore the ability of standard dosing and alternative intensified dosing regimens to achieve pharmacodynamic (PD) targets in plasma as well as in interstitial space fluid as the target site of infections in four heterogeneous populations.

Methods: Simulations were performed in NONMEM® 7.2 using a population pharmacokinetic (PK) model built upon pooled plasma and microdialysis data (of s.c. adipose and muscle tissue) obtained from healthy volunteers and patients with sepsis, diabetes-related foot infections or cystic fibrosis (n_{tot}=51) [1]. The influence of the covariates creatinine clearance (CLCR) and weight (WT) on plasma

and target site exposure of LZD was assessed both for standard dosing and intensified dosing regimens (600 mg thrice daily (TID) vs. loading dose preceding standard dosing). For this purpose, the PK/PD indices AUC/MIC and $fT_{>MIC}$ (time during which free concentrations exceed the MIC) were calculated for Day 1 and Day 4 of therapy and compared to the respective target values (AUC/MIC=100, $fT_{>MIC}$=100%. [2,3]) for the MIC_{90} of LZD against *S. aureus*.

Results: For median values of CLCR and WT of the pooled population, septic patients achieved lowest PK/PD indices (AUC_{0-24}/MIC 57.6, $fT_{>MIC\_adipose}$ 68.7%, $fT_{>MIC\_muscle}$ 67.0%). Furthermore, LZD exposure decreased with increasing CLCR and decreasing WT. A loading dose of 1200 mg prior to standard dosing led to slightly higher AUC/MIC values on the first day of therapy, while TID dosing resulted in tendentiously higher $fT_{>MIC}$ (e.g. septic patients (TID vs. loading dose): AUC_{0-24}/MIC 85.5 vs. 90.2 , $fT_{>MIC\_pl}$ 98.8% vs. 86.8%). Whereas continued TID dosing seemed advantageous for septic patients (typical CL=11.2 L/h), diabetic patients, the subgroup displaying lowest LZD CL (6.35 L/h), were more prone to LZD overexposure (AUC_{24} 400 mg·h/L [4]).

Conclusions: Linezolid exhibits substantial PK variability between and within different populations, exposing patients to a risk of either therapeutic failure or adverse events. Given the importance of rapidly achieving effective concentrations especially in critically ill patients, intensified dosing regimens, e.g. including front-loading, might be particularly beneficial for septic patients.

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Jonathan Mochel Evaluating the dose-response relationship of furosemide on diuresis and renin-angiotensin aldosterone activation in dogs combining multiple comparisons and modeling techniques

J.P. Mochel (1,2), B. Bornkamp (2), and B. Bieth (2)
(1) Department of Pharmacology, Leiden-Academic Centre for Drug Research, 2300 Leiden, The Netherlands. (2) Integrated Quantitative Sciences, Novartis Pharmaceuticals, Werk Saint Johann 4056 Basel Switzerland

Objectives: Congestive heart failure (CHF) is a leading cause of morbidity and mortality which is commonly associated with fluid overload and shortness of breath in canine populations. Furosemide is a non-potassium sparing loop diuretic prescribed for the majority of patients suffering from heart diseases. Although furosemide provides an overt clinical benefit in reducing fluid retention, it also has the disadvantage of activating the renin-angiotensin aldosterone system (RAAS), which further contributes to the accelerated progression of CHF. Despite the widespread use of loop diuretics and concerns regarding activation of the RAAS in dog patients, no detailed information on the dose-response relationship of furosemide is presently available. Our objective was to quantify the effect of several increasing doses of furosemide on diuresis, renin activity (RA) and aldosterone (AL) in dogs, using a model-based approach.

Methods: 24 healthy beagle dogs were allocated to 4 treatment groups (saline control, furosemide 1, 2, and 4 mg/kg I.M., q12 hrs for 5 days). Dogs were placed in metabolism cages for collection of urine. RA was determined using a dedicated enzyme immunoassay, while AL concentrations were quantified in plasma by mass spectrometry. Data from trough RA and AL values, as well as 24-hr diuresis were analyzed at steady state using dose-response modelling based on a multiple comparison procedure and modelling (MCP-Mod) approach [1]. To cover a broad range of anticipated dose-response shapes, a set of candidate models was characterized, and a multiple contrast test was performed to assess the presence of a dose response signal (MCP part). Finally, a model averaging technique was used to derive the dose-response curve for each endpoint of interest (Mod part).

Results: Sigmoid E_{max} models were found to adequately describe the dose-response relationships of furosemide. The derived ED_{50} and ED_{90} values were estimated to be lower for 24-hr diuresis (0.6 and 1.3 mg/kg q12 hrs, respectively), compared with RA (1.0 and 1.9 mg/kg) and AL (1.0 and 2.1 mg/kg).

Conclusions: MCP-Mod is a powerful tool for evaluating dose-response relationships in veterinary pharmacology. Our data show that furosemide produces a sub-maximal effect on diuresis at doses lower than those identified to activate the systemic RAAS.

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Dirk Jan Moes Exploring risk factors for everolimus discontinuation and serious side effects in renal transplant recipients on everolimus and prednisolone dual therapy.

DJAR Moes (1, 3), S Jönsson (2), J den Hartigh (1), T van der Straaten (1), JJ Homan van der Heide (4), JS Sanders (5), FJ Bemelman (4), H-J Guchelaar (1), MO Karlsson (2) & JW de Fijter (3)
(1) Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands. (2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (3) Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands. (4) Department of Nephrology, Academic Medical Center, Amsterdam, The Netherlands. (5) Department of Nephrology, University Medical Center Groningen, Groningen, The Netherlands.

Objectives: Everolimus is an emergent non-nephrotoxic alternative for calcineurin inhibitors with substantial potential non-renal benefits in renal transplantation. Despite its proven efficacy and close therapeutic drug monitoring, everolimus is also known for relatively high discontinuation rates and some serious side effects. The primary objective of this study was to develop time-to-event models for the time to drug discontinuation and the key side effect (i.e pneumonitis, infection and new onset diabetes mellitus) to identify risk factors that may determine therapy outcome.

Methods: An extensive dataset consisting of demographic, transplant related and pharmacogenetic data of 99 stable adult renal transplant recipients on a regimen of everolimus and prednisone dual therapy was used for a systematic analysis using a parametric survival model for each different endpoint to describe the time to discontinuation and the most hazardous side effects including pneumonitis, infection and new onset diabetes mellitus. Modelling was performed using NONMEM v7.3.0 and R statistics was used for summary statistics and plotting.

Results: The baseline hazard of discontinuation, pneumonitis and infection data, respectively, was best described by a Gompertz function and an exponential hazard function was used to describe the baseline hazard of new onset diabetes mellitus. Risk factors for everolimus discontinuation were excess everolimus exposure and increasing age. Furthermore, risk factors for the hazardous side-effect non-infectious interstitial pneumonitis were excess everolimus exposure and PXR(NR1|2)(-24113G>A):AA genotype. For infection and new onset diabetes mellitus no significant risk factors could be identified.

Conclusions: The current findings indicate that discontinuation rates and non-infectious pneumonitis in renal transplant recipients on everolimus can be prevented by avoiding excess initial and/or excess maintenance everolimus exposure.

Daniel Moj Is the ICRP reference man still suitable for physiologically-based pharmacokinetic (PBPK) modeling?

Daniel Moj (1), André Schäftlein (1), Nina Hanke (1), Wiebke Braun (2), Manfred James Müller (2), Thorsten Lehr (1)
(1) Clinical Pharmacy, Saarland University, Saarbruecken, Germany, (2) Institute of Human Nutrition and Food Science, Christian-Albrechts University, Kiel, Germany

Objectives: The body composition of the human population is constantly changing and recent changes were taken into account by the novel "Kiel reference man". We investigated the differences between the "old" ICRP and the "new" Kiel reference man on pharmacokinetic (PK) parameters determined in PBPK simulations.

Methods: The Kiel reference man is based on a healthy Caucasian population (n=208, 105 males, 103 females) aged from 18 to 78 years with a BMI from 16.8-35.0 kg/m^2. In addition to age, height and weight, the masses of brain, fat, heart, kidney, liver, muscle and spleen have been measured. The Kiel reference man has been implemented in PK-Sim 5.3.2 and used for simulation of concentration-time profiles after single oral doses of clarithromycin, midazolam, paracetamol and theophylline. The AUC, C_{max} and half-life of the simulated concentration-time profiles were compared to simulations using the ICRP reference man.

Results: The recently established Kiel reference man is taller, heavier and has a higher BMI value than the ICRP reference man, but shows e.g. a smaller liver size. PBPK simulation and analysis revealed that the changes in biometry have significant impact on descriptive pharmacokinetic parameters of clarithromycin, midazolam, paracetamol and theophylline. The AUC_{0-24} of the investigated drugs increased by approximately 30% in the Kiel reference population compared to the ICRP population. C_{max} and half-life increased by 7% and 20% respectively, except for midazolam where the half-life declined by 4%.

Conclusions: The Kiel reference man has been established and successfully used for PBPK simulations. The taller and heavier Kiel reference man shows a significant increase in AUC_{0-24}, C_{max} and half-life of various compounds. This analysis demonstrates that an update of the ICRP reference man, which is intensively used in PBPK modeling, is necessary.

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Morris Muliaditan Determinants of variability in drug exposure and implications for dose selection in tuberculosis patients

Morris Muliaditan (1), Oscar Della Pasqua (1,2)
(1) UCL School of Life and Medical Sciences, London, UK, (2) GlaxoSmithKline, London, UK.

Objectives: Despite promising advances in tuberculosis (TB) drug development, new integrated methods are still required to efficiently transition the growing number of novel compounds that are needed to shorten current first-line therapy. Clinical trial simulation (CTS) can be a valuable tool for informing robust study designs with respect to the population and dose rationale. This project aims to present the first component of a simulation-based framework for the evaluation of combination therapies in TB. A model for simulation of virtual patients was developed in conjunction with existing population pharmacokinetic (PK) models for all first-line drugs, with the objective of highlighting the implications of covariate effect on variability in systemic drug exposure following different dosing regimens.

Methods: Virtual demographic characteristics were simulated from a database using the multivariate distribution method [1]. Existing population PK models were used to simulate concentration versus time profiles based on WHO recommendations and crude weight band. The goodness of predictions was assessed against literature

values. The adequacy of each regimen was measured based on the variability in the simulated AUC0-24 and percentage of patients achieving the recommended minimum Cmax [2]. The development of the population demographic model was performed in R. Population PK simulations were performed using a non-linear mixed effects approach, as implemented in NONMEM 7.2.

Results: The use of a multivariate distribution method yielded a virtual population with comparable covariate correlations to those in the database and published studies. Evaluation of the weight bands revealed that WHO recommended regimens yielded the lowest exposure in patients weighing less than 40 kg. Median simulated AUC0-24 of the first-line drugs was found to be approximately 1.2, 1.3 or 1.4 fold lower when compared to patients weighing respectively 40-54 kg, 55-70 kg or >70 kg. The opposite trend was observed following crude weight band-based dosing regimen.

Conclusion: A population demographic model was developed that can be integrated into a TB CTS framework. Our results show potential limitations of WHO recommended regimen, in that patients with low body weight are potentially underexposed. Moreover, a fixed dose regimen based on three (<40 kg), four (40-70 kg) or five (>70 kg) tablets was proposed to ensure comparable drug levels across all the population.

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Helen Musther Extended Validation of a Peripheral Sampling Site in PBPK modelling using Clarithromycin, Dextromethorphan, Dextrorphan, Erythromycin, Lidocaine and Tramadol

Helen Musther (1), Kate Gill (1), Lu Gaohua (1), Shriram Pathak (1) & Masoud Jamei (1)
(1) Simcyp Limited, Blades Enterprise Centre, Sheffield, UK

Objectives: A corrective model to account for the observation that physiologically-based pharmacokinetic (PBPK) models often over-predict C_{max} for intravenous (i.v.) administration compared to in vivo sampling data has previously been presented [1]. The initial validation was limited to only seven compounds. The objective of this study was to extend the validation to additional compounds with varying physiochemical properties.

Methods: A peripheral site model has been developed and implemented within the Simcyp Simulator based on anatomy and physiology governing the blood supply at the site of sampling [1]. Additional compound datasets were identified where data required for modelling a compound and clinical studies with i.v. dosing and early sampling time points were available. Comparisons were made between predicted and *in vivo* observed C_{max} values for the central venous and peripheral site models.

Results: Physicochemical and *in vitro* metabolism data for six compounds (Clarithromycin, Dextromethorphan, Dextrorphan, Erythromycin, Lidocaine and Tramadol) with at least one relevant clinical i.v. study were collated for further performance verification. All studies investigated showed a C_{max} prediction within 2-fold of the observed value when using the peripheral site concentration, with many showing a marked improvement compared to the central venous concentration. The impact of using the corrective model may depend on the compound properties and the length of the intravenous administration.

Conclusions: Additional successful validation was performed for a model that allows a more realistic comparison of the predicted concentrations at a peripheral sampling site to those taken in clinical trials, particularly at early sampling time points and for compounds known to distribute into tissues. These models can be built into PBPK platforms to improve C_{max} predictions and potentially account for factors (such as effect of heat, variation in adipose and muscle content of the body) that may affect the initial mixing of the blood at the site of sampling and hence the simulated drug concentrations in blood or plasma at early time points.

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Efthymios Neroutsos Population pharmacokinetic study of Mycophenolic acid in patients with lupus erythematosus nephritis

Efthymios Neroutsos, Georgia Valsami, Aris Dokoumetzidis, E.Grika, P. Vlachoyannopoulos, P. Macheras
Laboratory of Biopharmaceutics-Pharmacokinetics, Department of Pharmaceutical Technology, School of Pharmacy, National and Kapodistrian University of Athens, Greece

Objectives: To develop a population pharmacokinetic (PK) model Mycophenolic acid (MPA) after administration of Mycophenolate Mofetil (MMF) in patients with nephritis caused by lupus erythematosus (LE).

Methods: The study consisted of n=93 patients and all patients were receiving daily MMF doses prior to study participation. MMF doses were 500 mg, 1 g and 1.50 g. Blood samples for MPA determination were collected at 0h (pre dose) 0.5h, 2h and 4h after commencement and were assayed by an HPLC method. After the development of the basic model covariates were screened. The final PK model was validated using nonparametric bootstrapping and a visual predictive check (VPC). Plasma concentration-time data of MPA were analyzed using NONMEM version 7.3.

Results: The final model was a two compartment model with first order absorption and prppotional error, with diagonal

interindividual variability on clearence. Body weight was identyfied as covariate of clearance. Final model parameter values were CL/F=11.3 L/h, V2/F=11.2 L, Q/F=13.6 L/h, ka=1.58 h^{-1} and V3/F was fixed to 300 L as reported in literature [1] with IIV of clearence 40.7%. Goodness of fit assessment using diagnostic plots such as DV vs PRED were considered reasonable. Internal validation by VPC resulted that the model describes well the data including the observed variability.

Conclusions: A preliminary PopPK model for MPA after administration of MMF was developed, that is intended to serve as a prior information for the Bayesian Individualization of MPA levels in Greek hospitals. The model will be enriched with more patients including also patients receiving MPA after renal transplantation.

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Ida Netterberg Assessment of the Predictive Properties of C-Reactive Protein and Interleukin 6 on Febrile Neutropenia

Ida Netterberg, Elisabet I Nielsen, Henrik Lindman, Angelica Quartino, Mats O. Karlsson, Lena E. Friberg
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Myelosuppression is the dose-limiting toxicity for many chemotherapeutic agents. Febrile neutropenia (FN) is a common and life-threatening complication among patients treated with chemotherapeutic agents, and the frequency depends on patient factors and tumor type [1]. Neutropenic patients with an infection typically present no signs of infection other than fever. Therefore, it is desirable to identify predictors of FN, in order to initiate appropriate (prophylactic) treatment, e.g. antibiotics or granulocyte stimulating factor (G-CSF). Such predictors include patient or myelosuppressive factors [2] or infection biomarkers, e.g. interleukin 6 (IL6) and C-reactive protein (CRP). The objective of this study was to characterize the time-courses of CRP and IL6 after chemotherapy and assess variables as predictors of FN.

Methods: Measurements of IL6 and CRP in cycle 1 and 4 were collected from 49 breast cancer patients treated with adjuvant chemotherapy [3]. The IL6 and CRP concentration-time profiles were described by an indirect-response model where abrupt

increases were captured by surge functions. Mixture models estimated the probability for observing a biomarker increase in each cycle. Predictors from the IL6- and CRP-models, an earlier characterization of neutrophil counts [3, 4], as well as patient factors, were evaluated in a logistic regression analysis of FN. The analysis was carried out using NONMEM 7.3.

Results: The peak time for IL6 was estimated to be shorter (3.9 days) than for CRP (7.8 days) which is in line with that physiologically IL6 stimulates the production of CRP. The probability of increased IL6 and CRP concentrations were estimated to 87 and 64 %, respectively. The data exploration clearly indicated a distinct connection between the magnitude of increased IL6 and CRP concentrations and FN. The combination of the estimated surge amplitude of CRP, IL6 baseline and age, significantly improved the prediction of FN. When only evaluating variables that would be available pre-chemotherapy, the estimated IL6 and neutrophil baseline were identified as significant predictors.

Conclusions: The magnitude of the increased CRP concentration, IL6 and neutrophil baseline and age, could be clinically valuable predictors of FN. This could potentially have an impact on the prophylactic therapy of patients at risk for developing FN.

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Thi Huyen Tram Nguyen Bayesian Fisher Information matrix for predicting estimation error and shrinkage of individual parameters with data below the quantification limit

Thi Huyen Tram Nguyen (1), Thu Thuy Nguyen (1,2), France Mentré (1)
(1) IAME-UMR 1137, INSERM and University Paris Diderot, Paris, France (2) CEA, LIST, 91191, Gif-sur-Yvette, France

Objectives: In nonlinear mixed effect model (NLMEM), good estimation of individual parameters are necessary for treatment optimization, for sequential analysis in pharmacokinetic-pharmacodynamic studies, for detecting covariate effect etc. Usually, individual parameters are estimated as the maximum a posteriori (MAP), i.e., the mode of the conditional distribution given the data. Individual designs influence the estimation of individual parameters which are shrinked toward the mean of population value in case of sparse designs. We aimed to illustrate the use of Bayesian Fisher information matrix (BFIM) implemented in the package PFIM 4.0 [1] to predict standard errors (SE) and shrinkage of individual parameters, using a pharmacokinetic/viral kinetic model for various designs [2]. In this study, we also proposed a method to handle data below the quantification limit (BQL) in BFIM.

Methods: BFIM is the sum of individual Fisher information matrix (IFIM) and the inverse of random effect variance (a priori information) [3]. We studied the influence of number of samples

(n), levels of inter-individual variability (w) and residual error (s) on the predicted SE and shrinkage. The contribution of BQL data in BFIM was calculated by deriving their log-likelihood, defined as the probability for the data to be under the limit of quantification.

Results: As expected, SE predicted by BFIM were lower than those predicted by IFIM. SE increased when n decreased or ω and σ increased; shrinkage increased when n decreased, ω decreased and σ increased. In absence of BQL data, RSE and shrinkage predicted by BFIM were closed to values obtained by simulation. In presence of BQL data, the new method for handling BQL data allowed for better prediction of RSE as compared to the method that ignored BQL information.

Conclusions:

BFIM can be used to predict shrinkage and SE of individual parameters estimated by MAP, either in absence or presence of BQL data. PFIM is a relevant tool to evaluate and optimize population and Bayesian design in trials analyzed by NLMEM.

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Elisabet Nielsen A pharmacokinetic-pharmacodynamic model characterizing the emergence of resistant Escherichia coli subpopulations during ertapenem exposure

Wanchana Ungphakorn (1), Thomas Tängdén (2), Linus Sandegren (3), Elisabet I. Nielsen (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden; (2) Department of Medical Sciences, Uppsala University, Sweden; (3) Department of Medical Biochemistry and Microbiology, Uppsala University, Sweden

Objectives: Antimicrobial resistance in *Escherichia coli* related to the production of extended-spectrum β-lactamases (ESBLs) is increasing worldwide. Further, resistant subpopulations with reduced expression of outer membrane porins have been observed in ESBL-producing *E. coli* exposed to ertapenem antibiotic [1]. However, to date, there is limited information on how ertapenem exposures influence the emergence of resistance. The aim of this work was to develop a pharmacokinetic-pharmacodynamic (PKPD) model to characterize the emergence of resistant *E. coli* during exposure to ertapenem and to predict bacterial killing following different dosing regimens of ertapenem in adult patients.

Methods: In vitro time-kill curve experiments were performed with three *E. coli* strains; native strain, ESBL-producing strain and ESBL-producing strain with reduced porin expression (*omp*R mutant).

Each strain was exposed to static ertapenem concentrations ranging from 1 to 512 times the MIC for 24 h using both standard and high starting inocula. Mechanism-based PKPD models were developed using NONMEM 7.3. Bactericidal activity of ertapenem and the emergence of resistance were predicted following different dosing strategies using a previously reported population PK model [2] and the developed PKPD model.

Results: Bacterial regrowth and increased MICs were detected for all three strains when exposed to intermediate ertapenem concentrations. The final PKPD model consisted of susceptible growing, less-susceptible non-growing and insusceptible non-growing bacteria. A pre-existing bacterial subpopulation explained the emergence of resistance. Results from dose predictions supported the effectiveness of commonly used ertapenem dosage regimens for the native strain, while regrowth of resistant subpopulations for the ESBL-producing and the ESBL-producing *omp*R strains was predicted. No clear advantages of extended infusions, or fractionated doses were found, questioning time above MIC as PD driver.

Conclusions: The developed PKPD model adequately characterized the emergence of resistance for the three *E. coli* strains investigated. This study supports that the time-course of emergence of resistance should be taken into consideration when selecting dosing regimens.

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Alanna Ocampo-Pelland Model-based Meta-analysis for Development of a Population-Pharmacokinetic (PPK) Model for Vitamin D3 and its 25OHD3 Metabolite

Ocampo-Pelland, A.S. (1,3), Gastonguay, M.R. (1,2,3), French, J.L.(2,3), Riggs, M.M. (2)
(1) Department of Biomedical Engineering, University of Connecticut, USA, (2)Metrum Research Group, LLC, Tariffville, Connecticut, USA (3)Metrum Institute, Tariffville, Connecticut, USA

Objectives: Association of Vitamin D3 (D3) and its metabolite (25OHD3) exposure with various diseases, including bone health, diabetes, and cancer, has become an active area of research[1]. Clinical studies investigating these relationships with D3 and 25OHD3 vary in dosing regimen, assays, demographics, and control of endogenous D3 production. This leads to uncertain and conflicting exposure-related associations with D3 and 25OHD3. To elucidate this parent-metabolite system, a population PK (PPK) model was developed to predict D3 and 25OHD3 from varied doses and administration routes. Sources of variability related to 25OHD3 baseline (BL), weight (WT), and assay type were explored.

Methods: Public source PK data pertaining to D3 and 25OHD3 in healthy or osteoporotic populations, including 57 studies representing 5406 individuals (25 individual-level and 122 group-level units), were selected using specified search criteria in

PUBMED. Data included IV, oral, single and multiple dose data: dose ranges for D3 (400-100000 IU/d) and 25OHD3 (15-1000 ug/d). A nonlinear (NL) mixed effects model was developed to simultaneously model the D3 and 25OHD3 PK (NONMEM v7.2). Model development explored 1- and 2-compartment (CMT) models with first-order absorption rate constant (ka) and linear or NL clearance (CLNL). Unit-level random effects and residual errors were weighted by arm sample size[2].

Results: D3 and 25OHD3 dispositions were described by 2-CMT models with NL and linear clearances (CL), respectively. D3 model estimates, apparent to oral administration were: CLNL (VMAX=1.62 nmol/h, KM=6.39 nmol/L), central volume (VC=15.5 L), intercompartmental clearance (Q=0.185 L/h), peripheral volume (VP=2333 L/h), BL concentration (3.75 nmol/L), and mean endogenous production rate (220 IU/d). For 25OHD3: CLM=0.0153 L/h, VCM=4.35 L, VTM=6.87 L, QM=0.0507 L/h. The same ka for D3 and 25OHD3 was assumed (0.323h-1); CLNL was set equal to 25OHD3 formation rate. Simulations showed an inverse relationship between 25OHD3 and BL 25OHD3. HPLC-MS was the reference assay for 25OHD3; RIA was most similar but differences in precision and bias were estimated for competitive protein binding assay and chemiluminescence. WT was too inconsistently reported in publications to discern its covariate effect in the PPK.

Conclusions: The PK of D3 and 25OHD3 suggest that estimation of CLNL was important when considering comparisons of D3 and 25OHD3 exposure across studies and dosing regimens.

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Jaeseong Oh Population pharmacokinetic analysis of fluconazole in premature infants

Jaeseong Oh (1), Su-jin Rhee (1), SeungHwan Lee (1), Juyoung Lee (2), Kyungho Jang (1), Seonghae Yoon (1), Kyung-Sang Yu (1), In-Jin Jang (1), Han-Suk Kim (2)
(1) Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea; (2) Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea

Objectives: Fluconazole prophylaxis is an efficacious therapeutic strategy to reduce invasive candidiasis mortality rates in premature infants with extremely low birth weight. However, the pharmacokinetic (PK) data of fluconazole in premature infants are limited to guide dosing. The aim of this study was to develop a population PK model for fluconazole in premature infants.

Methods: A total of 301 fluconazole plasma concentrations from 75 premature infants (post-natal age 3-8 days, post-menstrual age (PMA) 21.3-35.7 weeks, body weight (WT) 0.54-1.49 kg) who admitted neonatal intensive care unit of Seoul National University Children's Hospital were pooled to develop a population PK model using the nonlinear mixed-effects method in NONMEM (ver. 7.3). Subjects received intravenous (30 min infusion) or oral 3 mg/kg dose of fluconazole, with more than 72 hours dose interval. The First-Order Conditional Estimation with Interaction estimation method was implemented, which was followed by model

qualification using bootstrapping and visual predictive checks (VPCs).

Results: A one-compartment linear PK model with proportional residual error was chosen as the final PK model. The population mean clearance (CL) and volume of distribution (V) was derived by the following equations: CL (L/h) equals $0.0214 \cdot (WT)^{0.75} \cdot (PMA/30)^{0.468} \cdot (\text{serum creatinine}/0.5)^{-0.412}$; V (L) equals $1.06 \cdot (WT)$. The inter-individual variability of CL and V were 24%, 20.7%. The oral bioavailability of fluconazole was 91%. Model evaluation by bootstrapping and VPCs suggested that the proposed model was adequate and robust with good precision.

Conclusions: The final PK model of fluconazole adequately described the observed plasma concentration of fluconazole in premature infants. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of fluconazole in premature infants.

Andrés Olivares-Morales A reduced physiologically-based pharmacokinetic (PBPK) model for the prediction of regional gastrointestinal (GI) drug absorption

Andrés Olivares-Morales (1), Leon Aarons (1), Amin Rostami-Hodjegan (1,2)
(1) Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, University of Manchester, Manchester, UK. (2) Simcyp Limited, Blades Enterprise Centre, Sheffield, UK

Objectives: Most of the current PBPK absorption models represent the different regions of the human GI tract as a series of transit compartments, where the small intestine (SI) is typically described by seven compartments [1]. The aim of this work was to develop and validate a reduced, yet mechanistic, PBPK absorption model that can be used for the prediction of drug absorption and first pass intestinal metabolism in the different regions of the GI tract.

Methods: The model was implemented in Matlab® 2014a as a system of 18 ODEs. The GI tract was described by five compartments (stomach, duodenum, jejunum, ileum and colon), where a non-linear transfer function was implemented and optimised to describe the small intestinal transit time (SITT). The drug was modelled either in the solid or dissolved state. Dissolution was predicted using different derivations of the Nernst-Brunner equation [2]. Regional GI absorption was allowed only for dissolved

drug and it was assumed dependent on drug's effective permeability (P_{eff}). Regional variations in P_{eff} were implemented in the model [3]. All the drug-specific and system-related parameters were taken from the literature. The model was used to predict the fraction absorbed (f_{abs}) for 10 different drugs [4, 5]. In addition, the PK of the oxybutynin (OXY), a CYP3A-subtrate, was predicted when administered as immediate release (IR) and modified release (MR) [6, 7]. For the PK predictions, OXY's disposition parameters were derived by fitting a three compartment model to intravenous (iv) data[7], while allowing the model to predict OXY's absorption and first pass metabolism.

Results: The predicted f_{abs} for the 10 investigated drugs was in good agreement with the observed data [4, 5]; the average absolute fold error was 1.2, whereas the concordance correlation coefficient was 0.94. A similar agreement was observed for OXY's PK predictions, where the predicted PK parameters, AUC, C_{max}, CL_{po}, were 16 ng/ml/h, 6.6 ng/mL and 314 L/h, respectively for the IR formulation, while for the MR formulation, the parameters were 95 ng/ml/h, 4 ng/mL and 158 L/h, respectively [6, 7].

Conclusions: The new model allowed the description of the SITT with a reduced number of SI compartments. The model also proved useful for the f_{abs} predictions. The segmented structure of the model adequately captured the regional differences in absorption and first pass metabolism observed when OXY is administered as IR and MR [6,8].

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Edouard Ollier Clustering Absorption Profiles of Rivaroxaban Using Between Subject Model Mixture

E Ollier (1,2), I Gouin-Thibault (3), MA Loriot (4), P Mismetti (1), S Laporte (1), X Delavenne (1).
(1) Groupe de Recherche sur la Thrombose, EA3065, Université Jean Monnet - Saint Etienne (France), (2) U.M.P.A., Ecole Normale Supérieure de Lyon, CNRS UMR 5669 & INRIA, Project-team NUMED - Lyon (France) (3) Université Paris Descartes, INSERM U765 - Paris (France), (4) UF Pharmacogénétique et Oncologie Moléculaire, Hôpital Européen Georges Pompidou, Inserm UMR-S 775, Université Paris Descartes - Paris (France).

Objectives: Rivaroxaban is a direct oral anticoagulant that is characterised by a very low solubility independent from the pH conditions. Moreover for high dosing regimen, the bioavailability is incomplete and absorption could be delayed. This characteristic induces also high variability in the early rivaroxaban absorption phase (monophasic, multiphasic). The objective of this work was to characterize absorption profile of rivaroxaban and to classify it in different groups of absorption.

Methods: This work consists in the analysis of 60 rich pharmacokinetic profiles of rivaroxaban (40 mg) from the DRIVING study (ClinicalTrials.gov NCT01627665). The absorption rate of rivaroxaban was broken down into a sum of inverse Gaussian functions [1]. To regularize the identifiably issue due to the estimation of bioavailability only from oral data, we introduce prior

probability distribution on bioavailability, volume of distribution and clearance parameters. These priors were constructed using previously published data following intravenous administration of rivaroxaban [2]. Finally, a Between Subjects Model Mixture (BSMM) [3] was built in order to cluster absorption profiles (early monophasic vs. early biphasic absorption). Data analysis was performed using a non-linear mixed effect model with MONOLIX® software.

Results: A one-compartment model with absorption rate broken down into a sum of three inverse Gaussian functions (IG1, IG2, IG3) best described the data. These 3 inverse Gaussian functions have an increased mean absorption time (49.5 min, 3h14 min and 21 h for IG1, IG2 and IG3 respectively). The BSMM consists of two models corresponding to two different absorption profiles. The corresponding absorption rates are AR1 and AR2 respectively:

i) Early monophasic absorption and late absorption

AR1 = IG1 + IG3

ii) Early biphasic absorption and late absorption

AR2 = IG1 + IG2 + IG3

The proportion of subjects who are adequately described by an early biphasic absorption was estimated to 30%.

Conclusions: BSMM effectively classified rivaroxaban absorption into two separate early absorption profiles. Moreover, rivaroxaban 40 mg appears to undergo an unexpected late absorption. This last result will allow us to propose optimal strategy for anticoagulant effect reversion.

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Sean Oosterholt Population pharmacokinetics of NNZ-2566 in healthy subjects and Rett syndrome patients

Sean Oosterholt (1), Nancy Jones (2), Joe Horrigan (2), Larry Glass (2), Oscar Della Pasqua (1)
(1) Clinical Pharmacology & Therapeutics, UCL School of Life and Medical Sciences, London, UK, (2) Neuren Pharmaceuticals Limited

Objectives: NNZ-2566 is a synthetic analog of a naturally occurring neurotrophic peptide derived from insulin-like growth factor-1 (IGF-1). It has been developed as a treatment to reduce cognitive and neurodevelopmental symptoms in Rett syndrome, a rare genetic disease. Given the limited number and difficulties associated with frequent blood sampling in these severely impaired patients, a meta-analytical approach is proposed to characterise the pharmacokinetics of NNZ-2566 and most importantly evaluate the impact of clinical and demographic covariate factors on pharmacokinetic parameters and consequently on systemic exposure.

Methods: Rich pharmacokinetic data from three different phase I trials in healthy subjects were analysed in conjunction with sparsely sampled data from a phase II study in adolescent and adult female patients with Rett syndrome, yielding a pool of 97 subjects (age: 23 ±4.6, body weight: 60.9 ±17.1). The analysis was performed using a non-linear mixed effects approach using NONMEM 7.2.0. Model building was based on changes in the objective function (OFV) and goodness of fit plots (GOF). Covariate selection was based on a stepwise forward inclusion backward deletion procedure. Secondary

pharmacokinetic parameters including AUC, C_{max} and C_{tau} were used as measures of systemic exposure. Model evaluation was performed using goodness-of-fit and predefined predictive performance criteria. Using final parameter estimates and allometric scaling, NNZ-2566 levels were subsequently simulated to explore the dose rationale in the paediatric patients aged between 5-15 years.

Results: The pharmacokinetics of NNZ-256 was best described by a two-compartment model with first order absorption and elimination. There was no accumulation, metabolic inhibition, or induction observed during treatment. Body weight was found to be a significant covariate on clearance and volume of distribution. In addition, bioavailability after afternoon doses were systematically lower than after morning dosing suggesting that intake of food may have an effect on the absorption of NNZ-2566.

Conclusion: The analysis shows show how population pharmacokinetic modelling can be used to understand sources of variability in rare diseases, where the number of patients and blood samples available for analysis is limited. Moreover, our results show how clinical trial simulations can be used as basis for optimising the dose selection and design of prospective studies in rare diseases.

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Fernando Ortega Modelling Amyloid- ß levels in the presence of a gamma-secretase inhibitor

Fernando Ortega
Pharmacometrics Research Group. School of Pharmacy. The University of Manchester. UK

Objectives: To develop a mathematical model to describe Amyloid-β (Aβ) dynamics and to identify and analyze the factors in the amyloid processing pathway that contribute to the rise in Aβ levels at low inhibitor concentrations. The second aim is to examine whether the Aβ formation model can quantitatively describe in vitro dose response experiments in different cell lines.

Methods: Amyloid metabolism data was compiled from the literature [e.g. 1,2] and used to build a minimal kinetic model of Aβ production, in particular around APP degradation leading to Aβ formation. We propose that the processing steps obey Michaelis-Menten. The inhibitors dose response curves were fitted to the in vitro and in vivo data for model parameter estimation.

Results: Here, a minimal mathematical model has been developed that quantitatively describes the Aβ dynamics in cell lines which exhibit the rise of Aβ as well as in cell lines which do not. The model includes steps of APP processing through both the so-called amyloidagenic and non-amyloidagenic pathway. It is shown that the cross-talk between these two pathways account for the increase in Aβ production in response to inhibitor. With a minor extension, the

model also describes plasma Aβ profiles observed in man upon dosing with a GSI [3].

Conclusions: The mechanistic model rationalizes a series of experimental results that spans from in vitro to in vivo and to man. This has important implications for the development of drugs targeting Aβ production in AD.

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Aziz Ouerdani Effects of Bevacizumab and Everolimus for the treatment of Vestibular Schwannomas in patients with Neurofibromatosis Type 2

Aziz Ouerdani (1,4), Stéphane Goutagny (2), Michel Kalamarides (3), and Iñaki F. Trocóniz (4)
(1) NUMED Team, INRIA Rhône-Alpes, Grenoble, France, (2) Neurosurgery, Beaujon Hospital, Assistance Publique Hôpitaux de Paris, Clichy, France, (3) Neurosurgery, Pitié-Salpêtrière Hospital, Assistance Publique Hôpitaux de Paris, Paris, France, (4) Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy; University of Navarra, Pamplona, Spain

Objectives: To develop a mechanism-based mixed-effects model to evaluate and compare the efficiency of bevacizumab and everolimus for the treatment of vestibular schwannomas (VS) in patients with neurofibromatosis type 2 (NF2).

Methods: Data analysis included 22 patients with NF2. 13 patients received bevacizumab at 5 mg/kg every 2 weeks (reduced at every 3 or 4 weeks for some patients), 7 patients received everolimus at 10 mg once daily (reduced to 5 mg once daily for some patients), and the 2 last patients received both treatments at distinct periods. VS were classified into 4 stages (from I to IV) according to their tumor size that display a high variability (Initial VS size: median = 1.51 cm^3; range = 0.03 – 14 cm^3). Data were log transformed and analyzed in NONMEM 7.2 with the SAEM algorithm. We then used the model to

simulate different protocols of bevacizumab only and everolimus only.

Results: VS growth was described by a Simeoni growth model [1] where the proliferation and the cell death were depending on the VEGF levels. Bevacizumab and VEGF concentrations in nM are simulated from a published Target Mediated Drug Disposition (TMDD) model [2]. Everolimus reduces VEGF synthesis through mTORC1 inhibition. Cell death is 4 times higher with bevacizumab than everolimus. Tumor smaller than 7.5 cm^3 grow exponentially. After 7.5 cm^3 VS grow linearly at a rate of 0.3 cm^3 per month. Everolimus efficiency was decreased because of the deactivation of a negative feedback loop that increases tumor growth. Our model confirms the roles of the VEGF on the proliferation and survival of Schwann cells. Tumor shrinkage in patients treated by bevacizumab is more important than in everolimus treated patients. Simulations suggest that bevacizumab effect on VS might be dose-dependent. Moreover higher dose of everolimus does not improve tumor shrinkage and worsen the regrowth after the end of the treatment.

Conclusions: We developed a mechanism-based model to compare bevacizumab and everolimus efficacy. Our model confirms the roles of the VEGF on VS growth and the better tumor shrinkage induced by bevacizumab treatment.

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Theodoros Papathanasiou Response surface analysis of synergistic interactions of morphine and gabapentin in a rat model of postoperative pain.

Theodoros Papathanasiou (1), Rasmus Vestergaard Juul (1), Anne-Marie Heegaard (1), Mads Kreilgaard (1,2), Trine Meldgaard Lund (1)

(1) Department of Drug Design and Pharmacology, University of Copenhagen, Denmark (2) Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark.

Objectives

Despite much evidence that combination of morphine and gabapentin can be beneficial for managing postoperative pain, the nature of the pharmacologic interaction of the two drugs remains unclear. The aim of this study was to assess the interaction of the two drugs in a wide range of dose combinations and investigate whether co-administration can lead to synergistic effects in a preclinical model of postoperative pain.

Methods

The pharmacodynamic effects of morphine (1, 3 and 7 mg/kg), gabapentin (10, 30 and 100 mg/kg) or their combination (9 combinations of the above doses) were evaluated in a rat plantar incision model using an electronic von Frey device (1). The percentage of maximum possible effect (%MPE) and the area under

the response curve (AUC) were used for the evaluation of the antihyperalgesic effects of the drugs. Identification of synergistic interactions was based on three-dimensional response surface analyses based on the concept of Loewe additivity (2). Modeling of the pharmacodynamic data was performed using R (3). All models were fitted with generalized least squares modeling using the “gnls” function from the “nlme” library. Model selection was based on the AIC criterion.

Result

The combination of morphine and gabapentin resulted in synergistic antihyperalgesic effects. The synergistic combinations were 3+100, 7+10, 7+30 and 7+100 mg/kg for AUC and 1+100 and 3+100 mg/kg for %MPE. The synergistic interactions were found to be dose dependent and the increase in observed response compared to the theoretical additive response ranged between 26 and 58 % for the synergistic doses.

Conclusions

Combination of morphine and gabapentin resulted in dose-dependent synergistic antihyperalgesic effects in a preclinical model of postoperative pain. This finding highlight the theoretical advantage of using morphine and gabapentin in combination in order to minimize morphine related side effects and may encourage future clinical studies that will aim to clarify whether the synergistic interaction is present in post-operative pain in humans.

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Wansu Park Simulation of Scanning Time Point Selection for PET Scan Studies in Clinical Development of CNS Drugs: A Simple Fixed-time Design is Recommended over Scattered-time Point Designs

Wan-Su Park (1), Jongtae Lee (1), Sangil Jeon (2), Taegon Hong (1), Seunghoon Han (1), Dong-Seok Yim (1)
(1) Department of Clinical Pharmacology and Therapeutics, Seoul St. Mary's Hospital, (1) PIPET (Pharmacometrics Institute of Practical Education and Training), College of Medicine, The Catholic University of Korea, Seoul, Korea, (2)Clinical Trial Center, International St. Mary's Hospital, Catholic Kwandong University, Incheon, Korea

Objectives: PET is a tool frequently used to characterize the PK-PD relationship of plasma drug concentration and receptor occupancy in the brain. However, both the number of subjects and PET scans per subject are limited due to its high cost and time-consuming scanning procedures. We tried to determine the effect of PET scanning time points on the reliability of PD parameter estimates and to identify the scanning time point design that gives the most reliable PD parameter estimates.

Methods: We compared the performance of designs with various sets of sampling time points using the stochastic simulation and estimation method in Perl-speaks-NONMEM. Biases, relative standard errors, relative estimation errors, and root mean square errors were used to compare the performance of designs.

Results: Unlike the results of a previous report [1-4], we found that rather complicated designs where each subject or group of subjects are allocated to different scanning time points were not superior to the simple, conventional fixed-time designs regardless of whether effect compartment or receptor binding models were used.

Conclusions: The conventional fixed-time designs that have been used so far may give robust PD parameter estimates for occupancy data obtained from human PET studies of CNS drugs.

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Gab-jin Park Drug-Drug Interaction Analysis of a Drug with Long Elimination Half-life Using Population Pharmacokinetic Approach

Gab-jin Park(1,2,3), Dooyeon Jang(2,3), Jong nyeong Kim(1,2,3), Sunil Youn(1,2,3), Wan-Su Park(2,3), Jongtae Lee(4), Seunghoon Han(1,2,3), Dong-Seok Yim(1,2,3)

(1)Department of Clinical Pharmacology and Therapeutics, Seoul St. Mary's Hospital, (2)PIPET (Pharmacometrics Institute of Practical Education and Training), College of Medicine, The Catholic University of Korea, Seoul, Korea, (3)College of Medicine, The Catholic University of Korea, Seoul, Korea, (4)A2PG(Ann Arbor Pharmacometics Group), MI, US

Objectives: For drugs with long elimination half-life, multiple dosing drug-drug interaction (DDI) studies are challenging because of long-term administration and ethical considerations. The aim of the present study was to distinguish the effect of DDI from the drug accumulation itself by comparing the model-based simulation with the conventional, non-compartmental analysis (NCA).

Methods: Healthy male subjects were administered amlodipine and drug X for 10 days after amlodipine for 8 days. Full pharmacokinetic (PK) sampling was performed on day 8 and 18. Plasma concentrations of amlodipine were determined by LC-MS/MS. A population PK model was fitted to data of day 8 using nonlinear mixed- effects method (NONMEM, Ver. 7.2). The $C_{max,ss}$ and $AUC_{t,ss}$

for day 18 from the amlodipine PK model developed were compared with the NCA-based ones calculated using observed concentrations of day 18.

Results: Plasma concentration-time profiles of amlodipine were best described by a two-compartment model with first-order kinetics and absorption lag-time. The final parameter estimates were: CL (27.6 L/h), V2/F (784 L), V3/F (1730 L), Q/F (59.8 L/h), absorption rate constant (0.247 h^{-1}) and absorption lag-time (0.554 h). The geometric mean ratios (GMR) and their 90% confidence intervals (CI) of $AUC_{t,ss}$ were 1.187 (1.135-1.242) and 1.007 (0.892-1.136) for NCA and modeling approach, respectively.

Conclusions: The PK analysis method using modeling and simulation enabled to distinguish between the effect of DDI and the effect of drug accumulation. Likewise, the proposed method may be useful to evaluate DDI of drugs with long elimination half-lives that may not reach steady-state within the study periods.

Lorenzo Pasotti Automatic translation of Bayesian pharmacometric models: the PharmML-to-WinBugs converter

Cristiana Larizza (1), Lorenzo Pasotti (2), Enrica Mezzalana (2), Elisa Borella (2), Gareth Smith (3), Paolo Magni (2)
(1) Laboratory for Biomedical Informatics

Objectives: PharmML is a markup language for pharmacometric models description, under development by the DDMoRe consortium, that will enable the tool-independent formulation, exchange and integration of models and tasks [1]. The Modelling Description Language (MDL), also under development, is a human-readable standard language aimed to facilitate model writing and enable, via automatic translation, the generation of PharmML-encoded models that can be converted into the desired target language [2]. This work describes the efforts undertaken for the development of a PharmML-to-WinBugs converter, which will support Bayesian model estimation tasks in fully integrated interoperable workflows.

Methods: Converter development included 4 main steps. 1) Features for Bayesian model support, currently under revision, were proposed for PharmML and MDL, including extensions for parametric, non-parametric and empirical prior distributions. 2) A number of increasingly complex models were defined in PharmML and WinBugs to describe all the relevant situations. 3) A PharmML-to-WinBugs translation tool was developed via Java, using

libPharmML to read/validate PharmML files and some libraries to generate an intermediate model representation, suitable for final translation into WinBugs. 4) A conversion tool was developed via R to translate NONMEM-format data files into WinBugs input files, to create all the elements needed to use the model. PharmML 0.4, WinBugs 1.4.3, BlackBox 1.5, PKPD Model Library 1.2, and the WBDiff and WBDev interfaces were used.

Results: PharmML files are correctly translated into WinBugs and related Pascal files. The currently supported features are: single-subject and population models, algebraic and ordinary differential equations (ODEs), independent distributions at prior and inter-individual levels, multiple Observation Models with additive Gaussian error, time-varying continuous covariates, Function Calls, all Individual Parameter types, and transformation of Covariates, Individual Parameters and Observation Models. Three options are available to solve ODEs: 1) the inline ode block or 2) Pascal code via WBDiff, and 3) Pascal code via PKPD Library/WBDev, which can solve models with multiple dosing.

Conclusions: The converter supports a large number of situations of interest in Pharmacometrics. Its development will be completed to include the remaining PharmML features not currently implemented.
This work was supported by the DDMoRe project (www.ddmore.eu).

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Devin Pastoor Standardizing and accelerating data analysis and pharmacometric workflow with the PKPDmisc R toolkit.

Devin Pastoor
University of Maryland, Baltimore

Objectives: In pharmacometrics, modelers are exposed to heterogeneous data analytic projects, including data preparation, analysis, simulation, and visualization. Though each project presents unique challenges, many components of the workflow, including dealing with the behavior and quirks of R, are consistent across projects. Packages such as Xpose [1] and metrumrg [2] have been developed, their focus does not encompass specific components of the analytic process as they were developed primarily to ease interaction with NONMEM [3]. PKPDmisc aims to standardize and accelerate workflows by providing flexible and robust functions that address tasks common to many projects.

Methods: PKPDmisc is written in R, with a focus on code quality and performance. In many cases, by leveraging modern packages such as dplyr, and even writing custom C++ functions internally. As such, PKPDmisc can run 100's or even 1000's of times faster than traditional R implementations. PKDmisc also aims to easily address common issues with R, such as converting columns between data types, splitting data for plotting with ggplot2, and performing multi-step summary statistic calculations, where previously users may have resorted to unwieldy scripts or hacks.

Results: PKPDmisc offers functionality in the following areas:

- Quickly reading data, including non-standard nonmem simulation tables and Phoenix [4] tables with units.
- Convenient wrappers on common data manipulation operations
- Fast noncompartmental analysis
- Data preparation tasks such as handling BQL, missing data, and creating flags
- Summary statistic calculations for plots such as quantile plots
- Evaluating NONMEM run status and visualizing gradients during long runs
- Templates analysis folder structure and creating reports using Rmarkdown
- Curve stripping for initial estimates for two-compartment models
- Performing Wald's approximation for covariate model selection with NONMEM.
- Robust resampling functions for bootstrap or clinical trial simulations.
- Professional quality default themes for plots created with ggplot2.

Conclusions: PKPDmisc is open-source, free, and transparently developed on github (github.com/dpastoor/PKDPmisc), allowing users to easily ask questions, report issues, view documentation, and contribute.

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Eleni Pefani Drop-out estimation and PKPD analysis of a Phase 2a study for an anti-IL1R1 monoclonal antibody in Chronic Obstructive Pulmonary Disease (COPD)

Mark Penney (1), Eleni Pefani (1), René van der Merwe (1) and Paul Newbold (2)
(1) MedImmune plc, Cambridge, UK, (2) MedImmune LLC, Gaithersburg, MD, USA.

Objectives: To determine the drop-out rate from neutropenia in a Phase 2a study of the monoclonal antibody MEDI8968 (aka AMG 108). To develop PKPD models for the exposure of MEDI8968 in COPD patients and its effect on neutrophils and C-Reactive Protein (CRP) to demonstrate pharmacology and analyse the PKPD of MEDI8968 in reducing the rate of Acute Exacerbations of COPD (AECOPD).

Methods: A PKPD model based on data from previous studies in healthy volunteers, osteoarthritis and rheumatoid arthritis patients was adapted for COPD patients by simulating from baseline neutrophil counts typical of a COPD population; MEDI8968 PK and its suppression of neutrophil count were assumed to be conserved. This model was combined with the study process following a low count and the percent of subjects predicted to have the outcomes of skipping a dose or dropping out calculated.

Model-predicted PK exposure and neutrophil counts were compared to the results of a Phase 2a study in COPD patients. Both PK and PKPD models were updated and tested for study-dependent covariates. The pharmacology of MEDI8968 was investigated further by constructing a PKPD model for MEDI8968-induced suppression of CRP. AECOPD rate was investigated using a time to event analysis, using a constant hazard model and introducing average PK exposure as a covariate.

Results: The model correctly predicted negligible drop out from neutropenia with a per-protocol subject recruitment cut-off of 2.5x10^9 neutrophils/L. PK and neutrophil count were well predicted. The updated model had minimal changes and study was not a covariate, confirming that COPD subjects had similar PKPD to those previously tested. Exposure in COPD subjects was sufficient to cause maximum suppression of the neutrophil count. Suppression of CRP was maximal as judged by the similar suppression obtained in [2] and [3]; however, no relationship to exposure could be derived due to the single dose level of MEDI8968 used in the study. AECOPD rate was described well with a constant hazard model. However, no effect of MEDI8968 on the time-to-exacerbation was found.

Conclusion: The model could account for the differences in blood neutrophil count between COPD and previously tested patients with a simple adjustment of the baseline counts and so confirm appropriate recruitment criteria to prevent subject drop-out. The updated model could confirm full pharmacology was achieved with the MEDI8968 dose, although no improvement in AECOPD rate was observed.

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Sophie Peigne How modelling & simulation supported the drug development in children for a drug S

Sophie Peigné, Sylvain Fouliard and Marylore Chenel
Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier

Introduction: A study was conducted in paediatric patient population with drug S (marketed in adult), 80 % metabolized via CYP3A4. The objectives of this study were to describe the PK of drug S and its active metabolite in this population, to assess potential differences in PK between age classes, and to assess whether the blood/plasma ratio and the PKPD relationship are preserved between paediatric and adult populations.

Methods: The clinical study included a first titration period that should ensure that children started with a safe dose but were up titrated as rapidly as possible to an effective dose.PK data were obtained after 5 blood sampling using dried blood spot and one plasma sample in order to assess the relationship between blood and plasma concentration. PK measurements were available for 70 patients.To describe drug S and its metabolite blood concentrations in children, a joint population PK model was developed taking into account weight & age effects.Plasma PK exposure parameters were calculated in children using converted plasma PK profiles. To assess the PKPD relationship in children, a former adult PKPD model was used.

Results: Relationship between blood and plasma concentration was described using linear mixed effect models. 2- and 1- compartment models best described parent and metabolite dispositions, respectively. A first pass effect and the formation of the metabolite from the circulating drug S were included.Weight effects were fixed to the allometric values of 0.75 and 1 on CL and V, respectively [1]. In addition, a maturation function was added on metabolite formation clearance reflecting CYP3A4 enzyme maturation [2]. Other maturation processes that were investigated did not result in fit improvement.Plasma PK exposure comparison indicated that higher dose/kg were necessary to have similar exposure between younger and older children. No differences between age classes were observed in terms of range of exposure at the maintenance dose.Simulations were performed using adult PKPD model and individual plasma PK parameters and showed that the PKPD relationship in adult patients is conserved in children.

Conclusions: This work underlines the importance of modelling and simulations for the analysis of clinical studies for drug development in pediatric populations. The assessment of PK and PKPD relationship in children through the use of integrated analysis tools allowed to draw conclusions regarding the effects of dug S in children.

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Christina Pentafragka Population PK/PD modeling of granocyte colony-stimulating factors given as single and repeated doses in healthy volunteers.

Christina Pentafragka (1), Gilles Freyer (2) and Athanassios Iliadis (1)
(1) Aix-Marseille University, Faculty of Pharmacy, France; (2) Institut de Cancérologie des HCL, Lyon, France

Objectives: To develop a PK/PD population model to describe and compare the experimental observed profiles of two different formulations of lenograstim, a colony-stimulating factor of the hematopoietic chain, given as single and repeated doses in healthy volunteers.

Methods: PK (lenograstim concentrations) and PD (absolute neutrophil counts) data were supplied by two open-label, randomised, two-way crossover studies in which lenograstim AA (test product) and HSA (reference therapy) were administered by subcutaneous route within two periods to 16 healthy male volunteers at a single dose of 150 μg/m2 in the first, and to 24 healthy male volunteers at a dose of 10 μg/kg/day for 5 days in the second study. The basic model [1] was developed using MATLAB. For the population analysis of the experimental data, Naïve-Averaging-of-Data approach and Two-Stage method were performed by MATLAB. Single-Stage method was performed by Monolix [2].

Results: The most adequate model to describe the observed PK and PD profiles is (a) a two-compartment model for the PKs, including for the PDs (b) four differential equations depicting the maturation of neutrophils, (c) additional equations and parameters representing the down-regulation on stem cells' stimulation and up-regulation on lenograstim's clearance by the mature neutrophils' levels, and (d) two acceleration and one enhancement Emax-mechanisms, illustrating the effect of lenograstim on the hematopoietic chain. Some simplifications had to be done and parameters had to be fixed in order for the model to be structurally and numerically identifiable. Given the inter-subject variability, the obtained model establishes the equivalence between the two studied formulations of lenograstim.

Conclusions: The biggest technical difficulty for this type of modeling is the closed-loop biological system, controlled by two homeostatic feedbacks. This model could be used to describe the PK/PD behavior when anticancer drugs with hematological toxicity are co-administered with lenograstim to patients [3].

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Jonás Samuel Pérez-Blanco Age influence on clearance of phenobarbital in paediatric patients

JS Pérez-Blanco (1,2), P Teixeira (1), MJ Otero (2,3), E Laso Lucas (3), MJ García (1,2), D Santos Buelga (1,2)
(1) Department of Pharmacy and Pharmaceutical Technology, University of Salamanca, Salamanca, Spain; (2) Institute for Biomedical Research of Salamanca (IBSAL), Spain. (3) University Hospital of Salamanca, Spain.

Objectives: To describe the influence of AGE on phenobarbital clearance (CL/F_{PBT}) developing a pharmacokinetic (PK) model in a paediatric population.

Methods: The study has been conducted in 39 paediatric patients, aged 0-14 years old and treated with oral administration of PBT. A total of 71 PBT steady state serum concentrations were fitted to a PK model using non-linear mixed-effects modelling implemented in NONMEM V7.2 (FOCEI). Covariates were evaluated against CL/F by a stepwise forward inclusion (p = 0.05) and backward exclusion (p = 0.001) process to the base model. The covariates analysed were: AGE, WGT, HGT, BSA, BMI, LBM, SEX and concomitant treatments (phenytoin, lamotrigine, valproic acid, others). Missing data of covariates were handled considering as missing completely at random (MCAR) [1]. Evaluation of the final model was performed using bootstraps and VPC.

Results: A one compartment model with first order absorption and elimination processes (ADVAN 2 TRANS 2) has been selected as the best structural model. The values of the volume of distribution and absorption rate constant were fixed to those proposed in literature [2-3]. Missing HGT data (MCAR) were inputted following a simple linear regression performed with the available information of HGT and AGE (r^2=0.84) in the population studied. AGE and valproic acid treatment were included in the final model as covariates on the $CL/F_{PBT,}$ those account for a 48% of its variability and a 59% of the residual variability (proportional error):

$CL/F= (0.179-0.129 \cdot e^{-AGE*0.24}) \cdot 0.647^{VLP}$
V= 0.9 L/kg
Ka=1.33 h^{-1}
$CV_{CL/F}$= 23.4%
CV_{RES}= 10.9%

The relative standard error (RSE) for the fixed parameters was lower than 25%, except for the exponent of the AGE covariate (43%). RSE and estimated shrinkages for random parameters were lower than 30%. The proposed model was satisfactorily evaluated with a bootstrap (n=200) and VPC.

Conclusions: A suitable population PK model of PBT in paediatric patients has successfully been developed. The final model showed an important influence of AGE on the CL/F_{PBT}. Valproic acid treatment was included following statistics criteria (?OFV=-13.5) despite the fact that there were only 10% of the population concomitantly treated with this drug. Consequently, its real influence should be evaluated again with a more representative set of data of this covariate. The model proposed is useful for raising awareness of the PBT PK in childhood and could be helpful for TDM.

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Alejandro Pérez-Pitarch Growing evidence supporting therapeutic drug monitoring of erlotinib in non-small-cell lung cancer patients: a time-to-progression model.

Alejandro Pérez-Pitarch (1), Beatriz Guglieri-López (1), Virginia Merino (1), Amparo Nacher (1), Rafael Ferriols-Lisart (2), Matilde Merino-Sanjuán (1).
(1) Department of Pharmacy and Pharmaceutical technology, Faculty of Pharmacy, University of Valencia. Valencia. Spain. (2) Pharmacy Department. University Clinical Hospital of Valencia. Valencia. Spain.

Objectives: To develop a model describing the time-to-progression distribution of a sample of non-small-cell lung cancer (NSCLC) patients treated with erlotinib. To identify covariates as progression-free survival predictors (including drug exposure).

Methods: Time-to-progression data and relevant covariates were available from 26 NSCLC patients treated with erlotinib at the University Clinical Hospital of Valencia. Erlotinib plasma concentration data were simulated for the 26 NSCLC patients using a previously published pharmacokinetic (PK) model [1]. Time-to-progression was characterized with a time-to-event (TTE) model. TTE modelling and PK simulation was performed in NONMEM v 7.1.0 [2]. Exponential and Weibull TTE distributions were tested. Covariates, such as age, gender, NSCLC subtype, presence and location of metastases and tumour mutations, were evaluated as

progression-free survival predictors and inclusion was performed on basis of objective function value (OFV) decrease and graphical improvement of visual predictive check diagnostic graphics.

Results: The Weibull distribution model fitted the observed data significantly better than the exponential distribution model (ΔOFV=-6.13).

$h_0(t) = \lambda \alpha (\lambda t)^{\alpha - 1}$

$h_0(t)$: hazard at time t; λ: scale parameter; α: shape parameter.

Among the tested covariates, the following were included in the model in a stepwise manner: 1) epidermal growth factor receptor (EGFR) mutation on the shape parameter (α) (ΔOFV=-27.33); 2) erlotinib minimum plasmatic concentration on hazard (h) for patients with mutated EGFR (ΔOFV=-4.36); 3) presence of central nervous system metastases on the scale parameter (λ) (ΔOFV=-5.08). The model that best described the relationship between erlotinib minimum plasma concentration (Cmin) and progression hazard was:

$h_a(t) = h_0 \cdot (1-(Cmin/(Cmin + CE50))$

$h_a(t)$: hazard depending on drug exposure; CE50: minimum plasma concentration to achieve 50% of the maximum effect.

Conclusions: The described model supports therapeutic drug monitoring of erlotinib based on the evidenced relationship between drug trough concentrations and progression hazard. It is concluded that TTE modelling of disease progression has the potential to improve the efficacy of NSCLC treatment with erlotinib.

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Carlos Perez-Ruixo Platelets dynamics in peritoneal carcinomatosis patients treated with cytoreductive surgery and hyperthermic intraperitoneal oxaliplatin

Carlos Pérez-Ruixo (1), Belén Valenzuela (2), José Esteban Peris (1), Pedro Bretcha-Boix (2), Vanesa Escudero-Ortiz (3), José Farré-Alegre (2), Juan José Pérez-Ruixo (4)

(1) Pharmacy and Pharmaceutical Technology Department. University of Valencia, Spain ; (2) Platform of Oncology. Hospital Quirón Torrevieja. Torrevieja, Alicante, Spain; (3) Pharmacy and Clinical Nutrition group. University CEU Cardenal Herrera, Elche, Alicante, Spain; (4) Model-Based Drug Development. Janssen Research & Development, Beerse, Belgium

Objectives: We aimed to characterize the platelet counts dynamics in peritoneal carcinomatosis patients treated with cytoreductive surgery (CRS) and quantify the effect of hyperthermic intraperitoneal oxaliplatin (HIO).

Methods: Platelet counts from 45 patients treated with CRS and HIO diluted in isotonic 4% icodextrin (cohort A), 21 patients undergoing CRS followed by HIO diluted in isotonic 5% dextrose (cohort B) and 18 patients treated with CRS without HIO (cohort C) were used to estimate the system related and drug specific parameters of a modified Harker's cytokinetic model [1] to account for the effect of surgery and HIO on platelet dynamics. The surgery and HIO effects on the proliferation of precursor cell as well as the

surgery effect in the platelets lifespan were evaluated. The effect of age, sex, body surface area, total proteins, HIO carrier solution and splenectomy on model parameters was explored. Model evaluation and simulations were undertaken to evaluate the effect of the dose, treatment duration, and significant covariates on the incidence of severe thrombocytopenia and subsequent thrombocytosis.

Results: The time course of platelet counts was well characterized by the model developed, which simultaneously accounts for the acute-immediate thrombocytopenia response induced by the CRS and the HIO effect in bone marrow, as well as the subsequent thrombocytosis due to the natural defense mechanism to prevent mayor bleedings [2]. The model evaluation evidenced an accurate prediction of the time course of platelet counts and its associated variability, as well as the incidence of severe thrombocytopenia and thrombocytosis. Age, sex, body surface area, total proteins and HIO carrier solution were not associated with the model parameters. Simulations indicated that i) both thrombocytopenia and thrombocytosis were reversible and short-lasting, ii) the severity of the thrombocytopenia is inversely correlated with the thrombocytosis severity, iii) splenectomized patients have thrombocytopenia of lower severity and thrombocytosis of higher severity, relative to a non-splenectomized patients, and iv) the HIO dose and treatment duration were the main determinants of the severity and duration of the thrombocytopenia.

Conclusions: This model suggests that thrombocytopenia is the HIO primary dose limiting toxicity. Relative to the HIO dosing regimens used up to date, higher HIO dose or longer duration of HIO treatment could be used to treat peritoneal carcinomatosis patients, without substantially increasing the risk of major haematological toxicity.

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Aurelie Petain Inter-species comparison of semi-physiological pre-clinical PK/PD models to better predict the time course of myelosuppression in human: application to a novel vectorized epipodophyllotoxin (F14512)

A. Petain (1), B. Gomes (1), D. Tierny (2), A. Bidaut (1), P. Ferre (1) and L. Nguyen (1)
(1) Institut de Recherche Pierre Fabre, Research & Development center, Toulouse, France; (2) Oncovet Clinical research, Villeneuve d'Ascq, France

Objectives: A chemotherapy-induced myelosuppression model based on rat data was proposed to predict the time-course of myelosuppression in cancer patients [1]. The aim of the present study was to retrospectively assess the human predictability of semi-physiological PK/PD models built on rats, Beagle laboratory dogs and pet dogs. This comparative analysis was performed on F14512, a polyamine-vectorized anti-cancer drug which combines an epipodophyllotoxin core targeting topoisomerase II with a spermine moiety as a tumor cell-delivery vector [2].

Methods: In a first and prospective approach, the myelosuppression model was applied to rat data in order to predict hematotoxicity in a FIH trial including patients with solid tumors. A specific PK/PD study in Sprague Dawley rats using a wide dose range and various dosing schedules was performed to develop the model. Rat PK and

white blood cells (WBC) counts were fitted by NONMEM VI. The time-course of WBC in patients was predicted both on typical system related PD parameters (*i.e.*: MTT, Baseline and γ) previously defined in cancer patients [3] and the rat slope estimate (drug-related parameter) corrected for species differences in plasma protein binding and bone marrow sensitivity (*in vitro* CFU-GM assay).

In a second and retrospective step, PK/PD models were developed on Beagle dogs and pet dogs (patient dogs presenting spontaneous lymphoma tumors) data separately. For Beagle dog, data from toxicological studies were analysed. For the pet dogs, a specific PK/PD study was conducted by mimicking the dosing schedule used in human [4]. Leukopenia in human was predicted using drug-related PK parameters obtained in Beagle and pet dog models, respectively.

Results: The time-course of WBC in each species was adequately described by the PK/PD models. The estimated system parameters from the rat model were similar to those previously published. The PK/PD models in dogs predicted a more potent hematotoxicity in human compared to the predictions provided by the rat model. The preliminary clinical data showed that:

(1) actual myelosuppression in human was under-estimated by the rat model
(2) Myelosuppression from the dogs model was close to that observed in human
Updated results in pets will be presented.

Conclusions: PK/PD models based on larger species such as pet dogs may be a useful translational tool and its application in better predicting hematotoxicity in FIH trials can be valuable.

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Caroline Petit Designing a paediatric study for an antimalarial drug including prior information from adults

Caroline Petit (1), Vincent Jullien (2), Adeline Samson (3), Jérémie Guedj (4), Jean-René Kiechel (5), Sarah Zohar (1), Emmanuelle Comets (4,6)

(1) INSERM, UMRS 1138, Univ. Paris 5, Paris, France ; (2) Pharmacology Department, Inserm U1129, HEGP, Paris, France ; (3) LJK, UMR CNRS 5224, Univ. J. Fourier, Grenoble, France ; (4) INSERM, IAME, UMR 1137, Paris, France ; (5) Drugs for Neglected Diseases initiative, Geneva, Switzerland ; (6) INSERM, CIC 1414, Univ. Rennes 1, Rennes, France

Objectives: To investigate designing a pharmacokinetic (PK) study using adult prior information for a case-study on mefloquine and to evaluate robustness of the optimal design to different model misspecifications, comparing it with the empirical design.

Methods: PK data for adults and children were obtained from two different randomized studies for treatment of malaria with the same artesunate-mefloquine combination regimen, given once daily over 2 or 3 days. A recommended design for paediatric study on mefloquine was obtained by design optimisation on an extrapolated model built from adult data. The adult PK parameters were estimated using SAEM algorithm [1] with the software MONOLIX 4.2.2 [2]. Paediatric PK parameters were then obtained by adding

allometry and maturation [3] to the adult model and employed for designing the paediatric population study. Optimisation of the design is based on the Fisher information matrix [4] and was performed with PFIM 3.0. [5]. Robustness for the recommended design was evaluated in terms of the relative bias and relative standard errors (RSE) of the model parameters by simulating the paediatric population, keeping the distribution of doses and covariates from the actual study. Varying the parameters used in the simulation in four scenarios assessed the robustness, and the performance of the optimal design was compared to that of the empirical design.

Results: A two-compartment model with absorption was shown to best describe the adult data. When the children data was used as an external evaluation, differences between the two populations were apparent, especially in the early days after the beginning of treatment. The optimised design for children with 5 sampling times showed that early concentrations were needed to estimate the absorption phase accurately, recommending to collect the first sample 2 hours after the first dose and then during days 1, 5, 14 and 57. It gave good results in terms of bias and RSE and was robust across various model modifications, in stark contrast to the empirical design from the paediatric study.

Conclusion: Using prior information combined with allometry and maturation can help provide robust designs for paediatrics studies.

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We thank the Drugs for Neglected Diseases initiative for making their datasets available for this project.

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Philippe Pierrillas Improvement of parameter estimations in tumor growth inhibition models on xenografted animals: a novel method to handle the interval-censoring caused by experimental measurement on smaller tumor sizes

Pierrillas Philippe (1), Tod Michel (1), Bouzom François (2), Hénin Emilie (1)
(1) Université Claude Bernard, Lyon, France ; EMR 3738 Ciblage Thérapeutique en Oncologie (2) Technologie Servier, Orléans, France

Objectives: Censored data is a practical and overriding question when analysing data and handling it does not yield to a unique and simple answer. If not considered properly, censoring may cause bias and misspecification during data analysis [1,2]. The xenografted mice model is a widely used experimental model to evaluate anticancer effects of new compounds and possibly predict the efficacy in human thanks to translational approaches [3]. During tumor growth experiments on xenografted mice, the tumor size is measured by a technical operator using a caliper, and reported as the measures of 2 diameters, often converted into tumor volumes. For smaller tumor sizes, due to the imprecision induced by skin thickness and palpability of the tumor, when the length/width is less than 5 mm, reported tumor diameters are rounded to the nearest integer value, resulting in interval-censored tumor volumes. Hence we propose and evaluate a method to handle interval-censored data.

Methods: Different methods to handle this interval-censoring (including standard methods for handling below quantification limit values and our new method, the so-called interval-M3 method considering the likelihood of observations being in each interval) were compared using Stochastic Simulations and Estimations processes: 1000 datasets were simulated under a classical design of tumor growth experimental study in xenografted mice and then model parameters were estimated in each simulated datasets for each method. Simulation-based diagnostics, relative bias and relative root mean square error were consequently computed to compare each method.

Results: By not considering correctly the interval-censoring and by omitting or applying classical methods used for censored data, model parameter estimations appeared to be biased and especially the antitumor effect parameter, whose information lies mainly on smaller tumor volumes. Overall, the best performance was noted with the interval-M3 method giving less biased and more precise estimations for parameters (|bias|<0.55% and RMSE<12% for typical parameters) whereas for classical methods bias could reach up to 15%.

Conclusions: We showed that during xenograft mice experiments, parameters estimations with classical methods could be biased due to the limitation of caliper measurement. The new method proposed here, can thus be used to estimate parameters as precisely as possible and to optimally handle all the information provided by the available data in order to quantify the antitumor effect.

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Maiara Pigatto PK/PD modeling of tumor growth inhibition after etoposide administration in vitro and to tumor-bearing rats

Maiara Cássia Pigatto (1, 2, 3) Renatha Menti Roman (2) Letizia Carrara (3) Paolo Magni (3) and Teresa Dalla Costa (1, 2)
(1) Pharmaceutical Sciences Graduate Program, College of Pharmacy, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (2) Centro Bioanalítico de Medicamentos, College of Pharmacy, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (3) Dipartimento di Ingegneria Industriale e dell'Informazione, University of Pavia, Italy

Objectives: Describing the *in vitro* and *in vivo* anticancer effect of etoposide by a PK/PD model. Comparison of the *in vitro* and *in vivo* PK/PD parameters.

Methods: *In vitro* antitumor activity was determined against Walker-256 (W256) carcinosarcoma cells exposed to different constant concentrations and to dynamic concentration-time profiles that mimic the concentrations *in vivo* experiments. In *in vivo* tumor growth inhibition experiments, W256 tumor-bearing Wistar rats received etoposide 5 or 10 mg/kg i.v. *bolus* every day for 8 and 4 days, respectively. Tumor volume was monitored daily during and after drug treatment. The protocol of the *in vivo* studies was approved by UFRGS Ethics Committee on Animal Use (#22302). Data were analyzed starting from the Del Bene [1] and Simeoni [2] TGI

models (http://repository.ddmore.eu). An E_{max} function was introduced both *in vitro* and *in vivo* in the PD model to take into account nonlinearity in the k_2 (drug potency) parameter. A three-compartment popPK model was developed in a separate group of animals. Moreover, the drug concentration profile in tumor simultaneously measured with plasma data was also linked to the effect. PK/PD analysis was conducted using Monolix v.4.3.3, on average data for *in vitro* study and by mean of a nonlinear mixed-effect model for *in vivo* data.

Results: The nonlinear mixed-effect model was capable to describe the sources of between-subject variability in the *in vivo* tumor growth. In the *in vitro* experiments, the model estimated on data from constant exposure well predicted the antitumor activity from the dynamic concentration-time profile experiments. The comparison between *in vivo* and *in vitro* PK/PD parameters showed an increased etoposide anticancer activity *in vivo* than *in vitro.*

Conclusions: The same TGI model can successfully predict the etoposide effect after *in vivo* and *in vitro* exposure. In the *in vitro* approach, the antitumor effect following dynamic concentrations can be simulated using the parameters estimates from constant exposures, without the need of time-consuming experiments.

Acknowledgments: Financial support from CNPq/Brazil and doctorate scholarship from CAPES/Brazil.

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Poster: Drug/Disease modeling - Oncology | IV-59 | Thursday 15:20-16:40

Venkatesh Pilla Reddy Modelling and simulation of concentration-depth-time profiles in the urinary bladder wall following intravesical delivery

Venkatesh Pilla Reddy (1); Linette Ruston (1); Ian Grant (2); Gary Wilkinson (1); Barry Davies (3); Leigh Williams (3); Rebecca Ellston (3); Constanze Hilgendorf (4); Lars Lindbom (5); Jacob Brogren (5); Rhys DO Jones (1); Elizabeth Pease (6)
(1) iMED Oncology, DMPK, AstraZeneca, the UK; (2) PharmDev, AstraZeneca, the UK; (3) Bioscience, AstraZeneca, the UK; (3) iMED DMPK, AstraZeneca, Sweden; (5) qPharmetra, Sweden; (6) Global Oncology Projects, AstraZeneca, US.

Objectives: Localized release of an agent from a depot-type formulation in the proximity of the diseased tissue relative to systemic exposures could result in better therapeutic index in a cancer setting. Drug concentration-tissue/tumor-depth-time profiles can be predicted by Grabnar model (GM)[1] or by using physiology-based mechanistic model (PBMM). The main objectives of this work are 1) to reduce the existing 30 component GM, with aim of using this reduced model along with a minimal *in-vitro/ex-vivo* diffusion coefficient data to predict the rate and depth of tissue penetration and plasma levels *in vivo* after bladder local delivery (BLD) and 2) to develop an alternative model (e.g. PBMM) to predict tumour concentrations, and incorporate the possibility for permeability limited distribution.

Methods: *Grabnar Model:* Data from Grabnar paper was digitized and the model structure was implemented in NONMEM. The predictive performance of the models was assessed by comparison of simulated and observed concentrations across the thickness of bladder. The model parameters re-estimated with observations lumped according to what will be available in future in-house experiments: urothelium (x1-y1 µm), lamina propria (x2-y2 µm), and muscular layers (x3-y3 µm). Models with the number of compartments set to appropriate values between 3 and 30. *PBMM:* PBMM after systemic dosing was developed first by supplementing with tumour tissue: plasma partition coefficient (Kp) value[2] to predict tumour exposure followed by PBMM for BLD by including the permeability-limited bladder and a tumour compartments and using experimentally determined or in-silico predicted Kp value.

Results: *GM:* The reduced 7 compartment model in NONMEM was able to reasonably predict the urothelium exposure at different tissue layers, and this reduced model gave a better fit to the observed data over original GM. *PBMM:* Conceptual model in rats has been established using systemic dosing data to predict the tumour concentration, and then using data from orthotopic experiment for BLD. The results showed a good agreement with observed tumour and bladder levels.

Conclusion: In conclusion, GM for drug distribution in bladder tissue has been implemented and simplified in the NONMEM software. This analysis revealed that human bladder tissue-time profiles can be predicted with minimal *in-vitro*/*ex-vivo* data. If the bladder exposure cannot be described by a passive diffusion, it may be described with a membrane limited diffusion/transport using a novel PBMM approach refined for BLD or for systemic dosing + BLD.

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Elodie Plan Handling Underlying Discrete Variables with Mixed Hidden Markov Models in NONMEM

Elodie L. Plan (1), Joakim Nyberg (1), Robert J. Bauer (2), Mats O. Karlsson (1)
(1) Pharmacometrics Research Group, Department of Pharmaceutical Biosciences, Uppsala University, Sweden; (2) Pharmacometrics, R&D, ICON Development Solutions, MD, USA

Objectives: Concomitant infection impact on CD4 counts or rescue medication effect on pain score are examples of covariate relationships often not modeled due to missing information, potentially causing bias in drug effect estimation. Besides, modeling of latent variables that represent the underlying disease has become an interest, leading to attractive drug effect characterization.

Mixed Hidden Markov models (MHMM), capable of handling Markov chains of unobserved states, have been proposed [1] and require challenging maximum likelihood estimation (MLE) computation summing over all previous conditions. The objectives of this work were to explore various MHMM implementations in NONMEM and to expand on the investigation of the benefits of this methodology.

Methods: MHMM methodology was implemented in NONMEM 7.3 with an initial stationary distribution and a scaling of the forward probabilities. A subroutine involving the Viterbi algorithm was used

to evaluate the most likely hidden states chain during post-hoc analysis.

First, the model (a 2-state MHMM governing Poisson-based distributions) was applied to real clinical trial records (the 12-week screening phase of a study on 551 epileptic patients [2]). Then, 1000 copies of a hypothetical trial (60 HIV+ patients randomized to placebo or treatment with 60 observations each) were simulated and re-estimated with different models and MLE methods. Finally, an extension to a multivariate (MV) MHMM was developed (2 theoretical types of COPD records -1 measurement, 1 patient reported outcome- linked to presence or absence of relapse).

Results: The estimation of transition probabilities between hidden states associated with random effects was successful in all cases. While EM-based methods and Laplace provided similar estimates, EM-based methods were more consistent in reaching maximum likelihood with poorer initial estimates and Laplace, however, was faster.

Fitting a MHMM instead of a non-Markovian Poisson model to the simulated HIV trials led to a considerable OFV drop, a more accurate and precise drug effect estimate, and an improved power to detect drug effect.

Retrieving the effect of a hypothetical COPD drug on the hidden transition to relapse was possible with a MV-MHMM whereas it was not detectable when analyzing the observed variables with an open continuous model.

Conclusions: MHMM, here implemented in NONMEM, offer possibilities of better understanding and modeling of underlying data in numerous applications.

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Daniel Polhamus Assessment of propensity score and Mahalanobis distance matching in mixed outcome data

Daniel G Polhamus, Ph.D., Jonathan L French Sc.D.
Metrum Research Group, Tariffville CT

Objectives: Matching methodology in pharmacometrics has been used by the FDA [1] for determining drug effect in the presence of confounding variables. Common matching methods include Mahalanobis distance (MD) and propensity scores (PS). MD is cov matrix normalized Euclidean distance and expects continuous data, PS [2] models conditional treatment probability and allows mixed data. Assessment after matching is crucial and typically includes univariate measures like standardized bias and QQ-plots. Curiously, multivariate comparisons of the covariate distribution are rarely considered. In the case where all data is continuous, we can expect methods that explicitly account for the multivariate distribution of covariates (MD) will retain multivariate balance. However, in data more typical of medical trials can we expect the same? We investigate MD and PS methods to evaluate matching bias and examine new methods for comparing the covariance structure between matched patient samples of mixed data types.

Methods: Using publicly available oncology data (R::colon), we generate hypothetical exposure and confoundedness with exposure as a function of 8 qualitative + 2 quantitative covariates. Matches

are found on distances of: A) MD, B) MD (0.25 calipers), C) PS matching (0.25 calpers), and D) MD on continuous covariates (0.25 PS calipers). We bootstrap univariate and multivariate summaries of the matched data to quantify similarity. Heterogeneous covariance matrices (HCM) using appropriate correlations are used to correctly quantify mixed data type correlation for comparison.

Results: PS methods result generally in smaller bias between matched samples, with maximal standardized bias [90% CI] of A) 0.38 [0.25, 0.54], B) 0.37 [0.25, 0.55], C) 0.25 [0.14, 0.4], and D) 0.23 [0.14, 0.5]. MD methods better preserved the multivariate structure of the data per MSE on the element-wise difference of HCMs: A) 1.96 [1, 3.2], B) 1.92 [1.04, 3.47], C) 3 [1.72, 4.96], and D) 2.83 [1.59, 4.82].

Conclusions: Matching with mixed data is simplified by using propensity score methods, but it is important to assess both univariate and multivariate balance after matching. Our results indicate that while PS leads to low bias in matched samples, it does not preserve pairwise correlations as well as MD. We suggest use of MD within propensity scores when possible, and addition of multivariate screening using HCM's as an additional tool in the repertoire of selecting optimal matches.

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Teun Post Application of a Semi-Mechanistic, Integrated Glucose-Insulin Model to Graded Glucose Infusion Placebo Data to translate Glucose Insulin dynamics between Healthy Humans and Non-Human Primates

Rolien Bosch 1*, Wei Gao 2, Ryan Vargo 2, Chandni Valiathan 2, Craig Fancourt 2, P.A. Kothare 2, Maria C. Kjellsson 3, Mats O. Karlsson 3, Teun Post 1*

*1 PPDM: Quantitative Pharmacology & Pharmacometrics, MSD Oss B.V., Oss, The Netherlands, 2 PPDM: Quantitative Pharmacology & Pharmacometrics, Merck & Co, US, 3 Pharmetheus, Uppsala, Sweden, * Currently employed by LAP&P Consultants BV, Leiden, The Netherlands*

Objectives: To develop a foundational framework for the extrapolation of novel drug effects observed in non-human primates (NNP) to healthy volunteers utilizing the Graded Glucose Infusion (GGI) study paradigm. The GGI is a simpler method than the hyperglycemic clamp (HGC) for measurement of glucose-dependent insulin secretion (GDIS).

Methods: Placebo glucose and insulin data from three healthy subject GGI studies (N=47) and one NHP GGI study (N=11) were included for an analysis using NONMEM.

The IGI model developed by Silber et al [1] was the starting point. The need for adjusting parameters to fit the GGI data was assessed [2]. Translation to NHP was done by allometric scaling of the human GGI model [3]. Subsequently the need for parameter adjustments was assessed. The model was evaluated using VPCs and was externally qualified on human GGI data from a separate study.

Results: All disposition parameters of glucose and insulin were kept identical as presented by Silber et al. [1]. The Insulin-dependent Glucose Clearance (CLGI) and the Insulin on Glucose production (IPRG) feedback were estimated in combination with glucose and insulin baseline values (GSS and ISS) and residual errors (RESG and RESI) for both NHP and human data. Species differences between NPH and humans were observed for CLGI, IPRG and GPRG estimates.

Conclusions: The IGI was optimized to human GGI placebo data and allometrically scaled and optimized to the NHP GGI placebo data. Based on the VPC and external validation the final IGI model for each species adequately described the observed GGI data. Glucose appears to have a larger effect on decreasing the Glucose production (GPRG) in NHP compared to human (-19.9 vs. -2.97, respectively). Insulin on Glucose production (IPRG) seems to be comparable in NHP and human, although insulin levels in NHP reach much higher levels after Glucose infusion. This foundational framework for interspecies translation of placebo GGI data can be used as a starting point in the drug discovery setting, to explore the effect of novel diabetes treatments on GDIS and ISR from animal to human.

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Aurélie Premaud Mixed-effect models for longitudinal exposure to co-administered drugs and time-to-event data: prediction of risk of graft failure in renal transplant patients.

Zeinab Daher Abdi (1), Annick Rousseau (1,2), Aurélie Prémaud (1,2)
(1) INSERM, UMR-850, limoges, France, (2)Univ Limoges, Limoges, France.

Objectives: This study aimed to investigate, in adult kidney transplant recipients, the relationship between longitudinal exposure to co-administered immunosuppressive drugs (i.e mycophenolic acid (MPA) and an calcineurin inhibitor (either cyclosporine or tacrolimus) and a composite efficacy endpoint including acute rejection, graft loss and death.

Methods: Data from 222 patients were analyzed: 23 events were observed in 126 patients receiving cyclosporine against 15 in 96 patients receiving tacrolimus (p=0.61) in the two first years post-transplantation. Within NONMEM V7.2.0, the longitudinal drug exposures described using mixed-effects models were incorporated as time-dependent covariates in a parametric time-to-event model. An interval-censored approach was used for patients who had experienced an event to take into account that rejection occurred in a time interval prior to the time of diagnosis. Donor and recipient characteristics were tested as covariates.

Results: A sigmoid Emax model was selected to describe the time course of MPA exposure and exponential models were retained for the time course of cyclosporine and tacrolimus. Model-predicted time-varying distributions of MPA, cyclosporine and tacrolimus were in good agreement with observed values. The developed time-to-event model showed that the studied efficacy composite outcome was associated to longitudinal exposure to MPA and to onset of cytomegalovirus infection or disease. Within the observed ranges, calcineurin inhibitor exposures were not significantly associated with efficacy (i.e. acute rejection, graft loss and death). The risk of acute rejection, graft loss or death adjusted on the longitudinal calcineurin inhibitor co-exposures, decreased by 4% (95% confidence interval Hazard Ratio 0.93-0.99) per 1 mg.h/L increase of MPA area under the curve. The onset of cytomegalovirus infection/disease significantly increased this risk (Hazard Ratio=10.9; 95% confidence interval 6.5-21.7). Visual-predictive-check and Kaplan-Meier plots showed that the developed time-to-event model described well the rejection-free and failure-free graft survival curves.

Conclusions: For the first time, a time-to-event model that considers the combined longitudinal exposures to two co-administered drugs was developed. This work advocates for the avoidance of unnecessary high calcineurin inhibitors dosing and puts forward new arguments for MPA concentration monitoring.

Klaas Prins Acknowledging dispersion increases the power to detect central tendencies in under dispersed count data at low treatment arm size

Klaas Prins
qPharmetra LLC, Andover, MA, USA

Objectives: Traditionally, count data are modeled using the Poisson distribution that assumes mean and variance are the same. However, there are examples where variance is less (under dispersion) or more (over dispersion) than the mean count. A variety of distributions, including the Generalized Poisson (GP, [2]) are used to model the central tendency and data dispersion. Generally, the model fits improve substantially by estimating dispersion [1,3], but it has not been reported yet if this also leads to increased power to detect a certain effect. In the current simulation study a case of under dispersion this will be investigated.

Methods: The true model was based on under dispersed daily micturition frequency. The placebo model included a monoexponential decrease in base count (11 voids/d) reaching steady state effect after 8 weeks. The drug effect was modeled directly proportional to placebo effect via an Emax model (ED50 defined at 50 mg). Using PsN's [4] stochastic simulation-estimation (sse), an underdispersed data set (lambda=22, dispersion=-1) was simulated using a datasets of varying treatment arm size (n=10, 30, 50, 75, 100) including placebo, 25, 50, 100 and 200mg as

treatments. The model was re-estimated with a placebo and a placebo+drug effect model and the proportion ofplacebo+drug effect models being statistically superior to their corresponding placebo model was used to define the power to detect a drug effect (alpha=5%). This procedure was performed under the GP (estimating dispersion) and the Poisson distribution (by fixing dispersion to zero, making the GP collapse to a Poisson) and the success rates were compared between the two distributions.

Results: The model estimating the dispersion alongside the mean count (GP) was able to detect dose response at much lower treatment arm size than the Poisson. At n=10 and n=30, the 33% and 37% of the GP models detected a drug effect versus 1% and 3% for Poisson. At n=100 Poisson detected a significant drug effect in 47% of the cases, vs 51% for GP. Around 75-100 patients per arm the success rate was similar between the distributions.

Conclusions: Acknowledging dispersion in models for under dispersed count data using the GP distribution improves the power to estimate central tendencies in the data at relatively low treatment arm size. With increasing treatment arm size, this power advantage gradually fades out and becomes independent of the estimation of the degree of dispersion.

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Richard Pugh The Modeling & Simulation Workbench – Enabling Model-Based Decisions in Drug Development

Richard Pugh
Mango Solutions

Objectives:

The aims of this work was to develop a software platform that would:

- Provide a regulated environment for modeling work supporting health regulatory drug development activities
- Provide a secure, auditable model management system
- Allow for the storage, management and searching of modeling knowledge
- Provide a sophisticated model development platform
- Apply rigor to the modeling process without adding overhead to the modeler
- Provide a basis for standardisation and best practices across a modeling team

Methods:

The MSWB team collaborated to design an integrated knowledge management and model development platform, meeting the requirements of a health regulated system. The platform has been

deployed at Merck, and is required for all PKPD modeling activities at Merck.

The MSWB team developed requirements, architecture and software to create a platform that integrates several elements.

- Security and controlled access, allowing for blinded and due diligence modeling projects
- Searchable and annotated model repository
- Supports model development workflow around NONMEM, including R and Matlab scripting
- Execution of jobs on a high performance computing systems
- “Invisible” rigor (audit trail, versioning, meta data discovery)

Notably, the system supports a range of technical use, encompassing everything from “command line” access to visual “model review” tools.

Results:

Key system features will be demonstrated via screenshots, highlighted by the factors driving the design (such as model review, knowledge integration, remote execution). Conclusions: Navigator Workbench provides a knowledge driven modeling platform that effectively supports the use of modeling for decision-making on drug development programs at Merck

Conclusions:

Mango and Merck formed a cross-functional team that designed and delivered a model development and knowledge platform that meets the needs of a modern pharmacometric team. This close collaboration combined with a phased development approach enabled the creation of a best-in-industry modeling platform that is truly fit for purpose

Didier Renard Modeling of pharmacokinetic data using nonlinear mixed-effects: a paradigm shift in veterinary pharmacology. A case study with the nonsteroidal anti-inflammatory robenacoxib in cats

L. Pelligand1, D. Renard2, A. Soubret2, J. N. King3, J. Elliott1, J. Mochel2

1 Royal Veterinary College, Hawkshead Lane, Hatfield, UK; 2 Integrated Quantitative Sciences, Novartis Pharmaceuticals, Werk Saint Johann 4056 Basel Switzerland.; 3 Clinical Development, Elanco Animal Health, c/o Novartis, 4002 Basel Switzerland

Objectives: In veterinary medicine, characterization of pharmacokinetic (PK) information is usually performed using a so-called 2 stages approach, thereby limiting most of the analyses to rich data. The objective of the study was to model the PK of robenacoxib in cats by pooling data from diverse sources in order to leverage the richness of the intensively sampled individuals to inform parameter estimates of the more sparsely sampled patients.

Methods: Data from 83 cats were pooled from 7 preclinical (laboratory cat) and 1 field (client-owned cat, perioperative sampling) robenacoxib PK studies. Cats received robenacoxib subcutaneously (SC) and/or intravenously (IV). Sampling was rich for 47 laboratory cats (24 SC, 9 IV, 14 both) and sparse for 36 clinical cats (SC, 1 to 2 samples per cat). The exact dose ranged from 1.6 to 2.3 mg/kg. Data from both routes were modelled simultaneously with NLMEs in Monolix 4.3.2, using a combined additive and

proportional error model. Standard goodness-of-fit diagnostics, NPDEs, as well as VPCs were performed to evaluate the adequacy of the selected model. The influence of individual characteristics on population parameter estimates was assessed from the visual inspection of the full posterior distribution of the random effects.

Results: A two-compartment mammillary model with first-order absorption and elimination best described the PK of robenacoxib in blood. The precision of the final models parameters was considered satisfactory (RSE<20% for most parameters). Total body clearance was estimated to be moderate (0.518 L/kg/h) and the global extraction ratio E was 0.06. The SC bioavailability was high (83.6%) and the steady state volume of distribution was 0.280 L/kg. The absorption constant (K_a=0.85 h^{-1}) was lower than the elimination constant of the combined model (K_{10}=2.19 h^{-1}), thus confirming flip-flop SC PK. None of the population characteristics, in the investigated ranges herein, was found to explain the between-subject variability observed in the present studies.

Conclusions: Joint modelling of the IV and SC routes enabled to unveil the flip-flop disposition kinetics of robenacoxib in cats. Estimates of exposures from perioperative (sparse) and conscious (rich) sampled cats did differ substantially. The use of population modelling to leverage information from densely sampled cats to estimate PK parameters of anaesthetized (sparse) patients is innovative in veterinary pharmacology.

Su-jin Rhee A population pharmacokinetic analysis of once-daily intravenous busulfan in pediatric patients undergoing hematopoietic stem cell transplantation

Su-jin Rhee1, Seung Hwan Lee1, Ji Won Lee2, Kyung-Sang Yu1, Hyoung Jin Kang2, In-Jin Jang1, Howard Lee1,3
1Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea; 2Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; 3Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University

Objectives: Busulfan is a bifunctional alkylating agent, which is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation (HSCT). The aims of this study were 1) to characterize the population pharmacokinetics of once-daily intravenous (IV) busulfan in pediatric patients undergoing HSCT, and 2) to identify significant covariates that might affect the pharmacokinetic parameters of busulfan in this population.

Methods: A population pharmacokinetic analysis was performed using 2183 busulfan concentrations in 137 pediatric patients, who received an IV busulfan and cyclophosphamide regimen for 4 days before undergoing HSCT. The First-Order Conditional Estimation with Interaction estimation method implemented in NONMEM

(version 7.2) was used, which was followed by model qualification using bootstrapping and visual predictive checks (VPCs).

Results: A one-compartment open linear model with proportional residual error, which also included inter-individual (IIV) and inter-occasion variability (IOV) for clearance (CL), and IIV for volume of distribution (V), and their covariance, adequately described the concentration–time profiles of busulfan. Body surface area (BSA) was a significant covariate for CL and V, while plasma ferritin level and dosing day were significant only for CL. The typical population estimates of CL and V for an adult with BSA of 1.73 m^2 were 11.2 L/h and 43.8 L, respectively. The IIV of CL and V was 23.4% and 22.5%, respectively, while the IOV of CL was 10.5%. Model evaluation by bootstrapping and VPCs indicated that the proposed model was adequate, robust, and stable, and the parameters were estimated with a good precision.

Conclusions: The population pharmacokinetic model for IV busulfan can be utilized to develop and improve the dosing regimen in pediatric patients undergoing HSCT.

Marie-Karelle Riviere-Jourdan Evaluation of the expected Fisher information matrix without linearization, in nonlinear mixed effect models for discrete and continuous outcomes

Marie-Karelle Riviere, Sebastian Ueckert, and France Mentré
IAME, UMR 1137, INSERM, F-75018 Paris, France University Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

Objectives: In recent years, estimation algorithms for NLMEMs have transitioned from linearization-based approaches towards more exact higher-order methods. Optimal design, on the other hand, has mainly relied on first-order linearization (FO) to calculate the expected Fisher information matrix (FIM) [1]. Although efficient in general, FO precludes the application of optimal design with complex non-linear models and in studies with discrete endpoints [2,3]. The objective of this work was to apply integration algorithms, which have proven to be efficient for estimation, to evaluate the asymptotically exact FIM in NLMEM for both discrete and continuous outcomes.

Methods: In NLMEMs, the FIM has no analytical form as its calculation involves multiple integrations. We used either Adaptive Gaussian Quadrature (AGQ) [4] or Markov Chain Monte Carlo (MCMC) to integrate the derivatives of the log-likelihood over the random effects, and Monte Carlo (MC) approximation to evaluate its expectation w.r.t. the observations. The proposed methods were

implemented in R and used the probabilistic programming language STAN for MCMC sampling [5]. Evaluation was performed with models for continuous, binary, count and repeated time-to-event outcomes by comparing the FIM based relative standard errors (RSE) to the relative root mean square errors (RRMSE) from clinical trials simulation. The RRMSEs were obtained by simulating 1000 data sets in R and subsequently analyzing them with MONOLIX [6].

Results: Both AGQ and MCMC-based approaches showed good performance on scenarios for continuous and discrete outcomes with RSEs close to the RRMSEs obtained by simulations. In general, RSE predicted by linearization gave close results for rich designs, but showed larger deviations for sparse designs and very non-linear models. We compared the pros and cons of the proposed methods: especially computation of the FIM with AGQ took only seconds for models with few random effects (as commonly encountered in discrete outcome models), but models with more than 4 random effects became infeasible. The MCMC approach on the other hand was notably slower than AGQ for simple models, but can be applied to complex ones with similar time calculation.

Conclusions: Two complementing methods for calculating the exact FIM were proposed and evaluated: AGQ as fast algorithm for simple discrete models, and MCMC which suited even for large complex models where FO fails to correctly evaluate the FIM.

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Dirk Garmann RTTE analysis of repeated bleeding events in haemophilia A after recombinant factor VIII treatment

Dirk Garmann (1) Matthias Frede (2) Anita Shah (3) Bart Ploeger (4)
(1,2,4) Bayer Pharma AG, Wuppertal/Berlin, Germany (3) Bayer HealthCare, Whippany, NJ, USA

Objectives: to evaluate different dosing regimen for their clinical effectiveness through a quantitative understanding of the occurrence of repeated bleeding events after recombinant factor VIII treatment by a Repeated Time To Event (RTTE) analysis.

Methods: Bleeding data after recombinant factor VIII (FVIII) treatment were used to develop a RTTE model using non-linear mixed-effects modelling [1]. The following factors were evaluated as possible factors affecting bleeding rate: Time below a certain FVIII level/standardized to 1 week and complete FVIII activity time profiles for each subject both estimated using population PK modelling, number of target joints, reported bleedings in past year.

Results: A RTTE model assuming a decreasing repeated bleeding risk over time was chosen as a base model. Reported bleedings in the past year and the individual FVIII activity time profile were identified as significant covariates. The effect of the change in FVIII over time was highly significant ($p < 0.00001$) and was a better predictor compared to time below FVIII thresholds. Simulations show that the

final model describes the observed occurrence of bleeding events adequately.

Conclusions: A RTTE model was established to describe bleeding events in haemophilia A. This model can be used to simulate and evaluate several clinical relevant scenarios e.g. the effect of different dosing schedules or a factor VIII exposure guided approach of keeping patients above a threshold of 1IU/dL factor VIII.

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Leire Ruiz Cerdá Systems Pharmacology Model of the Co-stimulation Process of Immune Response in Systemic Lupus Erythematosus.

Leire Ruiz Cerdá (1), Itziar Irurzun-Arana(1), Ignacio Gonzalez-Garcia(1) (2), Chuanpu Hu(3), Honghui Zhou(3), An Vermeulen(4), Iñaki F. Trocóniz(1), José David Gómez-Mantilla(1)
(1)Pharmacometrics & Systems Pharmacology, Department of Pharmacy and Pharmaceutical Technology, University of Navarra, Pamplona 31080, Spain (2) Pharmacy and Pharmaceutical Technology Department. University of Valencia. Valencia, Spain (3) Janssen Research and Development, LLC, Spring House, PA 19477, USA (4)Janssen Research and Development, a division of Janssen Pharmaceutics NV, Beerse B-2340, Belgium

Objectives: To mechanistically characterize the co-stimulation process within immune responses with emphasis on alterations occurring in Systemic Lupus Erythematosus (SLE) using a Systems Pharmacology approach.

Methods: The co-stimulation process involves antigen presentation to T cells [1]. The network was built based on a rigorous bibliographic review, focused on the components of the immune responses that have been reported to be altered in SLE. Boolean expressions [2] and scripts to simulate the evolution of the entire network, were written in the R environment. We simulated a continuous autoantigen exposure and evaluated the differences in

the network dynamics by perturbation of different nodes. The network was validated through simulations (10,000) to obtain relative expression profiles for each component of the network.

Results: The network consisted of 50 nodes, 16 of which have been reported to be altered in SLE, and 140 relationships. From the 50 nodes, 17 corresponded to cytokines, 9 to Antigen-presenting cell (APC) surface molecules, 17 to T cell surface and intracellular molecules, 5 to differentiated T cell subpopulations and the remaining nodes corresponded to the autoantigen and T cell activation signals. The established network was considered validated based on the good agreement obtained when comparing expression profiles reported in literature for selected nodes and the corresponding relative expression simulated profiles. In addition, performing virtual knockout of nodes reported to be altered in SLE led to expression profiles similar to those presented in real SLE patients.

Conclusions: A systems pharmacology model for co-stimulation, a fundamental step in the mechanism triggering immune response, has been developed and validated. In its actual status, the model can be challenged by testing the effect of blocking or activating different pathways to help in target identification. Current ongoing developments involve (i) applying reduction methods towards a mechanistic model that can be handled in PKPD analyses, and (ii) expanding the network including T cell differentiation mechanisms and antigen presentation to B cells.

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Alberto Russu Modelling pharmacokinetics and CSF Abeta1-40 reduction in humans after dosing with JNJ-54861911, a novel oral BACE inhibitor

Alberto Russu (1), Johannes Streffer (2), Luc Tritsmans (3), An Vermeulen (1)
(1) Model Based Drug Development, (2) Experimental Medicine, and (3) Neuroscience Development, Janssen Research & Development, Beerse, Belgium

Objectives: Amyloid reduction via BACE inhibition is a potential therapeutic target in Alzheimer's Disease [1]. JNJ-54861911 is a potent oral BACE inhibitor tested in Phase I clinical trials [2]. The objectives of this work are: (i) to model the plasma and CSF pharmacokinetics (PK) of JNJ-54861911, (ii) to model the pharmacodynamic (PD) effect of JNJ-54861911 on CSF Abeta1-40 reduction as a marker of target engagement, and (iii) to assess the dose- and exposure-response of JNJ-54861911 on CSF Abeta1-40 after repeated daily dosing.

Methods: Plasma and CSF concentrations of JNJ-54861911, dosed as a suspension or a tablet, were obtained from healthy elderly volunteers in a Phase 1 multiple ascending dose trial, and analyzed via population PK modeling with NONMEM 7.1.0 [3]. Serial CSF samples to assess JNJ-54861911 PK and the time course of amyloid markers were obtained via 36-hour catheterization [2]. Drug effect was modeled by linking JNJ-54861911 CSF concentrations to CSF

Abeta1-40 reduction via a semi-mechanistic indirect response PK/PD model (see e.g. [4]).

Results: A two-compartment PK model with sequential zero and first order absorption with linear disposition captured the PK of JNJ-54861911 in plasma. Individual CSF PK profiles were essentially parallel to the respective plasma profiles and were described as a scaled version of the plasma concentration (mean ratio between CSF and free plasma concentration = 62%, plasma free fraction = 6%). JNJ-54861911 resulted in a potent and sustained CSF Abeta1-40 reduction (plasma IC50 = 21ng/mL; apparent CSF Abeta1-40 turnover half-life = 13h). Simulation of steady-state average CSF Abeta1-40 reduction evidenced that (i) a dose of 10mg q.d. results in >50% reduction in the majority of subjects, (ii) a dose of 25mg q.d. attains robust (>80%) reduction in most subjects, and (iii) Abeta reduction approaches 90% at a dose of 50mg q.d. and improves only marginally for higher doses.

Conclusions: The integrated, semi-mechanistic population PK/PD model captured the time course of JNJ-54861911 PK and allowed to link plasma concentrations to CSF concentrations, which are possibly reflective of brain penetration [5]. Modeling and simulation of CSF Abeta1-40 time course helped to quantify the dose- and exposure-response of JNJ-54861911 and allowed to infer a potential range of therapeutic doses for long-term treatment.

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Yevgen Ryeznik Adaptive designs for dose finding clinical trials with time-to-event outcomes

Yevgen Ryeznik (1,2), Andrew C. Hooker (2), Alex Sverdlov (3)
(1) Department of Mathematics, Uppsala University, (2) Department of Pharmaceutical Biosciences, Uppsala University, (3) EMD Serono

Objectives: Many clinical trials use time-to-event (TTE) outcomes as primary measures of efficacy or safety. For instance, in dose finding cancer trials the goals may be to estimate a dose-response relationship and to identify a dose level that yields the longest progression-free survival for testing in subsequent studies. Efficient designs for such trials are needed but finding such designs in practice may be complicated due to uncertainty about the model for event times, delayed responses and censored observations. In this work we develop optimal and adaptive designs for dose finding clinical trials with TTE outcomes.

Methods: We consider an accelerated failure time (AFT) model [1] assuming a quadratic dose-response model for log-transformed TTE outcomes with a Weibull distribution that are subject to right censoring with a fixed or random censoring time. We obtain the D-optimal design for the most precise estimation of the dose-response curve applying the general equivalence theorem [2]. Both the case when the dose is assumed to be a continuous factor and the case when the dose levels are chosen from a discrete set are studied. The censoring mechanism [3] is explored and the robustness of the designs to model misspecification is assessed. For implementing optimal designs in practice we propose a multi-stage adaptive

design. The effect of delayed response and different recruitment patterns on statistical properties of adaptive designs is examined.

Results: The proposed optimal designs generate allocation of patients to the most informative dose levels and achieve higher efficiency in estimating the parameters of interest compared to the popular equal allocation designs in the presence of censoring. Adaptive designs can be used to approximate the optimal designs; however, a sufficient amount of outcome data must be observed during the recruitment phase of the trial to facilitate adaptations. Further research on the robustness of the proposed designs to model misspecifications is ongoing.

Conclusions: The proposed designs can improve efficiency of clinical trials with time-to-event outcomes by reasonable allocation of study patients to dose levels that are most informative for the given study objectives.

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Muhammad Waqas Sadiq A whole-body physiologically based pharmacokinetic (WBPBPK) model of ciprofloxacin for prediction of bacterial killing at the site of infection

M. W. Sadiq (1,2), E. I. Nielsen (1), M. O. Karlsson (1), L. E. Friberg (1)
(1) Uppsala University, Sweden; (2) CVMD iMed DMPK, AstraZeneca R&D, 431 83, Mölndal, Sweden

Objectives: Aim of this study was to develop a WBPBPK model for ciprofloxacin to predict the tissue concentration time profiles in patients with only plasma concentrations data available. WBPBPK model was further combine to a PKPD model to illustrate the time-course of bacterial killing for infections with *E. coli* strains with different levels of resistance.

Methods: Based on 102 adult ICU patient's plasma concentration data, a WBPBPK model for ciprofloxacin was developed [1]. NONMEM was used to apply population approach for data analysis. Tissue to plasma distribution coefficients (Kp) for ciprofloxacin in 10 different tissues including lung, muscle, kidney and adipose were taken from clinical studies available in literature. These literature Kp values were used as informative priors while estimating the individual tissue Kp values. Time-course of the bacterial killing for *E. coli* in different tissues were quantitatively predicted by coupling the final WBPBPK model to a pharmacokinetic-pharmacodynamic (PKPD) model [2].

Results: The developed WBPBPK model successfully characterized both the typical trends and variability of the available ciprofloxacin data, as demonstrated by visual predictive checks. Stable PK estimates including clearance and tissue Kp values were generated by model, comparable to previously reported literature values. By connecting the predicted PK profile of unbound ciprofloxacin with the PKPD model the rate and extent of take-over of mutant bacteria in different tissues could be predicted. A series of simulation scenarios of different dosing regimens, mixtures of bacterial population with different levels of resistance and immune response were performed to illustrate the concept and the impact of different PK-profiles.

Conclusions: For prediction of time course of bacterial killing in different tissues a novel method of combining the concentration time profile from WBPBPK with PKPD model was successfully implemented.

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Tarjinder Sahota Efficient argument settings for NONMEM 7 expectation maximisation methods

Tarjinder Sahota (1), Brendan Johnson (1)
(1) Clinical Pharmacology Modeling and Simulation, GSK, UK.

Objectives: NONMEM has traditionally used gradient based algorithms (e.g. FO and FOCE) to estimate model parameters of nonlinear mixed effects models. These algorithms may fail to converge for numerical reasons. Newer expectation maximisation (EM) algorithms were introduced in version 7.0 of NONMEM which offered the prospect of increased numerical stability and reduced bias in model parameter estimation [1]. Unlike FO and FOCE estimation however, these algorithms come with many options and settings for the users to define which can be bewildering at first. The aim of this work is to derive efficient starting arguments using algorithm performance in real data case studies.

Methods: Three case studies are presented. 1) Mixture model PK with active metabolite 2) plasma lung model and 3) Hgb lifespan KPD model 4) Count data example. EM method performance was assessed relative to FOCE (LAPLACIAN for example 4) using the following criteria: 1) Likelihood of convergence, 2) Sensitivity to initial estimates 3) Run time and 4) MC noise evaluation. OFV vs ITERATION plots for assessing stationarity were used to select convergence criteria.

Results: Plotting parameters/OFV vs ITERATION is important component of assessing convergence. When initial estimates were close to final estimates, initial estimation steps (e.g. METHOD=ITS or METHOD=FO) can add to total run time and in some cases destabilise some models. Monte Carlo (MC) error in OFV evaluation was inappropriately high for some models. Use of RANMETHOD=3S1 and RANMETHOD=3S2 options resulted in drastic reductions in MC noise. Separate convergence criteria were defined for IMP/IMPMAP and SAEM methods.

Conclusions: The proposed argument settings provided a sensible starting point for efficient convergence with IMP and SAEM estimation methods.

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Maria Luisa Sardu Xenograft experiments: assessing consistency between a drug-driven and a biomarker-driven tumor growth inhibition model

M.L. Sardu (1), I. Poggesi (1,2), G. De Nicolao (1)
(1) Department of Electrical, Computer and Biomedical Engineering , University of Pavia, Italy, (2) Model-based Drug Development, Janssen Research & Development, Beerse, Belgium

Objectives: Integrating biomarker dynamics to describe the effect of antitumoral drugs provides a deeper insight in the mechanistic aspects of tumor progression [1][2]. When the dynamics of a selective biomarker, causally and quantitatively related to the inhibition of an associated tumor is considered [3], it is worth asking what structures should have a biomarker-to-tumor model and a drug-to-tumor one, in order to produce consistent predictions. In this work we resort to steady-state conditions to check the consistency between some PKPD models published in the literature [4].

Methods: All PKPD data used in this work, were simulated according to the models proposed in [4], using NONMEM version. 7.2. We focused the analysis on three models: i) drug-to-biomarker (model I), ii) drug-to-tumor model driven by the concentration in the effect compartment (model III), iii) tumor growth inhibition model driven from the effect of AKT biomarker (model IV). To assess whether model III and the cascade of model I with model IV

describe compatible behaviors, a steady-state analysis was performed. In analogy with the method proposed in [5] [6], the so-called characteristic curves were computed.

Results: Steady-state behaviors described by the characteristic curves of model III and model IV differ especially for higher concentrations. In particular, model IV predicted higher tumor volumes than model I. In order to recover consistency between these models, a novel biomarker-to-tumor model was proposed. In the new model, tumor growth modulation induced by biomarker inhibition is compatible with that induced by drug-concentration. The new model eases the comparison and understanding of the relationships between parameters of drug-to-biomarker and biomarker-to-tumor submodels. This paves the way to more precise predictions of tumor growth inhibition resulting from different protocols, but also from administration of different drugs, provided that they act on the same causal pathway.

Conclusions:

With reference to xenograft experiments, we analysed the steady-state consistency between a drug-to tumor model and a biomarker-to-tumor one taken from [4]. Since a discernible discrepancy was highlighted, we proposed a novel biomarker-to-tumor model that ensures steady-state consistency. The proposed model was validated on both steady-state characteristic curves and simulated PK-PD experiments.

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Franziska Schädeli Stark Use of PBPK information to select the doses and criteria for early dose confirmation or adjustment with a minimum number of subjects in a pediatric proof of concept (POC) study

Franziska Schaedeli[1] Stark, Caterina Bissantz[2], Sian Lennon-Chrimes[1,3], Valérie Cosson[1], Neil Parrott[2], Nicolas Frey[1]
Roche Pharmaceutical Research and Early Development, Clinical Development[1], Pharmaceutical Sciences[2], Roche Innovation Center Basel[1,2], Switzerland; Roche Innovation Center Welwyn[3], UK

Objectives: DrugA is a small molecule being developed for a neurologic disorder in a pediatric target population. Dose selection for a POC study targeted adult-equivalent exposure. While PBPK modeling is an accepted tool for pediatric dose prediction, health authorities also requested pre-defined criteria for early dose confirmation or adjustment (EDC), and sufficient confidence in the key PK parameters (CL, Vss) in adolescents before dosing younger children. We propose a method for EDC with a minimum number of subjects based on combined PBPK and population PK (PopPK) modeling and bootstrap resampling techniques.

Methods: A PBPK model was developed for children aged 5-17 yr based on an adult model for DrugA utilizing the pediatric module in SimCYP for scaling to children. Drug exposure (AUCss) and CL were derived from 4000 simulated PK profiles, and initial selection of pediatric age-adjusted doses was guided by the ratio of pediatric vs.

adult predicted CL (relCL) to achieve acceptable variability in exposure with a limited number of dose adjustment age groups (DAG). Criteria for EDC were set as follows: the dose is confirmed if observed relCL in a DAG is within 70-140% of predicted, otherwise it needs to be adjusted. The impact of sample size on the confidence for EDC was assessed by bootstrapping relCL from the pediatric PBPK database. For each sample size (N=4…40), the median relCL and a 90% CI was obtained from 1000 bootstrapped datasets. The minimum sample size with the 90% CI falling within the pre-defined limits was recommended for EDC. The performance of the approach with respect to EDC decision and PK parameter precision was assessed using PopPK model based clinical trial simulation (CTS).

Results: Median pediatric simulated CL approximated adult CL at the age of 16, but was reduced to 27% at 5 yr. Age and weight were equal predictors for relCL, justifying age-based pediatric dosing, which is preferred over weight-based dosing by clinicians. Four DAG (5-7, 8-10, 11-14, and 15-17 yr) were proposed, targeting 30, 45, 65 and 95% of the adult doses, based on predicted relCL and variability, available dose strengths and exposure limits for safety. EDC criteria was met with the bootstrapped 90% CI for N>=10 subjects per DAG. Results of CTS demonstrating the value and limitations of the approach will be presented.

Conclusions: PBPK modeling together with bootstrap techniques offer a tool to assess the sample size and criteria for EDC in a pediatric POC study.

Sebastian Wicha TDMx: A web-application for therapeutic drug monitoring enhanced by pharmacometrics

Sebastian G. Wicha (1), Martin G. Kees (1,2), Alexander Solms (3), Iris K. Minichmayr (1), Alexander Kratzer (4), Charlotte Kloft (1)
(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) Dept. of Anaesthesiology and Intensive Care, Charité Universitaetsmedizin Berlin - Campus Benjamin Franklin, Berlin, Germany, (3) Institute of Mathematics, University of Potsdam, Germany, (4) Hospital Pharmacy, University Hospital Regensburg, Germany

Background: Pharmacometric models have evolved as useful tools to quantify and explain pharmacokinetic (PK) variability between patients and to explore its resulting pharmacodynamic (PD) consequences e.g. on probabilities of target attainment (PTA) of anti-infectives. The application of pharmacometric PK/PD models in clinical practice is yet limited, as available software is either difficult to use or lacks functionality. Hence, we aimed to develop 'TDMx' (www.tdmx.eu), an easy-to-use, but powerful modular software tool for bedside dosing decisions, making use of state-of-the-art pharmacometric techniques such as (i) probability of target attainment analysis without requiring drug measurements, (ii) Bayesian PK estimation and definite PK/PD target attainment analysis if drug measurements are available and (iii) (adaptive) optimal design to sample at the most informative time points. As a starting point, population PK models for the anti-infectives

gentamicin, amikacin, meropenem and piperacillin have been implemented.

TDMx features:

- TDMx is freely accessible via a user-friendly web interface from any common (modern) browser and quickly provides answers to the clinically relevant TDM-related questions.
- *Patient module*: Input module for all available patient data (e.g. demographics, laboratory measurements) as well as the dosing schedule provided to 'TDMx'.
- *Probabilistic dosing module*: Computes the PTA to select a likely effective dosing regimen solely using patient covariates, e.g. to initiate empiric therapy, or to guide institutions where no drug measurements are available.
- *Bayesian dosing module*: Estimates individual PK parameters for definite target attainment analyses if drug measurements are available.
- *Optimal design module*: Predicts the most informative sampling time points for precise estimation of either PK parameters (e.g. in a research setting) or PD surrogates (e.g. $T_{>MIC}$ as a relevant PK/PD index in clinical routine).
- 'TDMx' was successfully validated against NONMEN$^{TM.}$

Conclusion: With 'TDMx', we provide a user-friendly and powerful web-application, making use of state-of-the art pharmacometric techniques to support bedside dosing decision-making. In comparison to other currently available tools, 'TDMx' offers broader functionality and can entirely be used in a web browser.

Ruben Faelens Simulo: a new PK-PD-Disease model simulator

Ruben Faelens, Quentin Leirens, Philippe Jacqmin
SGS Exprimo NV

What is Simulo?

Simulo is a new PK-PD-Disease model simulator, providing a user-friendly interface available on the web. It was developed to be a shared and user-friendly platform, running simulations on a private dedicated computing cluster. It provides the ability to simulate and subsequently analyse clinical studies using public, published or custom-developed nonlinear mixed-effects models.

Why was it developed?

Many simulation software solutions are available for model and simulation experts within the pharmaceutical industry. However, they often require extensive and complex scripting, especially when implementing mixed effect models and designing clinical trials. This complexity and this large choice of tools do not facilitate communication between M&S consultants and in-house M&S experts. In addition, they may be difficult to install as well as validate and they need scientific clusters to run, which have to be administrated.

Simulo solves these problems by providing a user-friendly web interface. Complex scripting is replaced by a straight-forward

interface where you can define treatments, dose adjustment, observations, inclusion/exclusion criteria… Models are shared between colleagues, which enables collaboration.

Ability to organize and implement complex trial designs in a user-friendly interface

Simulo is comprised of three major parts allowing to build and understand a model easily while conserving a very high flexibility thanks to its use of R code.

The *drug model editor* - Structural equations defining the core of the drug model can be introduced through algebraic, ordinary differential and/or delayed differential equations. Model parameters are computed from variability generated at different levels (population parameters, covariates, IIV & IOV). This variability can be sampled from non-correlated parametric distributions (e.g. constant, uniform, normal, lognormal, logit, logistic, Poisson, negative binomial), correlated parametric distributions and discrete distributions. It can even be bootstrapped from existing databases (sequentially or at random, with or without replacement, independently or jointly). Error models can be easily built in order to reproduce residual variability. Conditional events brings the ability to intervene during the simulated trial (e.g. dropout, adverse event, TTE).

The *protocol editor* - Enrolment, inclusion criteria, treatments (route & mode of administration, dose and dosing schedule), observations (type and schedule), lead-in phase or a complex protocol (e.g. parallel, cross-over Latin-square designs) can all be defined in a user-friendly interface. Simulo can be used to simulate complex dose adjustment schemes or special drug effects with ease.

The analysis editor - Analysis methods can automatically be applied on the in-memory results at the end of each replicate through

customized R scripts. It allows you to only save final output graphs and tables.

Once these elements are defined, a clinical trial can be simulated. All element definitions are converted into R code and executed on a high performance cluster. The raw and/or analysis results can be downloaded.

On the top of that, Simulo has some tools valuable during the process of implementation. First, a *live validation* module checks constantly the implementation and shows problems. Secondly, for easily seeing how a drug model behaves, a *live simulation* was created. It simulates a limited number of subjects and displays the results graphically, allowing you to quickly verify how your model behaves in different situations. Finally, hypotheses for each population characteristic, model parameter and study design attributes can be configured in a *scenario view*.

Technically

Simulo is web-based, which means it doesn't require a specific installation: a recent web browser is sufficient to connect. It was built by professional software engineers at Altran under the close supervision of domain experts at Exprimo and F. Hoffman-La Roche. The principle is a Java-based application running on an R backend. Simulations are done by first translating the study model to R code, and then efficiently executing this code. Moreover, Simulo is installed on Exprimo's servers and therefore the maintenance, validation and version control are kept centralized.

Service

Simulo has already faced an extensive use within Exprimo for client projects and has been validated on more than 80 models. It is now offered as an integrated part of the consultancy service that

Exprimo delivers to clients during a project. The sponsor has the opportunity to reproduce the simulations performed at Exprimo and/or to independently run advanced simulation scenarios that he would like to test. The simulated data can then be remotely visualized and analyzed through customized R scripts and/or can be downloaded as .csv files for further local processing.

We will provide a live demonstration but you are also invited to visit the website www.simulo.eu.