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Software abstracts

SAEM in MATLAB: an alternative to linearization

Marc Lavielle(1) and the Monolix research group(2)

(1) Université Paris-Sud, Bât 425, Equipe de Probabilités, Statistique et Modélisation, 91405 Orsay Cedex, France; (2) http://www.math.u-psud.fr/~lavielle/monolix

poster

Stochastic Approximation EM (SAEM) is a powerful algorithm for maximum likelihood estimation in nonlinear mixed effects models [1-4]. This algorithm estimates the population parameters from pharmacokinetic (PK) or Pharmacodynamic (PD) data without any linearizing technique.

SAEM can handle covariates and nondiagonal covariance matrix for the random effects. The exact observed likelihood is very well estimated using an importance sampling Monte-Carlo scheme. Thus, Likelihood Ratio tests can be performed with accurate error probabilities. Standard errors of the estimated parameters are also computed without linearization.

We have implemented a rather generic version of SAEM in MATLAB. We have successfully used this method to analyze different sets of simulated and real clinical data. SAEM is fast in practice and converge in situations where other reference methods (NONMEM, nlme) do not.

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Day 1
Poster abstracts

1. Population pharmacokinetics of caffeine and its metabolites theobromine, paraxanthine and theophylline after inhalation in combination with diacetylmorphine

A.S. Zandvliet(1,2), A.D.R. Huitema(1,2), M.E. de Jonge(1,2), R. den Hoed(3), R.W. Sparidans(3), V.M. Hendriks(4,7), W. van den Brink(5,7), J.M. van Ree(6,7), J.H. Beijnen(1,2,3)

(1)Department of Pharmacy & Pharmacology, Slotervaart Hospital, Amsterdam, The Netherlands; (2)The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; (3)Department of Biomedical Analysis, Section of Drug Toxicology, Utrecht University, Utrecht, The Netherlands; (4)Parnassia Addiction Research Centre, The Hague, The Netherlands; (5)Amsterdam Institute for Addiction Research, Amsterdam, The Netherlands; (6)Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands; (7)Central Committee on the Treatment of Heroin Addicts (CCBH), Utrecht, The Netherlands

poster

Objectives: The stimulant effect of caffeine, as an additive in legal diacetylmorphine (heroin) preparations for study purposes, may interfere with the pharmacodynamic effects of diacetylmorphine. From this perspective it is important to obtain insight into the pharmacology of caffeine as an additive to diacetylmorphine after inhalation. The current study focused on the pharmacokinetics of caffeine and its dimethylxanthine metabolites (theobromine, paraxanthine and theophylline) after caffeine inhalation in heroin users.

Methods: Diacetylmorphine preparations (25-100 mg base) containing a 100mg dose of caffeine were used by inhalation in this trial by 10 subjects on 5 consecutive days. For inhalation, either the method of "chasing the dragon" or a laboratory heating plate was used. Plasma concentrations of caffeine, theobromine, paraxanthine and theophylline were measured by high performance liquid chromatography (HPLC). The non-linear mixed effects modelling (NONMEM) program was used to estimate population pharmacokinetic parameters of caffeine and three metabolites simultaneously and their interindividual, interoccasion and intraindividual variabilities. The model was evaluated by the jack-knife procedure.

Results: Caffeine was rapidly and effectively absorbed after inhalation. The process of inhalation could be described as a bolus administration into the central compartment. Population pharmacokinetics of caffeine and its metabolites theobromine, paraxanthine and theophylline after inhalation of the caffeine sublimate could adequately and simultaneously be described by a linear multi-compartment model. Caffeine plasma concentrations were best described by a two compartmental model, its metabolites by single compartment models. The smoking method and the amount of diacetylmorphine that was co-administered with the caffeine did not significantly influence caffeine pharmacokinetics. The extent to which the individual dimethylxanthines were formed was correlated within individuals and subject to high interindividual variability.

Conclusion: The presented model adequately describes the population pharmacokinetics of caffeine and its metabolites theobromine, paraxanthine and theophylline after inhalation of the caffeine sublimate of a 100mg tablet. Validation by the jack-knife procedure proved the stability of the model.

3. WAM (Wald's Approximation Method): A User-Friendly Software Program for Efficient Covariate Model Building

Ken Kowalski(1), David Hermann(1), and Wenping Wang(2)
(1) Pfizer Global Research & Development, (2) Pharsight Corporation
poster

A new software utility (WAM) based on the efficient covariate model building algorithm proposed by Kowalski and Hutmacher (2001) is presented and will be made available on the NONMEM repository(ftp://ftp.globomaxnm.com/Public/nonmem/). The WAM software is a user-friendly freeware utility that ranks all 2^k possible covariate sub-models (presence or absence of k covariate parameters) based on Wald's approximation to Schwarz's Bayesian Criterion (SBC). The efficiency of this methodology stems from an approximate ranking of all possible covariate sub-models based on information from a single full model NONMEM run. The utility generates subsequent NONMEM runs for the top M parsimonious models (i.e., highest M ranked SBCs where M is typically set to 15) and compares the actual (NONMEM) and approximate (Wald) SBCs to verify the adequacy of the approximation. The final parsimonious model is chosen corresponding to the model with the highest actual SBC among the conditionally ranked top M models.

The utility requires the following:
1) Minor coding conventions in the NONMEM control stream for the full model (all k covariate parameters included in the model simultaneously),
2) Successful COV step estimation for the full model run, and
3) Use of an external subroutine ($SUBROUTINE command) and/or verbatim code to output the estimates and covariance matrix from the full model fit.

The WAM utility was written in C and was developed, tested and validated in a Windows PC environment; however, it is expected that the utility will be portable and should run under any operating system where NONMEM is supported.

5. Different approaches to the development of a WBPBPK model with a series of barbiturates using population modelling

S. Gisbert, L. Aarons and M. Rowland.

Centre for Applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK.

poster

Whole body physiologically based pharmacokinetic (WBPBPK) models are complex as they incorporate a lot of information coming from different sources (literature, in vitro and in vivo experiments) but this allow the models to become predictive and to be used for extrapolation from animal to man. The complexity of the WPBPK model has meant that to date models have mainly been developed by a two-stage process (i) optimisation of the drug dependent parameters and (ii) simulations using literature data on parameter variability and uncertainty.
The aim of the present study was to estimate the parameters of a WBPBPK model with a one-stage process. As the model has a large number of parameters compared to the number of observations, the estimation is difficult. To overcome this problem three approaches were tested: (a) fixing some parameters; (b) using Bayesian priors[1] and (c) integrating mechanistically based equations to predict Kp in the model[2].

The in vivo studies were realised in the rat. Plasma and tissue concentration time profiles were obtained after i.v. bolus administration of a 30 mmol/kg dose of seven barbiturate homologues to standard 250 g male Sprague Dawley rats. The WBPBPK model is composed of 14 tissue and 2 blood compartments and integrates physiological variability. The mechanistically based equations to predict Kp take into account both compound and tissue specific parameters.
Models were developed within NONMEM.
The use of priors did not lead to improved parameter estimation, despite longer run time. The results from the different methods will be compared in the presentation.

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7. The Design of Population Pharmacokinetic Studies: Sample Size Determination

K. Ogungbenro, G. Graham and L. Aarons

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester

poster

There is a need for pharmacokinetic(PK) studies just like any other study to include an adequate number of subjects in order to have the required level of power. However there are no general tools for determining sample sizes for population pharmacokinetic studies. The principles of Generalized Estimating Equations (GEE) for Generalized Linear Models (GLM) have been widely used in biostatistics for longitudinal data analysis and recently used to calculate the minimum sample size required based on the exponential family of distributions. Our intention was to extend the principles of GEE to nonlinear models in PK studies since these also involve longitudinal data.

GEE uses the first two moments of the likelihood to specify the model. Suppose measurements are scheduled for a set of time points for all individuals enrolled in the study and tj is the jth time (j=1,....,T). The vector of expected values in the sth subpopulation is given by . Let h( ) be the link function (h( )=) and g( ) is the variance function where Xs is the design matrix and is the parameter vector. Under GEE the covariance matrix among repeated measures is given by Vs= where is the dispersion parameter, As=diag[g( ).....g( )] and R is the working correlation matrix among repeated measurements. Equations to solve for the number of subjects using the functions above can therefore be derived so that an hypothesis of the form H0 : versus H1 : can be tested at a particular level of (type I error) and 1- (power, =type II error) where H is an h´r matrix of full row rank and h0 is the null hypothesis value for the (contrast of) parameter values (h is the number of for hypothesis testing).

A number of approximations have been proposed for nonlinear models, and nonlinear models are often linearised for the purpose of analysis. These include using the Jacobian matrix (Js) in place of the design matrix and the covariance matrix (Vs) as described by mixed effects modelling for the different error models. The method was applied to a one compartment IV bolus model with different values for clearance in two populations with the aim of calculating the minimum number of subjects required to detect the difference. The results of GEE were compared to the results obtained by applying the likelihood ratio test (LRT) and Wald test to the same problem and GEE produced a good estimate of power in all cases.

GEE was applied to the example described by White et al (1992), which involved an investigation using the LRT and confidence intervals to compare the clearance between two populations. The results of GEE were comparable to the results of White et al (1992).

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9. Clock time as a control variable for gall bladder emptying in an enterohepatic circulation model

T. Lehr (1), C. Tillmann (2), A. Staab (2), D. Trommeshauser (2), H.G. Schaefer (2), C. Kloft (1)
(1) Dept. Clinical Pharmacy, Institute of Pharmacy, Freie Universitaet Berlin, Berlin, Germany (2) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach a.d.R., Germany
poster

Objectives & Background: Plasma concentration-time profiles of a drug in clinical development showed multiple peak phenomenon as well as a long half-life of about 200 h. Enterohepatic circulation (EHC) is often associated with such observations. In the literature, models are presented by Ezzet et al. [1] and Funaki [2] to describe the pharmacokinetics of drugs undergoing EHC. However, these models are limited in the number of gall bladder emptyings. Wajima et al. [3] proposed an improved model using a periodic sinus function to control gall bladder release. The goal of this study was to apply and optimize the sinus function model to explore whether EHC might be a possible explanation for the specific properties of the compound investigated.

Methods: PK profiles of 47 subjects from three studies (single and multiple oral dosing as well as iv infusion) with 997 plasma samples were analyzed. Sampling times ranged up to 1084 h after administration. The data were best described by a two compartmental model (central and bile) with first order absorption and first order elimination. The release of the bile compartment was controlled by a sinus function model, switching the bile compartment periodically on and off. Several modified sinus functions were tested and applied to each study separately as well as to the combined studies.

Results: Implementation of clock time rather than relative time from administration in the sinus function model [a)] was found to be a pre-requisite for successful application of the EHC model. The model described the plasma concentration-time profiles of all studies adequately. The frequency of the gall bladder emptying was found to be similar across the three studies. A study specific time parameter (TDEL) had to be implemented, to account for the different administration times of the studies.

Conclusion: The model presented by Wajima et al. has the limitation that the on- and offset of the gall bladder emptying do not occur at the same time points of a day. Thus, a successful application of this model to drugs with a long half-life and a resulting long sampling schedule over weeks is difficult.
By implementation of the clock time the sinus function is reset every day resulting in a stabilized model. In consequence, this model accounts for a similar gall bladder emptying rhythm every day. The model presented can explain multiple peak phenomenon and a long half-life.

[a)] [sin(2*pi*(CLOCK+TDEL)/OMEGA)]
OMEGA = period of the sinus function
CLOCK = clock time
TDEL = start time difference of the sinus function period for a particular study

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11. Pharmacokinetic-Pharmacodynamic Modelling of Raltitrexed in Patients with Advanced Solid Tumours

E.Y.L. Blair(1), D.R. Mould(2), S.J. Clarke(3), L.P. Rivory(4), A.J. McLachlan(1)

(1)Faculty of Pharmacy, University of Sydney, Sydney, Australia; (2)Projections Research Inc, Phoenixville, PA, USA; (3)Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, Australia; (4)Johnson and Johnson Research, Eveleigh, Australia

poster

Objectives: The goals of this analysis were to develop a population pharmacokinetic/pharmacodynamic model that describes the relationship between patient exposure to raltitrexed and leucopenia and to identify covariates which may account for between patient variability in the PK/PD relationship.

Methods: All data modelling was performed with use of NONMEM v5.1.1 software. The pharmacokinetic study involved 112 adult patients (55% male) enrolled in 4 different Phase I clinical trials of raltitrexed as a single agent. Patients were given doses ranging from 0.1 to 4.5 mg/m2 every 3 weeks. A total of 2101 plasma concentration-time observations (average of 16 per patient) were available for at least 24 hours and up to 29 days for the first two cycles of raltitrexed treatment. The pharmacokinetic model was constructed using the first-order conditional estimation method with an interaction option. Model performance was assessed by evaluation of diagnostic plots and measures of parameter precision. The pharmacodynamic study involved 136 patients (56% male), of whom 102 patients were from the pharmacokinetic study. Exposure was measured as area under the plasma concentration time curve (AUC) and was estimated using the following formula: AUC=DOSE/CL where DOSE was the actual administered dose in each cycle. CL was estimated for patients without pharmacokinetic data using the formula for clearance and the patients' relevant covariate information. Individual estimates of CL were used for patients with pharmacokinetic data. Adverse event data were collected up to 11 cycles of raltitrexed treatment. The exposure-leucopenia relationship was examined by a logistic regression analysis with use of the conditional Laplacian likelihood method.

Results: A linear 3-compartment model with an additive and proportional residual error model best described the data. Creatinine clearance and body weight were found to be determinants of raltitrexed clearance when evaluated as single covariates (OFV reduction of 37 and 26 respectively, $P<0.0001$). Creatinine clearance reduced 12% of the interpatient variability in clearance in the final model. The population mean clearance estimate was 2.5 +/- 0.2 L/h. The calculated raltitrexed AUC was found to be predictive of severity of leukopenia. Other covariates investigated (age, sex, body surface area, serum albumin levels, alanine aminotransferase, aspartate aminotransferase and total bilirubin levels) were not found to influence raltitrexed clearance or the predicability of leucopenia.

Conclusion: Patients with impaired renal function and low body weight can have a high raltitrexed exposure which may in turn lead to an increased risk of leucopenia. Careful monitoring of signs of toxicity in these patients is prudent.

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13. Effect of Uncertainty About Population Parameters on Pharmacodynamics-Based Prediction of Clinical Trial Power - A Method for Sensitivity Analysis

Holger Kraiczi (1), Marianne Frisén (2)

(1) Pfizer Consumer Healthcare, Lund, Sweden, and Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden; (2) Statistical Research Unit, Gothenburg University, Gothenburg, Sweden

poster

In clinical trial simulation (CTS), uncertainty about population parameters determining the shape of the simulation model will influence the degree of uncertainty about the variable predicted with the simulation, e.g., trial power. However, the impact of uncertainty about single model parameters on the CTS prediction may vary considerably. In this sense, 'important' parameters, required to be entered into simulations with a high degree of precision to allow reliable CTS outcomes can be distinguished from 'unimportant' parameters, uncertainty about which has no serious consequences for the predicted variable. If such discrimination is done prior to trial simulations, research resources expended to inform CTS can be focused on the 'important' model parameters.

Using a worked example, we illustrate how uncertainty about population parameters may be incorporated into CTS by simulating full Bayesian predictive distributions of CTS outcome variables. We then suggest a method of sensitivity analysis, based on 2^k factorial simulation experiments, to rank input parameters with respect to their influence on uncertainty about the predicted CTS variable.

The analysis used to exemplify our approach is applied to the simulation of a completely randomized, placebo-controlled parallel-groups efficacy trial, in which the effect of the study drug is measured as a continuous outcome variable during steady-state conditions. The structural trial model links dose, concentration, effect (assuming a sigmoidal Emax model) and trial power. Trial power is the predicted variable and defined as the probability of an observed treatment effect that significantly exceeds a pre-specified clinically worthwhile difference. Analyses were performed for 3 different doses and 4 different settings of hyperparameters for 10 population parameters (means and variances for each of 5 structural model parameters).

The example illustrates that Bayesian predictive simulation, combined with a suitable experimental design of simulation studies, may be used to estimate the amount of information required to enable reliable predictions in CTS and, thus, to guide the process of learning in early drug development.

15. The reversal of rocuronium-induced neuromuscular block by the cyclodextrin ORG25969: model development and validation

B. Ploeger(2), N. Houwing(1), A. Bom(3), M.P. van Iersel(1), D. Zollinger(1), M. Danhof(2)

(1) NV Organon, Oss, The Netherlands; (2) LAP&P Consultants BV, Leiden, The Netherlands; (3) NV Organon, Newhouse, United Kingdom

poster

Objectives: ORG25969 is a chemically optimized cyclodextrin designed to selectively bind to rocuronium, leading to a reversal of rocuronium induced neuromuscular block (NMB). It is hypothesized that this reversal is due to a rapid decrease in the unbound rocuronium concentration. This hypothesis was evaluated and validated using a model-based analysis, in which the in vitro dissociation constant determined by isothermal microcalorimetry was used as a predictor of the complexation process *in vivo*.

Methods: A population approach was applied using NONMEM, to evaluate if the complexation between ORG25969 and rocuronium could be described best either under the assumption of instantaneous equilibrium between unbound rocuronium (steady state model) or by assuming hysteresis between the association of rocuronium to, or dissociation from, the ORG25969-rocuronium complex (dynamic model). First, a PK-PD model for rocuronium alone was developed. After fixing the parameters of this model to the individual-specific posthoc estimates, both interaction models were optimized using data from a phase I study, in which 10 male subjects received 0.1-8 mg/kg ORG25969 3 minutes after 0.6 mg/kg rocuronium. Subsequently, the models were applied to predict the observed change in rocuronium-induced NMB after ORG25969 administration. The model with the greatest predictability was further validated using a predictive check of another study (n=99), in which ORG25969 (0-8 mg/kg) was administered 3, 5 or 15 minutes after 0.6 mg/kg rocuronium.

Results: As evaluated with a posterior predictive check, the dynamic interaction model describes the observed PK and PD data after administration of ORG25969 considerably better as compared to the steady state interaction model. Subsequently, external model validation with a predictive check confirmed that the optimized dynamic interaction model with the *in vitro* kd of 0.1 μM could adequately predict the observed increase in the total rocuronium concentration and reversal of rocuronium-induced NMB.

Conclusions: Model based evaluation showed that the reversal of rocuronium-induced NMB after ORG25969 administration is due to a rapid decrease in the unbound rocuronium concentration. As the model was validated on an external dataset, the model can be applied for simulation of clinically relevant questions, such as selecting the dose schedule for optimal reversal of rocuronium-induced NMB.

17. A Mechanistic Disease Progression Model for Type 2 Diabetes Mellitus and Pioglitazone Treatment Effects

Willem de Winter (1), Teun Post (1), Joost DeJongh (1,2), Richard Urquhardt(3), Ian Moules (3), David Eckland (3) and Meindert Danhof (1,2)

(1) LAP&P Consultants BV, Archimedesweg 31, 233 CM Leiden, The Netherlands. (2) Leiden University, Leiden / Amsterdam Center for Drugs Research, Division of Pharmacology, P.O. Box 9502, 2300 RA Leiden, The Netherlands. (3) Takeda Europe Research and Development Centre, Savanah House, 11-12

poster

Objectives: Type 2 Diabetes Mellitus (T2DM) is characterized by the progressive failure of pancreatic b-cells to compensate declining insulin sensitivity with increased insulin secretion. Traditional treatment options provide short-term relief, but the UK Prospective Diabetes Study has demonstrated that they typically fail to prevent the relentless progression of T2DM over the long term. Whereas T2DM progression continues over periods of years to decades, clinical trials of antidiabetic agents are usually restricted to timescales of weeks or months. This study aims to develop a population-based mechanistic model of T2DM disease progression that allows a more accurate and precise extrapolation of the results of clinical trials over periods pertinent to T2DM progression.

Methods: A population pharmacodynamic model was developed on the results of two Phase III, one-year efficacy studies comparing pioglitazone to metformin or sulphonylurea in mono-therapy in a total of 2408 newly diagnosed T2DM patients. Change in fasting plasma glucose and glycosylated hemoglobin was modelled as a cascading sequence. Data on insulin in the same subjects were used to model the homeostatic feedback relationships between fasting plasma glucose and insulin. This allowed a mechanistic description of T2DM progression and treatment efficacy in terms of insulin sensitivity and b-cell function, and a physiologically appropriate differentiation of the treatment effects of the various agents.

Results: The model yielded a satisfactory fit to the study data. It was found that sulphonylurea treatment resulted in an acute and pronounced reduction of glycemic levels that was counteracted immediately by a rapid deterioration of glycemic control due to on-going disease progression. In contrast, pioglitazone therapy showed a more gradual lowering of glycemic levels but subsequently maintained glycemic control at a constant level throughout the duration of the trial, reflecting the absence of disease progression. This was also reflected in lowered fasting insulin levels throughout the duration of the trial. Metformin also had a gradual onset of action but showed evidence of continuing disease progression.

Conclusions: This study shows that T2DM disease progression can be modelled more accurately with a mechanistic model approach based on the fasting plasma glucose - insulin homeostasis. It suggests that pioglitazone has a protective effect against T2DM progression in newly diagnosed T2DM patients, and may be better than currently available monotherapies in maintaining glycemic control over the long term.

19. A Bayesian design and analysis for dose-response using informative prior information

Michael K. Smith(1), Scott Marshall(2), John Huggins(2).

(1) Biostatistics and Reporting, PGRD Sandwich; (2) Clinical Sciences, PGRD Sandwich.

poster

Objectives: We wish to optimise the design of a dose-response trial and obtain good estimates of relative potency when information is available on a previous compound within the same drug class. Using Bayesian methodology this prior information can be used quantitatively in the design and analysis of the study. This allows us to bias randomisation towards the new compound and make accurate inferences about the magnitude of the relative potency with a small overall sample size.

Methods: An Emax model was used to describe the dose-response relationship of an existing drug. The estimates from this model were used to provide an informative prior which was used to optimise the design and analysis of a new study to establish the dose-response and relative potency of a related compound from the same drug class. The assumption is made that data from the previous trials and the new study are exchangeable. This can be assured by making the inclusion / exclusion criteria as similar as possible, but departures from this assumption can also be allowed for by increasing the sample size.

Results and conclusions: Simulation results show that a relatively modest overall sample size can yield very informative results about the magnitude of the relative potency using this approach. Biasing the randomisation from the existing drug towards the new compound (in the ratio 1:4) gives sufficient information about the new drug to be able to make decisions about the magnitude of the relative potency with very good precision. Type I and type II errors using this approach are very low. The bayesian approach also allows probabilistic statements about the magnitude of the effect - very useful in decision making. Departures from our assumptions increase the type I and type II errors, but these can be mitigated slightly by increasing the overall sample size in order to allow the study data to influence the posterior estimates. This approach has the potential to allow very efficient dose-response studies where prior information on a previous drug is available and is considered exchangeable with information from a new study.

21. Population Pharmacokinetics of Teicoplanin in Outpatient Home Parenteral Antibiotic Therapy (OHPAT)

E Lamont (1), AH Thomson (2,3), M Dawber (2), L Semple (4), E Bell (4), RA Seaton (4)

1 Pharmacy Dept, Gartnavel General Hospital, 2 Pharmacy Dept, Western Infirmary, 3 CAMS Division, University of Glasgow, 4 Brownlee Centre, Gartnavel General Hospital, Glasgow

poster

Introduction. The Outpatient Home Parenteral Antibiotic Therapy (OHPAT) service has been developed to manage infections in patients who require intravenous antibiotic therapy but do not require hospitalisation. Teicoplanin is a glycopeptide antibiotic with a long elimination half-life, which makes it ideal for outpatient use. Currently, it is administered three times per week but there are no established guidelines for the optimal dosage regimen to use in this setting.

Objectives. The aims of this study were to determine the population pharmacokinetics of teicoplanin from routine data collected from the OHPAT clinic and to develop dosage guidelines for clinical use.

Methods. Patients received loading doses of 15 - 25 mg/kg/day for three days followed by 15 - 25 mg/kg on Mondays, Wednesdays and Fridays. Teicoplanin concentrations were measured once weekly on Mondays and the dose was adjusted to maintain troughs of 20-30 mg/litre (deep seated infections) or 10-20 mg/litre (bacteraemia or cellulites). Population pharmacokinetic analysis was performed using NONMEM with FOCE interaction. One and two compartment structural models and additive, proportional and combined error models were compared. The following clinical factors were investigated for their influence on teicoplanin pharmacokinetics: age; sex; teicoplanin dose; albumin concentration; total body weight (TBW); ideal body weight (IBW); height; serum creatinine concentration. Creatinine clearance (CrCL) estimates obtained using the Cockcroft Gault (CG) equation [1] with TBW ($CrCL_{CGT}$), the CG equation with IBW ($CrCL_{CGI}$) and the Salazar Corcoran ($CrCL_{SC}$) equation [2] were also evaluated.

Results. The data set comprised 93 patients whose ages ranged from 15 to 94 years and weights from 43 to 146 kg. Fifty percent of the patients were >20% above their ideal body weights. Estimated $CrCL_{CGT}$ ranged from 17 to 195 (median 65) ml/min There were 471 teicoplanin concentrations ranging from 6.7 to 58.3 mg/L. The data were adequately described by a one-compartment model with proportional residual error. Preliminary covariate analyses identified a relationship between CL and $CrCL_{CGT}$ i.e. CL (L/h) = 0.533 x (1 + 0.01 x ($CrCL_{CGT}$ -65)) and had an IIV of 22%. Volume (L) = 95 x (1 + 0.00597 x (weight - 72)) with an IIV of 38%. Residual error had a cv of 13%.

Conclusions. This study has established a model to describe the pharmacokinetics of teicoplanin in OHPAT patients receiving 15 - 25 mg/kg three times a week. The model will be used to develop dosage guidelines to achieve target concentrations for this group of patients.

References

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23. Development and Evaluation of a Population PK/PD Model for Fc-OPG in Healthy Postmenopausal Women

Matthew L. Zierhut(1), Mark C. Peterson(2), Marc R. Gastonguay(3), Steven W. Martin(2), Paolo Vicini(1), Pirow J. Bekker(2), Donna Holloway(2), Philip T. Leese(4)

(1) Department of Bioengineering, University of Washington Box 352255, Seattle, WA, 98195-2255; (2) Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA, 91320; (3) Gastonguay Consulting LLC, Simsbury, CT, USA; (4) Quintiles, Lenexa, Kansas, USA

poster

Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissue. This leads to increased bone fragility and risk of fracture, particularly of the hip, spine and wrist. Osteoprotegrin (OPG) is a promising alternative medication for osteoporosis. It is a member of the tumor necrosis factor (TNF) family, and works to decrease bone resorption by inhibiting osteoclast differentiation through the RANKL/RANK/OPG pathway. We describe the development of a PK-PD model for the fusion protein, Fc-osteoprotegrin (Fc-OPG), in healthy postmenopausal women. The model describes data from 8 cohorts (n = 13 subjects/cohort; OPG:placebo = 10:3) classified by dose level (0.1, 0.3, 1.0, or 3.0 mg/kg) and route of administration (intravenous (IV) or subcutaneous (SC) injection). OPG serum concentrations following IV or SC administration and urinary N-telopeptide (NTX) levels were available. The model was developed in a stepwise fashion and results in an adequate fit to the data with physiologically plausible parameter estimates. Model robustness was tested via a posterior predictive check with the model performing well in almost all cases. Clinical trial simulations with the model clearly showed that 2 weeks after a single 3 mg/kg SC dose, Fc-OPG produces a median urinary NTX percent change (w.r.t. baseline) of 45% (with a 95% confidence interval ranging from 34 to 60%). Simulations were evaluated using local and global sensitivity analysis methods. The model selection and simulation strategies we applied are rigorous, useful, and easily generalizable.

25. Propagation of population pharmacokinetic information using a Bayesian approach

Aris Dokoumetzidis and Leon Aarons

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK.

poster

Objectives: To investigate the propagation of population pharmacokinetic information across clinical studies by applying Bayesian techniques. The aim is to summarize the population pharmacokinetic estimates of a study in appropriate statistical distributions in order to use them as Bayesian priors in consequent population pharmacokinetic analyses.

Methods: Various data sets of simulated and real clinical data were fitted with WinBUGS, with and without informative priors. The posterior estimates of fittings with non-informative priors were used to build informative priors and the whole procedure was carried on in a consecutive manner. The estimates of fittings with informative priors where compared with meta-analysis fittings of the respective combinations of data sets. Also, approximate estimates of the population parameters were calculated by applying the Bayes theorem directly on the posterior distributions of the population parameters obtained by fittings with non-informative priors.

Results: Good agreement was found between the fittings with informative priors and the respective meta-analysis fittings, for the simulated datasets. Agreement was found not only on the population parameter estimates but also on the respective precisions. Also, reasonable agreement was observed in the clinical data, for most model parameters. Further, the computational times were much smaller for the prior method compared to the meta-analysis, due to the large datasets used with the latter.

Conclusions: The results of a population pharmacokinetic analysis may be summarized in Bayesian prior distributions that can be used consecutively with other analyses. The procedure is an alternative to the meta-analysis and gives comparable results. It has the advantage that is much faster than the meta-analysis, and can be performed when the summarized data are not actually available.

27. Characterization of Cortisol Circadian Rhythm and Lack of Cortisol Suppression by a New Corticosteroid, Ciclesonide

M. Pfister, S. Krishnaswami, S. Rohatagi
Aventis Pharmaceuticals, Bridgewater, New Jersey
poster

Objective: Ciclesonide (CIC) is a new inhaled glucocorticoid for the treatment of asthma that is converted into the active metabolite desisobutyryl-CIC (des-CIC) in the lungs. Study objectives were to characterize the circadian rhythm of endogenous cortisol release and to quantify the effect of systemic des-CIC concentrations on the endogenous cortisol release.

Methods: Demographic and pharmacokinetic/pharmacodynamic data from 12 Phase I and 3 Phase III studies in adults and 2 Phase III studies in pediatrics (ex-actuator dose: 40-2880 μg) were pooled for population analysis by NONMEM. Des-CIC concentrations were evaluated using one or two compartment models with appropriate covariates. Endogenous cortisol concentrations were characterized by various models such as the cosine model and a modified one-compartment model with first order elimination and first order input. The potential effect of des-CIC on the circadian rhythm of endogenous cortisol release was evaluated using dose and AUC as covariates and applying the E_{max} model.

Results: There were 635 subjects in this analysis with 5238 and 4470 observations recorded for des-CIC and cortisol concentrations, respectively. A one-compartment model with first order absorption adequately described the des-CIC concentration-time profile. A simple one-compartment model with first order absorption, an endogenous "pre-dose" cortisol concentration at dose-interval and a lag-time based on a fixed, hypothetical cortisol dosing time of 10 PM could adequately characterize the circadian rhythm of endogenous cortisol release and was superior to other models such as the cosine model. The doses of CIC (up 1280 μg) and the AUC were not significant covariates for cortisol concentrations suggesting negligible effects on endogenous cortisol concentrations. Using an E_{max} model, an EC_{50} of des-CIC of 1.96 ng/mL was estimated. Less than 1% of all observed des-CIC concentrations are higher than the EC_{50}, indicating a negligible effect of des-CIC on cortisol concentrations.

Conclusion: The novel one-compartment model adequately described the cortisol rhythm and des-CIC has a negligible effect on endogenous cortisol concentrations in adults and pediatrics at therapeutically relevant doses.

29. Population pharmacokinetic analysis of concentration data after implantation of sirolimus-eluting Bx Velocity stent in patients

V. Piotrovsky(1), G. Kopia(2), G.W. Vetrovec(3), D. Rizik(4), David Snead(2)

(1)J&J Pharmaceutical Research & Development, Beerse, Belgium; (2)Cordis Corporation, Warren, NJ; (3)MCV Hospitals at VCU Health Systems, Richmond, VA; (4)Scottsdale Heart Group at Scottsdale Health Care, Scottsdale, AZ

poster

Objectives: The Bx Velocity, sirolimus-eluting balloon-expandable stent has shown remarkable results in terms of reducing the occurrence of in-stent restenosis following coronary intervention. The current work was aimed to elucidate the sirolimus (SL) pharmacokinetics in patients with *de novo* coronary artery lesions.

Methods: Two PK trials were conducted in the United States (19 patients) and in Japan (20 patients). After implantation of one or two stents (149.4 - 177.7 mcg SRLM/stent), blood samples were collected serially and assayed for SL using a validated liquid chromatography method. NONMEM V software and the first-order conditional estimation method was used to fit mixed-effects models to concentration-time data.

Results: The structural model was based on animal data and mechanistic considerations. It assumed two-compartment (CMT) linear disposition of SL and included also the stent CMT and the artery tissue CMT. The fraction F of the total drug amount is released from the stent CMT to the blood stream. The rate is controlled by the rate constant K_{sb} (h^{-1}). The rest of the drug (1-F) is released to the artery tissue with the rate constant K_{sa} (h^{-1}). From the artery the drug is transferred to blood (K_{ab}, h^{-1}). Other parameters are listed below:

CL: Total blood clearance, L/h
V_c: Volume of the central CMT, L
V_p: Volume of the peripheral CMT, L
Q: Inter-CMT exchange flow, L/h

The model provided a good fit. Structural PK parameters were well defined. In a typical patient of 77 kg body weight, CL was 1.3 L/h (5.3) and Q 0.67 L/h (20), both increased with body weight. In parentheses standard errors of estimates expressed as % CV are given. K_{sa} differed between studies: it was 0.0039 h^{-1} (12) and 0.0064 h^{-1} (8) in the US and Japan studies, respectively. The remaining parameters did not depend on patient characteristics: V_c was 0.22 (20), V_p 59 L (27), F 0.091 (18), K_{sb} 0.051 h^{-1} (11), and K_{ab} 1.8 h^{-1} (15), respectively. Random inter-individual variability could be estimated in CL (18% CV), V_c (49), V_p (86), and Q (34) only. SL terminal half-life ($T_{1/2}$) was assessed *via* simulation using individual Bayesian parameter estimates. It was found to be substantially longer (210 and 150 h in the US and Japan studies, respectively) than after oral SL administration (62 to 82 h, literature data).

Conclusion: SL-eluting stent releases more than 90% of the drug directly to the artery tissue, and $T_{1/2}$ is controlled by the release rate. As predicted by the model, at 168 h since implantation (the last sampling time), approx. 50% of SL still persists in the artery.

31. Population pharmacokinetics of a new anticoagulant drug in clinical development

K.H. Liesenfeld, EU. Gräfe-Mody, A. Staab, H.G. Schaefer
Boehringer Ingelheim Pharma GmbH & Co. KG
poster

Objectives & Background: A population pharmacokinetic model for an intravenous anticoagulant drug in clinical development that acts as a direct factor IIa and Xa inhibitor was to be developed based on available data from healthy subjects. The model development should include an initial screening for covariates that might influence the pharmacokinetic properties of the drug substance. The purpose of the final model was to simulate and evaluate various scenarios (different dosing schedules, changes in pharmacokinetic parameters) for the further clinical development.

Methods: Pharmacokinetic profiles of 95 subjects from three studies (short and long term infusions with and without loading doses) with 1842 plasma samples were analysed. Sampling for pharmacokinetics was performed before start of infusion, during infusion and serially up to 80 hours after start of infusion. The demographic characteristics age, weight, height and body surface area (BSA) as well as creatinine clearances were to be tested as covariates on the pharmacokinetic parameters. The distribution of the demographic characteristics was narrow due to the inclusion criteria of the studies.

Results: The plasma concentration time profiles were best described by a 4-compartment model with first order elimination from the central compartment. The typical estimates of clearance (CL) and volume of the central compartment (V1) were 8.1 L/h and 10.0 L, respectively. The volumes of distribution for the peripheral compartments (V2, V3, V4) ranged from 12.4 L to 13.6 L and the corresponding intercompartmental clearances (Q2, Q3, Q4) from 21.4 to 0.691 L/h. Interindividual variability included in CL, V1, V2 and Q2 was low to moderate (21.9 to 43.7%). CL and thus steady-state concentrations were not influenced by any covariate investigated. Age and height were found to have a statistically significant influence on V2. However, the impact on the plasma concentration time profile was negligible.

Conclusion: A pharmacokinetic model based on all available phase I data is available to simulate and evaluate the influence of dosing schedules and changes of pharmacokinetic parameters (e.g. CL) on the pharmacokinetic profiles of the anticoagulant drug. Steady-state plasma concentrations in healthy subjects are not influenced by age, weight, height, body surface area, or creatinine clearance. However, this finding has to be confirmed in patient populations that will probably exhibit much wider distributions of the covariates tested so far.

33. Population Pharmacokinetic Analysis of Trastuzumab (Herceptin) following Long-Term Administration Using Different Regimens.

Jean-Eric Charoin(1), Philippe Jacqmin(2), Ludger Banken(3), Sian Lennon(4) and Karin Jorga(1)
(1) Clinical Pharmacology, F. Hoffmann-La Roche, Basel; (2) Exprimo Consulting LLP ; (3) Biostatistics, F. Hoffmann-La Roche, Basel; (4) Clinical Pharmacology, F. Hoffmann-La Roche, Welwyn
poster

Objective: To investigate trastuzumab pharmacokinetics and to assess the effect of covariates after long term trastuzumab administration using two different dosing regimens in patients (once weekly and every three weeks).

Material and Methods: Four Phase II/III studies, two with once weekly (loading dose of 4 mg/kg, maintenance dose of 2 mg/kg) and two with every three weeks (loading dose of 8 mg/kg, maintenance dose of 6 mg/kg) administration, were included in the database. In these studies, trough and full concentration-time profiles were collected. In total, 194 patients contributed to 2508 trastuzumab concentrations. A population pharmacokinetic analysis was conducted and individual Empirical Bayesian estimates of trastuzumab clearance, volume and distribution rate constants were estimated. The influence of demographic and clinical characteristics on clearance (CL) and central volume (Vc) were examined using the forwards selection and backwards deletion. For population pharmacokinetic analysis, NONMEM (version V) was used. Simulations were performed with Pharsight Trial Simulator (version 2.1.2). A bootstrap resampling technique (dataset replicated 800 times) was used to estimate confidence interval for the parameters.

Results: A two compartment linear PK model best described the data. Basic population PK parameters were: CL of 0.226 L/day (90% CI was 0.212-0.242), Vc of 3.17 L (90% CI was 3.05-3.32).
Trastuzumab CL increased significantly in patients with higher body weight. The drug regimen had no significant effect on trastuzumab CL and Vc. Based on individual post-hoc estimates, the median steady state AUCs over a period of 3 weeks were 1677 and 1793 mg*day/L, for once weekly and every three weeks regimens, respectively.

Discussion and Conclusion: PK parameter estimates were similar to the ones obtained in a previous population PK analysis performed by Genentech [1]. There was no effect of dosing regimen on trastuzumab PK parameters. The half-life of equilibrium was 26.3 days, which might be the basis for an every three weeks regimen. Trastuzumab CL depended on body weight, which is consistent with the medical practice to adjust the dose on body weight.

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35. Esmolol Population Pharmacokinetics in Critically-ill, Pediatric Patients

JS Barrett (1,4), A Zuppa (1,3), M Schreiner (5) and PC Adamson (1, 2, 4)

(1) Division of Clinical Pharmacology; (2) Division of Oncology; (3) Division of Critical Care Medicine, The Children's Hospital of Philadelphia, (4) Pediatrics Department, College of Medicine, The University of Pennsylvania, (5) Children's Clinical Research Institute, Philadelphia, PA

poster

Introduction: Esmolol has recently been studied in two clinical trials from which population pharmacokinetics have been derived: ETHIC, "Esmolol In Pediatric Patients Undergoing Treatment of Hypertension in Infants and Children After Surgical Repair of Coarctation of the Aorta" and ESCAPE, "Esmolol In Pediatric Patients with Supraventricular Arrhythmias."

Objectives: To describe esmolol pharmacokinetics in pediatric patients via population PK modeling and identify covariate, demographic and clinical factors that are important predictors of variability in esmolol PK parameters.

Methods: The ETHIC trial contained 107 patients: 22 newborns, 42 infants, and 43 children at doses of 125, 250, or 500 µg/kg/min after receiving a 125, 250, or 500 µg/kg respective bolus over 10-20 seconds. ESCAPE contained 34 patients, 3 to 17 years of age administered esmolol as a loading dose of 1000 mg/kg, immediately followed by an infusion of 300 mg/kg/min for 15 minutes. Dosing, covariate and PK data were merged across study and the final population PK database was comprised of 135 individual patients and 552 plasma esmolol concentration observations. Data was analyzed with NONMEM version 5 on a PC platform (Pentium IV; 2.6 GHz processor).

Results: The structural model was a two-compartment linear model with staged zero-order infusions. Inter-individual random variability was described by exponential variance for clearance (CL) and volume of distribution (Vd). Residual random variability was described by a combined additive and proportional variance model. Base model diagnostic plots revealed a large degree of unexplained variability. When an allometric model (fixed exponent of 0.75 for CL) was used to describe the change in PK parameters as a function of body weight, a significant improvement was evident. Race, sex, and age were also explored individually as covariates on clearance and volume. Population estimates of clearance and volume estimates were 10.2 L/hr and 9.96 L, which is similar to historical data on esmolol in pediatric populations.

Conclusions: The pediatric population PK model provided a robust description of esmolol PK across a wide range of ages (0.01 - 16.7 years) and body weights (2.6 - 114.1 kg). Model predictions were consistent with a linear, time-independent system. Newborns and infants appear to clear esmolol faster than children greater than 1 year of age. Clearance in children greater than 1 year of age is similar to that observed in adults.

37. Learning about Covariate Relations in the Patient Population Based on Data from Multiple Studies - Consequences of Different Approaches

Jakob Ribbing and E. Niclas Jonsson
Division of Pharmacokinetics and Drug Therapy, Uppsala University
poster

Identification and quantification of covariate relationships is an important part of population pharmacokinetic/pharmacodynamic modelling and is usually based on data from a single study. However, the individuals in a clinical study are merely a sample from, and may not faithfully reflect the underlying patient population. Thus, basing covariate selection on data from a single clinical trial may lead to false covariates being included in the model (type-I error), true covariates being omitted (type-II error) and to estimated coefficients being biased due to data-driven selection of covariates (selection bias). Overall this will have negative consequences on the predictive performance of the model. (1)

In this simulation study we investigate to what extent different approaches to covariate identification lead to lower type-I and II errors, less biased estimates of the covariate coefficients and better overall predictive performance.
The approaches examined include:
1. analysing the most recent dataset independently of any previous dataset(s)
2. merging all available datasets into one
3. estimating the model hypothesized from a previous dataset on the most recent.

Six covariates were sampled with replacement from an empirical distribution containing 1492 patients (2). For each replicate, three PK datasets were simulated using a one-compartment model with first-order absorption and a multivariate-linear-covariate model on typical value of clearance (TVCL). The first and second dataset contained 200 subjects in total. The third dataset consisted of 1000 subjects and was used only to assess the predictive performance on individual TVCL. The first and second datasets were analysed according to the different approaches and the results were compared.

The initial results show that the data-driven approaches all suffer from selection bias in situations where the power of identifying the correct covariate(s) is low. The approach of estimating on the second dataset the model hypothesized from the first dataset is non-data driven and thus produces estimates without selection bias. In situations where selection bias has substantial impact on the predictive performance this approach is considerably better than not using the first dataset at all. However, in all situations examined the approach of merging the two datasets, although producing somewhat biased estimates, performed the best in terms of predictive performance.

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39. Simultaneous fit of competing models as a model discrimination tool in Bayesian analysis

L.E. Friberg, C. Dansirikul and S.B. Duffull

School of Pharmacy, University of Queensland, Brisbane, Australia

poster

Objectives: The most common method to discriminate between nested models in frequentist analyses is the likelihood ratio test with some predefined level of significance. In addition to dichotomous model discrimination decisions, estimation methods, such as Markov chain Monte Carlo (MCMC), that are based on simulation platforms also allow for model discrimination to be based on predictive or posterior distributions. When using MCMC, competing models can be fitted simultaneously as a joint model with an added parameter to indicate which model is preferred.[1,2] Quicker mixing has been found when competing models were linked with a common residual error.[1] Here we examined the use of this approach to discriminate between population pharmacokinetic models.

Methods: Data sets, with 20 individuals in each, were simulated from 1- and 2-compartment models in MATLAB. The two competing models were simultaneously fit in WinBUGS as a mixture model with a mixing population parameter drawn from a uniform distribution. The posterior odds that one model was preferred over the other was calculated based on computation of the expectation of the mixing parameter. The mixture model was fit with both common and independent residual variances as well as with informative and low-information priors on the model parameters. The methodology was then applied in two examples, for citalopram and sirolimus.

Results: For all simulated data sets the mixing parameter supported the true model. The posterior odds were similar with and without a common residual variance. Parameter estimates for the true model were closer to the nominal simulation values when the models were not constrained to have a common residual variance, but chain mixing was slower. The posterior odds for the true model were higher and the autocorrelations lower with informative priors than with low-information priors. The mixing parameter showed that the 1-comparment model was preferred for the citalopram data (posterior odds=52) while the 2-compartment model was preferred for the sirolimus data (posterior odds=8.0).

Conclusion: Analysing two competing models simultaneously with a mixing parameter seems to be a promising tool for model discrimination in WinBUGS which can be performed on-the-fly.

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41. Comparison of sumatriptan and naratriptan using a markov model approach

Hugo Maas, Meindert Danhof, Oscar Della Pasqua
LACDR, Leiden University, Division of Pharmacology
poster

Triptans (such as sumatriptan and naratriptan) are efficacious and specific medications in the treatment of migraine. Yet, assessing clear pharmacokinetic-pharmacodynamic (PK-PD) relations for these drugs is difficult. In most clinical studies the actions of triptans in the trigeminal system are measured indirectly using pain-rating scales. As a consequence , sources of variability originating from the multiple levels of pain control are added to the original trigeminal signal. Furthermore, little is known about the kinetics of pathophysiological mechanisms involved in migraine, which complicates the design of predictive mechanism-based models.

In principle a PK-PD model for triptans should be based on a set of physiologically meaningful parameters. The facts that little information on the disease is available and that the endpoint is a categorical variable, impose that the model be stochastic. A class of structural models that provide these features are the hidden Markov models.

To test the hidden Markov model concept, a model was developed to describe the course of a single migraine attack treated with either sumatriptan or naratriptan. It consists of two layers: i) a hidden layer representing the (unobserved) states of trigeminal activity and ii) an observational layer that transforms trigeminal activity into a headache score. The parameters in the first layer of the model include the elements of the intensity matrix, which can be considered rate constants of the trigeminal activation process. Triptan plasma concentrations act as covariates increasing the forward transition rates. The headache scores returned by the observational layer are multinomially distributed conditional on the unobserved state. The parameters in this layer are the elements of the emission matrix, reflecting the influence of pain control processes on the trigeminal pain signal.

The model estimates disease-related parameters (transition rates and score probabilities) and drug-related parameters (EC50 and Emax). In this study, parameter estimates obtained from analysis of sumatriptan data are compared with those obtained from analysis of naratriptan data.

43. An example of application of the population approach to toxicological studies.

F. Fiorentini (2), M. Simeoni (1), I. Poggesi (2), G. Westerberg (2), M. Rocchetti (2)

(1) Dipartimento di Informatica e Sistemistica, Pavia University, Pavia, Italy. (2) Global Drug Metabolism, Pharmacia, Nerviano, Italy

poster

Usually, pharmacokinetic information is obtained from satellite groups of animals during toxicological studies. This approach provides a characterization of the toxicological findings only in relation to the average estimates of the systemic exposure (typically C_{max}, t_{max}, AUCs) in the satellite groups. In this way, the individual toxicological observations remain difficult to interpret in absence of a direct comparison with the exposure of the main study animals. A sparse sampling design together with a population analysis could however allow merging the individual toxicological observations with the corresponding estimate of the systemic exposure in the same animal. This allows a considerable expansion of the degree of information obtainable from the toxico-pharmacokinetic profile of the compound and, in addition, could provide reduction of costs in the subsequent phases of development.

An example of a real application of this kind of approach is provided here. Three typical studies that constitutes part of a toxicological program of a new intravenous anticancer drug were considered: an acute study after single administration, a short term study (7 days repeated administration) and a cyclic dose study. The data were analysed by using a 2-compartment model with elimination from the central compartment and a model of errors including random effects and fixed effects for gender, dose and cycle. The results compared with those obtained with more traditional approaches confirmed the adding value of the population analysis.

45. Modeling the complex pharmacokinetic profiles of cyclosporin and of mycophenolate observed in the early post-transplantation period.

Annick Rousseau, Aurélie Prémaud, Pierre Marquet
Department of Pharmacology and Toxicology, University Hospital, Limoges, France
poster

Background: In the early post-grafting period, the pharmacokinetic profiles of immunosuppressive drugs are complex. The time-blood concentration curves of cyclosporine (CsA) frequently exhibit delayed absorption and secondary peaks. Complex absorption profiles and time-dependent clearance were reported for mycophenolate (MPA), whose pharmacokinetic profiles also frequently present multiple peaks. Clinical evidence advocates for the rapid achievement of sufficient and stable exposure of these drugs in the early post-transplantation period, which may require dose adjustment based on pharmacokinetic modeling (1).

Objectives: To develop a pharmacokinetic model able to fit the complex pharmacokinetic profiles of CsA (Neoral(r)) and MPA (Cellcept(r)) in the early post-grafting period in renal transplant patients.

Methods: Pharmacokinetic evaluation was performed in 20 patients who had undergone de novo renal transplantation and received an immunosuppressive therapy including corticosteroids, MPA (Cellcept(r)) and CsA (Neoral(r)). In each patient, 11 blood samples were collected on the 3rd day of treatment, immediately before (T0) the morning dose and 0.33, 0.67, 1, 1.5, 2, 3, 4 6 9 and 12 hours after dosing. The pharmacokinetic analyses were performed using nonlinear mixed effect modeling with the NONMEM program version V (2) through the Visual-NM graphical interface (3).

Results: The different profiles of CsA could be adequately described using a model taking into account a discontinuous absorption (4). Briefly, this model assumes that (i) absorption from the stomach is negligible; (ii) a given oral dose is absorbed sequentially in two portions, (iii) at the same absorption site (i.e. a gut compartment). So, after oral administration a first fraction (f) of the dose is transferred from the stomach to the gut while the transfer of the remaining fraction (1-f) is delayed. This is described by first-order processes with lag-times, whereas absorption from the gut compartment is described by a first order rate constant. Six patients presented pharmacokinetic profiles with two peaks, while the 14 others had apparently a single, sometimes delayed and wide peak. A one-compartment model with first order elimination in association with the double absorption model best fitted the data, as shown by a highly significant decrease in the objective function (OF) (110 points less than with one- or two-compartment models with first-order absorption and a lag time). Residual variability consisted in a combined additional and proportional error of respectively 21 µg/L (close to the analytical limit of quantification of 20 µg/L) and 13.1%. The First-Order Conditional Estimation (FOCE) interaction method was used.

For mycophenolate, a two-compartment model with first order elimination in association with the double absorption model better fitted the kinetic data (OF = 398) than an absorption model based either on a first order process with lag time (OF = 450) or on Weibull distribution (OF = 436). However, the residual variability remained fairly high, consisting in a combined additional and proportional error of respectively 0.6 mg/L (i.e. 6 time the limit of quantification) and 18 %. Interestingly, in the only previously reported population pharmacokinetic study of MPA, few structural pharmacokinetic models including non-linear absorption processes were tested, i.e. the *E*max model, Weibull function and a dual, sequential first-order absorption process. The authors concluded that these models did not improve the fit as compared to a two-compartment model with first order absorption with a lag-time and first-order elimination (5).

Conclusion: The pharmacokinetic model developed in the present study is suitable for the analysis of CsA population pharmacokinetics in the first days after renal grafting. It reliably described the pharmacokinetics of cyclosporine whether a double peak was present or not on the concentration-time profiles. For mycophenolate, this multi-exponential absorption model provided a better fit than the other models tested,

though improvements are still needed. The influence of covariates, enterohepatic circulation and of a potential timedependentelimination process are still to be investigated.

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47. Modeling the occurrence of orthostasis using a longitudinal logistic regression model

Vermeulen, An; Piotrovsky, Vladimir and De Ridder, Filip

Advanced PK/PD Modeling & Simulation, J&JPRD

poster

Introduction: A new drug candidate in development was associated with an increased risk to develop orthostasis at the start-up of therapy. Orthostasis was defined as a drop in systolic blood pressure of more than 20 mmHg when changing posture from supine to standing. This side effect was especially predominant in healthy volunteers, and was less common in the target patient population. It was postulated that the rate of change in plasma concentrations could explain this finding. Therefore, a slow release formulation (SR) was developed such that the rate of change in plasma concentrations was substantially decreased, but C_{max} remained similar, i.e. T_{max} occurred at a much later time point than for an oral solution (~22h versus ~2h). Subsequently, two clinical trials were designed, a single dose trial in healthy volunteers, and a multiple dose trial in patients to proof the concept.

Objectives: The objectives of the current analysis were:
to model the pharmacokinetics (PK) of the compound after administration of an oral solution and a SR formulation to healthy volunteers and patients;
to model the incidence of orthostasis as a function of plasma exposure;
to check the robustness of the model by performing a posterior predictive check.

Methods and results: Two population PK models were developed using NONMEM software: one for the oral solution and the other one for the SR formulation. The two-compartment models only differed in their absorption parameters (lag times, duration of the zero order input and absorption rate constants), whereas apparent oral clearance, intercompartmental flows and apparent volumes of distribution were shared parameters in the two models.

Model predicted individual empirical Bayes estimates of basic PK parameters were obtained, and used as input in the longitudinal logistic regression model. The probability to develop orthostasis at each time point was estimated. The population PK/PD model contained a baseline model, a placebo model and a drug effect model. The drug effect model was an E_{max}-type model, characterized by an EC_{50}, a Hill coefficient, E_{max}, and an additional parameter describing the tolerance.

The final population PK/PD model was used consecutively to perform posterior predictive checks on the two trials.

49. Population PK and PK/PD Analyses of an Enzyme Inhibitor in Healthy Volunteers

B. Mc Hugh, N. Frey

Clinical Pharmacology, F. Hoffmann-La Roche, Basel, Switzerland

poster

Objectives: To develop a structural PK model and a structural PK/PD model in healthy volunteers.

Methods: Single doses of 10, 25, 50, 100, 200, and 400 mg were administered to 48 healthy volunteers. Data consisted of 16 plasma enzyme inhibitor concentration and enzyme activity measurements between dosing and 30 hours. A NONMEM population analysis to describe the PK commenced with a simple model and progressed with adding complexity. A NONMEM population analysis to describe the PK/PD relationship was implemented by considering effect-compartment, indirect effect, and slow-binding models (Äbelö, et al.). Since the baseline enzyme activity was observed to vary greatly, pre-dose enzyme activity was treated as a covariate for each volunteer.

Results: A two-compartment model with first order absorption and a combination of first order and Michaelis-Menten elimination adequately described the PK. The First Order (FO) method of NONMEM was used. The multiplicative error component had a standard deviation near 17% and the additive component was three times the limit of quantification. With the exception of Michaelis-Menten constant and the metabolism velocity, the PK parameters were well-estimated (standard error < 30%). No bias was observed when the individual weighted residual error was depicted versus either time or predicted concentration. After a time lag estimated to be 0.24 [h], the absorption was rapid (k_a= 9.3 [h^{-1}]). Complete metabolic saturation resulted in a total clearance one third lower than its maximum value (the first order clearance was estimated to be 31 [L/h]; the Michaelis-Menten constant and maximum metabolism velocity were estimated to be 272 [mg/L] and 4.5 [mg/h], respectively). Regarding the population PD parameters, the slow-binding model, i.e., a slow dissociation of the drug from the enzyme, best described the PK/PD of the drug. The FO method of NONMEM was used, no bias was observed, and the parameters were well estimated (standard error < 10%). The estimated rate constants for enzyme deactivation and subsequent activation were 0.075*C [h^{-1}] (C [mg/L] is the inhibitor concentration) and 0.85 [h^{-1}], respectively. In all cases other than very low drug concentrations, the binding rate to the enzyme was predicted to be much faster than the dissociation rate.

Discussion/Conclusion: This present PK model with a Michaelis-Menten component of elimination is consistent with the existing knowledge of the drug, i.e., there is a high likelihood to saturate a metabolic pathway. The poorly estimated Michaelis-Menten parameter and the metabolism velocity can be attributed to the small study population. The preliminary structural PK and PK/PD models in healthy volunteers will be enhanced as additional study information becomes available and will facilitate the analysis of data from patients.

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51 Application of Population Pharmacokinetic Analysis for Quantification of in vivo Binding Properties in the Rat Brain by Positron Emission Tomography

C. Lia Liefaard (1), Bart A. Ploeger (1,2), Carla F.M. Molthoff (3), Ronald Boellaard (3), Adriaan A. Lammertsma (3), Meindert Danhof (1,2), Rob A. Voskuyl (1,4)

(1)Division of Pharmacology, LACDR, Leiden University, Leiden, The Netherlands; (2)LAP&P Consultants BV, Leiden, The Netherlands; (3)PET Center, VU University Medical Center, Amsterdam, The Netherlands; (4)Epilepsy Institute of The Netherlands, Heemstede, The Netherlands

poster

Objectives: Changes in $GABA_A$ receptor density and affinity play an important role in many forms of epilepsy. Using Positron Emission Tomography (PET) receptor binding properties, maximum binding capacity (B_{max}) and receptor affinity (K_D) of specific $GABA_A$ ligands (e.g. Flumazenil, FMZ), can be determined non-invasively. A novel full saturation approach is presented, which, in contrast with presently available methods, allows simultaneous estimation of B_{max} and K_D from a single PET-study, using population analysis.

Methods: Following a saturating intravenous injection of [11C]FMZ, the concentration time curves of FMZ in brain (using PET) and blood (using HPLC-UV) were measured. The data were analysed with NONMEM. The structural PK model consisted of a 4-compartment model, containing a blood, a tissue and 2 brain compartments: Brain Free and Brain Bound. In the model the total FMZ concentration in the brain as measured by PET, reflects the sum of the concentrations in the Brain Free and the Brain Bound compartment. All exchanges between compartments are described using first order rates. Specific binding is dependent on both the concentration of free ligand and the concentration of receptors available for binding. The PK model includes inter-individual (IIV) and inter-occasion (IOV) variability in the volume of distribution of the brain (VBr). The residual error was assumed to be proportional to the concentration in blood and brain. Finally, a residual error was added to take into consideration the greater uncertainty in blood concentrations that are close to the detection limit. This residual variance was fixed to the square of half of the detection limit.

Results: Analysis of all data with the proposed model resulted in the precise estimation of all parameters, including the specific binding of FMZ in the brain, as characterised by B_{max} (32.7 ± 7.95 ng/ml) and K_D (10.1 ± 2.61 ng/ml). Variability in the positioning of the animals in the scanner resulted in variation in the location of the region of interest in the brain. This variation was successfully characterised by a significant variability (IIV and IOV, CV = 28.7%) in V_{Br}.

Conclusions: In conclusion a novel full saturation approach is reported, which allows simultaneous estimation of both B_{max} and K_D in a single experiment. This model will be used to assess changes in $GABA_A$-receptor properties in relation to progression of epilepsy.

53. Comparing efficacy of 10mg vs 20mg ARAVA in treatment of rheumatoid arthritis: A Population PK / PD Analysis

Willi Weber, Diether Rueppel, Heiner Speth
Aventis Pharma, Germany
poster

ARAVA is an isoxazole with immunosuppressive and anti-proliferate activity used for the treatment of rheumatoid arthritis. We investigated the relationship between ARAVA's active metabolite concentration at steady state, and the clinical responder rate classified according to the ACR20 [1] criterion and the Paulus criterion [2]. The pharmacokinetic and pharmacodynamic data of a 10 mg and a 20 mg dose group are investigated and compared in the light of the
-Drop out rate,
-The onset of efficacy,
-The concentration effect relationship, and
-The fraction of patients obtaining the full therapeutic potential of ARAVA after at least 23 weeks of treatment

Methods: We used the NONMEM software [3] with the FO method and a one-compartment PK-model with first order input. In a 2nd step we used a naive logistic model with steady state concentration as a predictor of clinical outcome observed after at least 23 weeks of treatment.

Results: Our results are summarized as follows:

- Drop out rate: In adult patients the rate of discontinuations was higher in the 10 mg group than in the 20 mg treatment group.
- Onset of efficacy: A tendency for an earlier onset of the effect of the treatment was found in the 20 mg dose group when compared to the 10 mg dose group.
- ACR20 criterion: Using a priori knowledge of the PK/PD relationship between C_{SS} as predictor variable and ACR20 as dependent variable, the individual estimates of the probability of success were more than 88% of the maximal ACR20 effect at concentrations above 24 mg/L.
- Paulus criterion: Using a priori knowledge of the PK/PD relationship between C_{SS} as predictor variable and the Paulus criterion as dependent variable, the individual estimates of the probability of success were more than 88\% of the maximal effect (Paulus criterion) at concentrations above 13 mg/L.

Conclusions:

1. In the adults, the observed higher rate of discontinuations in the 10 mg group may be interpreted as lack of efficacy in a larger fraction of RA patients than in the 20mg treatment group.
2. Using a loading dose of 100mg for the first 3 days followed by a 20 mg maintenance dose showed a trend of an earlier onset of efficacy than starting treatment with a single 100mg loading dose followed by 10 mg maintenance dose.
3. When rheumatoid arthritis is diagnosed, early aggressive treatment using a 20 mg daily maintenance dose should be more effective in avoiding irreversible joint destruction than using a 10 mg dose.

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55. Non-Linear Mixed Effects Models with Stochastic Differential Equations - Implementation of an Estimation Algorithm

R. V. Overgaard(1,2), E. N. Jonsson(3), C. W. Tornøe(4), H. Madsen(2)

(1) Pharmacometrics, Experimental Medicine, Novo Nordisk A/S, Denmark; (2) Informatics and Mathematical Modelling, Technical University of Denmark; (3) Department of Pharmaceutical Biosciences Uppsala University; (4) Experimental Medicine, Ferring Pharmaceuticals

poster

Objectives: Stochastic Differential Equations (SDEs) could potentially aid some parts of PK/PD modelling by better parameter estimates, as a diagnostic tool, to pinpoint model deficiencies, by incorporating true variations in the parameters, etc. These models offer a general intra-individual error structure, where the residuals are decomposed into dynamical noise from the SDEs and uncorrelated measurement noise. The focus of the present study is on two fundamental issues concerning the implementation of SDEs in non-linear mixed effects models. The first is how the likelihood function of non-linear mixed-effects models with SDEs can be approximated to facilitate estimation in these models. The second focus concerns identifiability: Can the inter-individual variability, the measurement- and the dynamical noise be separated?

Methods: The likelihood function was approximated by combining the First Order Conditional Estimation (FOCE) method used in non-linear mixed-effects models, with the Extended Kalman Filter (EKF) [1] used for SDEs. This aproximation was implemented in MATLAB for a non-linear mixed-effects model with SDEs corresponding to a one-compartment model. Several simulations of- and successive estimations with this model have been used to test the estimates produced by the proposed approximation of the likelihood function.

Results: Simulations confirm that the estimated dynamical noise is small when none is used in the simulations, such that only few type I errors are likely to occur. Other simulation studies demonstrate that the algorithm is able to detect a significant amount of dynamical noise when it is present in data (no type II errors), and that higher levels of dynamical noise do not produce higher estimates of the measurement noise or the inter-individual variability.

Conclusion: A novel approximation of the likelihood function was presented for non-linear mixed-effects models based on SDEs. It was confirmed that inter-individual variability, measurement- and dynamical noise can be separated, such that these models can be treated meaningfully.

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57. The cytochrome P450 3AP1 variant genotype shows correlation with the true clearance in a renal transplant population

John C Lukas(1), Martina Samiotaki(2), Maria Kontou(2), Rosario Calvo(3), Panos Macheras(1), Tasos Zografidis(3), Georgios Kyriakides(4)

(1) Laboratory of Biopharmaceutics and Pharmacokinetics, School of Pharmacy, University of Athens, Athens 15771, Greece, (2) Biomedical Sciences Research Center 'Alexander Fleming', Athens, Greece, (3) Department of pharmacology, School of Medicine, University of the Basque Country, Leioa, Spain, (4) Kyriakides transplantation center, Nicosia, Cyprus

Background. Cytochrome P450 3AP1 is important for the metabolism of sirolimus (SRL). Polymorphisms in the gene affect the production of the enzyme and hence possibly the pharmacokinetics of SRL. We attempt to resolve part of the observed variability in the ratio of the observed predose SRL concentrations (Cmin) relating it to the genotype as well as to the individual patient pharmacokinetic parameters.

Methods. Trough SRL blood concentrations (Cmin; n = 768) in renal transplant patients (n = 41), receiving combination SRL and cyclosporine for immune system suppression, were analyzed retrospectively. The promoter of the CYP3AP1 pseudogene was genotyped for polymorphisms. The association between the therapeutic surrogate Cmin/Dose and genotype was explored with standard methods and mixed effects models. A Bayesian method was used to resolve the patient specific pharmacokinetic parameters. The systemic clearance was regressed against the genotype, weight and sex as covariates in general additive models.

Results. A subgroup of 34 homozygotes (82.9%) and one of 7 heterozygotes (17%) were found. Mixed effects modeling of Cmin/ Dose showed a significant difference between the two subgroups in this variable (mean ± SD) (3.63 ± 1.17 [1000 x L] -1 and 2.86 ± 0.72 [1000 x L] -1, respectively; $p < 0.0001$) and insignificant effects for covariates weight and sex. A general additive model between individual CL and genotype resulted in a significant explanatory relationship ($p < 0.05$; F-test).

Conclusion. Polymorphisms in the CYP3AP1 gene appear to associate with different subpopulations of Cmin/Dose and of patient specific systemic SRL clearance. However, controlled prospective testing in much larger populations is needed to verify this result, preferably including haplotypic analysis with full pharmacokinetic population screens on the patients.

Day 2
Poster abstracts

2. Development and validation of a mechanism-based PK/PD model for the in vitro-in vivo prediction of QT prolongation by dofetilide

Daniel M. Jonker (1), Derek Leishman (2), Rob Wallis (2), Peter E. Milligan (2) and E. Niclas Jonsson
(1) Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Sweden, (2) Pfizer Global Research & Development, Sandwich Laboratories, Sandwich, Kent, UK
poster

Objectives: Drug-induced QT prolongation is an important biomarker for assessing the risk of heart arrhythmias and reflects blockade of the hERG potassium channel. The aim of the present work is to be able to predict the magnitude and variability of QT prolongation in patient populations from in vitro and preclinical studies. Dofetilide is a pure class III antiarrhythmic drug and as such an ideal starting point. In the present study, an integrated population PKPD model was developed for the action of dofetilide at the hERG potassium channel in vitro and in man.

Methods: A joint analysis was performed of 5 clinical studies, including 80 healthy volunteers and 17 patients with ischaemic heart disease. The affinity and activity of dofetilide was determined in recombinant cell cultures expressing the hERG potassium channel.
The analysis was performed in NONMEM in two steps. In the first step, the PK model was developed and covariates were identified in a semi-automated fashion. In the second step, the individually estimated dofetilide concentrations were used to drive the PD model. By including the in vitro dofetilide affinity in the operational model of pharmacological agonism, an estimate was obtained for the efficiency of the transduction from ion channel binding into the QT effect.

Results: A three compartment PK model with first-order absorption after oral administration characterized the time course of dofetilide concentrations well. Three covariates were identified by using stepwise forward selection followed by backward elimination at the 1% significance level: age for clearance, body weight for peripheral volume and body weight for clearance. Fridericia-corrected QT values were adequately described with the operational model including an effect compartment. Based on the in vitro affinity of 4.79 ng/ml, the transducer ratio was estimated at a value of 5, indicating the presence of a modest ion channel reserve. Upon chronic administration of dofetilide, tolerance was found to develop until a maximum was reached after four days.

Conclusion: In this work, the magnitude and variability of dofetilide-induced QT prolongation was estimated with a single mechanism-based PKPD model. This model will be extended to other compounds to explore its capability to predict the degree and variability of QT prolongation in a heterogeneous patient population from preclinical drug characteristics.

4. Population modeling of tumor growth inhibition in vivo: application to anticancer drug development

Simeoni M (1), Poggesi I (2), Germani M(2), De Nicolao G(1), Rocchetti M(2).
(1)University of Pavia, Italy; (2)Pharmacia Italia S.p.A., Nerviano, Italy
poster

Introduction: The in vivo evaluation of the antitumor efficacy of compounds in animal models is a fundamental step in the development of anticancer drugs. In these experiments, efficacy is expressed as percentage of decrease of the tumor weight in treated animals compared to control animals. We developed a minimal pharmacokinetic-pharmacodynamic model linking the dosing regimen of an anticancer agent to the tumor growth in animal models. The growth of tumors in non-treated animals (unperturbed growth) is described by exponential growth followed by a linear growth phase. The rate of tumor growth in treated animals (perturbed growth) is considered decreased by a factor proportional to both plasma drug concentrations and number of proliferating tumor cells. A transit compartmental system is used to model the delayed process of cell death. The parameters of the pharmacodynamic model are related to the growth characteristics of the tumor, to the drug potency and to the kinetics of the tumor cell death. Since the unperturbed and perturbed growths are measured in different groups of animals and considering that in this model the perturbed growth collapses into the unperturbed one in the absence of treatment, the simultaneous fitting of the two average growth curves was adopted for estimating the model parameters.

Aim: In this communication we report examples of the use of population approaches for modeling the outcome of these experiments. This would allow estimating the different sources of variability.

Methods: The examples refer to treatments with paclitaxel and an anticancer candidate synthesized as part of our discovery programs. Pharmacokinetics were described using 2-compartments open models with first order elimination from the central compartment. Tumor weights were modeled using the approach described above. The PK-PD model was implemented using NONMEM (v. V). For both PK and PD data inter-group and inter-animal variability were described using multiplicative models. Different models were used for describing the random error.

Results: The model fitted well the experimental data. The use of the population approaches allowed the identification of the PK-PD parameters and the description of the relevant sources of variability.

Conclusion: The use of the non-linear mixed effect model allowed the full exploitation of the capabilities of the PK-PD model of tumor growth. Since the model was proven effective also in predictive mode, based on the outcome of a preliminary experiment, stochastic simulations can be implemented for efficiently simulating the whole campaign of tumor growth inhibition studies for a novel anticancer agent.

6. Population Pharmacodynamic Analysis of QTc Prolongation vs. Plasma Concentration

Xuejun Chen, Al Corey, Suresh Mallikaarjun, Steve Bramer
Otsuka Maryland Research Institute
poster

Purpose: QT_c prolongation has been extensively investigated as a predictor of cardiac toxicity, and has been shown to correlate with plasma concentrations for some drugs. Exploratory analyses may indicate trends in QT_c prolongation as a function of plasma concentration but cannot account for covariate effects, high inter-individual variability and prediction of this relationship for new doses. The purpose of this study is to investigate the relationship between the pharmacokinetics and QT_c prolongation, using population-based techniques.

Methods: Data from 2 phase III studies were used for a population pharmacodynamic analysis using NONMEM. Based on the lack of hysteresis, and since the relationship between QT_c and concentration appeared to be stationary, it was decided that the QT_c - concentration relationship would be analyzed directly. The types of models to be evaluated were limited to those that reflect direct action (E_{max} type models, simple linear relationships). Different models and covariate effects were tested and compared in terms of the objective function and diagnostic plots.

Results: The best model, Sigmoid E_{max} with a Circadian Baseline, provided adequate fit to the pooled data. Baseline effect parameters (placebo dose) are consistent with literature. Baseline QT_c and gender have effect on baseline effect parameters. The typical values (% Relative standard error) for maximum possible effect (E_{max}, msec), concentration required to attain 50% of E_{max} (EC_{50}, µg/mL), exponent describing steepness of the effect-concentration curve (γ), Midpoint of the range of circadian fluctuation in QT_c (E_{avg}, msec), amplitude of the circadian fluctuation in QT_c, relative to E_{avg} (Amp, msec) and time of the maximum circadian deviation from E_{avg} (t_{circad},h) are 61.5 (23%), 4.72 (28%), 1.3 (8%), 381 (0.3%), 4.28 (9%) and 8.09 (3%), respectively. The value for E_{avg} was predicted by a combination of the subject's first QT_c measurement on study (BSF) and the subject's gender. Inter-subject variability was characterized for the key parameters except EC_{50} and was estimated to be approximately 27, 25, 2, 54 and 3 %CV for E_{max}, γ, E_{avg}, Amp and t_{circad} , respectively.

Conclusions: The model developed is suitable for the PK/PD analysis of QT_c prolongation. It accounts for covariate effects and inter-individual variability, which cannot be explained by a noncompartmental analysis.

8. A Population PK Model for Recombinant Factor XIII in Congenitally Deficient Subjects

Michael G Dodds(1), Paolo Vicini(1), Jennifer E Visich(2) and Mark Rogge(2)

(1) Department of Bioengineering, University of Washington, Seattle, Washington, USA (2) ZymoGenetics Inc., Seattle, Washington, USA

poster

Purpose: To develop a population pharmacokinetic model to describe the fate of recombinant FXIII-A2 (rA2) subunit administered to patients congenitally deficient (CD) in Factor XIII A2 subunit. The model incorporates the rate and extent of complexation of recombinant A2 (rA2) with available endogenous FXIII-B subunit to form the heterotetramer, rA2B2. Circulating FXIII is activated by calcium and thrombin, and the A2 subunit is liberated, activated and is responsible for cross-linking fibrin and stabilizing clots.

Methods: Previously, a three-compartment, nonlinear population PK model was implemented in NONMEM V, and then used to analyze data from randomized, double-blind, placebo controlled Phase I studies of rA2 in healthy volunteers. Immunoassay data included plasma levels for FXIII activity and A2B2, total A2 and free B concentrations. This model was extended to include a genetic covariate (FXIII A subunit deficient or normal) and differences in assay matrix composition. Phase I studies in CD subjects were then assessed using this model.

Results: The half-life of FXIII was found to be similar in healthy volunteers and CD subjects. Endogenous production rates of FXIII-B subunit were unchanged, but endogenous production of A2 in CD patients was estimated to be very small, as expected. Assay scale factors, in the form of volume of distribution, were found to be different in CD subjects.

Conclusions: The model well described immunoassay data prior to and following single- and multiple-dose administration of rA2 and its subsequent incorporation into rA2B2 in both healthy and CD subjects. This mechanistic model can be used for prospective simulation of other dosing schemes and modified to account for both congenital and potentially acquired FXIII deficiencies.

10. Population PK Analysis in Sparse Data and Flexible Sampling Time Conditions

F. Hourcade-Potelleret, C. Weber, B. Fotteler and N. Frey
Clinical Pharmacology, F. Hoffmann-La Roche, Basel
poster

Objective: Characterize the pharmacokinetics including effects of covariates of a tested drug, based on a phase II dose-ranging study (5, 10 and 20 mg) in patients during daily repeated administration.

Material and Methods: Trough PK samples were taken at steady-state during three occasions. Two additional samples were taken between 1 and 8 hours postdose based on the investigator's choice after 6 and 12 weeks of treatment. These data were pooled with full PK profiles from a phase I study (3 to 40 mg) performed in patients in order to facilitate the structural pharmacokinetic model definition. The potential influence of the following baseline covariates on drug clearance was explored: gender, age, BMI, albumin, AST, ALT, bilirubin, creatinine clearance and dose, time, disease duration, drug naïve or pre-treated patients, comedication with ACE-inhibitors, CYP2C19 genotype (homozygous extensive metabolizers versus heterozygous extensive and 3 homozygous poor metabolizers). A non-linear mixed effect model approach using NONMEM software version V level 1.1 was used to analyze the 1829 exploitable concentrations from 209 patients.

Results: A two-compartment model with first order absorption and lag-time was used to fit the data. IOV was coded on clearance and central volume. Pharmacokinetics was linear with time. A non linearity with dose occurred at the highest doses and was coded on F. The degree of accumulation was close to 1. AST and genotype for CYP2C19 exhibited a statistically significant influence on CL/F. CL/F was 233 mL/min for a homozygous extensive metabolizer and was 13 % lower for the combined subgroup of heterozygous extensive and poor metabolizers. CL/F decreased as AST increased and reached a plateau at the upper values of AST normal range. The residual error expressed as a coefficient of variation was 37 %.

Discussion and Conclusion: The PK seems easy to handle in clinical routine: linearity with time, no drug accumulation for the dose regimen selected. Although the interaction between CL/F and CYP2C19 genotype is very small and not clinically relevant, this covariate merits further investigation. Regarding AST, patients with higher values are likely to have lower drug clearance. This relationship is rational as the drug is mainly metabolized but needs to be confirmed in phase III. The residual variability is high as expected with a fragmentary PK sampling design.

12. Cerebral uptake of mefloquine enantiomers with and without theP-gp inhibitor elacridar (GF1210918) in mice

Emmanuelle Comets, France Mentré and François Gimenez
INSERM
poster

Objectives: Mefloquine is a chiral neurotoxic antimalarial agent showing stereoselective brain uptake in humans and rats. It is a substrate and an inhibitor of the efflux protein P-glycoprotein. We investigated the stereoselective uptake and efflux of mefloquine in mice, and the consequences of the combination with an efflux protein inhibitor, elacridar (GF120918) on its brain transport.

Methods: Racemic mefloquine (25mg/kg) was administered intraperitoneally to OF1 female mice, with or without elacridar (10mg/kg). Six to seven mice were sacrificed at each of 11sampling times between 30min and 168h after administration. Blood and brain concentrations of mefloquine enantiomers were determined using liquid chromatography. We modelled the pharmacokinetics of the two enantiomers jointly in blood and brain using non linear regression weighted by the empirical variance.

Results: A three-compartment model with zero-order absorption from the injection site was found to best represent the pharmacokinetics of both enantiomers in blood and brain. (-)Mefloquine had a lower blood and brain apparent volume of distribution and a lower efflux clearance from the brain, resulting in a larger brain/blood ratio compared to (+)mefloquine. Elacridar did not modify blood concentrations or the elimination rate from blood for either enantiomers. However, cerebral AUC of both enantiomers were increased after elacridar administration, with a stronger effect on (+)mefloquine. The efflux clearance from the brain decreased for both enantiomers, with a larger decrease for (+)mefloquine.

Conclusion: After administration of racemic mefloquine in mice, blood and brain pharmacokinetics are stereoselective, (+)mefloquine being excreted from brain more rapidly than its antipode, showing that mefloquine is a substrate of efflux proteins and that mefloquine enantiomers undergo efflux in a stereoselective manner. Moreover, pretreatment with elacridar reduced the brain efflux clearances with a more pronounced effect on (+)mefloquine.

14. Can clinically useful population PK models for carbamazepine in pediatric epilepsy patients be developed based on routine therapeutic drug monitoring (TDM) data?

K.C. Carlsson (1), N.O. Hoem (2), T. Glauser (3), A. A. Vinks (4).
(1)School of Pharmacy, Faculty of Mathematics and Natural Sciences
poster

Objectives: Population pharmacokinetics (PPK) models for implementation in Bayesian adaptive control strategies have been developed for several drugs and patient populations. A prerequisite for a good structural PK model is informative data. Therapeutic drug monitoring (TDM) data are available for routinely monitored drugs. This analysis explores the utility of sparse carbamazepine TDM data for the development of clinically useful population PK models.

Methods: Patient and TDM data were identified from our neurology outpatient clinic database. For carbamazepine 556 entries with one or more serum concentration measurements were found. Each entry contained information on patient demographics, date of birth, gender, ethnicity, drug used and concomitant meds, dosing regimen, time and amount of last dose and a laboratory result from a draw made at a stated time. Exclusion criteria were; combination therapy with other anticonvulsants, concomitant medication known to interact with carbamazepine, carbamazepine therapy of shorter duration than one month, suspected non-compliance and missing or conflicting information in the database vs. medical chart. Data were analyzed with an iterative-two stage Bayesian (IT2B) and a nonparametric EM algorithm (NPEM).

Results: 57 carbamazepine mono therapy patient data sets were identified from the database and used in the analysis. A one-compartment model with first-order absorption based on mean population data gave poor predictions. The individual Bayesian posterior models gave better predictions for all subjects, but showed large inter patient variability in the estimated parameters. To explore the potential benefits of splitting the data set into groups depending on drug formulation used several other models were tested.

Conclusion: Routinely collected TDM data can be used for PPK modelling. However, it will be necessary to combine such data with additional richer data. This will allow for the development of more informative and clinically useful PPK models that can then be used as part of Bayesian individualization strategies.

16. Modeling of drug- and system-related changes in body temperature: application to drug-induced hypothermia, long-lasting tolerance development and diurnal variation in body temperature

Sandra A.G. Visser (1), Björn Sällström (1), Tomas Forsberg (2), Svante B. Ross (3), Lambertus A. Peletier (4) and Johan Gabrielsson (1)

(1) PK/PD DMPK&BAC, (2) General Pharmacology, (3) Bioscience, Local Discovery Research Area CNS & Pain Control, AstraZeneca R&D Södertälje, SE-151 85 Södertälje, Sweden. (4) Mathematical Institute, Leiden University, Niels Bohrweg 1, P.O. Box 9512, 2300 RA, Leiden, The Netherlands.

poster

Objectives: Clomethiazole (CMZ), an agonist for the GABA(A) receptor, has been shown to induce rapid and long lasting tolerance to its hypothermic effects in rats. However, quantification of the drug- and system-related changes in body temperature is complicated by a diurnal variation in body temperature and an influence of handling. Therefore, the objective of the present investigation was to develop a model for the characterization of diurnal variation in baseline, animal handling effects, CMZ-induced hypothermia and tolerance development.

Methods: CMZ-induced hypothermia and tolerance development was characterized using body temperature telemetry in male Sprague Dawley rats after subcutaneous (sc) bolus administration of 0, 15, 150, 300 and 600 μmol/kg and 24 h continuous administration of 0, 20 and 40 μmol/kg/h using osmotic pumps. The duration of tolerance was studied by repeated injections of 300 μmol/kg with 3-30 days interval. Plasma exposure to CMZ was obtained in different groups of catheterized rats.

Results: Concentration-time profiles of CMZ displayed typical nonlinear kinetics with increasing dose and quantified with a two-compartment model with capacity-limited elimination. Simulated individual concentration-time profiles served as input to the pharmacodynamic model. The asymmetric diurnal variation in body temperature was successfully described with a negative feedback model, which was subject to external light-dark conditions. An exponential function characterized the animal handling effects. The baseline behavior was fed into a feedback model for temperature regulation allowing estimation of CMZ potency. The long lasting tolerance was described by inactivation of a moderator with an estimated turnover half-life of 30 days.

Conclusions: A pharmacokinetic-pharmacodynamic model featuring components for description of diurnal variation in baseline and influence of handling was able to quantify the CMZ-induced hypothermia and tolerance development in rats.

18. Identifying and minimizing major sources of variability in population pharmacokinetic studies

E. Tousset (1), C. Reners (1) & B. Vrijens (1-2)
(1) AARDEX Ltd., Visé, Belgium (2) University of Liège, Belgium
poster

Objectives: Occasional sampling of the concentrations of drug in plasma is used to study the pharmacokinetics of the drug in question, and to determine whether or not dosing is optimal. Both purposes are compromised by variance in the concentration of plasma, the origins of which include variations in both the sources and sinks for drug in the body. The main variation in the source of drug in ambulatory patients is variable execution of the prescribed regimen of drug administration. The main variations in the sinks for drug arise from food- and/or drug-induced changes in pharmacokinetic parameters, changing the relation between dose and concentration. To minimize these variations, sampling is routinely done at a 'trough' point in an interval between scheduled doses, i.e., just prior to the next scheduled dose in the prescribed dosing sequence.

The main objective of this research is to determine the magnitude and sources of variability in trough concentrations collected during ambulatory care.

Methods: Therapeutic drug monitoring data issued from several HIV studies were combined in order to quantify the within- and between-patient variability in trough concentrations and to identify major sources of PK variability in HIV studies. Electronically compiled dosing histories data were used to identify the proportion of variability in PK studies that could be attributed to patient non adherence to prescribed therapy.

Results: When therapeutic drug monitoring is used, many samples turned out not to be taken at the trough, but at some other point in the dosing cycle, and, furthermore, many samples turned out to be taken during an inter-dose cycle when the assumption of a steady-state is not justifiable, because of prior irregularities in dosing times. Those deviations result in considerable within-patient variability inducing sometimes difficult clinical interpretation of the results. Surprisingly, in some circumstances, the within-patient variability exceeds the between-patient variability. Through simulations we were able to show that electronically compiled times of dose taken prior to blood sampling can explain more than 50% of the residual, within-patient variability in trough concentrations.

Conclusions: These results suggest that electronically-compiled dosing histories may greatly improve information derived from both population PK studies and therapeutic drug monitoring.

20. A Population PK/PD Model for Cortisol Suppression

Isabelle Pouliquen, Lutz Harnisch
GlaxoSmithKline, CPDM, CPK, M&S, Greenford, London, UK
poster

Cortisol levels in the plasma follow a circadian variation with its peak in the early morning and a trough in the late afternoon. A well-known negative feedback loop exists in which ACTH partly via CRH release controls cortisol levels.
Any interaction with the natural cycle of cortisol production, release, and metabolism is prone to cause adverse side effects. The therapeutic administration of cortisol derivatives in the treatment of asthma, COPD or other inflammatory diseases will make a certain amount of the drug systemically available even if administered non-orally, i.e. per inhalation.
Especially in the chronic treatment of inflammatory diseases it is highly desirable to keep systemic exposure of drugs low and also to optimise the time course of the administration to cause the least impact on the cortisol life cycle.
Aim of the present work is to develop a population PK/PD model for cortisol, its daily variation and its dependency on exogenous administration of cortisol derivatives.
Based on literature information a structural model for the cortisol population data was developed using the work of Chakraborty[1], Rohatagi[2], and Meibohm[3] who used single subject data and different models to describe the circadian variation. The main purpose of the present work was to integrate the different models and to develop a *population* PK/PD model allowing extensive clinical trial simulations for new compounds and various dosing regimens.
A positive constrained 3-harmonic Fourier series input function was best in describing the cortisol baseline characteristics. The steroid induced suppression of the endogenous cortisol release was introduced via an Emax link function to the systemic exposure of the exogenous administered drug.
In order to derive the population PK/PD model data from various previous sources were used, i.e. cortisol response data after placebo and drug administration and also drug exposure data.
The potential clinical target was defined as the minimal cortisol suppression during a 24hour daily cycle. To achieve an optimal separation of desirable and adverse reactions simulations can be performed based on the derived model using any given dose, exposure, administration site, or potency of a given compound.

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22. Comparison of several prediction errors on concentrations for model evaluation

K. Brendel (1), E. Comets (1), C. Laveille (2), R. Jochemsen (2), F. Mentré (1)

(1) INSERM E 0357,Bichat hospital, Paris (2) Servier, Courbevoie

poster

objectives: The aim of this study is to compare criteria for the evaluation of a population pharmacokinetic model built with data from phase II studies. Several types of prediction errors on concentrations are proposed and evaluated on simulated data.

Methods: The model was built from 2 phases II studies of an antidiabetic drug. It was one compartment model with zero order absorption and first order elimination with exponential random effects on the apparent volume of distribution (V/F) and on the apparent clearance (Cl/F) and proportional error model. Two phase I data sets (12 subjects and 16 pharmacokinetic samples) were simulated according to the design of a real phase I study: the first (Vtrue) was simulated with the parameters values estimated previously; the second (Vfalse) was simulated using the same model, but with the mean value for V/F and Cl/F divided by two. We evaluated the following metrics on both datasets: Standardized Prediction Errors for Concentrations (SPEC) (WRES in NONMEM); Standardized Prediction Error for Concentrations with Simulations (SPECS), where simulations are used to estimate the mean and standard deviation of the predicted distribution of concentrations at each sampling time, and Normalized Prediction Distribution Error with Simulations (NPDECS), where the whole distribution of predicted concentrations is taken into account [1, 2]. Under the assumption that the model and parameter estimates are correct, NPDECS should follow a normal distribution N(0, 1). Under the additional approximation of linearity for the model and normality for the parameter distribution, SPEC and SPECS should also follow a normal distribution N(0, 1). For each criteria, we tested normality using the Shapiro-Wilks test. We then performed a Wilcoxon signed-rank test to test whether the mean was significantly different from 0. The pharmacokinetic evaluations and simulations (1000 for SPECS and for PDECS) were performed with NONMEM version V software. Graphics and tests were performed using SAS version 8.2 software.

Results: Even on Vtrue, both SPEC and SPECS were found to differ significantly from a normal distribution. NPDECS followed a normal distribution and the mean was not significantly different from 0 for the 3 statistics. On Vfalse, SPEC, SPECS and NPDECS were not found to follow a normal distribution and showed a mean significantly different from 0. In conclusion, NPDECS was able to validate Vtrue and reject Vfalse, while SPEC and SPECS showed less discrimination.

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24. Robust Population Pharmacokinetic Experiment Design

Michael G Dodds(1), Andrew C. Hooker(1) and Paolo Vicini(1)

(1) Department of Bioengineering, University of Washington, Seattle, Washington, USA

poster

Objectives: The population approach to estimating mixed effects model parameters of interest in pharmacokinetic (PK) studies has been demonstrated to be an effective method in quantifying relevant population drug properties. The information available for each individual is usually sparse. As such, care should be taken to ensure that the information gained from each population experiment is as efficient as possible by designing the experiment optimally, according to some criterion.

Methods: The classic approach to this problem is to design good sampling schedules, usually addressed by the D-optimality criterion. This method has the drawback of requiring exact advanced knowledge (mean values) of the parameters of interest. Often, this information is not available. Additionally, if such prior knowledge about the parameters is misspecified, this approach yields designs that may not be robust for parameter estimation. In order to incorporate uncertainty in the prior parameter specification, a number of criteria have been suggested. We focus on ED-optimality. This criterion leads to a difficult numerical problem, which is made tractable by a novel approximation of the expectation integral usually solved by stochastic integration techniques.

Results and Conclusions: We present two case studies as evidence of the robustness of ED-optimal design in the face of misspecified prior information. Estimates from replicate simulated population data show that such misspecified ED-optimal designs recover parameter estimates that are better than similarly misspecified D-optimal designs, and approach estimates gained from D-optimal designs where the parameters are correctly specified.

26. Quantification of 5-HT7 receptor efficacy distribution throughout the canine stomach using the operational model of agonism.

Pieter Janssen(1,2), Nicolaas H. Prins(2), Pieter J. Peeters(2), Klaas P. Zuideveld(3) and Romain A. Lefebvre(1)

(1)Ghent University, Ghent, Belgium; (2)Johnson & Johnson Pharmaceuticals, Beerse, Belgium; (3)F. Hoffmann-La Roche, Basel, Switzerland

poster

Objectives This study aimed to determine, quantify and explain regional differences in 5-HT_7 receptor efficacy throughout the canine stomach using the relaxant response of the selective 5-$HT_{1/7}$ receptor agonist 5-carboxamidotryptamine (5-CT).

Methods From 6 dogs, longitudinal muscle strips from 8 gastric corpus regions and 6 antrum regions were mounted for isotonic measurement. The 5-CT-induced relaxation was examined on a prostaglandinF_{2a}-induced submaximal contraction. The resulting concentration-effect relationships were subsequently analyzed using the Hill equation and the operational model of agonism to estimate the operational affinity (pK_A) and efficacy (log t) in a population approach (nlme, S-PLUS). The efficacy estimate (log t; ratio of receptor density and coupling efficiency) obtained was compared with estimates of 5-HT_7 receptor mRNA expression.

Results 5-CT inhibited PGF_{2a}-induced tonic contraction (corpus) and increase of phasic contraction amplitude (antrum). The consistent antagonism produced by the selective 5-HT_7 receptor antagonist SB-269970 (10 nM, pA_2 estimates 8.2-8.9) confirmed that in every region, the inhibition by 5-CT was 5-HT_7 receptor-mediated. Differences in the maximum effect (61-108%) and potency (pEC_{50} 6.4-8.6) were consistent by region in all animals. Using the operational model of agonism these differences could be quantified by estimating the efficacy parameter t (log t estimates ranging from 0.1-2.1). The log t decreases going from the lesser to the greater curvature. A proportional difference (68%) in the relative expression of 5-HT_7 receptor mRNA between the lesser and the greater curvature indicates that differences in receptor density contribute to the observed functional differences.

Conclusions This study illustrates that 5-HT_7 receptors are present throughout the ventral wall of the canine stomach but the efficacy is clearly greater close to the lesser curvature. Regional differences in intrinsic efficacy are likely to be due to changes in receptor density as shown by 5-HT_7 mRNA receptor expression. Regional differences in efficacy support the hypothesis that using partial agonists for the 5-HT_7 receptor it may be possible to obtain pharmacological and physiological selectivity.

28. A non-parametric (NPAG) population PK model of orally and intravenously administered linezolid.

N.O. Hoem (1), P. Beringer (2)

HPC, Oslo, Norway; (2) School of Pharmacy, University of Southern California, Los Angeles, U.S.A.

poster

Objectives: Population PK of linezolid (LNZ) has been characterized in several relatively recent publications, but with divergent conclusions regarding linear or non-linear elimination. This analysis applies a non-parametric EM method (Non Parametric Adaptive Grid - NPAG) to data densely collected from patients administered LNZ both orally and intravenously. The study design permitted the fraction absorbed (Fa) to be explicitly defined in the model.

Methods: PK-data were from a prospective, randomized, cross-over study in 17 hospitalized patients; 11 receiving continuous enteral feedings and 6 serving as controls. Patients had been were randomized to receive a single dose of either LNZ 600mg IV or 600mg PO suspension, with a 48 hour washout period between dosage forms. Data were analyzed with an iterative-two stage Bayesian (IT2B) method to estimate initial parameter ranges and subsequently with the NPAG method. Model discrimination was determined using log-likelihood values, mean error (ME), root mean squared error (RMSE) and Akaike's information criteria. Maximum *a-posteriori* Bayesian analysis was performed to determine the individualized pharmacokinetic parameters. Estimates of Fa and Total clearance were compared with those obtained by non-compartmental analysis.

Results: In this population of elderly hospitalised patients the oral and/or enteral absorption of LNZ was, regardless of PK-model applied, found to be fast (ka >2) and complete (Fa = 1). Volume of distribution was linearly correlated with total body weight for all models tested. Creatinine clearance was not found to correlate with any model-parameter. For models incorporating a distributive compartment, elimination was very well described by either a simple linear or by a Michaelis-Menten (MM) saturable model. Administration of the same dose in all experiments restricted the actual analysis of MM parameters to the Vm/Km ratio (Km fixed at 3.6 mM). In general, non-distributive models gave substantially poorer model fits. Interestingly, for such models, linear-elimination gave superior fits as compared to MM-elimination. Although the predictions given by the individualized PK parameters were excellent (R^2>0.97), mean-parameters predicted individual observed levels well (R^2>0.8) in both MM and linear 2-compartment models.

Conclusion: At doses below 600mg in this population of elderly hospitalised patients, analysis by the NPAG-algorithm demonstrated excellent predictions for 2-compartment distributive models both with MM- or with linear elimination. The MM- had less bias than the linear model. Taken together, this might indicate that the elimination of linezolid is indeed saturable at high plasma levels, as will be present initially before distribution equilibrium (Deq) is achieved, but becomes close to linear at levels usually present after Deq. Individual variability, at least in this group of patients, seems to be small enough to make the population mean parameter estimates useful for individual prediction.
Analysis of Fa could be directly incorporated into the model, and gave results that were essentially identical to a conventional comparison of AUCs. Explicit determination of Fa with compartmental modelling offers the ability to perform bioavailability assessments in patients with intermixed IV/oral dosage regimens (no washout necessary).

30. Evaluating the predictive power of the Fisher information matrix in population optimal experimental design

Andrew Hooker, Michael G. Dodds, Paolo Vicini

Resource Facility for Population Kinetics, Department of Bioengineering, University of Washington, Seattle, Washington, USA

poster

Objectives: In previous work, we evaluated computed population optimal designs via simulation studies [1]. Others have evaluated optimal designs without simulation by looking directly at the Fisher information matrix (FIM) and the predicted parameter variances (the diagonal elements of the FIM) [2]. However, the FIM is only an asymptotic lower bound on the covariance matrix of the model parameter values and it is not clear how well the FIM predicts experimentally measured variances in studies where the number of samples and number of individuals are not close to the asymptotic limit. In this work, we compare population D-optimal pharmacokinetic (PK) designs using both the asymptotic Fisher information matrix (FIM) predicted model parameter variances and model parameter variances derived from simulation studies. Previous work has looked at this problem for one specific model [3], here we expand this comparison and look at three separate models.

Methods: Taking three models from the literature, we compute various optimal designs for each. Then, for each optimal design strategy we calculate the predicted asymptotic percent coefficients of variation (CVs) for all model parameters from the FIMs for each design. Next, using NONMEM, we simulate numerous replicate experiments and compute the simulated parameter CVs for each optimal design. Finally, we compare the two designs by looking at their percent difference.

Results: The results of this study indicate that the asymptotic FIM CVs can, in general, be a good predictor of the trends seen in the CVs of simulation/estimation experiments. However, the CV values predicted by the asymptotic FIM do not seem to reliably predict the CV values seen in simulation/estimation experiments. In general, the CV values seen using the asymptotic FIM will tend to underestimate the actual CV values of simulation/estimation experiments. These results are similar to those found by Retout and Mentre [3]. However, in their work, no differences were found between the FIM CVs and the simulation/estimation CVs for the fixed effects of their model. We expect the difference, when present, to be model and design dependent.

Conclusions: Our results imply that using the FIM to compare different designs is possible, but using the FIM to predict actual values (not the trends) of estimated parameter variances may not be reliable. In practical terms, it appears that we can use asymptotic variance values as a guide to investigate designs, but conclusions should be drawn from a combination of asymptotic variance values and simulation studies. It should also be noted that the asymptotic FIM variance values can give us no information about the likely bias in the parameter estimates; simulation studies must be done to examine bias.

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32. Comparison between the Fedorov-Wynn algorithm and the Simplex algorithm for population designs optimisation using a model of the HIV viral load decrease

Sylvie Retout, Emmanuelle Comets and France Mentré
INSERM - University Paris 7
poster

Context We have recently developed PFIMOPT 1.0 for population designs optimisation . This generic Splus or R function is based on the optimisation of the D-optimal criterion, that is the maximisation of the determinant of the Fisher information matrix. This function can determine the best sampling times of the population design as well as its best structure, that is the number of groups, and for each group, the number of subjects, the number of sampling times and the allocation of the times. PFIMOPT uses the Simplex algorithm to maximise the D-optimal criterion. It is a general algorithm which optimises the sampling times in some given continuous intervals of times. A more specific algorithm has been proposed for designs optimisation, the Fedorov-Wynn algorithm, already used in . It optimises also both the group structure and the sampling times but in a given finite set of times.

Objectives To compare the performance of the Simplex algorithm to the Fedorov-Wynn algorithm for population designs optimisation. In particular, to evaluate the amount of information provided by the designs optimised with those two algorithms.

Methods We use the example of the simple biexponential model of HIV viral decay. This model involves 4 fixed effects. An additive error with an homoscedastic variance characterised by σ^2 is assumed. The vector of the population parameters is then composed of the four fixed effects, plus the variance of their additive random effects and σ^2. A priori values are given to those parameters from HIV literature. Based on those values, several designs with different groups structures are optimised with both the Fedorov-Wynn and the Simplex algorithms: designs with 8, 5, or 4 samples per subject are optimised. The allowed sampling times for the Fedorov-Wynn is the set of 12 sampling times from 0 to 56 days used in . The optimisation with the Simplex algorithm allows sampling times from 0 to 56 days in a continuous interval. To be clinically feasible, the sampling times are rounded to the nearest day. Moreover, a minimum delay of 1 hour between two successive sampling times is imposed. Some optimised designs are then selected to be simulated by replication of 1000 data sets analysed with the nlme function of Splus.

Results Designs optimised with the Simplex and the Fedorov-Wynn algorithm may be different but lead to a quite similar group structure and a same efficiency. Whatever the algorithm, the optimised designs provide precise parameter estimates, both on the fixed effects (CV < 4%) and on the variance of the random effects (CV < 43%). Preliminary simulations on designs with 5 samples per subject have already confirmed those results.

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34. Population pharmacokinetic/pharmacodynamic modeling of the possible tolerance development after a single oral dose of different BZD-GABAa agonists.

M Valle, M Yritia, R Antonijoan, G Urbano, MR Ballester, MJ Barbanoj

Centro de Investigación de Medicamentos, Institut de Recerca del HSCSP, Departamento de Farmacología y Terapéutica, Universidad Autónoma de Barcelona, Barcelona, Spain.

poster

Introduction: A commonly described situation for benzodiazepines (BZD) is the tolerance development after chronic administration. However, although many investigators have pay attention to the possible development of acute tolerance, due to the employed methodology for data analysis, it is not clear whether all the BZD-GABAa agonists develop tolerance after a single oral dose.

Aim: To test and compare the tolerance development pattern after single oral doses of different BZD-GABAa agonists administered to healthy volunteers, when evaluating the relative alpha and relative beta activities of the EEG as pd measures.

Methodology: Data from two different studies were combined during the analysis. In the first study a single oral dose of placebo, lorazepam (4 mg) or zolpidem (20 mg) were administered randomly, in a double- blind study to 36 volunteers. In the second study alprazolam (2 mg) was administered as single oral dose to 24 healthy volunteers. In both studies different blood samples were withdrawn to determine plasma levels of the different drugs, and 16 leads EEG was measured at different times before and after drug administration. The variables derived from EEG were relative alpha (7.5-13 Hz) and relative beta (13-30 Hz). Data analysis was performed in two steps: first pharmacokinetics was analyzed using NONMEM V with FOCE interaction. The individual predicted plasma concentrations were used for the development of the pharmacodynamic model using the FO option, in the second step.

Results: A two compartmental model with first order absorption and elimination from the central compartment best described the lorazepam pK profiles including weight as covariates in volume of the central compartment and plasma clearance, whereas a one compartmental model with first- order absorption and elimination best described alprazolam and zolpidem PK profiles. None of the other studied covariates except the mentioned one, were found to influence any of the parameters.

For the PD a sigmoidal inhibitory model (relative alpha) and a sigmoidal stimulatory model (relative beta) best described the PD profiles of alprazolam and lorazepam. Different values of Imax, IC50, Emax and EC50 were estimated for each of the drugs. Tolerance was only found for zolpidem and it was best described assuming the formation of a metabolite with antagonistic properties.

Conclusions: : Acute tolerance development after single oral dose is not present for the non-selective BZD-GABAa agonists alprazolam and lorazepam, whereas a clear acute tolerance is developed in the same situation when zolpidem, a selective BZD-GABAa, agonist is used.

36. Fitting Proportional Odds model to Ordered Categorical Data using the NLMIXED Procedure

Maria C. Kjellsson, Mats O. Karlsson
Division of Pharmacokinetics & Drug Therapy, Uppsala University, Sweden
poster

Introduction & Objective Ordered categorical data are commonly used to describe subjectively scored symptoms and side effects and a majority of the observations are often at one extreme of the possible outcomes, i.e. the distribution of response is skewed. The standard approach for modelling ordered categorical data is with the proportional odds model. For repeated measures, a mixed effects modelling approach is applied by adding interindividual variability on baseline, enabling the -2 logarithm of the likelihood to be minimized. Minimizing the logarithm of the likelihood, using the Laplacian method may result in severely biased parameter estimates, related to the skewness of response distribution and magnitude of interindividual variability [1]. Because of this, we intend to investigate the bias in parameter estimates, when the proportional odds model is fitted to ordered categorical data using the Gaussian quadrature method available in the NLMIXED procedure in SAS.

Method This is a Monte Carlo simulation study where 100 original data sets were derived from a known model with fixed study design. The simulated response was a 4-category variable on the ordinal scale with categories 0, 1, 2 and 3. The model used for simulation was fitted to each data set for assessment of bias, once with the Laplacian method and once with the Gaussian quadrature method. In particular, we have focused on situations with non-even distribution of the response categories and the impact of interindividual variability.

Results & Conclusion The bias in the parameters estimated using the Gaussian quadrature method was markedly reduced, compared to the results from the estimations using the Laplacian method. Thus, the Gaussian quadrature performes well also in those situations where the Laplacian method does not.

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38. Comparison of different models to describe simultaneously the kinetics of parent drug and metabolites after oral administration.

O. Sayar(1), L. Bueno(1), M.J. Garrido(1), F. Rombout(2), I.F. Trocóniz(1)

(1) Department of Pharmacy, School of Pharmacy, University of Navarra, Pamplona, Spain; (2) Department for Modelling and Simulation, Grünenthal GmbH, Aachen, Germany

poster

Introduction: The two most popular models used to fit drug and metabolite kinetics are: Model I, where the drug is absorbed and once it has reached systemic circulation, metabolite is appearing in plasma due to the continuos pass through the liver; and model II, where both, parent drug and metabolite are simultaneously absorbed with equal or different input rates. Model II would reflect a lost of parent drug due to a hepatic first past effect. Models I and II have the advantage that if the analyst chooses to first fit the parent data, the model parameters can be used in the analysis of the metabolite data. However, there are cases where those two models, despite of increasing the number of disposition compartments, and extra routes of elimination do not provide an adequate fit. In those situations, a model incorporating a liver compartment (model III) has been shown to improve model performance. Such model has been used rarely and still is not very well documented.

Purpose: To explore by means of computer simulations situations where the liver compartment model can provide better fits, which trends appearing in the goodness of fit plots suggest the inclusion of liver compartment, and interpretation of the model parameter estimates.

Methods: Simulations were performed assuming first order input kinetics, one compartment distribution kinetics from both drug and metabolites, and only one elimination route for the parent and metabolite. Combinations of restricted and non-restricted parent compound and metabolite characteristics together with different input rates values were explored. Models II and III were used to simulate concentration vs time profiles, which were analysed by models I to III. For the case of the simulations with model III, different distribution rates from and to the liver compartment were also used. Simulations and analyses were performed with NONMEM, and model discrimination was based on the minimum value of the objective function and visual inspection of the goodness of fit plots.

Results and conclusions: In general the kinetics of the parent drug was adequately described for the three models. With regard to the metabolite, Model I performed usually very poorly, performance of model II was affected by the ratio between the clearance of the drug and metabolite. Model III performed the best in most of the scenarios. After single administration, delayed predicted C_{max} for the metabolite was the major indication for choosing model III.

40. A Deconvolution Method for Linear and Nonlinear Systems based on Stochastic Differential Equations

Niels Rode Kristensen
Pharmacometrics, Experimental Medicine, Novo Nordisk A/S
poster

Objectives: The objective of this contribution is to demonstrate the performance of a new deconvolution method based on stochastic differential equations (SDEs). The new method is equivalent to an existing impulse-response based stochastic deconvolution method for linear time-invariant systems, but, unlike the existing method, the new method can easily be extended to handle nonlinear, time-varying systems. Being based on SDEs, the new method facilitates reconstruction of unknown input signals (with confidence intervals) based on arbitrarily irregularly sampled data using arbitrarily fine discretization.

Methods: A stochastic state space model structure is used to describe the relationship between the unknown input and the observed output of the system, and the reconstruction of the unknown input signal is performed by means of a smoothing algorithm based on state filtering. Different assumptions may be applied for the evolution of the unknown input signal, e.g. a random walk or an integrated random walk, which corresponds to applying a penalty on the first or second derivative, respectively. This penalty may be adjusted manually or determined automatically using a maximum likelihood criterion.

Results: Simulated as well as real data was used to demonstrate the performance of the new deconvolution method. Using data from a simulated glucose clamp study, the new method provided a reconstruction of the unknown glucose disposal rate (with confidence intervals), which was identical to the one provided by the existing impulse-response based stochastic deconvolution method. Results obtained with the two methods where also similar when reconstructing C-peptide and LH secretion profiles using real data. The ability of the new method to handle nonlinear, time-varying systems was demonstrated using simulated data by showing that the unknown rate of appearance, following extravascular administration, of a drug with nonlinear elimination kinetics could be reconstructed.

Conclusion: The performance of a new deconvolution method based on SDEs, which may be applied to linear as well as nonlinear systems, was investigated. The new method was demonstrated to be equivalent to an existing method for linear time-invariant systems, while facilitating extension to nonlinear, time-varying systems, which was also demonstrated. Furthermore, the use of SDEs within the new method was shown to provide flexibility in terms of allowing arbitrarily irregular sampling and arbitrarily fine discretization.

42. Population semi-parametric modelling of the pharmacokinetics of rofecoxib in rats

Dymphy Huntjens (1), Anne Chain (1), David Spalding (2), Meindert Danhof (1) and Oscar Della Pasqua(1,3)

(1) Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden University, The Netherlands (2) GlaxoSmithKline, Drug Metabolism & Pharmacokinetics, United Kingdom (3) GlaxoSmithKline, Clinical Pharmacology & Discovery Medicine, United Kingdom

poster

Objectives: Rofecoxib is a potent and highly selective cyclo-oxygenase-2 inhibitor and is often prescribed for human ailments such as acute pain and osteoarthritis. Previous investigations have demonstrated that the PK of rofecoxib displays enterohepatic recycling (EHC) in rats[1]. The objective of this study was to develop a population pharmacokinetic (pPK) model for rofecoxib in rats.

Methods: Male rats, instrumented with one or two cannulas, received an IV (6, 10 mg/kg in 5 min, 0.5 mg/kg in 60 min) an IP (10 mg/kg) or a PO (5 mg/kg) dose of rofecoxib. Plasma samples were taken at pre-defined time-points to obtain concentration-time profiles. These profiles displayed large inter- and intra-individual variability and multiple secundary peaks at different time-points. To describe the data, various models were investigated in NONMEM, including EHC models, the Wajima model and constrained longitudinal spline (CLS) models with different breakpoints.

Results: The EHC model and Wajima model were not able to accurately describe the observed concentration-time profiles. A fourth order CLS model with 4 breakpoints best decribed the PK profiles independent of the route of administration. A proportional and additive error model described intra-individual variability. Addition of data of bile duct-cannulated rats enabled the determination of relative bioavailability and thus total exposure in a quantitative manner. EHC resulted in increased bioavailability in normal rats (approximately 150%) as compared to bile duct-cannulated rats.

Conclusions: The CLS method was able to describe the noisy EHC-related fluctuations in plasma concentrations of rofecoxib in rats. A accurate estimation of total exposure is required to estimate the relevance of the increase of EHC in bioavailability.

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44. Population modeling of tumor growth in untreated xenografted mice

Poggesi I (1), Simeoni M (2), Germani M(1), De Nicolao G(2), Rocchetti M(1)
(1)Pharmacia Italia S.p.A., Nerviano, Italy; (2)University of Pavia, Italy
poster

Introduction: We developed a minimal pharmacokinetic-pharmacodynamic model describing the effect of an anticancer agent to the tumor growth in animals (PAGE 2004, Simeoni et al.). In this model, the growth of tumors in non-treated animals (unperturbed growth) is described by an exponential growth followed by a linear growth phase. Three parameters are estimated: the initial tumor mass, the rate constant of the exponential growth and the rate of the linear growth.

Aim: A substantial inter-experiment variability was observed in the tumor growth of non-treated animals. Since this was considered a possible limitation for the prospective use of the PK-PD model, a population analysis was implemented for studying the different sources of variability.

Methods: the weights of tumors in control animals obtained from different experiments were modeled using NONMEM (v. V). The frequency distributions of the various parameters were evaluated. The variability contributions describing the inter-individual and the inter-experiment components were considered.

Results: The model fitted well the experimental data. The distribution of the parameters indicated that, whilst the specific rate of exponential growth was reasonably constant across all experiments, the other parameters were more variable. The inter-individual variability of these parameters was well described using a lognormal distribution.

Conclusion: This population approach allowed a better comprehension of the meaning of the model parameters. The specific rate of exponential growth was more constant across experiments, suggesting that this parameter is related to the growth characteristics of the inoculated cell lines. The initial burden of tumor cells was affected by a higher inter-experiment variability, likely due to possible differences in the experimental procedure of inoculation. Also the rate of tumor growth in the linear phase was variable, possibly due to different immunological reactions among the animals.

46. Modelling of the effect of Topotecan on B cell subsets in tumor bearing rats.

C Segura1, E Bandrés2, I F Trocóniz1, J García-Foncillas2,O Sayar1, C Dios-Vieitez1, M J Renedo1, M J Garrido1

1Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Pamplona.

poster

Propose: To increase the understanding of the dynamic regulation involved in the hematopoietic alterations observed after the administration of topotecan (TPT) by fitting simultaneously im- and mature B cells.

Methods: Two groups of BDIX rats bearing tumor were used. Group I and II received saline or 6mg/kg of TPT. 30 days later, group II was divided in other two groups receiving TPT as a single 6mg/kg dose or as two consecutive administrations of 3mg/kg dose. Blood samples were withdrawn from each animal every 48h for five weeks. In each sample, the absolute number of leukocytes measured by Coulter counter and different lymphocyte subsets measured by flow-cytometric analysis were quantified. Absolute B lymphocyte counts were calculated on the basis of total leukocyte number. The pk of TPT was previously evaluated in a separate group of rats.

Results: It was expected that temporal alterations in the mature circulating cells are preceded by similar changes in immature cells. However, the results showed that after TPT treatment both type of cells decreased in parallel reaching the nadir at day 3-4, but while mature B-cells returned to baseline at day 8, immature B-cells were maintained at very low levels until approximately day 9 increasing slowly to reach baseline 21 days after TPT administration. The time course of the immature cells was described with a model incorporating a self-renewal of the stem cells, a maturation chain, a feedback mechanism, and a drug effect over the proliferation of the stem cells. [1] To fit the mature cell data an extra compartment (located outside the maturation chain) was incorporated into the model. Such compartment would resemble the spleen, where mature B-cells with a relative long life span, are stored in a number higher than in blood or bone marrow. [2] A decrease in the number of circulation mature B cells triggers the release from the spleen to the blood stream, allowing therefore a faster recovery of the mature B cells.

Conclusion: The proposed model could describe simultaneously two different stages of B cell providing new aspects about the dynamics of the hematopoietic system.

References:

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48. PsN Toolkit, a collection of computer intensive methods for population PK/PD

Lars Lindbom, Pontus Pihlgren and E. Niclas Jonsson
Div of Pharmacokinetics and Drug therapy, Dept Pharmaceutical Biosciences,
poster

Objectives: Many computer intensive methods useful in model building and model validation have been described in the literature [1, 2]. Their uses in population pharmacokinetics and pharmacodynamics have however been limited due to the lack of computing power and software. One way of addressing the limited computer power problem is to use distributed computing in the form of clusters or grids. This in turn requires software that supports parallel execution within a distributed computing environment. Perl-speaks-NONMEM (PsN)[3] is a programming library previously written by the authors to facilitate the development of software around the mixed effect modelling program NONMEM. Here we describe PsN-toolkit, a collection of computer intensive methods developed using PsN, intended for use in population pharmacokinetic and pharmacodynamic modelling.

Methods: The programming language Perl and the programming library PsN were used to implement the computer intensive methods. Support for parallel execution of the methods was constructed using the Perl module Parallel::ForkManager[4]. The object oriented structure of PsN was retained in the PsN toolkit methods. Nested dependencies between method classes were permitted, allowing for general inter-method communication.

Results: A collection of computer intensive methods intended for use in population pharmacokinetic and pharmacodynamic modelling using NONMEM has been constructed. Included methods are for example the Bootstrap, Cross Validation and a Stepwise Covariate Model Building tool. The methods share a common structure for preparation of data and model files, execution of NONMEM and handling of their output. Where such relations are deemed as relevant, the methods classes are aware of each other's functionality and capable of responding appropriately to the output from other methods. This makes it possible to construct new routines by combining the available procedures, e.g. using a Log-likelihood Profiling within Case-deletion Diagnostics to assess the influence of individuals or groups on the confidence intervals of estimates of model parameters. PsN-Toolkit supports parallel execution on multiple processor computers as well as on clusters that support whole process migration such as openMosix.

Conclusions: Using PsN-Toolkit on computers with multiple processors or on computer clusters allows the application of methods in model building and validation that otherwise would have been practically impossible due to long run times.

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50. A population pharmacokinetic-enzyme model for rifampicin autoinduction and bimodal absorption in pulmonary tuberculosis patients

Justin J Wilkins (1), Grant Langdon (1), Helen McIlleron (1), Goonaseelan Pillai (2), Peter J Smith (1) and Ulrika SH Simonsson (3)

(1) Division of Pharmacology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; (2) Novartis Pharma, Basel, Switzerland; (3) Division of Pharmacokinetics and Drug Therapy, Department of Biopharmaceutical Sciences, Uppsala University, Uppsala, Sweden

poster

Objectives: This study was designed to describe the pharmacokinetics of rifampicin in South African pulmonary tuberculosis patients on daily treatment with a standard rifampicin-containing drug regimen, using nonlinear mixed-effects modeling. In addition, the pharmacokinetic model was built to account for the considerable interindividual and interoccasional variability inherent in the drug's pharmacokinetic properties.

Methods: Three datasets containing 2 913 rifampicin plasma concentration-time data collected from 261 South African pulmonary tuberculosis patients were pooled. All subjects had been receiving rifampicin (7.01-15.78 mg/kg) once daily for 5 days per week, with a drug holiday on weekends, for at least 10 days. A mechanistic pharmacokinetic model encapsulating an enzyme turnover model to describe rifampicin's autoinductive properties and a mixture model to describe bimodality in the drug's absorption was developed using NONMEM. Parameters describing interindividual and interoccasional variability were included.

Results: The model comprised absorption, central plasma and enzyme pool compartments. The enzyme submodel was a positive feedback system - increases in rifampicin plasma concentration increased the enzyme production rate which accelerated the drug's rate of elimination. Total clearance and volume of distribution were similar to published values for tuberculosis patients. The absorption rate constant was bimodal, being more than threefold faster in one subpopulation. The estimated enzyme turnover corresponded to an enzymatic half-life of approximately one day.

Conclusion: The model presented here describes the time course of autoinduction of rifampicin metabolism in tuberculosis patients and confirms the previously-reported phenomenon of bimodality in the drug's absorption.

52. Population pharmacokinetic analysis of high-dose oral busulphan for bone marrow transplant in adults and children

CMJ Kirkpatrick(1), SB Duffull(1), ML Barclay(2), N Patton(3), GA Moore(4), MP Doogue(1)

(1)School of Pharmacy, University of Queensland, Brisbane, Australia; (2)Clinical Pharmacology, Christchurch Hospital, Christchurch, New Zealand; (3)Haematology, Christchurch Hospital, Christchurch, New Zealand; (4)Toxicology, Canterbury Health Laboratories, Christchurch, New Zealand

poster

Objectives: To undertake a population analysis of high dose oral busulphan for bone marrow conditioning prior to transplantation in adults and children.

Methods: A population pharmacokinetic analysis of busulphan was performed using NONMEM (using FOCE with interaction) on a population of 24 patients [11 adults/13 children, 8F/16M]. Age ranged from 1 to 50 years. Blood samples were available from 3 occasions for most patients. Initial non-compartmental analysis by the investigators suggested a systematic change in AUC during the treatment regimen.

Results: The best base pharmacokinetic model was a one-compartment model with first-order absorption and elimination with between subject variability (BSV) on Ka, CL and V and between occasion variability on Ka, CL and V. The mean population parameters were similar to previous studies. The final model included weight (kg) as a covariate on Vd. For CL, however, two competing covariate models were identified, i) $weight^{0.75}$ (allometric scaling) and ii) body surface area (BSA). The allometric scaling model had a slightly lower reduction in Obj (-3.5 units) compared with BSA, but both models provided a similar reduction in the unexplained BSV. To assess the best covariate model, 1000 non-parametric bootstrapped datasets were generated, and both competing covariate models fitted to the data. The difference in NONMEMs objective function, ΔObj, between both models was computed. The density of the distribution of the $\Delta Obj < 0$ was 0.75, indicating that the allometric model was preferred (odds = 3). A visual inspection of a predictive check was undertaken to evaluate the full model, this was performed for the full data set and for children and adults separately.

Conclusions: The population analysis provided similar parameter estimates to previous population studies. A possible way to assess biologically plausible competing covariate models is presented.

54.A disease model for the regulation of the glucose-insulin system

H. Silber (1), P. Stetina (1), B. McHugh (2), R. Gieschke (2), N. Frey (2), P. Vicini (3), U.S.H. Simonsson (1), M.O. Karlsson (1)

(1) Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Sweden; (2) Clinical Pharmacology, Modeling and Simulation Group, F. Hoffmann-La Roche, Basel, Switzerland; (3) Resource Facility for Population Kinetics, Department of Bioengineering, University of Washington, Seattle, Washington, USA

poster

Objectives: The aim of this project was to develop a mechanistic model to describe the glucose and insulin regulation following different kinds of glucose provocations, such as an intravenous glucose tolerance test (IVGTT), in healthy volunteers and type II diabetic patients.

Methods: The model was developed based on mechanistic knowledge of the insulin-glucose regulation. Data without drug-effect from four different trials with a total of 72 individuals (30 volunteers and 42 patients) were used. All patients and 24 of the volunteers received a single intravenous dose of glucose (250-330 mg/kg). The glucose was enriched with [6,6-$^{2}H_{2}$]glucose, on average 10% of the total glucose dose. After 20 minutes the patients and 10 of the volunteers received a 5-minute insulin infusion (patients 0.05 U/kg and volunteers 0.03 U/kg). The remaining 6 volunteers received a single bolus dose of [3-^{3}H]glucose at basal (14 µU/ml) and at elevated (110 µU/ml) insulin levels. Glucose was kept constant at 87.5 mg/dl. Blood samples were drawn pre-dose and until 240 minutes post-dose for the determination of plasma glucose, [6,6-$^{2}H_{2}$]glucose, [3-^{3}H]glucose and insulin concentrations. These concentrations versus time data were modeled simultaneously by non-linear mixed effect modeling using NONMEM.

Results: The glucose sub-model contained a two-compartment disposition model with endogenous production and insulin dependent and independent elimination. The insulin sub-model contained a two-compartment disposition model with endogenous production and release. Labeled glucose was also described with a two-compartment disposition model with insulin dependent and independent elimination. Feedback loops were incorporated into the model to account for the regulation of glucose production and elimination and for insulin production. Parameters with similar values for volunteers and patients were merged whereas other parameters were estimated separately for the two subpopulations in the model.

Conclusion: The model presented here allows the simultaneous prediction of insulin, glucose and labeled glucose levels without drug effect in volunteers and patients which can be of use in the development of antidiabetic drugs.

56. Population Pharmacokinetics and Response of ICL670 a Novel Oral Iron Chelator in Beta-Thalassaemia Patients

C. Ambery (1), L. Aarons (1)

(1) School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK

poster

Objectives: To develop a population pharmacokinetic model for ICL670 and the iron-complex Fe-$[ICL670]_2$.

Methods: A population approach (implemented with NONMEM) was used to analyse the pharmacokinetics of ICL670 and Fe-$[ICL670]_2$ from 18 subjects who received daily oral doses of ICL670 (10, 20 or 40 mg/kg) for 12 days. The relationship between ICL670 exposure and the efficacy variable faecal iron excretion was explored.

Results: A three-compartment pharmacokinetic model (including two-compartments for ICL670 and one-compartment for Fe-$[ICL670]_2$ formation) best described the ICL670-Fe-$[ICL670]_2$ pharmacokinetics. ICL670 apparent clearance (CL/F), apparent volume of distribution (V_1/F) and Fe-$[ICL670]_2$ apparent clearance (CL/Fm) and apparent volume of distribution (V_3/Fm) were 2.9 L/h, 31.6 L, 12.1 L/h and 16.3 L respectively. An empirical linear effect model was fitted to describe the relationship between exposure to ICL670 (daily ICL670 AUC) and daily faecal iron excretion. The linear relationship was described with an intercept of 2.53 mg/L and slope of 3.26 mg/L/h.

Conclusions: The analysis provides a model which characterises the pharmacokinetics of ICL670 and Fe-$[ICL670]_2$ in plasma and the effect of ICL670 administration on feacal iron excretion in beta-thalassaemia patients.