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Meindert Danhof & Bart Ploeger Implementing Receptor Theory in PK-PD Modeling

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Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) models differ from conventional PK-PD models in that they quantitatively characterize specific processes on the causal path between drug administration and effect. This includes target site distribution, target binding and activation, pharmacodynamic interactions, transduction and homeostatic feedback mechanisms. Consequently, the effects on disease processes are considered. It has been demonstrated that, compared to traditional descriptive models, mechanism-based PK-PD models have improved properties for extrapolation and prediction. Hence, they constitute a scientific basis for rational drug discovery and development [1,2].

Mechanism-based PK-PD models utilize receptor theory concepts for characterization of target binding and target activation processes. In this respect, receptor theory constitutes the basis for 1) prediction of *in vivo* drug concentration-effect relationships and 2) characterization of target association-dissociation kinetics as determinants of hysteresis in the time course of the drug effect.

Prediction of *in vivo* concentration-effect relationships

In the traditional PK-PD modeling approach rather empirical models such as the Hill equation are used to describe *in vivo* drug concentration-effect relationships. However, the Hill equation does not provide insight into factors determining the shape and location (in terms of concentration) of the concentration-effect relationship.

In theory, the relationship between drug concentration and biological response depends on drug and biological system specific factors. Therefore, the prediction of *in vivo* drug concentration-effect relationships requires distinguishing ‘drug-specific' and ‘biological system-specific' parameters. Classical receptor theory can be applied for making this separation, since it describes drug action by 2 independent parts, which relate to drug-specific (i.e. the agonist-dependent part) and system specific properties (i.e. the tissue-dependent part). Hence, receptor theory constitutes a scientific basis for the prediction of *in vivo* concentration-effect relationships [3].

Receptor theory has been incorporated in pharmacodynamic modeling in semi-parametric and full-parametric approaches. Both approaches use a hyperbolic function for describing target binding and activation, but differ in the way they describe the system-specific transducer or stimulus-response function. In the semi-parametric approach no specific assumptions are made with regard to the transducer function, making this approach particularly suitable for exploratory data analysis [4], whereas the full parametric approach requires the shape of the transducer function to be known. Particularly in systems with a high receptor reserve a hyperbolic transducer function is commonly observed, which can be implemented using the ‘Operational Model of Agonism' [5,6].

Mechanism-based PK-PD models can be identified by simultaneously analysing concentration-effect relationships of a variety of compounds with different target affinity and intrinsic efficacy. In this manner the system-specific transducer function, describing the unique relation between target

activation and effect, can be identified. In addition, for each of the compounds estimates of the *in vivo* operational affinity and intrinsic efficacy are obtained. In a series of investigations on drugs acting at G-protein coupled receptors (i.e. adenosine A_1, μ-opioid and serotonin 5-HT_{1A} receptors) and at the $GABA_A$ receptor complex, close correlations have been observed between estimated *in vivo* values and corresponding values derived from *in vitro* bioassays [6 - 9]. This shows the utility of receptor theory models for predicting *in vivo* concentration-effect relationships using *in vitro* bioassays data. This modeling approach has been successfully applied in the characterization of tissue-selectivity of drug effects [10], inter-species extrapolation of concentration-effect relationships [11] and analysis of inter-individual variability in pharmacodynamics resulting from 'receptor down regulation' [12]. Most recently the application of receptor theory in PK-PD modeling has been extended to pharmacodynamic drug interactions [13].

Target association-dissociation kinetics as determinants of hysteresis

Target association-dissociation kinetics can be a significant determinant of hysteresis between plasma concentration and effect. Estimation of the rate constants of *in vivo* target association-dissociation is often complex as it may be confounded by the biophase distribution kinetics and the kinetics of transduction. However, a number of studies [14 - 19] have shown that measuring drug concentrations in the biophase and/or the availability of data from dedicated pharmacological experiments allows accurate and precise estimation of target binding kinetics. An investigation in rats has shown that advanced imaging technologies (e.g. positron emission tomography) enable direct estimation of the target association and dissociation kinetics by PK-PD modeling [14]. Alternatively, simultaneous fitting of a series of *in vitro* binding experiments allows estimating the receptor association and dissociation rate constants [15]. Biophase distribution and target association-dissociation kinetics of semi-synthetic opioids were simultaneously estimated using data on the time-course of their analgesic and respiratory depressant effect in rats [16,17] and in humans [18,19]. A crucial factor in these analyses was the availability of dense data on the time course of drug concentration and effects following administration of a wide dose range. These models have been successfully applied for extrapolation of the pharmacodynamics of buprenorphine from rats to humans [20] as well as the design of optimized dosing regimens for the antagonism of buprenorphine-induced respiratory depression with naloxone [21].

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Mats Karlsson & Nick Holford A Tutorial on Visual Predictive Checks

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The visual predictive check (VPC) is a model diagnostic that can be used to: (i) allow comparison between alternative models, (ii) suggest model improvements, and (iii) support appropriateness of a model. The VPC is constructed from stochastic simulations from the model therefore all model components contribute and it can help in diagnosing both structural and stochastic contributions. As the VPC is being increasingly used as a key diagnostic to illustrate model appropriateness, it is important that its methodology, strengths and weaknesses be discussed by the pharmacometric community.

In a typical VPC, the model is used to repeatedly (usually $n \geq 1000$) simulate observations according to the original design of the study. Based on these simulations, percentiles of the simulated data are plotted versus an independent variable, usually time since start of treatment. It is then desirable that the same percentiles are calculated and plotted for the observed data to aid comparison of predictions with observations. With suitable data a plot including the observations may be helpful by indicating the data density at different times and thus giving some indirect feel for the uncertainty in the percentiles. Apparently poor model performance where there is very sparse data may not as strongly indicate model inadequacy as poor performance with dense data. A drawback of adding all observations to the VPC, in particular for large studies, is that it may cloud the picture without making data density obvious. A possible intermediate route is to plot a random sub-sample of all observations.

The percentiles chosen for plotting are often the 5^{th}, 50^{th} and 95^{th} percentile. However, for small data sets, less extreme percentiles (e.g. 25^{th} and 75^{th}) may be more appropriate. The stochastic components of the model will be of particular importance for predicting extreme percentiles. Thus such percentiles would be expected to act as useful diagnostics for that part of the model. At the same time, with small data sets, large differences between extreme percentiles based on simulated and observed data can occur by chance. The trade-off for suitable choice of percentiles, versus data set size and model component to diagnose has not been clearly outlined. However, identification of the 5^{th} percentile is normally based on 1000 values or more. Between subject variability is often the dominating variability component, and, therefore extreme percentiles such as the 5^{th} and 95^{th} maybe should probably be reserved for large studies (more than 500 subjects).

Stratification may be necessary to make a VPC illustrative when observations at the same value of the independent variable have different simulated distributions. Such differences will occur for: different response variables, different arms of a trial (placebo, varying doses, and active control), different routes of administration, different dose intervals, and whenever there are covariate relationships influencing any of the parameters of the model. However, stratification into many separate VPCs may also hamper diagnosis and a suitable balance has to be found. For some (small) data sets such a balance may be difficult to find and they may not be suitable for the VPC.

Binning is a procedure that may be necessary when observation times are heterogeneous between subjects. It involves grouping observations in different time intervals so that there are suitably large

number of observed values can be used to define the percentiles of the observed distribution. If this is not performed, the resulting percentiles may be very noisy and give little helpful information. One possibility is to use nominal (protocol) times for all observations and simulations. This procedure assumes that observations and simulation distributions are similar for neighbouring times. An alternative is to allow all observations/simulations within a time interval to contribute to defining a prediction interval that is common for the time interval. Binning will always lead to a certain distortion of the relationship between model simulations and the observations. It may therefore be useful to assess the sensitivity of the resulting graph to the binning choices that have been applied.

Uncertainty in the discrepancy between the percentiles of the observed and simulated data can make it hard to conclude whether differences represents model misspecification or not. This can be investigated by inspecting the variability that would be expected due to random chance. The uncertainty in the prediction intervals from the simulated data is related to the number of simulations performed. Thus, the number of simulations should be sufficiently large for this variability not to play an important role. The observed data is finite sample and may therefore show deviation from the expected behaviour, even if the model is correct. A procedure for assessing how large random variations can be expected involves calculating prediction intervals for each of the simulated data sets. From a suitably large number of simulated data sets confidence intervals based on the replicate prediction intervals can then be calculated.

The VPC, like other simulation-based diagnostic, relies on the appropriateness of the simulations that are performed. This may be difficult when adaptive designs are being employed. If the criteria for all adaptations are defined prospectively, creating simulations is "only" a technical difficulty. If, however, adaptation of doses, dosing intervals, observation frequency and other treatment aspects are based on subjective judgment by the physician or the patient, it can be extremely difficult to perform adequate simulations.

Missing data and protocol violations represent other situations which can be challenging with respect to simulations. Censoring of pharmacokinetic data due to data below limit of quantification and censoring of pharmacodynamic data due to patient dropout are situations where often a model should be constructed for predicting the censoring. It such situations it is also important to assess that the number and timing of the censoring mimics that of the real data. If the model is adequate, the full distribution of uncensored data can be realistically recreated in the simulations.

The VPC is rapidly becoming one of the most important diagnostic tools available. Therefore it is important to fully understand when it is suitable and how it can be made as informative as possible, and to understand the decisions and trade-offs necessary when constructing it.

Marilee Andrew Effect of Cranberry Juice on Population Pharmacokinetics of Amoxicillin and Cefaclor

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Objectives: Consumption of cranberry juice with low-dose oral antibiotics is often prescribed as long-term therapy/prophylaxis for recurrent urinary tract infection. β-lactam antibiotic disposition is moderated by multiple carrier-mediated pathways that also may be modified in the presence of cranberry juice. In addition, amoxicillin disposition is known to exhibit strong dose dependence [1]. The aim of this study was to determine whether co-administraton of cranberry juice alters β-lactam antibiotic population pharmacokinetics

Methods: In a crossover design, 18 healthy women received treatments of 500 mg or 2 g amoxicillin p.o. with water or 8 oz cranberry juice cocktail, or 500 mg cefaclor p.o. with water or 12 oz of cranberry juice cocktail. Blood samples were collected pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6 and 8 hr post-dose. Urine collections were made pre-dose and at 2 hr intervals for 8 hr post-dose. Population pharmacokinetic analysis of serum data was performed using SAAM-II, SPK (University of Washington, Seattle, WA, USA) and NONMEM ver. V (Globomax LLC, Hanover, MD, USA). Candidate structural models investigated prior to final model selection included a two compartment model with first order absorption and elimination, a two compartment with delay and first order absorption and elimination, and a two compartment with Michaelis-Menten absorption and first order elimination [2]. The final structural model consisted of one compartment with Weibull nonlinear absorption (profile based on the Weibull distribution) and first-order elimination [3]. Standard-Two-Stage population analysis was used to seed nonlinear mixed effects model runs with full covariance matrices in order to investigate appropriate covariance models. Reduced covariance matrix structures based on block diagonal and diagonal elements were selected. Between Subject Variability (BSV) and Between Occasion Variability (BOV) were modeled as lognormally distributed. Additive and proportional models were investigated for the Residual Unknown Variation (RUV) error model. FO and FOCE estimation methods were explored. The influences of dose, juice consumption and bodyweight on apparent clearance, apparent volume and the Weibull absorption shape (S) and scale (TD) parameters were examined. Several goodness-of-fit measures were used to evaluate model fit.

Results: FO method was selected due to difficulties achieving convergence with FOCE method. True likelihood profiling was used to verify the adequacy of FO method in select cases. Visual inspection revealed that individual predictions fit the data well. Data values were noted to be evenly distributed around the individual predictions, and the weighted residuals were evenly distributed around zero. The population predictions for amoxicillin exhibited a slight bias, overpredicting data values for the highest predicted concentrations. This latter is hypothesized to result from the model failing to capture some of the variation due to approaching the limits of parameterization. Population predictions of cefaclor were well distributed with respect to the data values.

Amoxicillin was best described using an additive error model (RUV of 0.689 mcg/ml), while cefaclor was best described by a proportional error model (RUV of 26.5%). Final amoxicillin and cefaclor models included as covariates a juice consumption effect on the Weibuill scale parameter TD and a bodyweight effect on apparent volume. The amoxicillin final model also included dose-dependence effects on CL/F, VOL/F and the Weibull scale parameter TD.

Amoxicillin CL/F of 22.1 ± 1.04 (standard error) L/hr for a 500 mg dose, with 10.6 ± 1.05 L/hr ΔCL/F due to high dose, correlated well with noncompartmental estimates of 20.8 – 22.0 L/hr for CL/F at 500 mg and 32.3-33.6 L/hr for total CL/F at 2 g dose. BSV and BOV on CL/F were 18.7 and 15.0%, respectively. Estimated dose-dependence covariates on amoxicillin CL/F and VOL/F were found to exhibit relative bioavailability comparable to an independent estimate obtained using urinary excretion data. Population values of amoxicillin VOL/F were 22.5 ± 1.06 L for low dose with 10.6 ± 1.05 L ΔVOL/F due to high dose administration. BSV and BOV were 72.6 and 35.6%, respectively. Weibull population values S and TD were 2.86 ± 0.11 (unitless) and 1.31 ± 0.19 hr, respectively, with BSV of 32.9 and 10.8%, respectively, and BOV of 32.7 and 13.4%, respectively. Bodyweight produced a change in VOL/F of 105 ± 93 ml per kg-bodyweight difference from median. High dose administration increased TD from baseline by 0.375 ± 0.164 hr, or 29%. Juice co-administration increased TD from baseline by 0.533 ± 0.074 hr, or 41%. In simulations using the population parameter values, increased TD produced a modest decrease in Cmax and increase in Tmax. This correlates well with the statistically significant increase in Tmax observed in noncompartmental results for doses co-administered with juice.

Cefaclor CL/F of 24.4 ± 1.24 L/hr correlated well with noncompartmental estimates of 23.8 – 24.5 L/hr. BSV on CL/F was 19.7%; no BOV was indicated. VOL/F was 21.5 ± 1.27 L, with 17.4% BSV and 10.5% BOV. Weibull population parameter values of S and TD were 1.73 ± 0.18 (unitless) and 0.704 ± 0.05 hr, respectively, with BSV of 69.7 and 26.8%, respectively, and BOV of 55.2 and 27.8%, respectively. Bodyweight produced a change in VOL/F of 146 ± 43 ml per kg-bodyweight difference from median. Juice co-administration increased TD from baseline by 0.160 ± 0.060 hr, or 23%, which resulted in a slight decrease in Cmax and increase in Tmax. This change correlates with the statistically significant decrease in Cmax observed in noncompartmental results for co-administration with juice.

Conclusions: The Weibull nonlinear absorption function and model parameterization to accommodate dose-dependent relative bioavailability provide a useful framework for assessing changes in absorption and overall disposition. Cranberry juice cocktail has a statistically significant but modest effect on the population pharmacokinetic profiles of amoxicillin and cefaclor. Changes in the absorption profile of both drugs cause slight to modest increases in Tmax and decreases in Cmax. Amoxicillin also exhibits a strong dose dependence that appears both to affect relative bioavailability in the form of significantly reduced Cmax and AUC, and to cause a slight increase in Tmax at high doses. These findings are consistent with previously published clinical pharmacokinetic results. The modest effects of cranberry juice consumption on disposition suggest that β-lactam antibiotics may be safely co-administered with typical servings of cranberry juice cocktail.

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Michael Barras Individualized compared with conventional dosing of enoxaparin.

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Introduction: There is widespread belief that individualizing dosing regimens of drugs will further optimize outcomes for each patient. However there are few prospective studies that have assessed the benefits or risks of such interventions. A compelling prior example showed that individualized pharmacokinetically guided chemotherapy in children with acute lymphoblastic leukemia provided a 15% improvement in 5-year complete remission over conventional dosing [1]. Enoxaparin is a low-molecular-weight-heparin used to treat thromboembolic disorders, however limited information is available that quantifies its safety in patients who are obese and / or have renal impairment. Two population PKPD studies [2, 3] have however quantified the influence of these covariates on the pharmacokinetics of enoxaparin and proposed individualized dosing regimens to maintain effectiveness and minimise toxicity.

Objectives: To evaluate if individualized enoxaparin dosing reduced the incidence of adverse events whilst ensuring therapeutic anti-Xa concentrations.

Methods: Two methods were used:

1. A confirmatory randomized, controlled, double blind clinical trial was performed to compare conventional (product label) with individualized dose guidelines. Patients randomized to the individualized arm were dosed using lean body weight if obese and total body weight if non-obese. Patients were dose adjusted at 48 hours according to renal function. Those in the conventional arm received a dose as determined by the treating physician, in accordance to the product label. The primary endpoint was the prevalence of bleeding events and the secondary endpoint a combination of bleeding or major bruising events (single bruise ≥ 20 cm2). This trial constituted the confirmatory component to the learn-confirm paradigm [4].

2. Within the confirmatory trial a learning component was included to quantify the result as a function of drug exposure. A categorical PKPD analysis was performed using NONMEM, to describe the severity of an adverse event as a function of exposure and demographic variables. Severity categories were defined a priori to match those used in the confirmatory component of the trial: S (0) no event or bruise < 1cm2; (S1) minor bruise (≥ 1 cm2 & < 20 cm2); and (S2) major bruise or bleed. The model was used to explore the likely occurrence of adverse events in patients with obesity and / or renal impairment dosed using either the individualized or conventional dose strategies.

Results: 118 patients were randomized to treatment; 56 in the individualized arm and 62 in the conventional arm. There were no significant differences between the two arms in their baseline demographics, mean duration of therapy and mean dose per day. The primary outcome (bleeding) occurred in one patient (2%) in the individualized arm and nine (15%) in the conventional arm (RR = 0.12, 95%CI = 0.01-0.89; P = 0.03). Six patients (11%) in the individualized arm and 21 (34%) in

the conventional arm had a composite bleeding or major bruising event (RR = 0.30, 95%CI = 0.12-0.71; P = 0.003). In both arms of the study there were no recurrent thromboembolic events during treatment and no deaths had occurred at 30 days [5].

PD data were obtained from 103 of the 118 patients. The final categorical model included cumulative AUC (cAUC) & age:

Logit (S0) = 2.83 - 2.75 * cAUC / 23 IU ml/hr - 0.54 * Age / 61 yr

Logit (S1) = Logit (S0) + 2.05

Simulations showed that dose individualization reduces the probability of a major bruise or bleeding event. This was most noticeable in patients with both obesity and renal impairment.

To further support the confirmatory study, data (cAUC and age) from patients in both treatment arms were introduced into the final categorical model. Plots of the probability of a major bruise or bleeding event versus cAUC clearly demonstrate the benefits of using an individualized dosing strategy.

Conclusion: Individualized dosing regimens for enoxaparin, based on prior population PKPD analyses, reduce the prevalence and severity of bleeding and bruising events when compared to conventional dosing, without apparent loss of effectiveness.

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Jeff Barrett Enhancing Methotrexate Pharmacotherapy in Children with Cancer: A Decision Support System Integrating Real-time PK/PD Modeling and Simulation with Patient Medical Records

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Objectives: The use of pharmacokinetic (PK) and pharmacodynamic (PD) measurements in the clinical care of patients is often limited to clinical pharmacists and pharmacologists; with the exception of few medications, treating physicians and caregivers are often unfamiliar with the value of such assessment to guide the day-to-day management of their patients. Methotrexate (MTX) is an anti-folate chemotherapeutic agent used in the therapy of several childhood cancers, including acute lymphoblastic leukemia, non-Hodgkin lymphoma, and osteosarcoma. MTX dosing is protocol-driven, however rescue from MTX toxicity with leucovorin can be modified by drug exposure over time. While there is no precise relationship between methotrexate serum levels and antineoplastic efficacy, levels below approximately 0.02 uM/L are seen as necessary for resumption of DNA synthesis. The correlation between serum methotrexate drug concentration and duration of tumor cell exposure in predicting methotrexate toxicity has been demonstrated. While a well-defined MTX therapeutic window has not been established, there are exposure targets which generally inform the caregiver on whether a patient is being effectively managed. Our objectives were to design an interface to the hospital's electronic medical records system which facilitates the management of MTX therapy, develop a decision support system (DSS) that provides early assessment of high dose MTX renal toxicity and recommendation for leucovorin rescue, verify the outcomes of the DSS against historical controls and current best practices, and design a testing strategy for this system's ultimate implementation.

Methods: Patient data used to develop the MTX population pharmacokinetic model and prototype dashboard application were obtained from source medical records from the Chartmaxx and Sunrise Clinical Manager (SCM) systems. Dosing histories and the visit-based demographics (e.g., weight, height, etc) were ultimately hand entered in Excel. Patient records including methotrexate TDM concentrations, laboratory values and medical record number were abstracted from Oracle tables in SCM. From these two sources, the joined data was generated in NONMEM and SAS dataset format and ultimately loaded into the Oracle database supporting the MTX dashboard using SQL loader. MTX disposition is described by a two-compartment model with first-order elimination. Although MTX clearance changes over time in patients with renal dysfunction, clearance is approximated with a simple model defined by two different clearance distributions for the two populations. The Bayesian forecasting model utilizes the NONMEM PRIOR subroutine to incorporate population priors into the model. Fixed effects parameters obtained from the final pop PK model were implemented for the initial Bayesian model. Prior distributions of the fixed effects parameters were obtained from the variance-covariance matrix from the final pop PK model as well. Prior distributions for random effects parameters were specified as an inverse Wishart distribution. Clearance was implemented as a mixture model, where a patient is assigned to a

population (normal or impaired clearance) based on the probability of that patient belonging to either population given their MTX plasma concentrations. The Bayesian forecasting model was evaluated using MTX plasma concentrations that were not used during model construction. The model reliably predicts future MTX plasma concentrations from two prior concentrations in all patients except a small number who develop renal toxicity at delayed times (> 48 hours). In these patients, the addition of a third concentration after 48 hours increases the precision of the prediction of concentrations at later times.

The MTX dashboard was developed based on a three-tier architecture comprising a back end database tier, a business logic middle tier and a data presentation/user interface tier at the front. The database tier consists of patient records from our electronic medical records system (SCM) merged with data from patient registration system (IDX), lab data management system (Clarity) and adverse event management system. Data fields are processed for gaps and can be manually entered (from patient charts) when missing data is critical for functionality. Views and summary tables are created from the relational tables for quick retrieval by the application. Predictions are conducted in an external computational platform - the modeling and simulation (M&S) workbench which can execute code in a variety of languages provided they can run in a batch mode (e.g., NONMEM, SAS, SPLUS and R). All analytics are gated in the middle tier through logic to ensure that minimally required data sets are available for each patient or sets of patients. The user interface is web-based and utilizes a combination of HTML, JavaScript and XML content.

Validation of the MTX dashboard contains three distinct components: (1) qualification of the population pharmacokinetic (PPK) model and the forecasting algorithm derived from this model, (2) assessment of the clinical performance of the decisions and decision logic derived from the forecasting routine and interface and (3) the system validation of the dashboard integration with the existing electronic medical records system.

Results: The MTX pop-PK model has been validated and is generalizable across a broad range of paediatric patients (age, size, renal function, etc). The clinical validation of the forecasting tool confirms that predictions of MTX exposure and guidance for leucovorin rescue. Dashboard views can toggle between the most recent MTX dose event with the complementary monitored MTX plasma concentrations and safety markers, the MTX exposure projected after the dosing guidance menu button is selected, a view of the individual patient projection overlaid against a nomogram used to assess the potential for MTX toxicity with consideration for drug rescue with leucovorin and an update of the model fit when the additional blood collection time points were added to the patient data set. Histoical pharmacotherapy summarizations within and across patients are also available. A working demo of the application will be shown at the meeting.

Conclusion: We have created a prototype web-based tool that utilizes MTX PK/PD defined in paediatric patients with cancer to forecast individual patient response to MTX therapy and provide guidance with respect to rescue therapy. In addition, this application provides real-time views of complementary data related to the clinical care of these patients that is also essential for the management of MTX therapy (e.g., urine pH, hydration, serum creatinine, etc). Future development of this tool will provide prediction of increased risk of MTX toxicity and drug interaction potential. Integration of the production application for the clinical management of patients at the Children's Hospital of Philadelphia is expected within the year; additional international test sights are being sought to provide additional feedback on the system.

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Laurent Claret A modeling framework to simulate Xeloda dose intensity and survival in colorectal cancer

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Objectives: Capecitabine (Xeloda®) is approved for colorectal cancer ("CRC") as a monotherapy at 1250 mg/m2 BID x 14 days every 3 weeks. A reduced starting dose has frequently been used off-label in clinical practice and will also be recommended for the combination with oxaliplatin (XELOX) and with other chemotherapeutics. A modeling framework has been developed to simulate dose intensity and survival for lower starting doses of Xeloda.

Methods: Models for longitudinal tumor size and for survival were previously developed [1, 2]. In the tumor size model, drug effect simulations were conditioned on observed dose intensity. A new model for the probability of dose modifications as a function of time and dose has been developed based on data from 596 patients with CRC from two phase III monotherapy studies [3, 4]. The full simulation framework was assessed in predicting dose intensity (starting dose of 1250, 1000 and 850 mg/m2), tumor shrinkage at week 6, and survival. The predictive distributions were derived from 500 replicates of 1000 patients and compared to observed values.

Results: The probability of dose modifications increased with time and dose. The simulations showed that reduction of the starting dose from 1250 to 1000 and 850 mg/m2 would result in 1) a nearly proportional reduction of median dose intensity, 2) a reduction in the extent of tumor shrinkage at week 6 from 13.1% to 9.0% and 6.6%, respectively, and 3) a minor change of expected survival from 423 to 400 and 387 days, respectively.

Conclusions: This modeling framework is a useful tool to simulate expected clinical response and support dosing decisions for Xeloda® monotherapy. The minor impact on median survival time supports tailoring Xeloda dose in case of toxicity, older age or impaired performance status to retain a favorable therapeutic ratio in clinical practice. This approach has been proven for dose reduction of Xeloda in combination therapy [5].

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Stephen Duffull A system model for the clotting cascade challenges clinical management of snake bites.

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Introduction: A procoagulant toxin is found in taipan snake venom. This toxin activates the coagulation cascade and causes venom-induced consumptive coagulopathy (VICC). This condition is associated with an initial phase of unopposed consumption of clotting factors including fibrinogen, followed by a prolonged period of hypocoagulation. Snake bite antivenom is the main stay of treatment.

Objectives: 1. To develop a system model for the clotting cascade that is sufficiently detailed to fully describe the effects of VICC. 2. To use the model to describe the change in the turnover of the clotting factors in the coagulation cascade due to introduction of a procoagulant toxin. 3. To use the model to investigate the influence of snake-bite antivenom.

Methods: A review of the literature was performed to identify relevant articles describing the clotting cascade. The production, elimination and activation of each of the clotting factors/proteins were described by a set of turnover models. The model was built in MATLAB (ver 2006b). Deterministic simulations were undertaken to assess the performance of the model to describe the time course of change of 12 clotting factors/proteins for which data were available from a prior study of 74 patients [1]. This study was not included in the original model building. The model was then used to simulate the effects of antivenom in different clinical settings.

Results: A system model was developed based on literature findings and included 35 compartments. The model performed well in predicting the concentration of clotting factors over time following taipan envenomation. Simulations from the model revealed that the upper limit of the half-life of the toxin in the blood was approximately 1 hour although based on the data available it was estimated to be closer to 10-15 minutes. Simulations from the model also indicated that unless the antivenom is given almost immediately, it is unlikely to influence either the extent or recovery time of the coagulation profile.

Conclusions: The developed model described the available data well. The model predicts the use of antivenom, although accepted as the therapy of choice, may have a more limited role in the treatment of VICC caused by taipans than previously believed. Recent independent data on the half-life of the venom supports the models estimate.

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Lena Friberg Modeling and Simulation of the Asenapine Exposure-Response and Drop-Out in Acute Schizophrenia

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Objectives: To characterize the efficacy time-course and drop-out in schizophrenic patients following placebo or asenapine treatment, to substantiate, by simulations, the efficacious dose range of asenapine and to improve the understanding of trial outcomes.

Methods: In three Phase 2 and three Phase 3 placebo-controlled 6-week trials in patients with schizophrenia asenapine was administered sublingually in doses ranging from 0.2 to 10 mg bid. In schizophrenia trials, substantial drop-out rates and variable placebo responses are commonly observed, and both may affect traditional LOCF analysis outcomes. Therefore a pooled population exposure-response analysis was performed in which both the time-course of the primary efficacy parameter Total PANSS as well as drop-out were analyzed using NONMEM.

Results: The placebo effect ($EFF_{Placebo}$) and the asenapine exposure response relationship ($EFF_{Asenapine}$) were proportional to the underlying Total PANSS:

$$\text{Total PANSS}=PANSS_{baseline}*(1-EFF_{Placebo})*(1-EFF_{Asenapine})$$

$$EFF_{Placebo} = PMAX*(1- e^{-(TIME/TD)^{POW}})$$

$$EFF_{Asenapine}=EMAX*AUC/(AUC+AUC50)*f(TIME)$$

$$f(TIME)=TIME/42 \text{ if } TIME\leq 42 \text{ Days and } 1 \text{ if } TIME>42 \text{ Days}$$

The maximum placebo effect (PMAX) was 69% higher and $PANSS_{baseline}$ was 3.5 units lower in Phase 3 studies compared with Phase 2 studies. Patients who had active schizophrenia for more than one month had a 3.4% lower baseline than those with a shorter duration of the present episode.

The most important factors in the drop-out model were related to the observed PANSS scores; a high PANSS score on the preceding observation, an increase between the two last scores, and an increase in score from baseline increased the probability to drop out.

The observed LOCF time-courses were well described in simulations from the combined PANSS and drop-out model. The original trial outcomes were within the 95% prediction interval for all placebo arms and the majority of the treatment arms. Simulated success rates indicated that in the applied study setting the probability of detecting a statistically significant change in PANSS LOCF from placebo at Day 42 for 5 and 10 mg bid asenapine was 24-64%.

Conclusions: The model-based analysis demonstrated a significant exposure-response for asenapine. Simulations indicated that the post-hoc probability of success of the performed trials was

relatively low. Overall, this analysis supported the dose range of 5-10 mg bid asenapine as effective in the treatment of schizophrenia.

Joga Gobburu How Disease Models can reduce late phase attrition rate to half by 2015

Joga Gobburu
FDA

Only 5% of new molecules make it to the market in oncology, lowest compared to other therapeutic areas. Yet, cancer is one of the leading causes of deaths in US, and non-small cell lung cancer (NSCLC) being the top cause within cancer deaths. Given the urgent need for more effective NSCLC treatments and the low yield drug development, we elected to understand risk factors for death in patients with NSCLC and whether anticancer drug activity can be characterized more precisely early in clinical development based on predictive biomarker, such as tumor size. This knowledge might then aid drug developers to better screen drug molecules, design trials and select doses. Four registration trials for NSCLC provided nine different regimens that are either first-line or second-line treatments for locally advanced or metastatic NSCLC. Tumor size dynamic data were described with a disease model that incorporates both the tumor growth property and the regimen's anti-tumor activity. Patient survival times were described with a parametric survival model that includes various risk factors and tumor size change as predictors. Among 11 potential risk factors for survival, ECOG score and baseline tumor size were found to be significantly related to survival in almost all regimens. The disease model describes the longitudinal tumor size data fairly well, especially for early weeks after treatment initiation. The survival model based on one regimen predicted the survival outcomes for the other eight regimens reasonably well despite that these regimens have different mechanism of actions and were studied in different trials.

The drug effects on tumor size from early clinical trials in conjunction with the NSCLC model can be applied to screen compounds, simulate NSCLC clinical trials to optimize designs leading to more successful registration trials.

Alwin Huitema Application of modelling and simulation in clinical oncology

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Most of the cytotoxic agents currently used in cancer chemotherapy have been discovered decades ago. Dosing of these agents is usually based on the concept of the maximum tolerated dose (MTD) as assessed in phase I study in cancer patients. As a result, treatment with these drugs is often a delicate balance between dose intensity and toxicity. Most cytotoxic drugs have haematological toxicity as dose limiting toxicity but also severe (cumulative) organ toxicity may occur.

Modelling and simulation may provide an efficient tool for treatment optimization of these cytotoxic drugs. Retrospective population pharmacokinetic studies have characterized the pharmacokinetics and metabolism of many cytotoxic drugs and effects like saturable elimination, auto-induction and drug-drug interactions have been quantified.

Several approaches for treatment optimization have been explored. Co-variate based dosing has frequently been investigated, but co-variates (including body surface area) usually only explain a minor part of the observed pharmacokinetic variability. Pharmacokinetically guided dosing has also been investigated, but, prospective studies are scarce.

A (semi)-physiological PK/PD model for haematological toxicity has been developed and has been validated for a wide range of cytotoxic drugs. Subsequently, this model has been used for optimization of treatment regimens. Under the concept that cytotoxic drugs should be dosed at the MTD, this PK/PD model can be used to select the optimal dose or combination. In the clinical development of the investigational anticancer agent indisulam, this approach has led to the establishment of optimal doses of combination regimens with indisulam and for a dosing algorithm of this drug based on patient characteristics. Moreover, this PK/PD model may allow for a more efficient phase I program of novel agents with haematological toxicity as dose-limiting toxicity as assessed in a simulation study.

The last decade an increasing number of targeted agents has been introduced in clinical oncology. These agents (monoclonal antibodies and small molecules) have a completely different toxicity profile compared to the cytotoxic agents. Furthermore, the MTD concept for dosing, may not be valid for these drugs. Biomarkers for quantification of the pharmacodynamic effects of these drugs are in development as is PK/PD modelling and simulation of these drugs.

Søren Klim Deconvolution of Insulin Secretion Rates

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Abstract is based on Master Project [4] and article [3] by Soren Klim and Stig Mortensen

Objectives: Insulin and C-peptide are secreted in equi-molar amounts from the beta-cells then passing through the liver before entering systemic circulation. The variable first pass effect on insulin due to hepatic extraction makes the insulin observations unusable for determining the secretion rate. C-peptid passes completely through the liver and has well-established kinetics. These properties of C-peptide enable deconvolution of C-peptide secretion which is equivalent to insulin secretion rate (ISR).

Methods: Deconvolution of C-peptide measurements has been performed in many different ways. Classic deconvolution is very sensitive to observation noise. A modelling approach is to model insulin secretion rates as piecewise constant and then estimate the secretion levels. This method was presented at PAGE in Copenhagen by C. Dansirikul [1].
In this project the deconvolution was performed using a framework able to handle Non-Linear Mixed Effects models based on Stochastic Differential Equations (SDEs). The framework was first developed for Matlab but has recently been made available to R.
The structural model and parameters were based on the article by Van Cauter et al. [2]. The insulin secretion rate was modelled as a random walk. This assumption is useful for quantifying the insulin secretion as the estimated parameter then becomes the variance scaling factor. This is an unrealistic assumption but it enables the compromise between observation noise and natural variation in secretion. The final deconvolved secretion rate is the optimal according to both stochastic factors.
The assumption on insulin secretion rate being modelled as a random walk induces problems when the model is extended into simulation purposes. The insulin secretion rate can under this assumption assume unphysiological negative values. A model structure using 2 compartments to build a double exponential decay to model the insulin secretion was added to the assumed random walk. This model was named the intervention model from the inspiration in time series analysis. It uses the information on when the meals are served to trigger insulin secretion. The insulin secretion rates were estimated using this extended model for ISR.

Results: The insulin secretion rates and uncertainty can be estimated with the framework. The stochastic deconvolution technique is less sensitive to observation error and enables the incorporation of existing model structures.
The intervention model is furthermore able to fit insulin secretion rates and provides a model with simulation properties.

Conclusions: The stochastic deconvolution technique can be used to determine insulin secretion rates. The deconvolved rates are optimal according to measurement noise and structural model. The technique enables a possibility to determine rates and uncertainty at any time point based on all observations i.e. smoothed estimates.

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Ines Paule Model-based dose adaptation of capecitabine for prevention of severe hand-and-foot syndrome: in silico comparison with the standard method

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Introduction:
Management of anticancer therapies is complex due to their narrow therapeutic indices (interval between minimum effective and toxic doses) and high inter-patient variability. With identical dosage, some patients may show no therapeutic response while others may experience severe side effects. One objective is to maximize anticancer effect for each patient without running unacceptable risks of severe toxicities. Individual dosage optimization is one of the tools to achieve this therapeutic goal.
Capecitabine (Xeloda®, Roche) is an orally taken prodrug of 5-fluorouracil (5FU), which is one of the most extensively used chemotherapeutic agents against solid tumours. As it is preferentially metabolized to the active molecule 5FU in the tumour tissue, capecitabine has the advantage of being less toxic to the healthy tissues [1], while having superior or at least non-inferior efficacy as compared to the intravenously administered 5FU associated to leucovorin (5FU/LV) [2, 4].
Although less toxic than 5FU, capecitabine shows toxicities as diarrhea and palmar plantar erythrodysesthesia, the so called hand-and-foot syndrome (HFS), which is much more frequently experienced by patients treated with capecitabine (54%) than those treated with 5FU/LV (6%) [3]. This syndrome manifests as a numbness or even desquamation of palm and sole skin, possibly disturbing daily activities. It is measured on an ordinal scale of severity from grade 0 (none) to grade 3.
While the common practice is to reduce doses by 25% after the 2nd occurence of severe toxicity (grade>=2), then by 50% after the 3rd episode, without taking into account other information about the patient, a more rational individualized dose adaptation approach might allow better control of toxicity and thus improve the therapeutic benefit. The idea is to determine the most appropriate dose for the next treatment cycle according to the prediction of individual toxicity risk, evaluated dynamically and by taking into account the particular patient's characteristics.

Objectives:
To set up the methodology for individual dose adaptation on the basis of ordinal observations and evaluate its feasibility and performances, as compared to the standard approach, by randomized in silico clinical trials.

Methods:
HFS individual model
Individual prediction-based dose adjustment schemes for capecitabine were derived on the basis of individual HFS observations and a population longitudinal HFS toxicity model previously developed in [3], using a dataset of 595 metastatic or advanced colorectal cancer patients from two phase III studies[2, 4]. The mixed effects transitional and proportional odds model for longitudinal ordinal data links taken doses, basal creatinine clearance and previous toxicity to the risk of (the highest) HFS grade of the week. Due to absence of pharmacokinetic data, the drug effect is

quantified by a kinetic-pharmacodynamic (KPD) model [5], whose particular feature is to relate the pharmacodynamic outcome (here, toxicity grade) to the taken drug doses without specifying the true PK model. The main idea of this model is to assume drug accumulation in a virtual effect (KPD) compartment and a mono-exponential pseudo-elimination.
To use this model for individual dose adaptation, we need to (i) estimate random individual effects of the patient, conditional on the observations of his past HFS toxicity (the estimation step), (ii) then to choose the new dose producing an acceptable risk of severe toxicity for the next cycle (the dose calculation step).

Estimation of random individual effects (ETAs)

1. Individual likelihood. Individual parameters were estimated by maximum a posteriori (MAP) estimator. For this, a specific likelihood function for the ordinal observations was derived.
2. Optimization. Local (simplex, quasi-Newton) and global (Adaptive Random Search) optimization methods, as well as Bayesian estimation by MCMC were tested.

Dose determination rule: the most suitable dose for the next cycle was considered to be the one that correspondes to a certain tolerable limit of severe toxicity risk (in 2 weeks).

In silico clinical trial protocol: One treatment cycle corresponded to 2500 mg/m2/day for 2 weeks, followed by 1 week rest. Trial duration was 30 weeks (10 cycles). Patients were assumed to drop out of the trial if they could not receive any dose for more than 6 consecutive weeks or if severe toxicity occurred for the 4th time.
The “Standard” protocol corresponded to the approved dose adaptation rules of capecitabine which are currently used. The alternative “Individual” protocol adjusted the dose according to the individual model estimations, without increasing the dose over the nominal dose. The “Individual+” protocol was as the “Individual” one, except that it allowed an increase of the dose up to 50% in patients not showing any toxicity at all. Those 3 protocols are described in Table I.

Table I: Description of trial protocols

Protocol	Start of dose adaptation	Treatment interruption	Dose calculation	Dose limits
Standard	After the 2nd occurrence of severe toxicity	Grade ≥ 2 toxicity	-25% after 2nd occurrence of severe toxicity, -50% after the 3rd, 0% after the 4th	[50%, 100%]
Individual	After the 1st occurrence of at least grade 1 toxicity, when the risk of severe toxicity exceeds 1%	Grade ≥ 2 toxicity, or when allowed dose is lower than 50% of the nominal dose	Corresponding to predicted risk of severe toxicity in 2 weeks equal to 1%	[50%, 100%]
Individual+	After the 1s occurrence of at least grade 1 toxicity, when the risk of severe toxicity exceeds 1%	Grade ≥ 2 toxicity, or when allowed dose is lower than 50% of the nominal dose	Corresponding to predicted risk of severe toxicity in 2 weeks equal to 1%	[50%, 150%] for patients without any toxicity (start at the 4th cycle), [50%, 100%] for the rest

Proof-of-concept simulation and exploration of statistical power

For the proof of concept, three arms were simulated with 10.000 patients per arm. In order to explore the statistical power, 100 replications of trials with 300, 400 and 600 patients per arm were simulated. Wilcoxon test was used to estimate the significance of reduction of toxicity duration. The

simulations were run in Trial Simulator 2 (Pharsight®) [6], and required the writing of specific Fortran subroutines for individual parameter estimation and dose calculation that were linked to the simulator. Bayesian estimation was performed within WinBUGS software [7].

Results:

Optimization algorithm comparison. Simplex optimization method showed to be as accurate as Adaptative Random Search (ARS) and much faster. Quasi-Newton algorithm was slightly less accurate and slower than simplex. However, the precision of the estimates was not excellent. Large confidence intervals of estimates given by Bayesian estimation indicated identifiability issues for this particular model. However, tests performed with modified values of (dose-related) model parameters showed that it is possible to obtain rather accurate individual parameter estimates of an ordinal data model when the response (ie toxicity grade) is highly reactive to the input (doses)).
The **proof-of-concept** simulation showed that individual model-based adaptation would result in reduction of severe HFS toxicity incidence by 13%, of its average duration by 1.6 weeks (12 days); as well, an average reduction of HFS grade 1 duration by 3.3 weeks (23 days), as compared to the standard approach would be expected. Moreover, continuous control of severe toxicity risk resulted in earlier detection of patients intolerant to capecitabine, and therefore the mean treatment duration was 6 weeks shorter than with standard adaptation.
"Individual+" protocol simulation results suggested that patients without any toxicity could benefit of dose increase up to +50% without increase in severe HFS toxicity (29% population concerned).
A clinical trial comparing "Standard" and "Individual" dose adaptations should include 600 patients per arm to achieve at least a 90% statistical power for a significant (alpha=0.05) reduction of severe HFS duration.

Conclusions:

Individualized dose adaptation on the basis of ordinal observations, using the developed methodology, showed to be feasible and beneficial. In silico results indicate that in the case of hand-and-foot syndrome induced by capecitabine, severe toxicity incidence may be reduced by 13% and its mean duration by 12 days. Moreover, estimation of individual toxicity risk showed to be especially beneficial for allowing early detection of patients intolerant to capecitabine (at high risk of severe toxicity) and therefore better determination of the optimal moment to switch to another treatment.
There are several limitations to this work. Firstly, judgement of adaptation strategies is limited because impact on anti-cancer efficacy and other toxicities could not be evaluated. It should be considered that individual adaptation leads to 18% reduction of drug exposure as compared to the standard adaptation. The second restriction of this dose adaptation is related to the model which seems to assume inertia of HFS toxicity. This may be due to cumulative nature of the drug or model producing some bias for toxicity recovery. Nevertheless, this work shows that individual dose adaptation of oral anticancer drugs, performed on the basis of ordered categorical data, should be beneficial and feasible in clinical routine.

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Joe Standing Predicting Paediatric Tobramycin Pharmacokinetics with Five Different Methods

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Objectives: An investigation into using adult data to predict paediatric tobramycin pharmacokinetics was undertaken. Tobramycin is a narrow therapeutic index aminoglycoside derived from *Streptomyces tenebrarius*, which inhibits bacterial protein synthesis. This study had two aims: to evaluate using adult data in modelling paediatric tobramycin pharmacokinetics; and to choose a model for optimising tobramycin dosing for children with febrile neutropaenia.

Methods: Following ethical approval, children with febrile neutropaenia were prospectively recruited to a dose escalation study for once-daily tobramycin, and subsequent data were collected from therapeutic drug monitoring (TDM). Three data sets were used: the first index set from 112 children (age 1-16yrs, CrCl 16-173mL/min) from the escalation study (5-13mg/kg od) and cohort undergoing TDM; the second index set from 97 adults[1] (age 16-85yrs, CrCl 10-166mL/min, dose: 20-140mg tds); and the third, a test dataset, of 54 paediatric patients (age 1-12yrs, CrCl 29-101mL/min) undergoing TDM. In children CrCl was estimated using a physiological method[2], in adults using Cockroft-Gault.

A 2-compartment model with BOV on bioavailability was implemented in NONMEMVI (FOCEI). Linear scaling of CL with CrCl was added *a priori*, as was linear scaling of V1 and V2 with weight, and non-linear (weight^0.75) scaling of Q[2]. The model was applied to the adult index set, the paediatric index set, pooled adult and paediatric index sets, the paediatric index set analysed using NWPRIOR, and the paediatric index set analysed using TNPRIOR (in the 2 latter cases prior distributions were from the adults). Validation was performed using the test paediatric data.

Results: The NONMEM objective function values (OFV) for the test data estimated from the 5 methods were 309, 296, 304, 317, and 338 respectively, indicating the paediatric only model performed best. This model gave the least biased patient-averaged population prediction error (95%CI) of 9.2%(-5.2%, 23.6%). The paediatric index and test datasets were merged, and the model re-run: CL standardised to a CrCl of 80mL/min was 3.12L/hr and V1 was 17.2L/70kg.

To investigate at what point adding the adult data would become useful, the size of the paediatric index dataset was reduced to 56, 28 and 14 patients. These were analysed alone and pooled with the adult index set and validated against the test data. Paediatric minus pooled adult/paediatric test OFV was -6.39 and +13.99 for 56 and 28 children respectively. Satisfactory termination was not possible with 14 paediatric patients.

Conclusions: A model has been developed that adequately describes paediatric tobramycin pharmacokinetics, and can be used to predict optimum dosing. Adding adult data to the full paediatric index data marginally worsened predictive performance, but at some point between 28

and 56 paediatric patients, it was improved. Investigation into the use of priors with fewer paediatric patients is planned.

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Martin Bergstrand Modeling of gastro-intestinal tablet transit and its' effect on drug release and absorption for felodipine extended release tablet under fed or fasting conditions

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Background: Magnetic Marker Monitoring is a novel technique for visualising the transit of a solid oral dosage form through the GI tract. For dosage forms with erosion controlled drug release, the technique can also be used for obtaining an in-vivo drug release profile [3].

Aim: A model capable of simulating gastro intestinal transit, in vivo drug release and absorption of felodipine extended release tablet under fed or fasting conditions.

Methods: In a clinical crossover study the gastrointestinal transit and the in-vivo drug release of magnetically labeled extended release tablets containing felodipine were monitored under fasting and fed conditions in six healthy volunteers using Magnetic Marker Monitoring [4]. Observations from this study were of three kinds: GI location of the tablet, remaining non-disintegrated tablet and plasma concentration of felodipine.

An integrated mechanistic model describing in-vivo drug release and plasma concentration was constructed. Tablet GI position was included in the model as a covariate, governing the turning on and off drug release into corresponding absorption compartments. The systemic distribution of felodipine was described by a central observation compartment and two peripheral compartments. This part of the model was parameterized with clearance and volume parameters and allometric scaling is assumed a priori for all parameters [2]. NONMEM VI, FOCE I, was used for estimation of model parameters.

The transit between the distinct GI positions; fundus, antrum, proximal small intestine, distal small intestine and colon was described by a separate markov chain model. Since observations were made with varying frequency differential equations and first order rate constants were used to describe change in tablet GI position probability. The markov principle was kept by re-initializing all compartment amounts after each observation. NONMEM VI, LAPLACIAN LIKE, was used for estimation of all markov model parameters.

Results and Discussion: The in vivo drug release was best described with three different zero order rate constants depending on the position of the non-disintegrated tablet. A relatively slow release rate was seen for fundus (D1). An approximately three times faster release rate was estimated for antrum and the proximal small intestine (D2/D3). In the distal part of the small intestine and colon the drug release rate was estimated to be intermediate in comparison to D1 and D2/D3. The interindividual variability for the different rate constants was highly correlated and sufficiently described with only one variability term affecting all rate constants. The magnitude of the interindividual variability was also seemingly small, 9%.

Mixing of gut content in fundus is low which is manifested in the model by a slow first order distribution constant for released drug content passing down to the distal stomach (K23). As the tablet moves down to the distal part however, it is likely that released drug in the proximity of the tablet is also moved in a sudden fashion. This effect has been incorporated in the model. The distribution rate from distal stomach to small intestine (K34) was estimated to be considerably faster than K23 but showed the same pattern in terms of acceleration after tablet movement. Absorption can be rate limited by either dissolution or permeability. An observed three-fold faster absorption rate in small intestine (K47 and K57) compared to colon (K67) is thought to be due to a lower dissolution rate in colon. It was hypothesized during the model development that the pre-hepatic bioavailability (FA) might differ over the different GI parts, however no such significant effect was detected.

The model suggests that food intake decreases the rate with which released drug substance in the distal stomach is passed down to the stomach (K34 -70 %) and increases pre-hepatic bioavailability (FA +70 %).

In the markov model describing GI transit the tablet can move back and forward between the upper and lower part of the stomach (fundus and antrum). The probability of transiting through out the proximal small intestine is described by four transit compartments (P:1- P:4). Transit through out the distal part is similarly described by three transit compartments (D:1 D:3). In the model colon is assumed to be a final stage from which the tablet moves no further. Concomitant food intake prolongs the tablet stay in the stomach by decreasing probability of moving from fundus to antrum and from antrum to small intestine.

The model predicts a median time of gastric emptying at approximately 45 min for tablets taken in a fasting state. The corresponding time for the fed state is 4 hr and 45 min. Tablet transit from antrum to fundus is approximately ten times more probable when the table is taken together with food. On average this movement occurs once following each tablet intake together with food. Furthermore that model predicts a median time of colon arrival of 4.25 hr and 8.5 hr after fasting respectively fed tablet intake.

Conclusions: The joint information in tablet GI location, in-vivo drug release and plasma concentration can be utilized in a mechanistically informative way with integrated modeling of data from Magnetic Marker Monitoring studies.

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Jakob Ribbing Modelling the Dynamics of Glucose, Insulin, Insulin Sensitivity and Beta-Cells in Subjects with Insulin Resistance and Patients with Type 2 Diabetes

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Introduction: Type 2 diabetes mellitus (T2DM) is a progressive, metabolic disorder characterized by reduced insulin sensitivity (insulin resistance) and loss of beta-cell mass (BCM), resulting in hyperglycaemia. Insulin resistance is abundant among obese subjects.[1] In isolation, insulin resistance does not cause hyperglycaemia due to compensatory upward BCM adaptation. This leads to increased insulin secretion and normoglycaemia.[2] With time some insulin resistant subjects experience loss of BCM, meaning that the progression into T2DM has begun. Today, *in-vivo* quantification of BCM is not possible, but evolving imaging techniques have the potential to soon accomplish this.[3] Fasting plasma glucose (FPG) is a biomarker for glycaemic control.

Treatment with peroxisome proliferator-activated receptor (PPAR) agonists has been suggested to improve both the insulin resistance and the beta-cell mass.[4] Tesaglitazar is a dual PPAR $\alpha\gamma$ agonist previously in development for treatment of T2DM.[5] Clinical development was discontinued in May 2006 when results from phase III studies indicated that the overall benefit-risk profile was unlikely to give patients an advantage over currently available therapies.

The objective was to develop a mechanistic pharmacokinetic-pharmacodynamic (PK-PD) model that incorporates FPG, fasting insulin, insulin sensitivity and BCM, describing patients at various stages of disease, from non-diabetic, insulin resistant to long-term treated T2DM patients, and incorporating impact of drug treatment on these four variables.

Methods: Fasting biomarker data from 1460 subjects in three clinical trials with tesaglitazar were available: one phase IIb study in insulin resistant, non-diabetic subjects. One phase IIb and one phase III study in T2DM patients, which were either drug naïve or previously treated with oral antidiabetics. All model fitting and simulation were performed in NONMEM version VI.

A mechanistic model which integrates BCM, insulin and glucose dynamics in normal subjects has been proposed by Topp et al.[2] To our knowledge, this model, derived from different sources in the literature, has never been applied to clinical data. The model consists of three linked differential equations. One of these describes how BCM adapts to maintain glucose at a physiological set-point (5.6 mmol/L), but also include glucose toxicity which causes a negative spiral of BCM degeneration at high glucose levels. The modelling framework suggested by Topp et al. was used as a starting point and was further developed to incorporate impact of disease state and drug treatment on BCM and insulin sensitivity. The effects of tesaglitazar were investigated on insulin sensitivity and on the increased FPG set-point that is maintained by the BCM adaptation. In addition, a positive relation between insulin sensitivity and insulin elimination was included, which was necessary to describe the dynamic changes in FPG and FI within the mechanistic framework. The use of a population-modelling approach allowed estimation of inter-individual variability in model parameters. The final model was evaluated using non-parametric bootstrap and visual-predictive check, both stratified on disease stage and dose group.

Results: The mechanistic PK-PD model described a strong relation between insulin-elimination rate and insulin sensitivity and predicted 40-60% lower BCM in diabetic patients. Steady-state in insulin sensitivity required approximately six weeks of treatment (half-life 12 days) whereas the BCM adaptation to attain a new FPG set-point required about six months.

The mechanistic PK-PD model described all available data well in terms of median and 95% confidence interval over time. When tesaglitazar treatment was initiated in drug naïve T2DM patients both FI and FPG dropped sharply during the first few weeks, mainly due to the improved insulin sensitivity. The improvement of FPG continued at a slower rate until about six months, due to the slower adaptation of BCM. Fasting insulin, however, exhibited a small rebound (i.e. increase), due to the increasing BCM that becomes apparent after insulin sensitivity has reached a new steady-state. Insulin resistant, non-diabetic subjects displayed a comparable drop in fasting insulin during the first weeks, due to improved insulin sensitivity. However, FPG decreased only a few percent in these subjects since the FPG set-point was almost normal in the untreated state.

In the investigated dose range the exposure-response relation was nearly linear for insulin sensitivity (EC50 greater than the observed exposure range). Regarding the exposure-response on FPG set-point, EC50 was within the exposure range (but with 100% inter-individual variability around the typical value). The two EC50 parameters were highly correlated on the individual level, indicating a shared mechanistic pathway.

Discussion and Conclusions: The mechanistic PK-PD model described FPG and FI well in a heterogeneous population ranging from non-diabetic, insulin resistant subjects to T2DM patients. Model predictions that can not be evaluated on the available data were in agreement with literature. 40-60% reduction of BCM in T2DM compared to normal individuals is in agreement with published autopsy data.[6] Our model assumes that, in the fasted state, insulin secretion at a fixed glucose level is proportional to BCM, regardless of disease state. Since our prediction of BCM is in line with the literature, this indicates that beta-cells in T2DM patients indeed have similar function as the beta-cells in the normal subject (at fasting).

The positive correlation between insulin sensitivity and insulin elimination rate has been reported several times in the literature and both are affected by the level of free-fatty acids (FFA), which is lowered by PPAR agonists.[1, 7] Possibly, FFA plays a key role in several ways, since lipotoxicity has been suggested leading to beta-cell death (apoptosis).[8] Consequently, FFA may be part of the common mechanistic pathway indicated by the estimated correlation between the two EC50. Patients that greatly improve insulin sensitivity with tesaglitazar will also respond well in BCM, partly as a result of reduced glucotoxicity following the increased insulin sensitivity and possibly also because both variables are affected by FFA.

The mechanistic PK-PD model allows incorporation of heterogeneous study populations and data, e.g. regular phase I-III trials combined with actual observations of BCM plus clinical experimental studies such as glucose and insulin clamp studies. Merging such information into the same quantitative framework enables in depth insight to physiology, disease and drug effects and will likely be valuable for decision making in drug development by more accurate model extrapolations.

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Thuy Vu Time Course of Disease Status as a Predictor of Clinical Outcome in Parkinson's Disease

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Introduction:

There are two reasons for studying the time course of disease status as a predictor in time to event (T2E) analysis. Firstly, it is well understood that pharmacologic treatments may influence both the time course of disease progress and a clinical event such as death. Secondly, the two outcome variables (i.e., disease status and clinical event) are highly correlated e.g. the probability of a clinical event may be increased by the worsening disease status. Despite these reasons, separate analysis for each type of outcome measurements is usually done and only baseline disease status is often used as a time-constant covariate in T2E analysis. We contend that more useful information can be gained when time course of disease status is modeled as a time-dependent covariate providing some mechanistic insight for the effectiveness of treatment. Furthermore, an integrated model to describe the effect of treatment on the time course of both outcomes would provide a basis for clinicians to make better prognostic predictions of the eventual clinical outcome.

Objectives:

Using Parkinson's disease (PD) as an example, we achieved three specific aims that linked the time course of disease progress to clinical events: (1) described disease progression using time courses of total Unified Parkinson Disease Rating Scale (UPDRS) and its subscales (bradykinesia, tremor, rigidity, postural instability/gait disorder [PIGD], and activities of daily living [ADL]); (2) evaluated the influence of predicted disease status as a continuous time-dependent covariate in T2E models of death, disability, dementia and depression; (3) assessed the prognostic value of early disease status measurements on the probability of clinical events. The working hypothesis was that the UPDRS subscales would progress at different rates and their relative responses to anti-parkinsonian treatments would not be similar. Consequently, the predictive power of these subscales on clinical events would also be different.

Methods:

Treatment information, patient demographics, disease status assessments, and clinical events (i.e., survival times, and times to first event of disability, dementia, and depression) were obtained from the DATATOP cohort, which enrolled and followed 800 PD patients for 8 years.

(1) Quantitative models for the time course of Disease Status: Models for disease progress and pharmacodynamics were developed to describe the time course and quantify treatment responsiveness for each of the subscales using a nonlinear mixed effects approach as previously described for total UPDRS measurements [1]. A Gompertz model was used to describe the asymptotic natural disease progression. Symptomatic effects were modeled as an offset from the

baseline disease status and the disease-modifying effects were included as either a shift in the progression half-time or in disease status asymptote.

(2) T2E models to describe relationship between Disease Status and Clinical Events: Parametric distributions (i.e., exponential, Gompertz, and Weibull) were used to describe the baseline hazard function. To link time course of disease status to clinical events, we included the predicted time course of disease status (i.e., UPDRS and its subscales) in the hazard function. Individual parameter estimates (IPP) were obtained from the disease progress models in (1) to compute the predicted time course of disease status. Age, smoking status, and sex were also evaluated as potential predictors.

(3) Prognostic value of early measurements of Disease Status on the probability of Clinical Events: Clinical assessments of disease status up to 1 year were used to obtain IPP with the disease progress models in (1). Individual probability of clinical events at 5 years was computed using predicted disease status based on 1 year measurements. The probability distributions at 5 years based on 1 year or 8 year series of UPDRS measurements were visually inspected for predictive agreement.

Results:

(1) Quantitative models for the time course of Disease Status: The natural disease progression for all subscales was best described by a Gompertz model. Total UPDRS, PIGD, rigidity, bradykinesia and ADL progressed at similar rates (half-time range 2-5 y), whereas tremor progressed at a much slower rate (half-time of 11 y). Responsiveness to levodopa is lower for the PIGD subscale (ED_{50} ~ 1300 mg/d) but is similar for the other subscales (ED_{50} range 7-10 mg/d) Levodopa and deprenyl showed a disease modifying effect by decreasing the disease status asymptote for UPDRS subscales and by increasing the half-time to asymptote for total UPDRS.

(2) T2E models to describe relationship between Disease Status and Clinical Events: Except for dementia, time was an important explanatory variable in the base models for clinical events of death, disability and depression. Age had an independent effect on the hazards for death and dementia. Among the subscales, time course of ADL best explained the increased hazard of death in our patient population. Time course of total UPDRS was a better predictor than those of UPDRS subscales for T2E models of dementia, depression and disability. Visual predictive check plots were adequate in describing the goodness of fit.

(3) Prognostic value of early measurements of Disease Status on the probability of Clinical Events: Probability distributions of survival and dementia at 5 years predicted from 1 year measurements were well correlated with the predictions based on the full 8 year follow up (r=0.81 for death; r=0.9 for dementia). The correlation was not as good for disability (r=0.74) and depression (r=0.78).

Conclusions:

We have shown that hazards for 4 clinical events in PD are not constant over time. They are clearly influenced by PD progress, as measured by total UPDRS or its subscales. With the integrated models of time course of disease progress and clinical events, the differences in probability of clinical events could be explained by the symptomatic and/or protective effects of anti-parkinsonian medications on PD progression. The use of early disease status measurements may have clinical application in predicting the probability of clinical events and giving patients better individual prognostic advice.

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Sergei Leonov Stochastic pharmacokinetic models: selection of sampling times

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Introduction and Objectives: We discuss pharmacokinetic (PK) studies which are described by compartmental models. Traditionally, ordinary differential equations (ODE) are used for PK modeling, and two sources of randomness are introduced, measurement errors and population variability. In this presentation we focus on the intrinsic variability induced by the random terms in stochastic differential equations (SDE). Unlike the ODE-based models, the intrinsic variability leads to a "within-subject" correlation, or autocorrelation, between values of a stochastic PK process at different time points. This means that in serial sampling schemes, starting from certain sample sizes, the gain of information from adding extra observations for a given patient will diminish.

Methods and Results: Using the techniques of stochastic calculus, see [1] - [3], we find closed-form expressions for the mean and covariance function for a number of PK processes generated by SDE. Special attention is given to those cases where trajectories of the stochastic system are positive which is important from a biological perspective, cf. [4], [5]. The formulae for the covariance function allow us to address the problem of optimal design, i.e. finding sequences of sampling times that guarantee the most precise estimation of unknown model parameters. We use the first-order optimization algorithm, see [6], to construct D-optimal designs for a number of examples, including cases where experimental costs are taken into account.

Conclusions: We emphasize that all three sources of variability should be considered in stochastic PK models: within-subject, between-subject, and measurement errors. We recommend cost-based designs which allow for a meaningful comparison of sampling schemes with different numbers of samples.

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Joakim Nyberg Application of the optimal design approach to improve therapeutic drug monitoring for cyclosporine

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Objectives: Previously an intensive sampling schedule spread over 2 days was used to identify the pre-transplantation oral (PO) and intravenous (IV) pharmacokinetics (PK) of cyclosporine in paediatric renal patients and to predict the optimal post-transplant dosing strategy.[1] The aim of this study was to develop a reduced optimal pre-transplant design, within clinical restrictions, for estimation of individual empirical Bayes estimates (EBEs).

Methods: The newly developed monitoring schedule was supposed to be reduced to 3 samples/dose/patient and both doses administered within one day. Further constrains on maximum doses and infusion rates applied. The following design variables were optimized within these constraints: sampling times, doses of cyclosporine (IV,PO), time of second dose, duration of the IV infusion, administration order.

The model was based on a previously determined population PK model[1]with the population parameters being used as prior information. To optimize on the individual level, the EBEs of 8 parameters were transformed to fixed effects. The design was optimized across a discrete distribution of individual parameter vectors obtained from 77 patients, who received IV and PO cyclosporine.[1] The main covariate relationship between weight (discrete distribution), clearance (CL) and volume of distribution was included into the model and the doses were optimized as mg/kg. The ED-optimization was performed in PopED v.2.0. (http://poped.sourceforge.net/).

Results: The above method for maximizing the precision of EBEs using optimal design was implemented for the first time, as was the application of continuous distributions to represent prior information and discrete distributions for ED-optimality.

Several optimization options were explored incorporating different constraints. The pre-transplant monitoring schedule could be reduced to a total of 6 samples within an 8 hour observation interval. Both doses could be administered within this time interval complying with the constrains above. Clinically suitable designs were found for both combinations PO dose first or second. The designs were optimized to give precise individual estimates for CL and bioavailability (F) or for all PK parameters. The expected coefficient of variation on the EBEs for CL and F could be reduced on average by 50% applying these designs compared to the prior information.

Conclusions: Optimal design techniques can be applied for therapeutic drug monitoring schedules to maximize the information about the individual EBEs.

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Sylvie Retout Design optimisation in nonlinear mixed effects models using cost functions: application to a joint model of infliximab and methotrexate pharmacokinetics

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Objectives: We recently extended the R function PFIM [1] for population design evaluation and optimisation to deal with multiple response models and we proposed the Fedorov-Wynn algorithm to optimise both the group structure (number of groups, proportions of subjects and number of samples per group) and the sampling times [2]. However, optimisation is done for a fixed total number of samples without any consideration on the relative feasibility of the optimised sampling times or the group structure. Our objectives are to extend PFIM with cost functions to take into account those feasibilities and to illustrate this extension on design optimisation of a joint population model of infliximab and methotrexate pharmacokinetics administered in rheumatoid arthritis.

Methods: We introduce cost functions as described in Mentré *et al.* [3] in the Fedorov-Wynn algorithm allowing thus optimisation for a fixed total cost. Regarding the application, infliximab is administered every 8 weeks by infusion and is described by a one compartment model with first order elimination whereas methotrexate is orally administered every week and is described by a two compartment with first order absorption and elimination. We first evaluate a design at steady state (called empirical design) composed of 50 subjects with 12 sampling times per subject common to both drugs. We then optimise four designs, each one with a different cost function but for a same total cost. The four different cost functions investigated are the following: the first one is the classical one, i.e. the cost of an individual design is proportional to the number of samples; the second one penalizes samples late during the dose interval; the third one involves a cost for each new subject in the study; the fourth one combines the second and the third one.

Results: The optimised designs provide reasonable parameter estimate precisions. They are different according to the choice of the cost function, in term of sampling times but also group structure with, for instance, a higher number of samples per subject and thus a smaller number of subjects when penalising in the cost function the addition of new subjects.

Conclusions: Cost functions have been successfully introduced in PFIM. This work illustrates the usefulness of PFIM for design optimisation especially when substantial constraints on the design are imposed.

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Eric Snoeck The challenge of modelling hepatitis C virus dynamics after long term treatment: Application of MONOLIX

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Background: Mathematical models for hepatitis C viral (HCV) RNA kinetics have provided important insights into the life cycle of HCV and have increased the understanding of the mechanism of action of the current standard treatment of care: i.e. combination therapy of pegylated interferon (PEG-IFN) and ribavirin [1]. However, these models are unable to explain all of the observed long-term HCV RNA profiles under treatment and after cessation of therapy [2].

Objectives: 1) To develop a HCV viral kinetic model describing the individual HCV RNA profiles in chronic hepatitis C (CHC) patients after a long-term treatment with PEG-IFN alfa 2a (Pegasys®) and ribavirin (Copegus®). 2) To undertake exploratory mechanistic simulations explaining phenomena such as break-through during therapy and relapse after discontinuation of therapy.

Methods: A total of 18937 HCV RNA concentration-time data were available from 1773 CHC patients who participated in clinical trials evaluating different 24 or 48-week dosing schemes of PEG-IFN alfa-2a as monotherapy or in combination with different doses of ribavirin. The original model of HCV infection and treatment based on the Lotka-Volterra principle [3], including three differential equations representing the populations of target cells (T), productively infected cells (I) and virus (V), was modified and extended (e.g. liver regeneration and viral extinction) to allow fitting long-term viral load data. The MATLAB® version of MONOLIX 2.3 was used in combination with user-defined functions in C^{++} solving the ODE's describing the kinetics of T, I and V. Finally, an extension of the SAEM algorithm was used to handle left censoring due to the lower limits of quantification of the HCV RNA levels [4].

Results: The individual long-term HCV RNA *versus* time profiles were well described by the extended HCV viral kinetic model, with estimated free virus clearance rates and infected cells death rates similar to those previously found in the literature. The estimated effect of PEG-IFN alfa-2a was confirmed to be higher in HCV genotype non-1 patients as compared to patients infected with HCV genotype 1. The model provided a convincing picture of how ribavirin enhances the long-term outcome of interferon-based therapy. Analogous to HIV [5], exploratory mechanistic simulations revealed that the concept of the basic reproductive ratio (RR0) is playing a major role in predicting the individual outcome in CHC patients.

Conclusions and Perspectives: Hepatitis C virus dynamics after long-term treatment in 1773 CHC patients was successfully modelled using MONOLIX. Mechanistic simulations have provided additional insights into the understanding of the possible synergy between ribavirin and PEG-IFN and the factors explaining long-term individual outcomes in CHC patients which could assist in treatment decisions. The effect of other hepatitis C drugs with a new mechanism of action can be incorporated into the existing model allowing predictions for these other drugs or drug combinations to aid in optimizing the design of future clinical trials.

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Andrew Hooker Parameter estimation in non-linear mixed effects models using interval analysis

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Objectives: Parameter estimation for non-linear mixed effects models is an important aspect of model based drug development. Typically, these models are fit to data using a maximum likelihood approach requiring basic statistical assumptions, and often the models are linearized resulting in model misspecification. Further, the solution to these maximum likelihood based methods often require good initial estimates for parameters as they are prone to getting trapped in local optima. In this work we present a method of parameter estimation based on interval analysis (IA) to circumvent these problems [1]. Our method encloses the set of parameters for a given model that are consistent with the data set, and does not rely on maximum likelihood. As a result, no statistical assumptions are made, and model linearization is not needed. Further, the resulting parameter sets consistent with the data can be interpreted as confidence intervals for parameter estimates, so no asymptotic assumptions based on the Fisher information matrix, or bootstrap methodologies, are needed to compute standard errors. Finally, interval methods are global search methods that guarantee that no solutions within the search space are lost.

Methods: Both maximum likelihood (using the FOCE with interaction method in NONMEM) and IA methods (implemented in C++) were used to fit a variety of simulated pharmacometric data. The parameter interval estimates computed with IA were then compared to the parameter estimates and standard errors computed with maximum likelihood.

Results: Parameters with no between subject variability were shown to be in good agreement between the two methods. The IA method tended to have a larger range for possible parameter values as the method provides intervals for the parameter estimates that correspond to all the possible solutions that would allow the model to fit the data (compared to confidence intervals in the maximum likelihood approach).

Conclusions: Interval analysis is a suitable foundation for parameter estimation in non-linear mixed effects models. The proposed method reduces the assumptions and approximations needed to estimate model parameters, and the method guarantees finding all parameter values that are consistent with the model. Because of this, IA methods are a natural choice in investigating, among others, model identifiability, the presence of inter-individual variability and model misspecification.

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Christian Laveille Evaluation of the PK and PK-PD libraries of MONOLIX: A comparison with NONMEM

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Introduction: The statistical model for most population PK/PD analyses is the nonlinear-mixed effects model (NLMEM). As opposed to linear models, there are statistical issues to express the optimization criteria for these nonlinear models so that first approximation methods (FO and FOCE) based on linearization of the model were proposed. It is well known that these methods have several methodological and theoretical drawbacks.

The SAEM (Stochastic Approximation EM) algorithm avoids any linearization and is based on recent statistical algorithms. This algorithm is a powerful tool for Maximum Likelihood Estimation (MLE) for very general incomplete data models. The convergence of this algorithm to the MLE and its good statistical properties have been proven. The SAEM algorithm is implemented in the freely available MONOLIX software that can be downloaded at http://www.monolix.org.

A new version of MONOLIX will be released soon and therefore an exhaustive evaluation should be performed. At a first stage, the PK and PK-PD library were extensively evaluated. The other features of MONOLIX are also in the process of being reviewed and will be presented later on.

Methods:

1. To extensively test all the available models in the PK and PK-PD library of MONOLIX
2. To perform this evaluation with NONMEM V and NONMEM VI and the latest version of MONOLIX
3. To discuss and compare the results.

Results:

1. All available models within the PK and PK-PD library of MONOLIX were evaluated within either NONMEM version V and VI but also with the latest version of MONOLIX.
2. Trial Simulator version 2.1.2 was used to simulate all the datasets. For each data set, single dose and multiple doses were simulated. The single dose was administered at time 0 and observations were made up to 72h. Then multiple doses started at time 72h and a dose was given every day during 7 days. Trough measurements were made every day. A full profile was drawn at time 144h and after the last administration at time 216h. Overall 120 subjects were simulated for each dataset and allocated to one of the four dose group.
3. For the PK and PK-PD Library, all the random effects were simulated with a log-normal distribution. In most case, the inter-individual variability was set to 30% whatever the parameter and residual errors of 20% were used.
4. For NONMEM, as first trial, the First-Order Conditional Estimate (FOCE) method with Interaction was used after logarithm transformation. In case of convergence issues with the FOCE method, the First-Order (FO) method was used.

5. For the PK-PD models, both PK and PD were fitted simultaneously either in NONMEM or MONOLIX.

Conclusions: Preliminary results showed encouraging results for MONOLIX with all runs successful. The covariance matrix was obtained in 100% of the cases. As expected not all runs were successful with NONMEM using FOCE with Interaction. Whatever the method implemented within NONMEM, run times were significantly reduced when using MONOLIX.

Elodie Plan Maximum Likelihood Estimation Methods: Performances in Count Response Models Population Parameters

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Objectives: Count responses represent a full class of common pharmacodynamic outcomes, there is a need for greater knowledge in Non-Linear Mixed Effects approach for modelling discrete observations.
Laplacian approximation iteratively determines the 2nd derivative of the maximum of the Likelihood [1] based on 1 quadrature point, a value that can be increased using the Gaussian Quadrature (GQ).
The aim of this study was to explore different probability distribution models and the accuracy of the estimation of their population parameters using different methods (LAPLACE and GQ) and programs (NONMEM VI and SAS(NLMIXED)).

Methods: This methodological study was performed through stochastic Monte Carlo simulations followed by re-estimations. All simulations (100 data sets for each probability distribution) were performed in NONMEM; parameters values used were derived from a real case study on 551 epileptic patients [2].
Count models investigated during this study were: Poisson (PS), Poisson with Markovian features (PMAK), Poisson with a mixture distribution for individual observations (PMIX), Zero Inflated Poisson (ZIP), Generalized Poisson (GP) and Inverse Binomial (INB) [3]. Estimations of the simulated data sets were completed with LAPLACE in NONMEM and LAPLACE/GQ in SAS. Performances were evaluated by computing: (i) the absolute value of the relative bias (AVB) and (ii) the root mean square error (RMSE) of the estimated population parameters compared to the true ones.

Results: With LAPLACE in NONMEM, the AVB in fixed effects was < 3.4 % in all models; it was even < 0.8 % in PS, PMAK and PMIX. The RMSE was 3.9 – 10.4 % with lowest values for the mean count parameter (λ).
The estimation of the random effect of λ resulted in an AVB ranged 0.3 – 8.2 % in all models. The magnitude of the random effect of the dispersion parameter present in ZIP, GP and INB showed the largest bias (-25.9, -15.7 and -21.9 % respectively).
Analysis with GQ resulted in an adjustment of parameter bias (> -5.3 %) in ZIP. For the INB model, NLMIXED with LAPLACE/GQ could not produce parameter estimates. This inability appears related to the empirical Bayes estimation step.

Conclusions: The PS count model parameters were accurately estimated in NONMEM; addition of Markovian features or Mixture distribution did not harm the relative estimation error profile, but inclusion of a parameter allowing for inequality between λ and variance of the counts was associated with a marked bias in the estimation of its variability.

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Nick Holford Stuck in Modelling – Attempts to describe disease progress and the action of oral hypoglycaemic agents in type 2 diabetes

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Background: The modeling of time course of glucose and insulin changes during prolonged treatment with oral hypoglycaemic drugs has to consider disease progression mechanisms as well as drug action. De Winter et al. (1) proposed a mechanism-based model for changes in beta cell function and insulin potency during treatment with gliclazide (GLZ), metformin (MET) and pioglitazone (PIO).

Methods: Steady state solutions to modified HOMA for glucose-insulin regulation models (2-4) were used to describe glucose and insulin responses to changes in beta cell function (BF) and insulin potency (IP). Models for disease progress and effect compartment concentrations of drug treatments were implemented using differential equations. Predictions of glucose and insulin can be obtained by solving a system of algebraic equations. This solution is not required to solve the differential equations but NONMEM attempts to solve both algebraic and differential equations simultaneously. Parameter estimation used ADVAN9 in NONMEM VI level 1.3.

Results: Run times for this problem were extremely long even with the simplest glucose-insulin regulation model. The algebraic equation solver failed at initialization when random effects were added to the baseline BF and IP parameters for more complex regulation models. Therefore it was not possible to use these more realistic regulation systems.

Conclusions: Possible solutions to the problem include 1) calling a root finder subroutine to obtain the algebraic equation solutions independently of the solution to the differential equations 2) using a closed form solution to the algebraic equations (only possible for very simple regulation models) 3) using a more robust estimation method (e.g. MCPEM or SAEM) 4) using a parallel processing implementation (e.g. S-ADAPT).

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Anthe Zandvliet PK-PD model of multiple follicular development with corifollitropin alfa during controlled ovarian stimulation: application of Markovian elements.

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Background: Corifollitropin alfa is a novel gonadotropin that has different pharmacokinetic properties than follicle stimulating hormone (FSH) but similar pharmacodynamic features. A single injection is able to initiate and sustain multifollicular growth for an entire week. If necessary, follicular stimulation can be continued with daily injections of recombinant FSH (recFSH) from Day 8 onwards. Administration of hCG for induction of final oocyte maturation is indicated when 3 follicles of ≥ 17 mm are observed. Both follicle number and size are important parameters of treatment success.

Objectives: To develop a PK-PD model to describe the time profile of the number and size of follicles during treatment with corifollitropin alfa and recFSH.

Methods: In a phase II dose-finding trial and a phase III safety and efficacy trial, 479 subjects were treated with corifollitropin alfa and were evaluable for PK-PD analysis. Data from an absolute bioavailability study (n=16) were used to support PK model development. Ultrasound scans were performed regularly to assess the number of follicles in various size categories: 2-4, 5-7, 8-10 mm (Day 1 only) and 11-14, 15-16, 17+ mm (all days). A transit compartment model was used to describe follicular growth. Each compartment corresponded to a 1-mm size class, starting with follicles of 1 mm (or less) and ending with follicles of 17+ mm. Transit rate constants k_{tr} represented follicular growth and were estimated as an E_{max} function of the corifollitropin alfa concentration. k_{out} was complementary to k_{tr} ($k_{out} = E_{max} - k_{tr}$) and represented follicle decline. PK and PD data were analyzed sequentially using NONMEM VI. FOCE was used for the PK model and the LAPLACIAN method for the PD model.

Results: A 3-compartmental model adequately described the PK profile of corifollitropin alfa. In an initial attempt to describe follicular development, the amount in each transit compartment represented the lambda of a Poisson distribution. Simulations indicated overdispersion: the Poisson model was suitable to describe independent measurements, but the repeated count measurements of follicles were not independent. We did not manage to incorporate Markovian elements in this model. In a second attempt, the amount in each compartment represented the probability of a single follicle to have the corresponding size. Follicles were distributed over the compartments according to a multinomial distribution. Again, Markovian elements could not be incorporated in this model in NONMEM. As a work-around, posthoc estimates were used to perform a Markov simulation in SAS.

Conclusions: Follicular development during controlled ovarian stimulation was assessed by ultrasound scans resulting in repeated dependent multicategorical count measurements. The multicategorical nature of the data prevented flexible incorporation of Markovian elements in Poisson and multinomial models.

Discussion: During the "Stuck in Modeling" session, we would like to discuss how to apply Markovian elements. Is it feasible to develop a Markov model of follicular growth in NONMEM? Alternatively, is it acceptable to use posthoc estimates for Markov simulations in SAS?