Oral presentations

Graphical display of population data

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oral presentation

Graphical displays are important tools for exploration, goodness of fit assessment and presentation in any type of data analysis and become even more important as the complexity of the models and data structures increase.

The data encountered in non-linear mixed effects modeling are complex. First, the structure is hierarchical (individuals within populations) and it may be necessary or useful to consider visualization of all the levels in the hierarchy. Second, the amount of data (number of observations and/or individuals) may be very large. This requires efficient ways of producing or, sometimes, displaying, graphs. Third, the data are multivariate, i.e. there is potentially more than one independent variable that needs to be considered in the graphical displays.

Categorical data of the "proportional Cox model" type effectively disqualifies our standard graphical techniques. When the dependent variable is continuous, there is a direct relationship between the observations and the predictions from the model. With categorical observations, on the other hand, the model describes the probabilities of the different outcomes. This means that our graphical methods need to be adjusted such that they also relate to these probabilities.

The first part of this tutorial will review common strategies to address the general issues mentioned above, for cases when the dependent variable is continuous, for example drug concentrations. The second part of the tutorial will concern graphical exploration, goodness of fit assessment and presentation when the dependent variable is categorical. The tutorial will cover a variety of graphical displays and techniques suitable for this purpose, many of which up till now have had no or very little use in the population PK/PD community.

Using SAS for non-linear mixed modelling - An overview

Al Maloney
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oral presentation

The NLMIXED procedure in SAS fits nonlinear mixed models, that is, models in which both fixed and random effects may enter nonlinearly. The conditional distribution of the data (given the random effects) can be specified with either a standard form (normal, binomial, Poisson) or a general distribution. The mixed models are fitted by maximizing an approximation to the likelihood integrated over the random effects. Different integral approximations are available, the principal ones being adaptive Gaussian quadrature and a first-order Taylor series approximation. A variety of alternative optimisation techniques are available to carry out the maximization; the default is a dual quasi-Newton algorithm.

This presentation will give a brief overview of the integral approximation methods, the function optimisation methods, finite difference approximations of derivatives (for gradient and hessian determinations), and the specification of the model, initial estimates, and associated random effects. A selection of the 73 options shall be considered, including the specification of the convergence criteria, and requesting additional output. Obtaining all modelling results can be achieved using the Output Delivery System (ODS). To improve performance, some comments on coding will be made. The advantages and limitations of this procedure will also be discussed. Time permitting, an example of using NLMIXED to perform adaptive trial design with dynamic patient allocation will be presented.

Mixture Modelling for the Detection of Subpopulations in a Pharmacokinetic/Pharmacodynamic analysis

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oral presentation

Introduction and Objectives: To be able to estimate accurately parameters entering a nonlinear mixed effect model using the hypothesis that one or more subpopulations can exist rather than assuming that the entire population is best described by unimodal distributions for the random effects, we developed a methodological approach based on the likelihood approximation using the Gauss-Hermite quadrature. The idea is to combine the estimation of the model parameters and the detection of homogeneous groups of patients in the population using a mixture for the distribution of the random effects. This work presents an application of this methodology on a PKPD population analysis and we compared the results with those obtained by Frey *et al* (2002) who used NONMEM.

Methods: Accuracy of the likelihood approximation is likely to govern the quality of the estimation of the different parameters entering the nonlinear mixed effect model ; we propose to base this approximation on the use of the Gauss-Hermite quadrature. This work presents improvements of this quadrature that render it accurate and computational efficient for likelihood approximation. Moreover, a strategy allowing the detection and explanation of heterogeneity including the Kullback-Leibler test used to estimate the number of components in the mixture is proposed. In order to evaluate the capability of the method to take into account heterogeneity, this methodology was applied in a PKPD analysis using the same database as Frey *et al* and the structural model they selected. This analysis is based on data collected during the clinical development of a once-a-day modified release formulation of gliclazide, a second-generation sulphonylurea used in the treatment of Type 2 diabetes. Frey *et al* looked for non-responders and thus looked for a subpopulation of patients in whom therapeutic effect would be null. Here we look for subpopulations of patients whatever their specificity with respect to such and such parameter entering the effect description. For this reason the distributions of the random parameters are specified as mixture of Gaussian distributions. Each component of the mixture will be identified a subpopulation exhibiting specific characteristics.

Results: Looking at the heterogeneity in the population, same results in term of heterogeneity explanation were found on the parameter corresponding to the baseline of glycaemia. According to the other parameters, heterogeneity was pointed out in the distribution of two parameters entering the effect description. Part of this heterogeneity was explained specifying the relationships between the different subpopulations and covariates and a discussion about the resultant subpopulations was proposed. Looking at the parameters estimation, similar results were found using NONMEM and the proposed methodology with slight differences discussed in this work as partly due to the way non-responders were accounted for in the different methods.

References:

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Modelling and simulation of the incidence of adverse events in clinical trials.

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oral presentation

Objectives: Predict the incidence of a pre-defined adverse event in dose ranging trials of a new compound. The adverse event of interest is typical for the class to which the new compound belongs.

Methods: A PK/PD model was developed using data from Phase II/III trials of a marketed compound of the same class (10 studies, ± 2500 patients). A time-to-event (hazard modelling) approach was used to model the incidence of the adverse event of interest (number of patients with at least 1 episode of the event/total number of patients randomised). This approach utilizes all available information and allows a flexible incorporation of time-varying covariates, including drug exposure, varying trial duration and dropout. A parametric model was developed describing the hazard as a function of time and covariates, including drug exposure. A similar model incorporating the drop out mechanism was also developed. Patient-specific measures of drug exposure were derived from an available population PK-model (developed in NONMEM). The hazard models were fitted by maximum likelihood and implemented in the SAS-procedure NLMIXED. The model was validated against other trials with the same compound. Using these hazard models, a population PK-model based on early Phase I data of the new compound, and adopting a few basic pharmacological and pharmacokinetic assumptions, clinical trial simulations were performed to predict the incidence of the adverse event in the planned dose-ranging trials. Sensitivity analyses were performed to assess to impact of uncertainty in some aspects of the model.

Results: The hazard for developing the adverse event of interest was best described by a steep - virtually on/off - relationship, with patient-specific average steady state concentration. This translated into shallow dose-response relationship for the new compound. Clinical trial simulation allowed to assess the incidence for the planned dose-ranging trials and to balance safety and efficacy.

Conclusion: Hazard modelling is a flexible tool to model the occurrence of (adverse) events in clinical trials. In this application, it allowed to synthesize relevant data of a marketed compound. Simulation allowed studying what can be expected in planned clinical trials based on available knowledge and gaps therein.

What is the Value of Uncertainty Parameter Estimates provided by Different Population PK Methods?

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oral presentation

Background In population models, parameter uncertainty is estimated either by posterior distribution of fixed and random effect parameters or by standard errors (SE) derived from the Hessian matrix with maximum likelihood methods. The SE is a crucial, and controversial, piece of information which varies with the available quantity of information and can be considered as one of the very first steps of model evaluation as well as essential for any future simulations[1].

Purpose The purpose of this study is to compare by simulations the performances for estimating SE of a PK model with different population methods across various designs.

Method We simulate from one compartment PK model with oral absorption, inter-individual log-normal variability and additive error model. Simulation (true) parameters are based on Theophyline dataset provided with NONMEM and optimal sample times by PFIMOPT for all designs[2]. We simulate 100 datasets for each combination of number of subjects (30, 100, 500) associated with each sampling design (3, 6, 15 points/patient). Each of the 900 datasets is fitted using NONMEM methods (FO, FOCE, FOCE Inter) and SE computed either from default NONMEM covariance matrix ($COV) or by non-parametric bootstrap (n=200) after FOCE Inter. We compare, for each of the 4 methods, parameters with their true values and SE with expected values computed by PFIMOPT.

Results In terms of bias with sparse data, we observe no differences between various methods for fixed effect parameters, with all estimates close to true value. When number of points / patient increases, a slight bias appears with FO method (+10% on average). For random effect parameters, consistent bias (+35%) is observed across all designs and methods. Residual error bias disappears when number of points/patient increases. As expected, SEs decrease quickly when subject sample size increases. SEs of fixed effect parameters are close to expected SEs and consistent across all designs and all methods, bootstrap included. SEs of random effect parameters appear to be consistently different from expected ones across all methods and all designs, but highly variable from one data set to another. We find no noticeable difference between bootstrapped and $COV standard errors. Regarding CPU times, SEs are obtained 200 times faster with $COV compared with bootstrap.

Conclusion For all estimation methods, fixed effect parameter SEs, derived from Hessian, look reliable, while those of random effects appear to be highly variable and different from PFIMOPT expected ones. Bootstrap SE are very close to $COV SE. Those results have to be confirmed further with estimates from nlme, with and without bootstrap, and Bayesian posterior estimates from BUGS.

References

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Stochastic differential equations in NONMEM

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oral presentation

Objectives: The objective of the present analysis is to explore the use of stochastic differential equations (SDEs) in nonlinear mixed-effects modelling. The purpose of using SDEs in population PK/PD modelling is to account for correlated residual errors due to possible model misspecification. SDEs can furthermore be used as a diagnostic tool for model appropriateness and provide a framework for pinpointing model deficiencies. The focus of the presentation will be on the implementation and application of SDEs in population PK/PD modelling using NONMEM.

Methods: The intra-individual variability in SDE models is decomposed into two types of noise, i.e. a measurement noise term representing uncorrelated error due to e.g. assay error and a system noise term accounting for model misspecification or true random physiological fluctuations. Parameter estimation in SDE models involves the use of state filtering methods such as the Extended Kalman Filter (EKF) [1] which has been implemented in NONMEM. In the case of no system noise, the SDE model reduces to an ordinary differential equation (ODE) model traditionally used in NONMEM.

Results: Clinical data of GnRH antagonist degarelix was used to explore the use of SDEs in population PK/PD modelling. The PK/PD of IV administered degarelix was analyzed using a three-compartment PK model and a turnover PD model with a pool compartment. The estimated system noise in the PK model was significant but small and likely due to random physiological fluctuations. For the PD model, the estimated system noise was large indicating possible model misspecifications which were attempted pinpointed.

Conclusion:: The SDE algorithm was successfully implemented in NONMEM VI and applied to clinical PK/PD data of GnRH antagonist degarelix. The obtained results illustrated that it is possible to decompose the residual error into measurement and system noise in nonlinear mixed-effects models. Identified advantages of using SDEs compared to ODEs in population PK/PD modelling are: 1) More realistic description of the observed variations and thereby improved simulation properties, 2) can be used as a diagnostic tool for model appropriateness, and 3) provide a framework for pinpointing model deficiencies.

References:

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Using Stochastic Differential Equations for PK/PD Model Development

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oral presentation

Objectives: The objective of this contribution is to demonstrate the benefits of using stochastic differential equations (SDEs) instead of ordinary differential equations (ODEs) for individual PK/PD model development. Using SDEs facilitates more systematic model development by allowing information about structural model uncertainty to be extracted from data in a manner impossible when using ODEs. Allowing such information to be extracted not only provides a basis for constructing tools for performing model diagnostics, but also allows model deficiencies due to time-variations in specific parameters to be pinpointed. Furthermore, using SDEs facilitates tracking of such time-variations and in combination with nonparametric methods for feature extraction this provides a basis for intelligent model improvement.

Methods: The generic model structure used is a stochastic state space model consisting of a set of SDEs describing the dynamics of the states of the system in continuous time and a set of discrete-time measurement equations describing the relationship between the states and the observations obtained. Such models have a number of advantages compared to models based on ODEs. Most important is the inclusion of a diffusion term, the primary difference between an SDE and the corresponding ODE, which, when estimating model parameters, provides a decomposition of prediction error, which allows effects of model uncertainty, e.g. due to model structure misspecifications, to be decoupled from effects of measurement error, and also facilitates tracking of time-variations in model parameters via state filtering.

Results: Simulated as well as clinical data was used to demonstrate the performance of the proposed methodology in terms of facilitating the development of an appropiate model for the absorption kinetics of a drug. Starting from an assumption of first order absorption kinetics, simulated PK data was used for proof of concept by demonstrating that the nonlinear model used to simulate the data could be re-constructed via tracking of time-variations in the absorption rate. Using the same approach, practical applicability was demonstrated using clinical data obtained following SC administration of a long-acting insulin analogue.

Conclusion: Using SDEs for individual PK/PD model development was demonstrated to facilitate systematic model development by providing tools for performing model diagnostics and for intelligent model improvement.

A real time optimal design for model discrimination and parameter estimation for itraconazole population pharmacokinetics

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oral presentation

Introduction: Itraconazole is used in the treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Recent evidence suggests that itraconazole has a better absorption profile when administered as a solution compared to capsule. Itraconazole has an active metabolite hydroxyitraconazole.

Aim: To develop an optimal design for estimation of the population pharmacokinetics for itraconazole and hydroxyitraconazole following administration by solution and capsule.

Methods: The clinical study investigators required the design to have a maximum of 30 patients and a maximum of 4 blood samples taken on each of 2 occasions. Itraconazole is to be administered on two periods, one occasion as the capsule and one occasion as the solution. The time frame for the design was 2 months. Elicitation of prior information from the literature revealed that itraconazole and its metabolite could be adequately described by a 2 compartment model for the parent and a 1 compartment model for the metabolite. It was, however, unclear if the parent displayed linear or non-linear elimination from the central compartment. We developed an optimal population design (using POPT(r)) for two competing multiple response (parent and metabolite) repeated measures models. It was assumed that capsule and solution would follow the same structural model but have different input parameter values. We optimised the product criterion of the linear and non-linear models using simulated annealing. We assessed the performance of the optimal design using simulation and estimation in NONMEM (ver 5).

Results: The optimal population design consisted of 3 elementary designs for both capsules and solution. Joint sampling windows were provided using Monte Carlo simulation. Due to the constraints on the maximum number of blood samples per patient, it was required that we fix some of the parameters, thereby reducing the dimensionality of the model. These parameters were included within the information matrix to preserve their interaction with other parameters but the corresponding row and column were deleted from the information matrix prior to computation of the determinant in each step in the optimisation algorithm. The design took 7 days to optimise on a P4 2.8 GHz PC. Simulation from the optimal design revealed that the design was able to support the estimation of the expected and the alternative model in 100% of the simulated data sets. We also confirmed that the design was able to correctly discriminate between the two models on 74% of occasions when the correct model was linear and 100% of occasions when the correct model was non-linear. We are waiting on the results from the actual study.

Conclusion: We developed a real-time design for a complex population pharmacokinetic model which had multiple response types and where there was uncertainty in the structural pharmacokinetic model. The use of optimal design techniques made an otherwise difficult to construct sparse design manageable in a clinical setting.

Bayesian analysis of a patient dataset using prior information from normal volunteers and from another patient group

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oral presentation

In drug development, researchers have been using available information for designing trials, analysing data and, ultimately, making informed decisions. In particular it is desirable to use this information to maximise the gain from newly obtained data since the sampling frequency of PK/PD responses often lessens as the development progresses.

In this talk, we address common issues regarding Bayesian analysis of a patient dataset where relevant prior information is mainly available from normal volunteers and from patients belonging to another subpopulation. A simulated patient PK dataset is generated for a primarily-renally-excreted antibiotic based on relevant population PK analysis results that include patients with degrees of renal impairments. The knowledge gathered from PK analyses of normal volunteers and from another patient group, coupled with currently available methods to predict patients' renal function is utilised to aid the aforementioned data analysis.

First, the set-ups of numerical priors and population PK models for the analysis are defined to avoid retrospectional bias, while further sets of priors and/or models can be cautiously considered at a later time. The suitability of the analysis itself is then assessed in respect of model-based exchangeability; the assessment is also taken after the analysis. Additionally, we assume that a separate frequentist analysis of the patient dataset is already completed and that the results are available at this stage. A number of analyses of the dataset are then carried out using WinBUGS, adopting a vague prior and informative priors in conjunction with models that together take account of potential heteroscedasticity across the populations. The models are able to allow and/or detect potential differences across the populations so that, in conjunction with other related information, further systematic improvements in the modelling can be achieved. The performance of each analysis is examined in three ways: via a posterior predictive check that examines the general quality of the fit; via conditional predictive ordinates that aim to look at details of the fit; and via common assessment plots. Comparisons across these analyses are also made via plots. Finally, potential applications of the results as a whole are discussed, which focus especially on consequences related to the PD and on whether or not, and how, to address questions arisen from the analyses.

In conclusion, Bayesian analyses using a set of priors with varying degrees of informativeness and of models allowing moderate dissimilarity between different populations enable us to project truer state of drug investigation at any given point of time in a quantitative unified manner.

Stochastic Approximation EM algorithm in nonlinear mixed effects models: an evaluation by simulation

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oral presentation

Context:: Maximum likelihood estimation in nonlinear mixed effects models cannot be directly performed as the likelihood has no close form. Most of algorithms implemented in software are based on a linearization of the model. These algorithms could produce inconsistent estimates and an increase of type I error of Likelihood Ratio Test. To avoid the linearization of the models, Kuhn and Lavielle [1] proposed to combine SAEM, a stochastic approximation version of the EM algorithm [2], with a Markov Chain Monte Carlo procedure.

Objectives:: To implement the SAEM algorithm in R and an evaluation of the likelihood without linearization. To evaluate by simulation the estimation properties of SAEM and of the FOCE method implemented in the nlme function of Splus.

Methods:: We evaluate the likelihood of the SAEM estimates by importance sampling. The instrumental distributions used in the importance sampling procedure are gaussian approximations of individual posterior distributions. We simulate 200 datasets from a biexponential model of the viral load decrease during anti-HIV treatment, 100 datasets with N=40 subjects and 100 with N=200 subjects. This model involves 4 fixed effects with exponential random effects. An additive error on the log viral load with an homoscedastic variance is assumed. We assume identical sampling times for all subjects taken at 1, 3, 7, 14, 28 and 56 days. Parameter values of simulation are taken from Ding and Wu [3]. We evaluate the type I error of the Likelihood Ratio Test with both nlme and SAEM by testing a treatment effect on the first viral decay rate.

Results:: Some of the nlme estimates are significantly biased whereas they are not with SAEM. The RMSE are rather similar with SAEM and nlme. The type I error of the LRT with nlme is overestimated and is 13% when N=40 subjects and 18% when N=200 subjects for a nominal level of 5%. The type I errors of the LRT on the same example are respectively 6% and 5% with SAEM. SAEM is a powerful tool which provides maximum likelihood estimation in nonlinear mixed effects models without linearization.

References::
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Accurate Maximum Likelihood Estimation for Parametric Population Analysis

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oral presentation

Objectives: The statistical performance of estimators of fixed and random effects in parametric population PK analyses can be strongly degraded by the use of likelihood approximations such as FO and FOCE. Here we investigate the computational viability and statistical performance of a new implementation of a parametric expectation-maximization (PEM) method originally formulated by Schumitzky in 1994 [1] that maximizes an accurate parametric likelihood function.

Methods: The PEM algorithm alternates between computing various integrals representing expectations over the random effects distribution (the expectation step) and updating the random effects distribution (the maximization step). Remarkably, even though the accurate likelihood function is being maximized, no explicit evaluations of that function are necessary, although the expectation integrals are similar in form and computational difficulty to the integrals defining the likelihood function. The true likelihood can be shown to increase monotonically during each EM step provided the expectation integrals are evaluated accurately. The required numerical integrals were computed with high accuracy numerical techniques using quadrature points defined by low discrepancy (quasirandom) sequences. The algorithm was also instrumented with an explicit accurate likelihood evaluation at each iteration to verify the theoretical monotonic improvement of the likelihood function and convergence to a maximum. A variety of simulated one compartment IV bolus test cases spanning both sparse and rich data cases as well as different levels of inter-individual variability were analyzed with PEM as well as methods (IT2B, NONMEM) employing FO and FOCE integral approximations.

Results: Under all conditions tested the PEM algorithm converged rapidly and monotonically to a maximum likelihood solution, typically in 20-30 iterations. This was somewhat surprising, given the known linear (and often slow) convergence rate for EM algorithms in other contexts such as mixing distribution estimation and nonparametric population PK analysis. Analyses of individual cases generally took on the order of 1 to 10 minutes for several hundred simulated subjects on a current generation PC. The algorithms that use approximations converged to solutions that were suboptimal to varying degrees with respect to the true likelihood, with the FO method typically showing the largest likelihood deviation from the maximum likelihood solution and the poorest statistical performance. Overall, the statistical performance of the PEM estimators was markedly superior with respect to bias, consistency, and in particular statistical efficiency, the latter by factors up to 3 relative to FOCE and 100 relative to FO for cases with sparse data and/or high inter-individual variability.

Reference:

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PK extrapolation from animal to man: the good, the bad and the ugly. An overview of the performance of different methods applied across the project portfolio at Roche

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oral presentation

Background: In order to reduce failures related to pharmacokinetic (PK) issues and to determine the suitability of compounds for an intended dosing regimen, it is important to predict human PK as early as possible. A variety of different approaches are available for this purpose. Allometric scaling has been traditionally used, however recently mechanistic physiologically based PK (PBPK) models have been developed and made more useful and attractive to the pharmaceutical industry.

Objectives: The aim of this work was to compare empirical and PBPK approaches for the prediction of human PK for 19 Roche compounds that reached clinical development in the last 5 years and to identify the main limitations of the current models. In addition the PK modeling approach was compared to the mg/kg or body surface area (BSA) approach for starting dose determination.

Results: PBPK approaches gave more realistic predictions than the classical empirical methods for all 19 compounds; a greater proportion of the predicted parameters (e.g. Cmax, AUC, t1/2) and plasma concentrations were within 2-fold error of the observed values. For example, AUC was relatively well predicted with 76% of compounds within 2-fold error of the observed value using PBPK compared to only 42% using the Dedrick approach. For Cmax, there was a systematic tendency to underestimate the observed value, and the overall success rate was only 47% using PBPK approaches.

Any poor predictions were generally as a result of biliary elimination and/or enterohepatic recirculation processes that were not incorporated into the model.

Conclusion: In addition to improved prediction accuracy, PBPK approaches offer more potential in the early stages of the drug development process. However the prediction of some parameters such as Cmax remains challenging, for a number of reasons. The lack of prediction models for processes such as biliary elimination and active transport processes still limits the accuracy of the predictions and increases the level of uncertainty.

Incorporating uncertainty and variability into PBPK based predictions of human PK

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oral presentation

Background: PBPK (physiologically based pharmacokinetic) models are used in preclinical research to predict drug concentrations in plasma and various organs based on physiological (volumes, blood flows) and compound specific (partition coefficients, intrinsic clearance) parameters. In general, PBPK model parameters represent averages (often from a small number of measurements), literature data, or even educated guesses. Some PBPK model parameters might be very well characterized in terms of central tendency and dispersion (e.g. blood flow in human). When predicting drug concentrations such knowledge should be incorporated, thus addressing variability. Other PBPK model parameters might not be known enough to assign a firm statistical distribution. When predicting drug concentrations such (mis-)knowledge should be incorporated, thus addressing uncertainty.

Objectives: The objective was to characterize the impact of variability in physiological and compound specific parameters on PK predictions using PBPK models.

Methods: A PBPK model [1,2] was realized in ACSL (advanced continuous simulation language, AEgis Inc). Variability on physiological parameters was incorporated using the P3M database [3]. After selection of relevant records (e.g. male, 18-45 y), multivariate (log)normal random vectors were generated preserving the predefined variance-covariance structure. Compound specific variability was incorporated based on experimental results (in vitro incubations) and standard PK equations. The ACSL program generated the random parameter vectors for a specified number of subjects and summarized predicted plasma-concentration versus time profiles into median, 5% and 95% percentiles.

Results/Conclusion: So far, preliminary results from one iv administered compound suggest that physiologically related variability (as obtained from the P3M database) may not contribute much in addition to compound specific variability. However, the relationship between physiological and compound specific parameters and PK predictions needs to be investigated in more detail to better understand the sensitivity of the system.

References:

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NONMEM Implementation of Cell Lifespan Models for Hematological Drug Effects

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Johnson & Johnson Pharmaceutical Research and Development
oral presentation

Different PK/PD models for dealing with the hematological drug effects have been recently published in the literature [1,2]. The models assumed that cells produced by a zero or first order process, survive for a specific duration (cell lifespan) and then are lost. The rate of cell loss must be equal to the production rate but is delayed by the cell lifespan. Drugs can stimulate or inhibit the production rate of cells according to a general Hill function [1]. In order to model the proliferation and maturation stages of cells, different number of precursor pool compartments could be added to the models. In addition, anticancer agents are assumed to act on the precursor pool based on irreversible linear or capacity-limited cytotoxicity [2].

Due to the fact that delayed differential equations are needed for cell lifespan models, their implementation in NONMEM is not straightforward. The objective is to present the NONMEM implementation of five different cell lifespan models for dealing with the hematological drug effects and to evaluate NONMEM performance to estimate the model parameters.

Model 1 and 2 assume cells are produced by a zero and first order process, respectively. Model 3 and 4 assume a precursor pool indirect model to account for cell proliferation and removal from the circulation. In model 3, every process was quantitated with a specific cell life-span, after a zero order precursor rate production, whereas model 4 assume a zero order precursor rate production followed by a first order proliferation rate. In this model the removal from the circulation occurs after a cell lifespan. Model 5 assume a three-pool indirect model to account for the cell proliferation, maturation and removal from the circulation. Every process was quantitated with a specific cell life-span, after a zero order precursor rate production. Models 1 to 4 assume drug stimulated the precursor production rate. Model 5 mimics the anticancer drug effects and assumes drug effect takes place at the cell proliferation stage following a capacity-limited cytotoxicity.

Simulation followed by estimation were used to evaluate NM performance and the impact of the interindividual and residual variability magnitude on the estimates of the population parameters.

References:
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Adaptive Designs : Bayesian & Non-Bayesian Approaches

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oral presentation

The recent past has seen a considerable increase in the use of flexible and adaptive designs. However adaption is not new. In this tutorial I will discuss a taxonomy of clinical trial designs which will cover many of the adaptive designs which are available. These will run from very simple up-and-down designs which have been used for more than 50 years, to very complex designs involving surrogate end-points and Bayesian decision making.
All of the designs will be illustrated with examples.

An adaptive design for dose-response using the Normal Dynamic Linear Model.

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oral presentation

Objectives: Adaptive designs have an intuitive appeal in the drug development environment where we are trying to balance allocation of patients to efficacious doses with maximising our learning about the dose-response relationship while doing so in as cost-efficient a manner as possible. We suggest a pragmatic approach to running an adaptive dose-response trial on a VAS numerical rating scale endpoint, dropping ineffective doses and terminating the study early if there is no clear clinical benefit.

Methods: A Normal Dynamic Linear Model has been used to describe the dose-response relationship. This is a very versatile and flexible model which allows for non-monotonic response functions. This could be an important consideration in the chosen endpoint if subjects drop out of the study early. The NDLM also provides, within the bayesian context, access to probabilistic statements about features of the dose-response relationship. These probabilistic statements form the basis of decision criteria for dropping doses and terminating the study outright if there is a low probability of showing sufficient efficacy. Simulations were performed to investigate the performance of these rules when the simulated data were analysed at different interim analyses. The timing and frequency of these interims could be optimised using the simulation results.

Results and conclusions: The results of the simulated trials show that it is possible to run a cost-effective adaptive trial based on a parallel group study with equal allocation to treatments. A simple study design makes the execution of the study much simpler and we get the benefits of an adaptive design (dropping ineffective doses) without the complexity of some other adaptive designs in the setup phase. The interim analyses show good power and low Type I error with significantly lower average sample sizes than conventional studies run to completion. The inferences from the NDLM correctly pick out doses with low probability of success from those that are efficaceous. The estimated cost savings due to stopping the study early and dropping individual doses due to lack of efficacy could be as much as $486,000.

Adaptive dose-finding in two-dimensions: A phase 1 oncology example

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Cytotoxins are widely used in combination, despite similar toxicities, for example in the bone marrow or gastronintestinal tract. Finding an optimal dose in terms of toxicity with a single drug (one dimension) has proven to be far from simple, due to the ethical limitations on the trial design and complexities of dealing with noisy data concerning multiple-organ systems. The traditional Markov-style scheme used in one dimension has limitations, however uptake of continual reassessment methodologies has been slow. Further challenges arise in finding the optimal combination of doses for two or more agents. The typical approach of "collapsing" the two-dimensional problem into a one-dimensional series of ordered dose may not find the optimal balance of toxicity and efficacy. The application of adaptive designs in two dimensions requires explicit consideration of the toxicity and efficacy surfaces that are a function of dose of each drug and requires that we unmask several critical assumptions, particularly concerning synergy. A simple mathematical framework applicable to the incidence of DLTs is described and its limitations highlighted. This relatively simple model allows the application of a CRM-style dose finding scheme in more than one dimension, and some illustrative simulations help to assess performance. Practical aspects of adaptive designs are also considered, including elicitation of sensible priors and description within a protocol. Finally, an example of the successful application of this methodology at the University of Newcastle is presented, along with lessons learned. Approaches to extending the model, for example with biomarkers of toxicity or efficacy, are also discussed.

Pharmacokinetic/Pharmacodynamic Modelling of the Analgesic Effects of Tramadol in the Paediatric Population

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oral presentation

Introduction: The metabolite O-demethyltramadol (M1) is the main responsible for the analgesia after administration of tramadol (T). The ability of young children to form M1 is still not characterised.

Purpose: To develop a population pharmacokinetic/pharmacodynamic (PK/PD) model for T in paediatrics.

Methods: 104 children [mean age (range) = 4.55 (2-8) years; mean weight (range) = 19.65 (10-43 kg)] received postoperatively an initial 2.5 min i.v. infusion of T at 1 mg/kg. Depending on pain relief one third of the initial dose was given at 15, 30 and/or 45 min. Serum samples and several response variables related to pain relief were recorded for a 6 h period. The latter were modelled as ordered categorical variables using logistic regression in NONMEM V.

Results: PK. Disposition of T and M1 was described with a two and a one-compartment model, respectively. Weight showed significant effects ($p<0.001$) on T and M1 distribution and on elimination of T, respectively. Inter-subject variability did not exceed 52%. The mean (range) predicted maximum plasma concentration values for T and M1 were: 1914.7 (1067.6 - 3310) and 25 (9.7 - 87.4) ng/mL, respectively. PK/PD. M1 in the effect site was the best predictor of crying and agitation. Movement was best correlated with T in the effect site. Weight was found to have a significant ($P < .05$) effect on the baseline pain relief of crying and agitation. Typical steady-state plasma concentration levels of M1 and T of 10 and 120 ng.mL-1 in a 20 kg child, were associated with a 95 % probability of achieving complete pain relief.

Conclusions: T and M1 show predictable PK and both are important predictors of T induced analgesia. Children have the ability to produce enough M1 to achieve adequate pain relief safely.

Population Modelling of the Absolute Bioavailability and Pharmacokinetics of Phenobarbitone in Infants with Seizures

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oral presentation

Objectives: Seizures occur in 1-2 infants per 1000 term live births and constitute a medical emergency with significant risk of mortality and morbidity, such as impeded neuronal development. Phenobarbitone is the long-standing treatment of first choice, but it has adverse effects including inhibition of brain growth and neuronal toxicity. Little is known of the pharmacokinetics of phenobarbitone in these patients, especially the oral bioavailability. In this study we determined the pharmacokinetics of oral and intravenous phenobarbitone in order to provide guidelines for seizure management in combination with plasma concentration monitoring data.

Methods: A population pharmacokinetic analysis was developed using NONMEM with the G77 compiler and first order conditional estimation. Phenobarbitone concentration data were obtained retrospectively from medical records. Using a one-compartment model, estimates of clearance, volume of distribution, and fraction of absorbed dose were obtained. Interindividual and residual variabilities were estimated using an exponential and additive error model, respectively. The absorption rate constant was fixed to 2 h^{-1} because of lack of data in the absorptive phase. Several patient characteristics were screened for influence on the typical pharmacokinetic parameter values.

Results: From 1-9 (median 2) plasma samples per infant were obtained from 113 infants of mean (range) age of 13 (1-108) d, gestational age 36.8 (23-42) wk, and current weight of 3.0 (0.59-5.8) kg. The mean plasma concentration was 29.5 (1-93) mg/L. The typical values (interindividual variability) were 12.2 mL h^{-1} (38%) for clearance and 1.9 L for volume (33.9%) at median weight of 3.27 kg. A linear median-centred weight model on both parameters significantly improved the fit to the data. The systemic oral bioavailability was 0.61 (33.6%) and was unaffected by any patient characteristic. The elimination half-life (based on typical values) was 107.9 h. The residual variability was 20%.

Conclusion: Typical clearance, volume of distribution and half-life were similar to adult values, but the bioavailability was somewhat lower. The half-life was longer than reported in older children. Infants older than 14 d had lower drug levels indicating a possible need for upward dose adjustments. There was considerable interindividual variability in all parameters which justifies continued plasma phenobarbitone concentration monitoring in these patients.

The Value of Priors and Prior Uncertainty in Clinical Trial Simulation: Case Study with Actinomycin-D in Children with Cancer

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oral presentation

Introduction: Actinomycin-D (AMD) is an antineoplastic agent used for the treatment of childhood cancers since the 1960's. Despite its longstanding and widespread use, there is very little pharmacokinetic information from which safe and appropriate pediatric dosing can be derived.

Objectives: To assemble and review prior information about AMD's activity, PK/PD, and clinical experience in adults and children to construct a drug and study model to explore outcomes and evaluate trial designs. To examine the sensitivity of outcomes (PK, PD, safety and efficacy) to model assumptions and various parameterizations.

Methods: Compartmental and physiologically-based PK models were created based on prior information derived primarily from the literature. Likewise, clinical event rates for drug response and toxicity measures were obtained from the literature and incorporated into the outcome model as categorical data with assigned probabilities. Model evaluation was conducted using NONMEM (version V) and simulation models were built using Pharsight Trial Simulator (version 2.1.2). Available priors from which the drug model was created include the following: DNA binding and inhibition of cell proliferation data [1, 2]; ^{3}H-AMD animal disposition data[3,4]; AMD-^{3}H pilot PK study in 3 patients [5].

Results: Structural models (2 and 3 CPM and physiologically-based models with allometric scaling of drug clearance) for AMD agreed well with limited adult human and animal data. The appropriateness of the various model expressions is extremely dependent on the assumption that the ^{3}H-AMD accurately reflects the free, parent AMD in children, variability is modest and that typical scaling of drug clearance with body weight is appropriate. Assignment of the toxicity correlation is dependent on the assumption that other co-administered chemotherapeutic agents do not contribute to the AMD-associate toxicities and that we have appropriately aligned systemic versus peripheral toxicities based on the presumed exposure-response relationship. Based on our assumption of potency and composite PK model, we can discriminate dose groups independent of study design.

Conclusions: Compartmental and physiologic models used to define the underlying structural PK model of AMD are based on limited prior information. Despite the degree of parameter uncertainty, projected outcomes based on constructed models still permit the association of exposures to observed toxicities and confirms the utility of the approach. We plan to examine the validity of the proposed simulation model in an upcoming prospective, clinical trial. We further intend to construct an appropriate evidence-based pop-PK/PD model from which dosing guidance for children with cancer can be derived.

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Bayesian Population Pharmacokinetic Analysis of Sirolimus

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oral presentation

Objective: It is usual that data collected from routine clinical care is sparse and unable to support the more complex pharmacokinetic (PK) models that may have been reported in previous rich data studies. Informative priors may be a pre-requisite for model development. The aim of this study was to estimate the population PK parameters of sirolimus using a fully Bayesian approach with informative priors.

Methods: Informative priors including prior mean and precision of the prior mean were elicited from previous published studies using a meta-analytic technique. Precision of between-subject variability was determined by simulations from a Wishart distribution using MATLAB (version 6.5). Concentration-time data of sirolimus retrospectively collected from kidney transplant patients were analysed using WinBUGS (version 1.3). The candidate models were either one- or two-compartment with first order absorption and first order elimination. Model discrimination was based on computation of the posterior odds supporting the model.

Results: A total of 315 concentration-time points were obtained from 25 patients. Most data were clustered at trough concentrations with range of 1.6 to 77 hours post-dose. Using informative priors, either a one- or two-compartment model could be used to describe the data. When a one-compartment model was applied, information was gained from the data for the value of apparent clearance (CL/F = 18.5 L/h), and apparent volume of distribution (V/F = 1406 L) but no information was gained about the absorption rate constant (k_a). When a two-compartment model was fitted to the data, the data were informative about CL/F, apparent inter-compartmental clearance, and apparent volume of distribution of the peripheral compartment (13.2 L/h, 20.8 L/h, and 579 L, respectively). The posterior distribution of the volume distribution of central compartment and k_a were the same as priors. The posterior odds for the two-compartment model was 8.1, indicating the data supported the two-compartment model.

Conclusion: The use of informative priors supported the choice of a more complex and informative model that would otherwise have not been supported by the sparse data.

Evaluation of a transit compartment model versus a lag time model for describing drug absorption delay

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oral presentation

Background: Traditionally, a delay before the commencement of drug absorption has been modeled as a discrete lag time. At this lag time, the concentration-time profile is discontinuous, which is unattractive from a computational point of view and which does not have physiological basis. An analytical solution of a delay model which approximates a series of transit compartment may avoid these drawbacks of the discrete lag model.

Aim: To compare the performance of the standard lag-time model with an analytical solution of the transit compartment model, which allows the (non-integer) number of transit compartments to be estimated, on data from 4 different compounds.

Methods: Concentration-time data on glibencamide, furosemide, amiloride, and moxonidine was analyzed. In the transit compartment model, absorption delay was described by the passage of drug through a series of transit compartments with a single transfer rate. Drug transfer to the central compartment was described by a second rate constant. The optimal number of transit compartments was estimated from the data. The population pharmacokinetic analysis was performed in NONMEM using the FOCE method with interaction. Goodness-of-fit was assessed by the decrease in OFV value and by inspection of diagnostic graphs.

Results: For all investigated drugs, a significant absorption delay was estimated with both the transit compartment model and the lag time model. With the transit compartment model, the goodness-of-fit was visibly better in the absorption phase and around the concentration peak compared to the lag time model. A significant drop in the OFV up to 530 points was observed with all compounds. The estimated number of transit compartments for glibenclamide, furosemide, amiloride and moxonidine were 22.9, 9.7, 12.4 and 7.2 respectively. The estimates of the remaining PK parameters were similar between the two models.

Conclusion: Based on the results from this comparison with four drugs, the transit compartment model is an attractive alternative for modeling drug absorption delay, especially when the drug absorption phase is poorly described by a lag time model.

Disease Progression in Parkinson's Disease - Evidence for Protective Effects of Drug Treatment

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oral presentation

Objectives: The effects of drug treatment on the progression of Parkinson's disease have been studied in large clinical trials but no conclusion has been reached about their protective effects. This study investigated the time course of the Unified Parkinson's Disease Response Scale (UPDRS) in a large cohort of patients over 8 years to describe disease progression and drug effects.

Methods: 800 patients enrolled in the DATATOP study[1] were followed for up to 8 years. Time and drug treatments were used to model the progression of 15,236 UPDRS observations with NONMEM using the first order conditional method.

Results: The progression of UPDRS was adequately described by a linear model. An improvement in objective function was obtained with a Gompertz function which predicted an asymptotic 'burn-out' state. Levodopa, deprenyl, bromocriptine and pergolide had both symptomatic and protective effects. The symptomatic effects of levodopa were greater than the other drugs but protective effects were similar. The efficacy (Emax) of levodopa increased with time reaching its peak about 2 years after initial entry. The combination of levodopa and deprenyl had a greater protective effect than predicted from their separate effects.

Conclusions: Modelling disease progression has revealed both expected and unexpected features of drug action in Parkinson's disease. The model has been used successfully to predict the outcome of a trial designed to detect a protective effect of levodopa [2].

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