PAGE 2013 Oral Program

Tuesday June 11

15:00-18:30	**Registration**		
18:30-19:30	**Welcome reception at the Old Fruitmarket located on Candleriggs in the Merchant City area, close to the city centre. Please see the map on http://www.glasgowconcerthalls.com/maps**		

Wednesday June 12

08:00-08:45	**Registration**		
08:45-09:00	**Welcome and introduction**		
09:00-10:20	**Model-based approaches in benefit-risk assessment and decision making**		*chair: Oscar Della Pasqua*
09:00-09:40	*Dyfrig Hughes*	Quantitative benefit-risk analysis based on linked PKPD and health outcome modelling	
09:40-10:00	*Jonathan French*	Can methods based on existing models really aid decision making in non-small-cell lung cancer (NSCLC) trials?	
10:00-10:20	*Jonas Bech Møller*	Optimizing clinical diabetes drug development – what is the recipe?	
10:20-11:45	**Coffee break, poster and software session I**		
	Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter		
11:45-12:25	**Animal health (I)**		*chairs: Alison Thomson & Jonathan Mochel*
11:45-	*Jim Riviere*	Food safety: the intersection of	

12:25		pharmacometrics and veterinary medicine	
12:25-13:50	**Lunch**		
13:50-14:50	**Animal health (II)**		*chairs: Alison Thomson & Jonathan Mochel*
13:50-14:20	*George Gettinby*	Two models for the control of sea lice infections using chemical treatments and biological control on farmed salmon populations	
14:20-14:50	*Daniel Haydon*	From epidemic to elimination: density-vague transmission and the design of mass dog vaccination programs	
14:50-16:20	**Tea break, poster and software session II**		
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter		
16:20-17:40	**Modelling and evaluation methods with (potential) application to infectious diseases**		*chair: Leon Aarons*
16:20-16:40	*Wojciech Krzyzanski*	Physiologically structured population model of intracellular hepatitis C virus dynamics	

16:40-17:00	*Martin Bergstrand*	Modeling of the concentration-effect relationship for piperaquine in preventive treatment of malaria
17:00-17:20	*Matt Hutmacher*	A Visual Predictive Check for the evaluation of the hazard function in time-to-event analyses
17:20-17:40	*Celine Laffont*	Non-inferiority clinical trials: a multivariate test for multivariate PD

Thursday June 13

08:45-10:05	**Lewis Sheiner student session**		*chairs: Lena Friberg, Philippe Jacqmin & Leon Aarons*
08:45-09:10	*Abhishek Gulati*	Simplification of a multi-scale systems coagulation model with an application to modelling PKPD data	
09:10-09:35	*Nelleke Snelder*	Mechanism-based PKPD modeling of cardiovascular effects in conscious rats - an application to fingolimod	
09:35-10:00	*Nadia Terranova*	Mathematical models of tumor growth inhibition in xenograft mice after administration of anticancer agents given in combination	

10:00-10:05	**Presentation of awards**		
10:05-11:35	**Coffee break, poster and software session III**		
	Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter		
11:35-12:35	**Mechanistic modelling**		*chair: Nick Holford*
11:35-11:55	*James Lu*	Application of a mechanistic, systems model of lipoprotein metabolism and kinetics to target selection and biomarker identification in the reverse cholesterol transport (RCT) pathway	
11:55-12:15	*Rollo Hoare*	A novel mechanistic model for CD4 lymphocyte reconstitution following paediatric haematopoietic stem cell transplantation	
12:15-12:35	*Huub Jan Kleijn*	Utilization of tracer kinetic data in endogenous pathway modeling: example from Alzheimer's disease	
12:35-14:05	**Lunch**		
14:05-14:55	**Reproducibility and translation**		*chair: Katya Gibiansky*

14:05-14:35	*Niclas Jonsson and Justin Wilkins*	Tutorial: Reproducible pharmacometrics	
14:35-14:55	*Nick Holford (on behalf of DDMoRe)*	MDL - The DDMoRe modelling description language	
14:55-16:20	**Tea break, poster and software session IV**		
	Posters in Group IV (with poster numbers starting with IV-) are accompanied by their presenter		
16:20-17:20	**New methods for population analysis**		*chair: France Mentré*
16:20-16:40	*Vittal Shivva*	Identifiability of population pharmacokinetic-pharmacodynamic models	
16:40-17:00	*Leonid Gibiansky*	Methods to detect non-compliance and minimize its impact on population PK parameter estimates	
17:00-17:20	*Julie Bertrand*	Penalized regression implementation within the SAEM algorithm to advance high-throughput personalized drug therapy	
	Social evening		

Friday June 14

09:00-10:00	**Development and application of models in oncology**		*chair: Marylore Chenel*
09:00-09:20	*Shelby Wilson*	Modeling the synergism between the anti-angiogenic drug sunitinib and irinotecan in xenografted mice	
09:20-09:40	*Amy Cheung*	Using a model based approach to inform dose escalation in a Ph I Study by combining emerging clinical and prior preclinical information: an	

		example in oncology	
09:40-10:00	*Sonya Tate*	Tumour growth inhibition modelling and prediction of overall survival in patients with metastatic breast cancer treated with paclitaxel alone or in combination with gemcitabine	
10:00-10:10	**Preview of PAGE 2014**		
10:10-10:50	**Coffee break**		
10:50-12:10	**Stuart Beal methodology session**		*chair: Steve Duffull*
10:50-11:10	*Chuanpu Hu*	Latent variable indirect response modeling of continuous and categorical clinical endpoints	
11:10-11:30	*Anne-Gaelle Dosne*	Application of Sampling Importance Resampling to estimate parameter uncertainty distributions	
11:30-11:50	*Hoai Thu Thai*	Bootstrap methods for estimating uncertainty of parameters in mixed-effects models	
11:50-12:10	*Celia Barthelemy*	New methods for complex models defined by a large number of ODEs: application to a glucose/insulin model	
12:10-12:20	**Closing remarks**		
12:20-12:40	**Audience input for the PAGE 2014 program**		

Dyfrig Hughes A-05 Quantitative benefit-risk analysis based on linked PKPD and health outcome modelling

Dyfrig Hughes
Centre for Health Economics and Medicines Evaluation, Bangor University

Objectives: Health outcomes modelling, conventionally used in health technology assessment, is based on disease progression models with the probabilities of benefit and harm for health states based on epidemiological and clinical trial evidence, and the health state preferences based on utility estimates. During early phases of clinical drug development, and where randomised controlled trials may not be possible, outputs from PKPD models may serve as inputs to health outcome models to inform the balance of harms and benefits based on the quality-adjusted life-year (QALY). Here, a comparison is made of the net clinical benefits of genotype-guided warfarin with both standard, clinically-dosed warfarin and three new oral anticoagulants (dabigatran, rivaroxaban and apixaban).

Methods: A clinical trial simulation based on a PKPD model of S-warfarin was used to predict differences in time within therapeutic range (TTR) between genotype guided and clinically dosed warfarin. A meta-analysis of trials linking TTR with outcomes was conducted to obtain relative risks of different clinical events. A discrete event simulation model representative of the AF population in the UK was used to extrapolate event risks to a lifetime horizon. Modelled outputs included clinical outcomes and QALYs.

Results: In the base case analysis, genotype guided-warfarin, rivaroxaban, apixaban and dabigatran extended life by 0.003, 1.11, 2.06 and 1.47 months, respectively, compared with clinical algorithm dosed warfarin. The corresponding incremental net benefits were 0.0031 (95% central range [CR] -0.1649 to 0.1327), 0.0957 (95% CR -0.0510 to 0.2431), 0.1298 (95% CR -

0.0290 to 0.2638) and 0.1065 (95% CR -0.0493 to 0.2489) QALYs. In pairwise comparisons, using clinical algorithm dosed warfarin as the comparator, genotype guided warfarin, rivaroxaban, apixaban and dabigatran were associated with a positive incremental net health benefit in 57%, 83%, 90% and 85% of the simulations respectively.

Conclusion: Clinical trial simulations based on pharmacological models offer a new way to obtain estimates of net benefit in circumstances where trial data are not available. Based on our simulations, apixaban appears to be associated with the highest net benefit.

Jonathan French A-06 Can methods based on existing models really aid decision making in non-small-cell lung cancer (NSCLC) trials?

Jonathan L French (1), Daniel G Polhamus (1), and Marc R Gastonguay (1)
(1) Metrum Research Group, Tariffville, CT, USA

Objectives: The need for more efficient drug development in oncology is widely recognized. Wang et al [1] propose the use of % change in tumor size at 8 weeks (PTR8) as a marker of efficacy to aid decision making in NSCLC drug development. Sharma et al. [2] advocate M&S in oncology drug development through the use of adaptive Phase II-III trials. In this work we compare 3 approaches to using M&S for making decisions based on accruing data in a Phase II clinical trial.

Methods: We simulated clinical trials with 400 NSCLC patients randomized 1:1 to 2 groups receiving first-line treatment. We assume a recruitment period of 6 months with an additional 9 month follow-up period. Overall survival (OS) and PTR8 data were simulated using the NSCLC model of Wang et al. [1]. For each simulated trial, 3 interim analyses (IAs) were performed: 8 weeks after (1) 80 pts enrolled (~10 events), (2) 280 pts enrolled (~50 events), and (3) 400 pts enrolled (~90 events).

Two drug effect scenarios were evaluated. The first had a median difference in PTR8 of 40%, a difference in median OS of 100 days, and expected hazard ratio of 0.67. The second had no difference in PTR8 or OS.

We compared decision rules based on difference in PTR8 to Bayesian rules based on the posterior predictive distribution for the log hazard ratio (logHR) at the end of the study. For the Bayesian rules, the relationship between

PTR8 and OS was updated using the accruing data in the trial and prior distributions centered at the estimates from [1]. We also evaluated rules based on the estimated logHR using a Cox model. Decision rules were compared using ROC analysis (true positive rate, TPR, and false positive rate, FPR).

Simulation and analysis were performed using R 2.15.1 and OpenBUGS 3.2.1.

Results: Under scenario 1, all rules performed poorly at IA1. At IA2, the best Bayes rule performed notably better (TPR=.67, FPR=.29) than either the best PTR8 rule (TPR=.56, FPR=.46) or Cox rule (TPR=.65, FPR=.37). At IA3, the best Bayes and Cox rules (TPR~.75, FPR~.25) performed better than the best PTR8 rule (TPR=.55, FPR=.33). Scenario 2 showed similar results.

Conclusions: Model-based approaches can aid decision making in NSCLC trials. However, IA decision rules based on PTR8 alone have little ability to predict the outcome of positive or negative studies, consistent with recently published results [3]. The model-based Bayesian decision rules evaluated here performed notably better.

References:

[1] Wang Y. et al. Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin Pharmacol Ther. 86, 167--174 (2009).
[2] Sharma MR, Maitland ML, and Ratain MJ. Models of Excellence: Improving Oncology Drug Development. Clin Pharmacol Ther. 92, 548--550 (2012).
[3] Claret L. et al. Simulations using a drug-disease modeling framework and phase II data predict phase III survival outcome in first-line non-small-cell lung cancer. Clin. Pharmacol. Ther. 92, 631--634 (2012).

Jonas Bech Møller A-07 Optimizing clinical diabetes drug development – what is the recipe?

Jonas B Møller (1), Rune V Overgaard (1), Maria C Kjellsson (2), Niels R Kristensen (1), Søren Klim (1), Steen H Ingwersen (1), Mats Karlsson (2)
(1) Quantitative Clinical Pharmacology, Novo Nordisk A/S, Søborg, Denmark
(2) The Pharmacometrics Group, Uppsala University, Uppsala, Sweden;

Objectives: A key challenge in diabetes drug development is to extrapolate the results from early clinical efficacy assessments (clamp studies or glucose provocation tests) to late phase efficacy outcomes such as HbA_{1c}. With the increasing need for investigating anti-diabetic medicine in special populations (e.g. paediatrics), another challenge is to use available data to extrapolate from one population to another. These challenges call for a library of quantitative models to link and predict key endpoints in diabetes trials during the different phases of drug development. The objective of this presentation is to show how specific pharmacometric diabetes models, alone or in combination, can be applied to optimize clinical diabetes drug development.

Methods: By combining a PK model with a model for glucose homeostasis [1], a link between drug concentration and drug effect on plasma glucose can be established, as previously shown for an oral anti-diabetic (OAD) or insulin treatment [2,3]. By subsequently applying a model linking glucose to HbA_{1c} [4], the predicted plasma glucose response can be used for prediction of late phase efficacy outcome. Clearly, assessment of treatment dependence on the link between glucose and HbA_{1c} is crucial, and thus we applied individual data from 4 clinical trials covering 12 treatment arms (OADs, GLP-1 agonist, and insulins) to test our approach.

Results: The performance of the proposed framework is illustrated through a case study where trial outcome wrt. HbA_{1c} for each treatment arm was

predicted. The HbA_{1c} predictions were successful with a mean absolute error ranging from 0.0% to 0.24% across treatment arms. Calculations of the mean ΔHbA_{1c} vs. comparator and the corresponding confidence intervals were shown to provide identical conclusions based on predictions and observations at end-of-trial.

Conclusions: In this presentation we outlined and applied models for linking early phase assessments and late phase treatment outcomes within clinical diabetes drug development. Implementation and validation of these models were driven by a consistent focus on the ability to predict future trial outcomes and link data from different stages of clinical development. We find this a key ingredient in the recipe for optimizing diabetes drug development.

Acknowledgements: This work was part of the DDMoRe project.

References:

[1] Jauslin PM et. al: An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics, 2007
[2] Jauslin PM et. al: Identification of the mechanism of action of a glucokinase activator from oral glucose tolerance test data in type 2 diabetic patients based on an integrated glucose-insulin model, 2011
[3] Roege RM et. al.: PAGE poster n. l-61, 2012: Integrated model of glucose homeostasis including the effect of exogenous insulin
[4] Moeller et. al.: ADOPT (A Dynamic HbA_{1c} EndpOint Prediction Tool) - A framework for predicting primary endpoint in Phase 3 diabetes trials, *abstract accepted for ACOP 2013*

Jim Riviere A-09 Food safety: the intersection of pharmacometrics and veterinary medicine

Jim E. Riviere
Institute of Computational Comparative Medicine, College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA

Food animal veterinarians bear numerous responsibilities, not only to their sick patients, but also to the producers and consumers of animal food products, as well as the environment. A fundamental difference between food animal veterinary and human medicine relates to the fact that animals treated with drugs are often consumed as food after treatment is completed.

Unlike for humans where the physician isn't concerned about drug left in the patient after treatment, in food animal medicine the veterinarian must be sure an effective dose of drug is given (appropriate PK-PD regimen) and also that no potentially adverse levels of drug persist in the edible tissues and products (e.g. milk, eggs) of treated animals. A second difference is that drugs are administered to large populations of animals as disease is often diagnosed and treated on a herd basis.

Animals may be dosed in feed, water or dips, creating uncertainty in dose level and interval. Uncontrollable environmental covariates like temperature and humidity can further increase variability. These factors must be considered to insure that a safe food animal product free of toxic or allergic chemicals reaches the consumer. The regulatory determination of such tissue withdrawal times is performed in control groups of healthy animals. Although the pharmacometric approaches to the calculation of such parameters in various regulatory jurisdictions may differ, the experimental design of such trials is similar. Once approved, drugs are then used in natural clinical

populations where diseases processes for which the drug is labeled to treat are present, and concomitant medications are also often administered. This has resulted in a regulatory system with a reasonable degree of reproducibility relative to determination of the withdrawal time metric, but a lack of direct relationship to drug disposition processes seen in clinical populations of animals treated under diverse conditions.

Various authors have amply reviewed the impact of disease processes on the primary drug pharmacokinetic parameters, with focus being on drug elimination and distribution pathways and processes as they affect blood concentration-time profiles as a function of drug efficacy. However, the effect of such factors on very low residue-level concentrations (PPM, PPB) of drugs and their metabolites in edible tissues has rarely been addressed or even considered. Similarly, residue depletion trials are often conducted in homogeneous groups of animals using controlled dosing regimens in order to reduce animal numbers while still arriving at a statistical solution to the withdrawal time algorithm; yet variability in the actual treated populations relative to breed, production and environmental factors alone easily violates this assumption. This is particularly true when the withdrawal time algorithm is attempting to estimate behavior in 1-5% of the population with 95% confidence. Situations where concern arises include when the disease process alters the normal ratio of parent drug to marker residue produced by altered biotransformation processes, when a product of the disease process binds to and modifies the drug residue depletion profile in a target tissue, or when disposition processes fundamentally alter pharmacokinetic patterns.

Advances in population (mixed effect) pharmacokinetic modeling open up approaches to study, model and predict these factors; in many cases directly based on the mechanism of the interaction. Mixed effect models allow disease related and potentially pharmacogenomic factors to be directly estimated and modeled. Such considerations become increasingly important if global regulatory jurisdictions set residue tolerances based on the limits of analytical detection, which of late continually drops to levels where minor interactions at the molecular tissue level become important for model predictions and violations of tissue tolerances, but are totally irrelevant to their toxicological impact on human food safety.

George Gettinby A-11 Two models for the control of sea lice infections using chemical treatments and biological control on farmed salmon populations

George Gettinby (1), Maya Groner (2), Ruth Cox (2), Chris Robbins (3) and Crawford Revie (2)
(1) University of Strathclyde, Glasgow, Scotland, (2) University of Prince Edward Island, Canada, (3) Grallator Ltd, UK

Objectives: To formulate models to inform how best to manage the control of sea lice populations which are a major threat to aquaculture and salmon production worldwide.

Methods: Two types of models are used to investigate the interaction between sea lice and salmon populations. In the first model changes in lice population stages are represented using four differential-delay equations. Time dependent solutions are obtained using algorithms embedded in the Sea Lice Difference Equation Simulator software. This enables treatment regimens under different geographical and environmental conditions to be investigated. The second model adopts a different approach to facilitate the introduction of a further fish population i.e. wrasse. Wrasse along with several other fish species are increasingly being used as "cleaner" fish because they feed on lice which are attached to salmon [1][2]. Using an individual-based modelling approach and simulations implemented using proprietary modelling software the density relationship between wrasse and salmon populations was investigated.

Results: Early work using the population modelling approach provided a parsimonious mathematical representation of the growth of the sea lice population [3] [4]. Using numerical methods it was possible to obtain

solutions to the differential equations which reflected day-to-day changes in sea lice counts per salmon. The model identified when to apply treatments that would be less costly and more effective. The model lacked flexibility, stochasticity and did not take cognisance of sea water temperature and its effect on development and survival time of the lice stages. Experiences of adapting the model in Scotland and Norway [5] showed that it was not always stable and small changes in parameters could produce very different outcomes. The introduction of biological control and the use of cleaner fish led to investigating an individual-based modelling (IBM) approach [6][7][8]. A simple IBM which takes account of biological development rates associated with water temperature [9] showed that the use of wrasse fish to graze on sea lice in salmon production units can provide an effective way forward for salmon aquaculture.

Conclusion: Sea lice are a major threat worldwide to the sustainability of farmed and wild salmons stocks. They are affected by a large number of factors on salmon farms. Mathematical modelling offers a way of assessing the simultaneous impact of these factors.

References:

[1] Treasurer JW. Prey selection and daily food consumption by a cleaner fish, *Ctenolabrus rupestris* (L.), on farmed Atlantic salmon, *Salmo salar* L. Aquaculture (1994) 122:269-277.

[2] Treasurer JW. Wrasse (*Labridae*) as cleaner-fish of sea lice on farmed Atlantic salmon in west Scotland. In: Wrasse: Biology and Use in Aquaculture (ed by MDJ Sayer, JW Treasurer & MJ Costello), (1996) pp. 185-195. Fishing News Book, Oxford.

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[4] Robbins C, Gettinby G, Lees L, Baillie M, Wallace C, Revie CW, Assessing topical treatment interventions on Scottish salmon farms using a sea lice (*Lepeophtheirus salmonis*) population model. Aquaculture (2010) 306: 191-197.

[5] Gettinby G, Robbins C, Lees F, Heuch PA, Finstad B, Malkenes R and Revie CW. Use of a mathematical model to describe the epidemiology of

Lepeophtherius salmonis on farmed Atlantic salmon *Salmo salar* in the Hardangerfjord, Norway. *Aquaculture* (2011) 320: 164-170.
[6] Cox R, Groner M, Gettinby G, Revie CW. Modelling the efficacy of cleaner fish for the biological control of sea lice in farmed salmon. Proceedings of the 13th ISVEE Conference, Aug 20-24, 2012, Maastricht, Netherlands.
[7] Groner M, Cox R, Gettinby G, Revie CW. Individual-based models: A new approach to understanding the biological control of sea lice. Proceedings of the 9th International Sea Lice conference, May 21-23, 2012, Bergen, Norway.
[8] Groner ML, Cox R, Gettinby G and Revie CW. Use of agent-based modelling to predict benefits of cleaner fish in controlling sea lice, *Lepeophtheirus salmonis*, infestations on farmed Atlantic salmon, *Salmo salar* L. *Journal of Fish Diseases* (2012) doi:10.1111/jfd.12017.
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Dan Haydon A-12 From Epidemic to Elimination: Density-Vague Transmission and the Design of Mass Dog Vaccination Programs

Daniel T Haydon, Sunny Townsend, Sarah Cleaveland, Katie Hampson
Institute of Biodiversity, Animal Health and Comparative Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow

Objectives: Rabies is one of the most important zoonotic diseases in the world, causing an estimated 55,000 human deaths each year, primarily in Asia and Africa. Momentum is building towards development of a strategy for the global elimination of canine rabies, which has recently been identified as a priority by WHO, OIE and FAO as well as other international human and animal health agencies. This presentation will address several critical issues relating to the design of mass dog vaccination campaigns for the cost-effective control and elimination of canine rabies.

Methods: Our findings are based on the analysis of data generated from a high-profile and well-studied outbreak in Bali, Indonesia, and the on the results of a closely parameterized spatially explicit computer simulation of the dynamics of rabies outbreaks.

Results: We present three main findings. The first is that although dog densities on Bali are at least an order of magnitude higher than other populations in which rabies has been studied, our estimate for the basic reproduction number (R_0) of ~ 1.2 is similar to other populations with much lower dog densities, which suggests that, counter to expectations, R_0 for rabies is essentially density independent.

The second result follows directly from these consistent values of R_0: across a wide range of settings, and even in very high-density dog populations, control and elimination of canine rabies by dog vaccination is an entirely feasible control option. Additional measures to reduce dog population density are not likely to be necessary.

Our third result is that the effectiveness of vaccination depends primarily upon reaching a sufficient vaccination coverage (70%) across the population in successive campaigns, and does not improve with more complex, reactive or synchronized campaigns. However, even small 'gaps' in vaccination coverage can significantly impede prospects of elimination, and therefore regional coordination and participation in such campaigns is critical.

Conclusions: This study has enabled us to evaluate the impact of different vaccination strategies on human deaths averted and the time it will take for rabies to be eliminated from Bali under a range of plausible scenarios. Modeling can be used to develop simple, pragmatic and operational guidelines for regional rabies vaccination campaign that will be of immediate practical relevance for developing strategies for the global elimination of canine rabies.

Wojciech Krzyzanski A-14 Physiologically Structured Population Model of Intracellular Hepatitis C Virus Dynamics

Wojciech Krzyzanski (1), Xavier Woot de Trixhe (2), Filip De Ridder (2), An Vermeulen (2)
(1) University at Buffalo, NY, USA; (2) Janssen Research & Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium

Objectives: To develop a physiologically structured population model capable of describing intracellular dynamics of viral RNA and its integration with observable circulating HCV RNA levels.

Methods: The standard model of viral dynamics [1] consists of target cells (T), infected cells (I), and viral load (V). The circulating virus levels are determined by the production (pI) and elimination rate (cV). The drug inhibits the viral production rate. To explain the discrepancy in the estimates of the half-life of the circulating HCV RNA, the standard cellular infection (CI) model was expanded by including the drug effects on intracellular processes of viral RNA production and virion assembly [2]. The central part of this model is the intracellular level of HCV RNA (R). The link between the intracellular and cellular infection (ICCI) model and CI model has been achieved by replacing the constant p with a time dependent p(t) = rR(t). To account for the time scale of intracellular processes, the time from infection *a* was introduced [3]. *a* was interpreted as an individual cell characteristic (structure) and an *a*-structured population model was applied.We propose a new physiologically structured population (PSP) model where R rather than *a* is the individual cell structure. The production rate for circulating HCV RNA is expressed as $rR_{tot}(t)$, where the total intracellular viral RNA is a new link between ICCI and CI models. The drug effect is dose dependent [4].The p-state equations of the PSP model were integrated resulting in a CI model augmented by a new

variable $R_{tot}(t)$. The model parameters were obtained from [3]. Simulations were performed to compare the time courses of V(t) with the results presented in [3]. Additional simulations were done to study the impact of dose on V(t). All simulations were performed using MATLAB R2012b.

Results: The circulating levels of HCV RNA predicted by the R-structured population model overlap with that for the *a*-structured model. The dose effect on V(t) exhibits a critical dose $Dose_{crit}$. For Dose > $Dose_{crit}$, V(t) vanish for larger times implicating virus eradication. For Dose < $Dose_{crit}$, those variables approach new steady-states that are dose dependent.

Conclusion: The R-structured population model describes the drug effect on the intracellular processes and allows integration with the cell infection model. The viral load time courses predicted by the PSP model are similar to the time courses generated by the standard CI model.

References:

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Martin Bergstrand A-15 Modeling of the concentration-effect relationship for piperaquine in preventive treatment of malaria

Martin Bergstrand (1), François Nosten (2,3,4), Khin Maung Lwin (4), Mats O. Karlsson (1), Nicholas White (2,3), Joel Tarning (2,3)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (2) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. (3) Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK. (4) Shoklo Malaria Research Unit (SMRU), Mae Sod, Thailand.

Objectives: A randomized, placebo controlled trial conducted on the Northwest border of Thailand compared monthly to bi-monthly treatment with a standard 3-day treatment regimen of dihydroartemisinin-piperaquine [1]. A total of 1000 healthy adult male subjects were followed up weekly for 9 months of treatment. This project aimed to characterize the concentration-effect relationship for the malaria preventive effect of piperaquine and utilize it for simulations of dosing in vulnerable populations and in areas with piperaquine resistance.

Methods: Seasonal variations in baseline risk of malaria infection were investigated by applying one or two surge functions to a constant baseline hazard for placebo treated subjects. A mixture model was used to differentiate between a high- and low-risk subpopulation [2]. Monthly observations of piperaquine plasma concentrations were modeled using a frequentist prior [3] based on a published PK model [4]. A joint PKPD model was subsequently applied to explore the effect of piperaquine plasma concentration on malaria infection hazard. The model was sequentially

extended to account for the effect of dihydroartemisinin and the delay between the malaria diagnosis and the crucial point of prevention failure.

Results: One significant seasonal peak in malaria transmission was identified from May throughout June during when the hazard was increased with 217% (RSE 27%). The concentration-effect relationship was best characterized with a sigmoidal E_{max} relationship where concentrations of 7 ng/mL (RSE 13%) and 20 ng/ml were found to reduce the hazard of acquiring a malaria infection by 50% (i.e. IC_{50}) and 95% (IC_{95}), respectively.

Simulations of monthly dosing, based on the final model and literature information about PK, suggested that the one year incidence of malaria infections could be reduced by 70% with a recently suggested dosing regimen compared to the manufacture recommendations for children with a body weight of 8-12 kg [5]. Pregnant women were predicted to have a 12.5% higher incidence compared to non-pregnant.

Conclusions: For the first time a concentration-effect relationship for the malaria preventive effect of piperaquine was established. The established model has been useful in translating observed results from a healthy male population to that expected in other populations.

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Matt Hutmacher A-16 A Visual Predictive Check for the Evaluation of the Hazard Function in Time-to-Event Analyses

Matthew M Hutmacher
Ann Arbor Pharmacometrics Group (A2PG)

Objectives: To present methods for performing visual predictive checks (VPCs) specifically for evaluating the hazard function while modeling time-to-event (TTE) data. Binned and smoothed hazard estimators will be discussed for continuous single-event TTE data.

Methods: Pharmacometricians are becoming more involved in determining exposure-response relationships for efficacy and safety TTE endpoints. because these can be the most clinically informative for certain indications. Determining the hazard, or instantaneous risk, of an event has great utility. Changes in the absolute risk of an event over time contain information for supporting dosing or titration strategies. Methods for TTE analyses are being discussed ([1],[2]) and presented more frequently (for example, see [3]). However, little can be found for simulation-based model evaluation (or VPC) other than using Kaplan-Meier (KM) curves [1]. KM based methods evaluate the model through the survival function, which is an exponential function of the integrated (cumulative) hazard. Thus, hazard evaluation using KM curves does not provide a direct assessment of the hazard's features. It may also lack sufficient sensitivity in some cases [4]. A binned hazard estimate (BHE) approach is presented first. The method essentially considers a piecewise constant hazard for each bin and uses a simple hazard estimator for the bin. Conceptually straightforward extensions can be made using running line smoothers (RLS) with further smoothing using kernel regression. However, going back to Watson and Leadbetter (1964) [5], kernel smoothers (KS) can be directly applied. This method is more complex conceptually. Literature in this area is quite rich.

Results: Simulations were performed for various hazard functions. The BHE, RLS, and KS methods described above are introduced, implementation and considerations for their use are discussed, and the methods are contrasted to the KM method typically used.

Conclusions: Hazard-based VPCs provide a direct evaluation of the hazard function and provide a valuable simulation-based diagnostic tool for development of TTE models.

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Celine M. Laffont A-17 Non-inferiority clinical trials: a multivariate test for multivariate PD

Laffont C. M.(1), Fink M(2) and Concordet D(1)
(1) INRA, UMR 1331, Toxalim, F-31027 Toulouse, France. Université de Toulouse, INPT, ENVT, UPS, EIP, F-31076 Toulouse, France; (2) Novartis Pharma AG, Basel, Switzerland

Objectives: Composite PD endpoints are a common feature of clinical trials. This multiplicity poses a challenge for the statistical comparison of two treatments, generally the non-inferiority of a drug to a reference. Several strategies are possible. One is to test each endpoint separately but the risk is to have different conclusions and to fail to demonstrate non-inferiority because we have to correct for the multiplicity of the tests (loss of power). A second strategy is to derive a single variable from the multiple endpoints (either binary: responder/non-responder, or linear combination) and perform a single test. In that case, we lose part of the information. We have seen in previous works[1,2,3] that it is possible to model all endpoints simultaneously. In that context, we propose a multidimensional statistical test which exploits all the information and is *a priori* more powerful.

Methods: We assume that a multivariate population model is available where treatment differences are coded as ratio parameters on the PD parameters of interest. We define the statistical hypotheses of the test in a multidimensional framework. As previously discussed[4], several definitions are possible based on intersection/union principles. We propose a decision rule which can be interpreted geometrically as follows: the null hypothesis H_0 is rejected when the confidence region of the vector of ratio parameter estimates has no common point with H_0. Based on several simulation studies, we explore the advantages of this test over separate univariate tests. We

then apply the test to real clinical data where the efficacy of NSAIDs on chronic osteoarthritis is evaluated using four ordinal responses.

Results: We found that there is a balance between the dimension (the number of endpoints), the correlation between estimates, and the size of the dataset. When applied to real clinical data, non-inferiority was demonstrated with the multivariate test. When no correction was applied to account for the multiplicity of the tests, it was also demonstrated on each response separately. In contrast, when the multiplicity of the tests was accounted for as it should, non-inferiority could not be demonstrated for any response.

Conclusion: Multivariate testing definitely raises some challenges for the scientists and regulatory authorities (definition of null hypothesis, non-inferiority margin) but needs to be explored as it can be a powerful tool to increase power and thus reduce clinical costs.

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Abhishek Gulati A-18 Simplification of a multi-scale systems coagulation model with an application to modelling PKPD data

Abhishek Gulati (1), Geoffrey K Isbister (2, 3), Stephen B Duffull (1)
(1) School of Pharmacy, University of Otago, Dunedin, New Zealand; (2) Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, NSW, Australia; (3) School of Medicine and Public Health, University of Newcastle, NSW, Australia

Background

A comprehensive systems pharmacology model of the coagulation network was recently shown to describe the time course of changes in coagulation factors in response to Australian elapid envenoming [1]. The model consists of 62 ordinary differential equations (ODEs) and 178 parameters with multiple inputs and outputs. Based on any given set of available data relating to a specific input-output process, it is possible that some compartments are either less important or have no influence at all. Fixing the parameters that are not informed by the data would solve the issue of identifiability but not resolve model complexity. In this work, we describe the simplification of a multi-scale systems coagulation model and its application to describe the recovery of fibrinogen concentrations post-snake bite. Available data includes timed fibrinogen concentrations in patients with complete venom-induced consumption coagulopathy resulting from Brown snake envenomation [2]. The patients (N=61) were recruited to the Australian Snakebite Project from over 100 hospitals in Australia between January 2004 and May 2008.

Aims

The overall aim of this work was to explore a simplification of a coagulation systems pharmacology model for use in modelling pharmacokinetic-pharmacodynamic (PKPD) data. Four specific objectives were identified: (1) to create a simplified model for exploring fibrinogen recovery after envenomation that mechanistically aligns with the coagulation systems pharmacology model, (2) to extract the simplified model for use for estimation purposes, (3) to assess structural identifiability of the simplified model based on the inputs and outputs available in the dataset and (4) to develop a population PKPD model for fibrinogen concentration-time data based on the mechanisms apparent in the simplified model.

Methods

(1) Simplification of the coagulation systems pharmacology model: The technique of proper lumping, based on a previously published method [3], was used to simplify the 62 compartment ("original") model. Fibrinogen and Brown snake venom absorption and plasma compartments were left unlumped. For each of the remaining 59 lumpable compartments, the compartments were lumped randomly and a lumping matrix constructed. This lumping matrix was used to transform the full state parameter vector to the lumped state vector ("lumped" model). The simulated time courses of fibrinogen post Brown snake bite were compared among the lumped and original models to assess for loss of predictive performance. Simulations were carried out using MATLAB® R2011a. (2) Extraction of the simplified model: ODEs of the lumped model were "extracted" from the ODEs of the original model by eliminating the "unwanted" reactions that did not have any influence on the fibrinogen profile. ODEs of the lumped compartments that were formed as a result of merging of various compartments from the original model had to be explicitly written as if they had been unlumped compartments. The clotting factor that was most relevant to the Brown snake venom-fibrinogen relationship represented its respective lumped compartment. (3) Identifiability of the simplified model: The structural identifiability of the extracted model was assessed using an Information Theoretic Approach [4]. A criterion that consisted of two pre-defined conditions, as per [4], had to be met for a model to be structurally identifiable. Population OPTimal (POPT) design software was used for the analysis. (4) Modelling the fibrinogen concentration time data using the

simplified model: A full population approach was carried out to analyze the fibrinogen data using NONMEM® v7.2. The extracted model was used as the structural model and no further changes were made to the structure of the model. The unidentifiable parameters obtained from Methods (3) were fixed. BSV was considered for parameters that were identifiable. The models with BSV on one or more structural parameters were assessed for significance using the likelihood ratio test that required a decrease in the objective function value of at least 3.84. A visual predictive check (VPC) to evaluate the final model was performed by simulating 1000 replicates from the model and comparing the observed data and the prediction intervals derived from the simulated data graphically.

Results

(1) Simplification of the coagulation systems pharmacology model: The original 62 compartment model was lumped to a 5 compartment model that described the Brown snake venom-fibrinogen relationship. An *in silico* Brown snake venom bite followed by an *in silico* antivenom administration at 4 hours resulted in a similar consumption-recovery profile for fibrinogen using the lumped and original models. Lumping the compartments further significantly reduced the predictive performance of the lumped model. (2) Extraction of the simplified model: Extraction of the ODEs of the lumped model resulted in reduction of the total number of parameters to 11 compared to 178 in the original model. A Brown snake bite using the extracted model resulted in the nadir of fibrinogen depletion to 0.025 g/L compared to 0.018 g/L with the original model. (3) Identifiability of the simplified model: Assessment of identifiability of the extracted model using POPT found that 9 parameters out of the total 11 parameters were identifiable. The remaining two parameters were fixed. (4) Modelling the fibrinogen concentration time data using the simplified model: The decline and eventual recovery of fibrinogen after Brown snake envenomation was described by the 5 compartment model. A VPC showed that the model explained the observed data well. The half-life of fibrinogen was estimated to be 40 hrs (1.5 days) post Brown snake envenomation which was close to a half-life of 1 day observed in patients post Taipan snake bites [5]. The half-life of Brown snake venom was estimated to be equal to 55 minutes and refers to the procoagulant toxin in the venom and not the venom itself.

Conclusions

The technique of proper lumping was able to simplify a complicated systems pharmacology model to a much simpler model that retained a clear physical interpretation of the input-output relationship as seen in the original model. Coagulation factors - prothrombin and thrombin seemed to play the most important role in the Brown snake venom-fibrinogen relationship. The technique of structural identifiability analysis identified the parameters that could be estimated precisely after fixing the unidentifiable parameters. The techniques used in this study can be applied to other multi-scale pharmacology models.

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Nelleke Snelder A-19 Mechanism-based PKPD modeling of cardiovascular effects in conscious rats - an application to fingolimod

N. Snelder (1,2), B.A. Ploeger (1), O. Luttringer (3), D.F. Rigel (4), F. Fu (4), M. Beil (4), D.R. Stanski (3) and M. Danhof (1,2)
(1) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden, The Netherlands; (2) LAP&P Consultants BV, Leiden, The Netherlands; (3) Modeling and simulation department, Novartis, Basel, Switzerland; (4) Cardiovascular and Metabolism Research, Novartis Institutes for BioMedical Research, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

Objectives

Fingolimod (FTY720; Gilenya (trade name)) is a sphingosine 1-phosphate (S1P) receptor modulator, which is effective in the treatment of multiple sclerosis[1]. In 2010 fingolimod was approved for treatment of patients with relapsing forms of multiple sclerosis at a dose of 0.5 mg. However, early in clinical development a dose-dependent mild increase in blood pressure of 5-6 mmHG was observed at the supra-therapeutic doses of 1.25 and 5 mg. The mechanism of action (MoA) underlying this effect was not fully understood. In general, cardiovascular safety issues in drug development occur often. In this context, an adequate understanding of the cadiovascular system (CVS) which regulates blood pressure in both preclinical species and human is pivotal to efficiently anticipate clinical effects of drugs on blood pressure and ultimately improve translational drug research. The development of such a translational pharmacodynamic (PD) model requires a mechanistic understanding of blood pressure regulation. The physiological principles of the CVS including BP regulation are well characterized and the homeostatic principles of the CVS are thoroughly understood. Briefly, mean arterial

pressure (MAP) equals the product of cardiac output (CO) and total peripheral resistance (TPR) and CO equals the product of heart rate (HR) and stroke volume (SV). However, drug effects on this interrelationship have not been analyzed in a mechanism-based and quantitative manner. This investigation aimed 1) to describe, in a mechanism-based and quantitative manner, the effects of drugs with different MoA on the interrelationship between BP, TPR, CO, HR and SV and 2) to describe the effect of fingolimod on the CVS and to get a better understanding of mechanisms leading to blood pressure changes following administration of fingolimod using the developed drug-independent model.

Methods

The cardiovascular effects of 8 drugs with diverse MoA's, (amlodipine, fasudil, enalapril, propranolol, hydrochlorothiazide, prazosin, amiloride and atropine) following a single administration of a range of different doses were characterized in spontaneously hypertensive (SHR) and normotensive (WKY) rats. In addition, the effect of fingolimod following multiple administrations (maximal 4 weeks) of doses of 0, 0.1, 0.3, 1, 3 and 10 mg/kg were characterized in SHR and WKY rats. The rats were chronically instrumented with ascending aortic flow probes and/or aortic catheters/radiotransmitters for continuous recording of BP, HR and SV. Data were analyzed in conjunction with independent information on the time course of drug concentration using a mechanism-based PKPD modeling approach. The interrelationship between MAP, TPR, CO, HR and SV is expressed by the formulas 1) MAP=CO*TPR and 2) CO=HR*SV. Previously, we have developed a mechanism-based linked turnover model to describe the inter-relationship between MAP, CO and TPR[2]. This model consisted of two differential equations, one for CO and one for TPR, which were linked by negative feedback through MAP. Following a top-down modeling approach this model was extended in two ways. I) HR and SV were included in the model. The extended model consisted of three linked turnover equations involving the basic parameters of the CVS, TPR, HR and SV all linked by negative feedback through MAP. II) the circadian rhythm, which was observed in all 5 parameters of the CVS, was described by two cosine functions, one influencing HR and one influencing TPR. Linear, log-linear, power, E_{max} and Sigmoid E_{max} models were evaluated to describe the drug effects on TPR, HR

or SV. Subsequently, the developed drug-independent model was applied to identify the site of action of fingolimod and to describe the effect of fingolimod on the 5 parameters of the CVS. To this extend the system-parameters were fixed and only drug-specific parameters were estimated.

Results

By simultaneous analysis of the effects of 8 different compounds with diverse MoA's, the dynamics of the interrelationship between BP, TPR, CO, HR and SV were quantified. System-specific parameters could be distinguished from drug-specific parameters (all correlations < 0.95) indicating that the developed model is drug-independent. Model based hypothesis testing on the basis of the developed mechanism-based CVS model revealed that the increase in BP in rats, which was observed after treatment with fingolimod, is mediated by a primary effect of fingolimod on TPR. The effect of fingolimod on TPR was described by a combination of a fast (effect on the production rate of TPR (K_{in_TPR}) and slow effect on TPR (disease modifying effect on the dissipation rate of TPR (k_{out_TPR}). Both effects were found to be proportional to the baseline and the slow effect resulted in a permanent increase in BP as compared to the baseline at start of treatment. The slow effect was dependent on disease state (baseline TPR). This explains why the slow effect does not occur in WKY rats, which have a lower baseline TPR. Through the feedback-mechansims the drug effect on TPR results in an increase in MAP and TPR and a decrease in CO, HR and SV.

Conclusions

A system-specific model characterizing the interrelationship between BP, TPR, CO, HR and SV in rats has been obtained, which was used to quantify and predict cardiovascular drug effects and to elucidate the MoA for the effect of fingolimod. Ultimately, the proposed PKPD model may allow prediction of BP effects in humans based on preclinical evaluations of drug effect. It should be noted that the identified set of system parameters is specific for SHR and WKY rats. Consequently, applications of the developed model, using the identified set of system parameters, are limited to SHR and WKY rats. However, an advantage of a mechanism-based model is that it allows accurate extrapolation between different rat strains and from one

species to another[3,4] as the structure of the model is expected to be the same in all species. Therefore, future research will include the application of the developed drug-independent model to predict the clinical response based on preclinical data for fingolimod and other compounds. To this end the developed drug-independent model will be scaled to human and validated on human MAP and CO measurements.

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Nadia Terranova A-20 Mathematical models of tumor growth inhibition in xenograft mice after administration of anticancer agents given in combination

Nadia Terranova (1), Massimiliano Germani (2), Francesca Del Bene (2), Paolo Magni (1).

(1) Dipartimento di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Italy; (2) PK & Modeling, Accelera srl, Nerviano (MI), Italy.

Objectives

In clinical oncology, combination treatments are widely used and increasingly preferred over single drug administrations. Therefore, the R&D process is nowadays focused on the development of new compounds that can be successfully administered in combination with drugs already on the market. To this aim, preclinical studies are routinely performed, even if they are only qualitatively analyzed, on xenograft mice for the assessment of new combination therapies. The ability of deriving from single drug experiments a reference response to a joint administration, assuming no interaction, and comparing it to real response would be the key to recognize synergic and antagonist compounds.

This work is aimed at deriving quantitative information from standard experiments. In particular, the definition of no interaction between drug effects has been provided by means of a new mathematical model. On this basis, we have also developed a new combination model able to predict the tumor growth inhibition (TGI) in combination regimens and provide a quantitative measurement of the nature and the strength of the pharmacological drug interaction as well.

Methods

Experimental Methods

The experimental setting is that of a typical *in vivo* study routinely performed

within several drug development projects using human carcinoma cell lines on xenograft mice [1]. The typical combination experiment involves the control arm, the single agent arms and the combination arms. Average data of tumor weight of control and treated groups were considered. The PKs are evaluated in separated studies.

The no interaction model

Starting from a minimal set of basic assumptions at cellular level that include and extend those formulated for the single drug administration [2], a minimal model able to define and simulate the no interacting behavior of an arbitrary number of co-administered antitumor drugs has been formulated. The tumor growth dynamics is described by an ordinary and several partial differential equations. Under suitable assumptions, the model reduces to a lumped parameter model that represents the extension of the very popular Simeoni TGI model [3] to the combined administration of two non-interacting drugs. The TGI minimal model parameters relative to the tumor growth and to the drugs action were estimated from experimental data coming from single-drug administrations and used to simulate combination regimens under the hypothesis of no interaction. Fitting was performed by nonlinear least squares as implemented in the lsqnonlin routine of MATLAB 2007b suite with analytical computation of the Jacobian. Each residual was weighted proportionally to the inverse of the related measurement.

The combination model

Starting from the TGI minimal model, we have also developed a new PK-PD model able to predict tumor growth after the co-administration of two anticancer agents, assessing the nature and the strength of interaction as well. The tumor growth rate assessed in untreated mice is decreased by two terms proportional to drug concentrations and decreased-increased by one interaction term proportional to their product. In order to provide an understandable measure of the strength of the interaction, two indexes (called *synergistic/antagonistic combination index*) were defined.
PK and PD models were implemented in WinNolin 3.1 for the analysis of several experiments. Model identification was performed by using the nonlinear weighted least squared algorithm (with weights equal to the inverse of the related measurement). As for the minimal model the tumor-related parameters and the drug-related parameters were estimated by fitting the Simeoni TGI model on the single agent arms. Then, fixing these

parameters to the estimated values, the new proposed TGI model was fitted against the combination arms to obtain the value of the interaction term.

Results

The no interaction model

The minimal TGI model specialized for the case of two non-interacting drugs has been applied to analyze the study of irinotecan CPT-11 in combination with two different dosages of a novel compound (here call Drug B) on the HT29 human colon adenocarcinoma cell line. The validity of the no interaction hypothesis was then assessed by a suitable statistical test [4]. CPT-11 and Drug B showed a negative interaction, namely a (slight) antagonistic behavior in both combination arms.

The combination model

The model was successfully applied to four novel anticancer candidates, synthesized by Nerviano Medical Sciences, Nerviano, co-administered with four drugs already available on the market for the treatment of three different tumor cell lines. In total, six experiments, testing 11 different combination treatments involving more than 230 mice, were led. The estimation of the interaction term allowed an easy evaluation of the nature of the interaction. The combination indexes were then evaluated for the combination treatment in order to have an absolute measure of the strength of interaction. The model has also shown very good capabilities in predicting different combination regimens in which the same drugs were administered at different doses/schedules.

Conclusions

Starting from a minimal set of assumptions formulated at cellular level, the proposed minimal TGI model has been defined to describe the case of no interaction between co-administered drugs, in order to provide a theoretical definition of interaction. The model defines a general class of models and at least in one of its specialized form, can be used for the evaluation of drug combinations by exploiting simulations, providing a rigorous alternative to the subjective and qualitative visual comparison of experimental data. Starting from the concepts, a new PK-PD model has been developed and implemented aiming to be an approach of practical use in assessing combination therapy in standard xenograft experiments as well as identifying

synergistic drug combinations.
The relevance and applicability of the combination model were demonstrated analyzing several studies. This model can be considered an indispensable tool in the preclinical drug development and a crucial advance in the knowledge as it integrates the previous information to improve the decision making.

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James Lu A-23 Application of a mechanistic, systems model of lipoprotein metabolism and kinetics to target selection and biomarker identification in the reverse cholesterol transport (RCT) pathway

James Lu(1), Katrin Hübner(2), M. Nazeem Nanjee(3), Eliot A. Brinton(4), Norman Mazer(1)

(1) Clinical Pharmacology, F. Hoffman-La Roche Ltd., Basel, Switzerland; (2) Department of Modeling Biological Processes, BioQuant, University of Heidelberg, Heidelberg, Germany; (3) Division of Cardiovascular Genetics, University of Utah, Salt Lake City, UT, USA; (4) Atherometabolic Research, Utah Foundation for Biomedical Research, Salt Lake City, UT, USA

Objectives: The inverse association between the levels of high density lipoprotein cholesterol (HDL-C) with cardio-vascular (CV) risk has led to the "HDL-cholesterol hypothesis" whereby interventions raising HDL-C are expected to decrease CV risk [1]. However, the recent failures of HDL-C raising compounds (e.g., CETP inhibitors/modulators [2]) to reduce CV risk have prompted a revision of this hypothesis. The "HDL flux hypothesis" has been proposed [1]: interventions should aim to promote cholesterol efflux into the reverse cholesterol transport (RCT) pathway, leading to plague regression. This new conceptual framework calls for a re-evaluation of targets and biomarkers.

Methods: In contrast to the stochastic, particle-based model previously presented [3], the current work utilizes a coarse-grained model that describes the dynamics of cholesterol and apoA-I pools by a system of ODEs. Importantly, the cyclic process of HDL particle maturation and re-generation is described, employing geometrical concepts [4]. HDL re-generation results in a feedback loop linking the clearance rate of HDL-C back to the RCT input

rate. The 17 parameters in the model are estimated using the *maximum a posteriori* approach: prior estimates of key parameters are taken from published flux values in normal subjects, which are subsequently informed by the calibration data. "Virtual populations" are created by sampling model parameters from a multivariate normal distribution around the mean to understand epidemiological relationships. Using correlation and principal component analyses of simulation outputs, biomarkers are examined and selected based on further mathematical analysis.

Results: Our model predicts that CETP inhibitors raise HDL-C due to a reduction in its clearance rate, but do not increase the RCT input rate. We believe this provides an explanation for their lack of CV benefit. In contrast, we identify targets that increase both HDL-C and RCT: e.g., ABCA1. Using the model, we further predict that the ratio of lipoprotein parameters pre-b/apoA-I is a biomarker of therapeutic response under ABCA1 upregulation.

Conclusions: A challenge in understanding the effects of perturbations to the RCT pathway is the presence of a feedback loop due to the cyclic nature of HDL metabolism. To meet this challenge, a systems model has been built to help select targets and identify biomarkers. The model shows that only some targets which increase HDL-C are associated with increases in RCT.

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Rollo Hoare A-24 A Novel Mechanistic Model for CD4 Lymphocyte Reconstitution Following Paediatric Haematopoietic Stem Cell Transplantation

Rollo L Hoare (1,2), Robin Callard (1,2), Paul Veys (1,3), Nigel Klein (1,3), Joseph F Standing (1,2,3)

(1) Institute of Child Health, University College London, 30 Guilford St, London, UK; (2) Centre for Mathematics and Physics in the Life Sciences and Experimental Biology, University College London, Gower St, London, UK; (3) Great Ormond Street Hospital NHS Foundation Trust, Great Ormond St, London, UK

Objectives: Before a haematopoietic stem cell transplant (HSCT), a child will usually be given a conditioning regimen to reduce or ablate the host immune system in order to prevent graft rejection. Following HSCT, long-term successful outcomes and short-term complications are associated with the rate and extent of recovery in the child's immune system. Studying immune reconstitution in children presents a huge challenge as the rapidly developing immune system means that expected CD4 T cell counts (a key subset of lymphocytes) for age can vary by as much as three-fold [1]. This work presents a new mechanistic model that has been developed which describes the reconstitution of total body CD4 T cell count with time in children who have had an HSCT.

Methods: The fundamental model of the CD4 cell count has three parameters representing, the initial total body CD4 cell count, thymic output of CD4 cells, and the net loss rate of CD4 cells. The model is made more mechanistic in three ways: (1) accounting for age-related changes in the thymus with a functional form for thymic output [2]; (2) allowing for thymic output not recovering production immediately after the HSCT; (3) including the effects of competition for homeostatic signals leading to changes in the

net loss rate with cell quantities. We apply this model to longitudinal data collected in the bone marrow transplant unit in Great Ormond Street Hospital.

Results: Adding the effects of reduced thymic function and competition both significantly improved model fit, and the final model had good descriptive and simulation properties. In the long term, the modelled population average returned to, or very near to, the total body CD4 count expected for a healthy child. The dynamics of the thymus returning to full production agree well with experimental evidence [3].

Conclusions: A novel mechanistic model for the immune reconstitution of CD4 cells after HSCTs in children has been developed. The model brings together many ideas about the immune system in children, including the changes in the thymus with age, and appears to show clearly the necessity of including both the effects of reduced thymic function post HSCT, and of competition for homeostatic signals by CD4 cells in the body. It is now possible to carry out a multivariate analysis and find which parts of the immune system are affected by covariates such as disease type, drug pre-conditioning, and graft-versus-host disease prophylaxis.

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Huub Jan Kleijn A-25 Utilization of Tracer Kinetic Data in Endogenous Pathway Modeling: Example from Alzheimer's Disease

Huub Jan Kleijn, Tom Bradstreet, Mary Savage, Mark Forman, Matthew Kennedy, Arie Struyk, Rik de Greef, Julie A. Stone
Merck Research Laboratories, Whitehouse Station, NJ, US

Objectives: Tracer kinetic studies can be a valuable tool to gain understanding on the dynamics of protein pathways. However, results interpretation is difficult and requires a model-based evaluation to take full advantage of the data. In this example, timecourse data on CSF tracer and ELISA-based total CSF Aβ were obtained under unaltered, mild and potent production inhibition with a BACE inhibitor in healthy human to inform understanding of the amyloid pathway, which is central to plaque formation in Alzheimer's Disease. Our goal was to establish a mechanistic pathway model that describes the total Aβ, fraction labeled Aβ, and newly generated Aβ with a single drug action (inhibition of BACE) to enhance understanding of the utility and interpretation of tracer kinetic data.

Methods: Subjects (n=5/arm) received single doses of placebo, low or high dose BACE inhibitor with ^{13}C-labeled leucine infused from 5 to 15 hours post-dose. Serial plasma and CSF samples were obtained for assessment of drug concentration, total Aβ, and fraction of leucine and Aβ labeled.
Data were fit to a compartmental model reflecting brain pools for precursor protein, BACE cleavage product C99, gamma secretase cleavage product Aβ and distribution to the lumbar CSF sampling site. Duplicate pathways were needed, informed by the timecourse of fraction ^{13}C-labeled leucine, to separately describe the labeled and unlabeled fractions. BACE inhibition was modeled as an Emax function on the production rate of C99.

Results: The model was able to simultaneously describe the time courses of total Aβ, fraction labeled Aβ, and newly generated Aβ with a single drug action. Rate constants related to steps in the amyloid pathway could be separated from delays related to distributional processes. Simulations indicated that timing of ^{13}C-leucine infusion relative to dosing of the BACE inhibitor is key in obtaining informative data on the underlying system.

Conclusions: Tracer kinetic approaches together with mechanistic modeling enhance the understanding of endogenous pathway dynamics. A model-based analysis allowed to distinguish between steps in the amyloid pathway and distributional processes. This framework enables a more physiologically based approach to account for effects of Aβ oligomers and/or plaque pool in Alzheimer's disease. Finally, model-based simulations inform on improvements of the experimental design that will maximize derived knowledge on the underlying system pharmacology of the amyloid pathway.

Justin Wilkins A-27 Reproducible pharmacometrics

Justin J. Wilkins (1), E. Niclas Jonsson (2)
(1) SGS Exprimo NV, Mechelen, Belgium; (2) Pharmetheus AB, Uppsala, Sweden

Reproducibility is the cornerstone of scientific research, but is nonetheless a challenging area in pharmacometric data analysis. The large number of intermediate steps required, often involving multiple versions of datasets, combined with a mixture of software tools and the substantial quantity of results that must be tracked and summarized renders traceability an onerous and time-consuming business.

The concept of "reproducible research" is that the final product of scientific research is not just the text of a report or research article, but should also include the full computational environment used to produce the results, including all the associated code and data – and that this bundle of data and scripts should be shared with others who wish to reproduce these results. Although this is not often possible in pharmacometrics, given that data are usually confidential and that it may not be practical to reproduce hundreds of model fits, we can apply the process of reproducible research to our activities as far as possible to ensure that traceability is maintained.

Although there are many approaches that may be taken to adopting this principle, we shall focus on the combination of R, knitr and LaTeX. These tools together enable the end-to-end scripting of data file creation, capture of results from external software tools and subsequent analyses, and can automate the creation of publication-quality reports, articles and slide decks.

We shall demonstrate that applying techniques such as these is not particularly difficult, especially now that they are coming into general use and

support from software tools is maturing. We shall discuss the substantial benefits of doing so, which include increased accuracy, efficiency, reliability and credibility, elimination of transcription errors, built-in traceability, and the ability to reproduce an analysis, including article or report, in its entirety years later. A live demonstration will be available during the poster sessions.

Nick Holford A-28 MDL - The DDMoRe Modelling Description Language

Nick Holford (1), Mike Smith (2) on behalf of DDMoRe WP3 contributors
1. Department of Pharmaceutical Biosciences, Uppsala University, Sweden 2. Dept Statistical Pharmacometrics, Pfizer Global Research & Development, United Kingdom

Objectives: Definition of a modelling description language (MDL) is a key deliverable from the Innovative Medicines Initiative Drug Disease Modelling Resource (DDMoRe) project [1]. The MDL aims to provide a new standard in describing pharmacometric models consistently across software tools and brings together features of various existing modelling languages. It is intended to be flexible, extensible, easy to code, understand and use. Together with the associated computer-readable markup language, PharmML, the aim is to facilitate automated translation of models and modelling tasks into target application scripts for NONMEM, Monolix, Phoenix NLME, BUGS, R and Matlab.

Methods: A DDMoRe work-package group comprising members from European universities, small to medium enterprises (SME) and the pharmaceutical industry have collaborated for 2 years to develop the MDL. A draft MDL description was proposed and refined through review and input from colleagues across the project. Example models (Use Cases) have been proposed which test the ability of the language to describe a variety model features succinctly and unambiguously.

Results: A MDL specification document has been written that describes the structure and properties of the language. There are two components 1) the Model Coding Language (MCL) which is declarative and describes the mathematical model, parameters, data and task properties. 2) the Task

Execution Language which is procedural and defines the workflow of modelling tasks using a R like language which may include (but is not limited to) estimation, simulation, diagnostics, modelling summaries and data generation. Close integration with R is desirable to leverage existing and established modelling and simulation packages. Automated translation from NM-TRAN to MDL [2] and from MDL to NM-TRAN has been demonstrated for simple models. A "Rosetta Stone" has been constructed to assess whether key attributes within the target languages have been adequately expressed within the MCL and to identify how translation of MDL to the other target languages can be achieved.

Conclusions: It is expected that conversion to the remaining target application scripts will occur rapidly now that the feasibility of using NM-TRAN has been confirmed. Public release of the language specification will occur by June 2013. This work is presented on behalf of the DDMoRe project.

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Vittal Shivva A-30 Identifiability of Population Pharmacokinetic-Pharmacodynamic Models

Vittal Shivva(1)*, Julia Korell(1,2), Ian G Tucker(1), Stephen B Duffull(1)
(1)School of Pharmacy, University of Otago, Dunedin, New Zealand
(2)Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Background: Mathematical models are routinely used in clinical pharmacology to study the time course of concentration and effect of a drug in the body. Identifiability of these models is an essential prerequisite for the success of these studies [1]. Identifiability is classified into two types, structural identifiability related to the structure of the mathematical model and deterministic identifiability which is related to the study design. Though various approaches are available for assessment of structural identifiability of fixed effects models, no specific approaches are proposed to formally assess population models.

Aim & Objectives: In this study we developed a unified numerical approach for simultaneous assessment of both structural and deterministic identifiability for fixed and mixed effects pharmacokinetic (PK) or pharmacokinetic-pharmacodynamic models. The approach was based on an information theoretic framework [2]. The approach was applied to both simple PK models to explore known identifiability properties and also to a parent-metabolite PK model [3] to illustrate its utility.

Methods & Results: One compartment first order input PK models (Bateman & Dost) were assessed as fixed effects and mixed effects models using the criteria developed in this study. Results from the assessment of mixed effects models revealed that the bioavailable fraction F and its between subject variability (BSV) parameter ω_F were unidentifiable in the Dost model,

whereas only *F* was unidentifiable in the Bateman model. A parent-metabolite model that described the oral PK of ivabradine and its metabolite was assessed for identifiability of both fixed and mixed effects. Assessment of the model revealed that V_{m2} (volume of distribution of the metabolite in the central compartment) and F_i (bioavailable fraction of the parent) were unidentifiable in the model. All BSV parameters were identifiable in the mixed effects model of ivabradine.

Discussion & Conclusions: Results from the analysis of simple and more complicated (multiple response) PK models have demonstrated the ability of this approach to assess structural identifiability of population models. This method also enables the assessment of deterministic identifiability by examining the diagonal elements of the inverse of the Fisher Information Matrix for a candidate design. The current approach can serve as a unified method for assessing both structural and deterministic identifiability of population models.

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Leonid Gibiansky A-31 Methods to Detect Non-Compliance and Minimize its Impact on Population PK Parameter Estimates

Leonid Gibiansky (1), Ekaterina Gibiansky (1), Valerie Cosson (2), Nicolas Frey (2), Franziska Schaedeli Stark (2)
(1) QuantPharm LLC, North Potomac, MD, US; (2) F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: To develop and evaluate methods to detect non-compliance and obtain unbiased parameter estimates in a population pharmacokinetic (PK) analysis.

Methods: Data sets emulating clinical studies with different duration, sampling schemes and levels of compliance to a once daily oral dosing regimen were simulated using a 2-compartment model with first-order absorption and elimination and significant drug accumulation. Non-compliance was simulated as drug holidays preceding some observations in 20 to 80% of subjects. For each dataset, the original model was fit assuming full compliance to evaluate precision and bias on the parameter estimates. Two methods (CM1, CM2) to account for non-compliance were tested. CM1 introduced a random effect (ETAerr) on the magnitude of the residual error and re-estimated PK parameters with increasing fractions of subjects with high ETAerr removed from the data set. CM2 is the generalization of the idea proposed in [1]. It relied on rich data obtained immediately before and after an observed dose in the clinic, while trough PK samples related to unobserved doses outside the clinic (outpatient doses) were ignored. To account for possible non-compliance, individual relative bioavailability of the outpatient doses was introduced, estimated, and associated to individual compliance.

Results: When assuming full compliance, the PK parameter estimates were significantly biased. By introducing ETAerr in CM1 the bias was reduced and non-compliant subjects could be associated with a high ETAerr. Incremental removal of subjects with high ETAerr further reduced the bias until the parameter estimates converged to the true values, while the variance of the ETAerr decreased towards zero. However, precision of the obtained parameter estimates decreased with increasing number of subjects removed to obtain unbiased parameter estimates. CM2 yielded unbiased PK parameter estimates for the datasets with any fraction of non-compliant subjects. Non-compliant subjects could be associated with a low bioavailability estimate for the outpatient doses. However, the method heavily relies on the availability of rich data following an observed dose in the clinic.

Conclusions: The proposed methods offer ways to identify subjects with non-compliance and reduce or eliminate bias on PK parameter estimates based on rich or sparse PK sampling data in populations with prevalent non-compliance.

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Julie Bertrand A-32 Penalized regression implementation within the SAEM algorithm to advance high-throughput personalized drug therapy

Julie Bertrand (1), Maria De Iorio (2), David J. Balding (1)
(1) Genetics Institute, University College London, London, UK, (2) Department of Statistical Science, University College London, London, UK

Context: In a previous study, we have shown that penalized regression approaches (such as Lasso) in combination with a model-based population analysis were computationally and statistically efficient to explore a large array of single nucleotide polymorphisms (SNPs) in association with drug pharmacokinetics (PK) [1]. However, these approaches use two stages in which the effect of a SNP on model parameters is assessed after those parameters are estimated.

Objectives: To develop an integrated approach to simultaneously estimate the PK model parameters and the genetic size effects and compare its performance to a penalized regression on Empirical Bayes Estimates (EBEs) and a classical stepwise procedure.

Methods: At each iteration of the Stochastic Approximation (SA) Expectation Maximization algorithm, a penalized regression is realized on the values of the individual parameters issued from the SA to update the vector of fixed effects. In the Lasso procedure, the penalty function is the double-exponential (DE) probability density. Hoggart et al. [2] proposed the HyperLasso, a generalization of the Lasso, to allow the penalty function to have flatter tails and a sharper peak. HyperLasso uses the normal-exponential Gamma (NEG) distribution, which is the DE with the rate parameter drawn from a Gamma distribution. The shape parameter of the NEG was here set to

1 and the scale using a formula ensuring a given family wise error rate (FWER) [2] rather than permutations as in [1].

Our simulated PK model is based on a real-case study but with a design selected to ensure reasonable precision of parameter estimates of 300 subjects and 6 sampling times. The simulated array includes 1227 SNPs in 171 genes. Under the alternative, H_1, we randomly picked 6 SNPs per simulated data set which together explain 30% of the variance in the logarithm of the apparent clearance of elimination.

Results: The penalized regression on EBEs and the stepwise procedure obtained a FWER not significantly different from the target value of 0.2, while the integrated approach was more conservative with an empirical FWER of 0.1. Nevertheless, all three approaches obtain similar power estimates to detect each of the 6 causal SNPs with the integrated approach detecting almost no false positives. The integrated approach computing times were longer under the null and under H_1, 1.8 and 2.8h compared to 0.08 and 0.12h for the penalized regression on EBEs and 0.08 and 0.73h for the stepwise procedure.

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Shelby Wilson A-34 Modeling the synergism between the anti-angiogenic drug sunitinib and irinotecan in xenografted mice

S. Wilson, E. Grenier, M. Wei, V. Calvez, B. You, M. Tod, B. Ribba
INRIA Grenoble Rhone-Alpes, Numed Project Team, 655 avenue de l'Europe, 38330 Montbonnot-Saint-Martin, France

Objectives: We aim to evaluate a potential synergistic effect between sunitinib, an anti-angiogenic agent, when given in combination with irinotecan, a cytotoxic agent, in preclinical settings using tumor inhibition models.

Methods: We analyze a data set consisting of longitudinal tumor size measurements (1,371 total observations) in 90 colorectal tumor-bearing mice. Mice received single or combination administration of sunitinib and/or irinotecan. We model this data with a system of non-linear ordinary differential equations that describe tumor growth and angiogenesis. Sunitinib is modeled as acting by reducing the carrying capacity of the tumor, while irinotecan directly reduces the tumor bulk by inducing progressive cell death through transit compartments. Model parameters corresponding to tumor growth and monotherapy are estimated in a mixed-effect manner using Monolix (Lixoft) while parameters corresponding to drug synergism are estimated in a fixed-effect manner using a Nelder-Mead Simplex Method. We then evaluate the hypothesis that sunitinib and irinotecan interact synergistically when administered together.

Results: Through a chi-squared test on the residuals generated by the single and combination arm simulations, we conclude that there must be a synergistic interaction between these drugs ($p<0.0001$). We found that this interaction takes place in the rate parameter defining the speed in which cells die once affected by irinotecan, with this speed being proportional to the area under the curve of sunitinib given prior to the first dose of irinotecan. This increase in death rate can be related to re-oxygenation of cells due to the improved vasculature induced by sunitinib. A direct consequence of this interaction is the creation of a therapeutic window in which the relative timing between drug administrations is most effective. Irinotecan administered 5 days after onset of sunitinib administration leads to the maximum relative reduction of tumor size (9.52%).

Conclusions: Our model suggests that synergism between irinotecan and sunitinib is a necessary consideration for future studies. Model dynamics indicate the existence of an optimal timing of irinotecan administration with respect to that of sunitinib. This model can be used as a simulation tool to increase overall treatment efficacy by suggesting protocols based on the identification of optimal treatment windows created by the synergism between anti-angiogenic and chemotherapeutic drugs.

S. Y. Amy Cheung A-35 Using a model based approach to inform dose escalation in a Ph I Study by combining emerging clinical and prior preclinical information: an example in oncology

S.Y. Amy Cheung, James W.T. Yates, Peter Lawrence, Marcelo Marotti, Barry Davies, Paul Elvin, Christine Stephens, Paul Stockman and Andrew Foxley
AstraZeneca R & D, Macclesfield, UK

Objectives: Oncology Phase I studies are typically small, open-label, sequential studies enrolling 3-6 patients per dose escalation [1]. Deriving a recommended dose, schedule and potential combination option is one of the main goals.
Rule based methods are used to identify the recommended dose [1] based on clinical data generated during the study. The disadvantages of these methods are that they are unable to use all previous information on the study and cannot easily provide extrapolation to untested schedules. Model based approaches for human studies [2] allow utilization of all available data, and the relationship between dose, exposure and effect to be determined. This example of a first time in man trial demonstrates the benefits of incorporating model based approaches to inform dose escalation.

Methods: Prior to this study, pre-clinical information was reviewed to identify and prioritize key data for analysis that would provide useful signals for tolerability.
The predicted human PK profile was used as prior information to enable analysis of the sparse datasets emerging from the first few cohorts. Pharmacodynamic models developed from pre-clinical data were reapplied to the clinical data.
The models were updated with data from each successive cohort of patients

and then used to simulate the endpoints for a range of proposed dose escalations to inform the clinical team with predicted outcomes. These models were also used to explore options for further arms of the study to investigate alternative schedules.

Results: Even from small data sets the models developed were robust to inform escalation. This was demonstrated in part by the ability to predict to untested doses and schedules. The simulations of continuous variables allowed for dose increments and the starting dose for alternative schedules to be determined using a quantitative basis. This included the instigation and escalation of intermittent dosing arms that proceeded to identify the recommended dose more quickly than would have been the case with a classical approach.

Conclusions: The utilization of pre-clinical, clinical PK, safety and PD data in model based dose escalation allows rapid learning in early phase clinical development. This real-time approach using simulation of scenarios based on the available information has enabled a development program to identify the RD for a range of schedules efficiently thereby improving trial outcome.

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Sonya Tate A-36 Tumour growth inhibition modelling and prediction of overall survival in patients with metastatic breast cancer treated with paclitaxel alone or in combination with gemcitabine

Sonya C Tate (1), Valerie Andre (1), Nathan Enas (2), Benjamin Ribba (3) and Ivelina Gueorguieva (1)
(1) Eli Lilly and Company, Erl Wood, UK, (2) Eli Lilly and Company, Indianapolis, USA, (3) INRIA, Grenoble, France

Objectives: The aim of this study was to develop a modelling framework to a) characterise the tumour growth inhibitory (TGI) effects of paclitaxel and gemcitabine in metastatic breast cancer (MBC) patients, and b) investigate the predictive potential of change in tumour size (CTS) on overall survival (OS).

Methods: A randomised phase III trial was performed to evaluate the clinical benefit of gemcitabine for MBC patients receiving concomitant paclitaxel therapy [1]. Data from the study were collated and inclusion criteria were applied to align the WHO tumour size dataset with RECIST 1.0. A sequential modelling approach was applied to first evaluate tumour growth dynamics and to subsequently predict OS from CTS. The PK/TGI model was developed to incorporate the effect of combination therapy. A survival model was used to characterise OS as a function of various covariates, including CTS at weeks 1 to 12, baseline tumour size, treatment group, ECOG status, age and ethnicity.

Results: Of the 598 patients enrolled, 486 patients contributed 1477 measurements meeting the inclusion criteria. Survival data were available for 446 of those patients, of which 376 had died at the last follow up. A PK/TGI

model which was previously used to assess tumour growth dynamics in a range of tumour types [2,3,4] was successfully applied to MBC. To model drug combination, we included two distinct routes of tumour shrinkage, one by paclitaxel and another by gemcitabine. Drug exposure was incorporated into the model by simulating AUC0-24 from published PK models [5,6]. The median predicted CTS at week 8 was -11% from baseline for the paclitaxel arm and -26% for the gemcitabine/paclitaxel arm. OS was described using a survival model with a Weibull distribution, incorporating CTS at week 8 as the best predictor of OS. Additional covariates included in the survival model were ECOG status and baseline tumour size.

Conclusions: We have extended an existing clinical TGI model to incorporate combination therapy and successfully applied this model to analyse tumour size data in MBC patients treated with paclitaxel alone or in combination with gemcitabine. Notably, using this combination therapy model, we have found that CTS at week 8 was a good predictor of OS in accordance with previous studies for NSCLC and thyroid cancer [3,7]. These results support the use of this modelling approach in future clinical studies which incorporate combination therapy in a parallel design.

This work is supported by the DDMoRe project.

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Chuanpu Hu A-39 Latent variable indirect response modeling of continuous and categorical clinical endpoints

C. Hu(1), P. Szapary(1), A. Mendelsohn (1), H. Zhou(1)
(1)Janssen Research & Development LLC, Spring House, PA, USA

Objectives: Parsimonious predictive exposure-response modelling is important in clinical drug development. This study aims to introduce a general latent variable representation of Indirect Response (IDR) models, and apply it to simultaneously model the efficacy endpoints of Psoriasis Area and Severity Index (PASI) scores and the 20%, 50%, and 70% improvement in the American College of Rheumatology disease severity criteria (ACR20/50/70), in psoriatic arthritis (PsA) patients treated with ustekinumab.

Methods: A general approach of using a latent-variable representation of IDR models in a format of change from baseline for clinical endpoints is developed from a continuous underlying process. The approach extends to general link functions that cover logistic/probit regression. Placebo effect parameters in the new representation are more readily interpretable and can be separately estimated from placebo data, thus allowing convenient and robust model estimation. When applying to ordered categorical endpoints, the approach allows the testing of baseline constraint that the probability of achieving endpoint equals zero. Inherent connections with baseline-normalized standard IDR models are derived. This approach was applied to data through the primary endpoint (week 24) from two phase III clinical trials of subcutaneously administered ustekinumab for the treatment of PsA, where PASI scores and ACR20/50/70 were jointly modelled with accounting of their correlations.

Results: An earlier approach using latent variable IDR [1,2] to model clinical endpoints is shown to be equivalent to a baseline-normalized representation [3,4]. This is used to further prove an equivalence between Type I/III IDR models for clinical endpoints. The equivalence properties hold under general link functions that cover logistic and probit regression or continuous clinical endpoint modelling. In the current application, 925 PsA patients contributed to nearly 3,000 ustekinumab serum concentration measurements, 5,000 ACR and 3,400 PASI scores. External validation showed reasonable parameter estimation precision and model performance.

Conclusion: The latent-variable IDR model representation provides a parsimonious approach for predictive modelling of clinical endpoints. In this framework, Type I and Type III IDR models are shown to be equivalent, therefore there are only three identifiable IDR models. The joint model could be used to predict both psoriasis and arthritis components.

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Anne-Gaelle Dosne A-40 Application of Sampling Importance Resampling to estimate parameter uncertainty distributions

Anne-Gaëlle Dosne (1), Martin Bergstrand (1), Mats O. Karlsson (1)
: (1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Develop a method to assess parameter uncertainty for non-linear mixed effects (NLME) models based on Sampling Importance Resampling (SIR) [1]. Compare this method to existing methods for real and simulated data.

The uncertainty in parameter estimates in NLME models is commonly computed using the asymptotic covariance matrix. A well-known limitation of this method is the lack of considering any asymmetry in the parameter uncertainty. In this work, a method based on SIR was developed to improve uncertainty estimation based on the covariance matrix while limiting computational burden.

Methods: A high number (2000-10000) of parameter vectors were sampled from the covariance matrix. For each parameter vector, an importance ratio (IR) was computed by weighting the fit to the original data by the probability density value for the vector given the estimated covariance matrix. Non-parametric uncertainty distributions were then obtained by resampling parameter vectors according to probabilities proportional to the IR. The SIR method was applied to NLME models for real [2-4] and simulated data. Parameter confidence intervals (CIs) and density distributions obtained with SIR were compared to those obtained based on likelihood profiling (LLP), covariance matrix and bootstrap using the FOCEI method in NONMEM 7.2.

Results: Compared to CIs based on the covariance matrix, SIR provided a closer agreement with LLP, especially for parameters showing asymmetric CIs. SIR CIs were in agreement with CIs based on the covariance matrix when the uncertainty was symmetric. SIR also led to CIs in closer agreement to LLP for real data examples where the bootstrap confidence intervals were shown to be inflated [5].

Conclusions: SIR appears as a promising approach to assess parameter uncertainty. While based on the covariance matrix, it can address asymmetry in parameter uncertainty. As opposed to LLP, it directly generates a distribution that can be used for clinical trial simulation. In comparison to a bootstrap SIR allows every parameter vector to be evaluated using all data, which is valuable when the data set is not very large, yet at a very limited computational burden.

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Hoai Thu Thai A-41 Bootstrap methods for estimating uncertainty of parameters in mixed-effects models

Hoai-Thu Thai (1), France Mentré (1), Nicholas H.G. Holford (3), Christine Veyrat-Follet (2), Emmanuelle Comets (1)
(1) INSERM, UMR 738, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, UMR 738, F-75018 Paris, France; (2) Drug Disposition Department, Sanofi, Paris, France; (3) Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand

Objectives: Nonparametric case bootstrap is frequently used in PK/PD for estimating standard error (SE) and confidence interval (CI) of parameters [1-2]. Residual bootstraps resampling both random effects and residuals are an alternative approach to case bootstrap which resamples entire individuals [3-4]. These methods have not been well studied in mixed-effects models (MEM). We aimed to study and propose appropriate bootstrap methods in MEM and to evaluate their performance by simulation using examples of disease progression model in Parkinson's disease [5] (for linear MEM) and PK model of aflibercept (Zaltrap®) [6], a novel anti-VEGF drug (for nonlinear MEM).

Methods: Different bootstraps accounting for between-subject and residual variabilities were implemented in R 2.14. Corrections of random effects and residuals for variance underestimation were investigated [7]. The bootstrap performances were first assessed in LMEM with homoscedastic error by a simulation (k=1000 replicates and B=1000 bootstrap samples/replicate) with 3 balanced designs (rich, sparse, large error). The best bootstraps in LMEM were then evaluated in the NLMEM with heteroscedastic error by a simulation (k=100/B=1000) with 2 balanced (frequent/sparse) and 1 unbalanced designs. Bootstraps were compared in terms of bias of

parameters, SE and coverage rate of 95% CI. R 2.14 and MONOLIX 4.1 were used to fit the data in LMEM and NLMEM, respectively.

Results: Our simulations showed a good performance of the case bootstrap and the nonparametric/parametric residual bootstraps with a correction for variance underestimation in LMEM [8]. In NLMEM, these methods performed well in the balanced designs, except for the sparse design where they greatly overestimated SE of a parameter estimate having a skewed distribution. In the unbalanced design, the case bootstrap overestimated the SE of this parameter and the nonparametric residual bootstrap overestimated the SE of variances even with stratification on frequent/sparse sampling. The asymptotic method performed well in most cases, except for low coverage rates of highly nonlinear parameters.

Conclusion: The bootstraps only provide better estimates of uncertainty in NLMEM with high nonlinearity compared to the asymptotic method. The nonparametric residual bootstrap works as well as the case bootstrap. However, they may face practical problems, e.g skewed distributions in parameter estimates and unbalanced designs where stratification may be insufficient.

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Celia Barthelemy A-42 New methods for complex models defined by a large number of ODEs. Application to a Glucose/Insulin model

Celia Barthelemy and Marc Lavielle
INRIA Saclay and University Paris-Sud

Objectives: Modelers are increasingly faced with complex physiological models represented by a large number of ordinary differential equations (ODEs). Widely used modeling algorithms need to evaluate the structural model a large number of times, and for instance SAEM, MCMC and Monte-Carlo algorithms can be extremely time-consuming when the model is defined by a large system of ODEs. There is therefore a need for new efficient numerical tools to help the modeler deal with such complex models. We propose an extension of these algorithms that limits the total number of times the ODEs need to be solved.

Methods: This new approach consists in first evaluating the structural model on a well-defined grid of parameters. Then, the structural model is approximated by interpolating these isolated values. The number of points of the grid defines the quality of the approximation. "Exact methods" are obtained when this number tends to infinity.

The proposed method has been evaluated using simulations. Performance was assessed by computing the root mean square error (RMSE) and the computing time required for several tasks: estimation of the population and individual parameters, evaluation of the Fisher information matrix, evaluation of the log-likelihood, and creation of VPCs.

Results: We illustrate the method on simulated datasets from the glucose/insulin model proposed by Alvehag [1]. This model is composed of 29 EDOs, and 5 parameters are estimated. For a grid of 11^5 points, the elapsed time for each task is approximately divided by 7. For example, the times for the original and extended SAEM algorithms are respectively 3 minutes and 42 seconds, and the increase in the RMSE does not exceed 5%.

Conclusions: Encouraging results have been obtained with models defined by a large system of ODEs and a relatively small number of unknown parameters. In particular, the population parameters are estimated with little bias whereas the estimation is significantly faster compared to standard SAEM. This method makes feasible the use of more and more realistic physiological models.

Attempts can now be made to extend such approaches to models defined with a larger number of parameters. Application to spatial models defined by Partial Differential Equations (PDEs) could also be considered.

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Andrijana Radivojevic I-01 Enhancing population PK modeling efficiency using an integrated workflow

Andrijana Radivojevic, Martin Fink, Jean-Louis Steimer, Henning Schmidt
Novartis Pharma AG, Basel, Switzerland

Objectives: Population pharmacokinetic (popPK) modeling outlines a very significant area of Pharmacometrics, or *Modeling & Simulation*. PopPK activities need to be performed regularly during drug development - from first-in-human dose prediction until submission at the end of Phase III. Since such analyses currently can take a considerable amount of time, resources are bound and not readily available to support other aspects of model based drug development. Our aims were to examine how the process of building a popPK model can be supported in order to increase efficiency, to develop a user friendly implementation of a popPK toolbox as proof-of-concept, and to stimulate a scientific discussion about such an integrated approach.

Methods: Through an internal survey at Novartis Modeling&Simulation and review of published literature, the most typical popPK modeling scenarios (following the Pareto principle) were identified. Based on that information, a popPK workflow was defined, along with a standard dataset specification. A modular approach was chosen, allowing the modeler to use the workflow where possible and do additional assessments where needed.

Results: This investigation proposes a workflow for popPK analyses, including data standards, data exploratory and goodness-of-fit plots, model building, covariate search, model summary/comparison statistics. As a proof-of-concept, the workflow was implemented and documented within the user-friendly SBPOP Package [1]. It has already been tested internally at Novartis on analysis of Phase II and III data for several compounds.

Conclusions: While the literature offers guidelines on popPK model validation and reporting, recommendations on actual model building still remain limited. The given implementation of a step-wise popPK modeling workflow has been proven to bring a considerable gain in efficiency, but at the same time assuring compliance to regulatory and internal requirements, freeing the modeler from labor intensive repetitive coding tasks. The approach is easily extensible to sequential PKPD modeling. At the current stage, the discussed workflow and its implementation is meant to serve as a basis for scientific discussions on model building standards.

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Gauri Rao I-02 A Proposed Adaptive Feedback Control (AFC) Algorithm for Linezolid (L) based on Population Pharmacokinetics (PK)/Pharmacodynamics (PD)/Toxicodynamics(TD)

Gauri G. Rao (1), Neang S. Ly (1), Brian T. Tsuji (1), Alan Forrest (1)
(1) School of Pharmacy &Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, NY

Objectives:L has a complicated &variable population PK model with parallel saturable (non-renal) & first order (renal) pathways of elimination. The traditional dose of 600mg q12hr provides ~30-fold variability in area under the curve (AUC); only ~19% of this variability can be explained by patient covariates. Efficacy is well related to AUC/MIC with values of 100 to 200 needed to treat most sites of infection. The current MIC breakpoint for susceptibility is 4. TD (decreased platelet (PLT)) related to AUC & duration of L treatment. Our objective is to use population PK/PD/TD models & Monte Carlo simulations (MCS) to evaluate the ability to safely &effectively treat infections with an MIC>1.

Methods: We developed an integrated PK/PD/TD model from the literature1-4. MCS (ADAPT 5)was used to randomly select 5000 adult patients (with a full range of weights, creatinine clearance &baseline PLT) who were treated with 3 different regimens (600mg q12h (R1), 600mg q8h (R2) & a regimen individualized by AFC (R3)). For each subject ®imen resulting AUCs were used to compute, for MICs 2 &4, the probability for success for a lower respiratory tract infection (PLRTI2 & PLRTI4) & bacteremia (PBac2 & PBac4) & predicted platelet nadirs on days 7 (NPlt7) & 14 (NPlt14). For the AFC algorithm, a 1200mg loading dose was followed by plasma samples at 0.5, 1, 4, 12 & 24h, with random observation errors, (times according to optimal sampling

theory) &600mg q8h. These samples were fit with a MAP-Bayesian estimator & doses adjusted within 24h.

Results: The randomly selected patients had a median (range) weight (kg) 73.4(39-132), creatinine (mL/min) 67.8 (22.6-178) & baseline PLT 305 (135-595). Results for (R1/R2) for %Bac2 (91.8/95.9), %Bac4 (66.2/93.6), %LRTI2(75.5/77.9), %LRTI4(59.6/76.5), %NPLT7

Conclusions: R1 the MIC cutoff should be 2 & not 4. Given the substantial variability in PK poorly described by covariates, AFC of L appears the best approach to extend this to an MIC of 4.

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Sylvie Retout I-03 A drug development tool for trial simulation in prodromal Alzheimer's patient using the Clinical Dementia Rating scale Sum of Boxes score (CDR-SOB).

Sylvie Retout (1), Isabelle Delor (2), Ronald Gieschke (1), Philippe Jacqmin (2), Jean-Eric Charoin (1) for Alzheimer's disease Neuroimaging Initiative.
(1) F. Hoffmann-La-Roche Ltd, Basel, Switzerland, (2) SGS-Exprimo, Mechelen, Belgium

Objectives: Population Alzheimer's disease (AD) progression models have been developed using the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) scores to describe the dementia stage of the disease [1-2]. However, those models cannot be used in the context of drug development projects focusing on earlier stages of the disease such as with prodromal patients, and for which endpoint is assessed by CDR-SOB scores. Our objectives were then to support the development of an AD progression model based on CDR-SOB scores and to demonstrate, by simulation, the usefulness of such a model for clinical trial optimisation.

Methods: An AD progression population model was developed [3] using the CDR-SOB scores from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [4]. That model enables the estimation of a disease onset time and a disease trajectory for each patient. The model also allows distinguishing fast and slow progressing sub-populations according to, the functional assessment questionnaire (FAQ), the normalized hippocampus volume and the CDR-SOB score at study entry. We used that model in a simulation mode to explore its potential impact in terms of quantitative understanding design elements (inclusion, trial duration, etc) of a respective clinical trial.

Results: The AD model enables clinical trial design optimization, by 1- understanding the impact of inclusion criteria/disease severity on treatment

effect and required trial length; 2- simulating the time course of the placebo and treatment trial arms under different scenarios (e.g. alternative sample size, trial durations and measurement times) in order to determine how and when enough effect size should be achieved for differentiation. Furthermore, a robust analysis of the data can be performed at the end of a study, by implementing and quantifying a possible drug effect (e.g. time to maximal effect, effects that increase or decrease over time) on one or more of the parameters of the natural history disease progression model [3].

Conclusions: The use of this novel AD disease progression model is a powerful tool in the context of drug development to optimize clinical trial designs and therefore to maximize the likelihood to bring new medicine to Alzheimer's patients.

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Philippe Jacqmin I-04 Constructing the disease trajectory of CDR-SOB in Alzheimer's disease progression modelling

Isabelle Delor (1), Sylvie Retout (2), Jean-Eric Charoin (2), Ronald Gieschke (2), Philippe Jacqmin (1) for Alzheimer's Disease Neuroimaging Initiative
(1) SGS-Exprimo, Mechelen, Belgium, (2) F. Hoffmann-La-Roche Ltd, Basel, Switzerland

Objectives: To establish the disease onset time (DOT) and disease trajectory (DT) concepts[1] by developing an original natural history population disease progression model of Alzheimer's disease (AD)[2,3] based on the CDR-SOB scores from the ADNI database[4].

Methods: The final data set consisted of CDR-SOB records collected from 229 control (NL), 380 mild cognitive impaired (MCI) and 180 AD subjects for up to 4 years. A total of 19 covariates were included in the database. Model development was performed in NONMEM V7.2.0.[5] using the FOCE method and guided by the OFV and GOF plots.

Results: Subjects entered the study at different stages of the disease. DOT and DT were implemented in a differential equation to describe disease progression:

$$dCDR/dT=(RATE+CDRxALP)xT^{30}/(DOT^{30}+T^{30})$$

At the time the disease was estimated to start in a subject, DOT activated the increase in CDR-SOB score (CDR) based on a disease rate (RATE) adjusted to the subject's progression velocity by an additive term (CDRxALP). A transient drop of the score in some subjects just after study entry was captured by a 'placebo' effect function. In addition, it was detected that the disease progression evolved significantly more slowly in 40 to 50% of MCI subjects.

To capture this difference in DTs, a mixture model was implemented allowing two different disease rates, coupled with the additive term only for the fast rate. Modelling was performed in the logit domain. CDR-SOB and ADAS-cog scores were identified as covariates of DOT and the Mini Mental Score Exam (MMSE) as covariate of ALP. Covariates for assignment to slow or fast progressing subjects were functional assessment questionnaire (FAQ), normalized hippocampus volume and CDR-SOB score. Based on these 3 prognostic factors at study entry, more than 78% of MCI subjects could correctly be assigned to the slow or fast progressing subpopulations. The final model could predict 85% of MCI-AD conversions. Finally, synchronization of biomarker time-profiles on individual DOT estimated by the CDR-SOB model virtually expanded the observation period of these biomarkers from 3 to 8 years.

Conclusions: The use of a DOT-DT model is powerful for detecting different disease progression rates in a population and identifying corresponding prognostic factors. Estimation of DOT allows the synchronisation of biomarker-time profiles on disease onset rather than on study entry and provides insights on long-term changes in biomarkers.

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Rachel Rose I-05 Application of a Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Model to Investigate the Effect of OATP1B1 Genotypes on the Cholesterol Synthesis Inhibitory Effect of Rosuvastatin

R.H. Rose (1), S. Neuhoff (1), K. Abduljalil (1), M. Chetty (1), M. Jamei (1), A. Rostami-Hodjegan (1,2)
(1) Simcyp Ltd (a Certara company), Sheffield; (2) School of Pharmacy and Pharmaceutical Sciences, The University of Manchester; UK

Objectives: To develop a PBPK/PD model that links the hepato-cellular concentrations of rosuvastatin (RSTN), predicted by a permeability-limited liver model within a full PBPK model, to the rate of cholesterol synthesis over time and to use the model to estimate the impact of OATP1B1 c.521TT, TC and CC sequence variations on the response.

Methods: PK/PD of RSTN in the Healthy Volunteer population was constructed in the Simcyp Simulator (v12.2). Using clinically observed concentration-time data, the Simcyp Parameter Estimation module was used to obtain the uptake clearance of RSTN into the liver for OATP1B1 genotypes with c.521TT, TC and CC sequence variations [1]. The structural model for the effect of RSTN on cholesterol synthesis was coded using the Simcyp custom PD scripting facility and was based on the report by Aoyama *et al*., (2010) [2]. The parameters for baseline were kept as in the original publication. However, the drug effect (inhibition of mevalonic acid synthesis) in our model was driven by the unbound intracellular water concentration (Cu_{IW}) in liver (as opposed to plasma). Therefore, associated values were obtained by re-fitting the data in dominantly wild type OATP1B1 genotypes. Simulations were performed to predict the PD response for the three OATP1B1 genotypes.

Results: The model allowed adequate recovery of clinical PK [1] and PD [2] profiles. Simulations indicated that while the mean plasma $AUC_{0\text{-}48h}$ was increased by approximately 50% and 90% for the heterozygote and CC-homozygote genotypes relative to the wild type, the liver Cu_{IW} AUC was reduced by 6% and 9%, respectively. The corresponding mevalonic acid AUC relative to baseline was reduced by 2.5% and 5%, respectively.

Conclusions: While some studies have indicated an association between the OATP1B1 c.521T>C sequence variations and reduced therapeutic response to statins, others have failed to support this [3]. The PBPK/PD modelling approach used in this study suggests only a small contribution of the c.521T>C sequence variation on interindividual variability in cholesterol synthesis effect of RSTN. Linking the PD response to the concentration at the site of action predicted by a full PBPK model allowed better insight into the impact of transporter genotype on PD response. Models which mechanistically account for local PK variability improve understanding of the apparent observed PD variability and helps in dissecting out the true system mediated variations in response [4].

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Elisabeth Rouits I-06 Population pharmacokinetic model for Debio 1143, a novel antagonist of IAPs in cancer treatment

E.Rouits(1), P. Olsson(2) , J.M. Sorensen(3) and V. Nicolas-Métral(1)
(1) Debiopharm S.A., Chemin Messidor 5-7, CP 5911, 1002 Lausanne – Switzerland (2) SGS Exprimo NV, Generaal De Wittelaan 19A b5, 2800 Mechelen – Belgium (3) Ascenta Therapeutics, Inc., 101 Lindenwood Drive, Malvern, PA 19380 – USA

Objectives: Debio 1143 is an orally available small molecule antagonist of the inhibitors of apoptosis proteins (IAPs), developed as a therapy for cancer. Debio 1143 pharmacokinetics (PK) were evaluated in two dose-escalating phase I studies; one in monotherapy and one in combination with cytarabine and daunorubicin.

Methods: A population PK model was developed using NONMEM 7.2, to fit the plasma concentration-time data (n=961) from 48 evaluable patients. The clinically relevant dose range (80 - 900 mg q5d21 in the monotherapy trial in patients with advanced cancer or lymphoma and 100/200/300 mg q5d21 in the combination trial in Acute Myelogenous Leukemia (AML) patients) was explored in the model.

Results: A two-compartment model proved sufficient to describe the distribution of Debio 1143. The absorption was best described by two sequential zero-first order absorption phases. Typically, the first absorption phase corresponded to 12% of the absorption, though this varied substantially between dosing occasions. The zero order absorption phases lasted for 31 and 52 minutes respectively, the second phase starting at the end of the first phase, though the duration of the phases varied considerably between individuals. Inter-individual variability was estimated for CL/F, LAG1, D1, Ka2 and D2. Parameters were estimated with good precision. Relative

bioavailability was found to decrease by 22% for doses after the second dose. Residual error was modelled using a proportional model, with separate error terms for the two studies, as separate bioanalytical assays have been used.

Conclusions: The pharmacokinetics of Debio 1143 was well described by a two-compartment model with two absorption pathways. The bioavailability appeared to change after repeated administrations, suggesting a possible time-dependent PK, which is in line with what has been observed *in vitro.* The model will be updated with data from on-going studies using alternative schedules of administration to 1/ help designing optimal trials and 2/further explore PK/PD relationships.

Alberto Russu I-07 Second-order indirect response modelling of complex biomarker dynamics

A. Russu(1), E. Marostica(2), G. De Nicolao(2), I. Poggesi(1)
(1) Model-Based Drug Development, Janssen Research & Development, Beerse, Belgium; (2) Department of Industrial and Information Engineering, University of Pavia, Italy

Objectives: Biomarker dynamics in response to drug action may not always be fully understood. Redundant pathways, tolerance, feedback and counter-regulation may be such that the response to a drug stimulus can show complex patterns [1-3]. This motivates the present work, where a new pharmacokinetic/pharmacodynamic (PK/PD) approach inspired by indirect response modelling (IRM) [4] and precursor-dependent IRM [5] is investigated.

Methods: We propose a novel family of PK/PD models that feature a zero-order rate constant k_{in} of precursor formation, and a first-order rate constant k of conversion from precursor to response. Drug concentration is assumed to modulate simultaneously k_{in} and k (potentially by stimulation or inhibition) through specific SC_{50} or IC_{50} parameters. The rate of response dispersion can be assumed equal to k to reduce model complexity. The proposed models can structurally describe complex patterns, such as the combination of (i) inverse response (i.e. a drop of response levels immediately after dosing, followed by an increase above baseline level), (ii) fast achievement of peak response followed by slow return to baseline, after single dose, and (iii) average increase from baseline at steady-state, after repeated dosing. The mathematical properties of the proposed PK/PD models and the sensitivity of response profiles to parameter changes were investigated by simulation. Model identifiability was assessed using NONMEM version 7.1 [6] to perform parameter estimation.

Results: In the sensitivity analysis, the new approach could describe a wide range of response profiles, following both single and repeated-dose administration. In particular, different real-life patterns of response could be reproduced. Simulations showed that, under a suitable study design, model parameters could be estimated with good precision. Moreover, the proposed approach was able to reconstruct both population and individual profiles.

Conclusions: These results confirm the feasibility of a modeling approach for longitudinal data characterized by complex features. This approach extends and complements the well-known methodology of IRM [2,5], and is especially appealing when the mechanism of action of a drug is known (or assumed) to impact both the response itself and a precursor of response. Additionally, the proposed approach can be used effectively to describe inhibition of clearance for both a parent drug and its metabolite, in presence of a second drug that inhibits certain metabolic pathways (e.g. CYP3A4).

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Teijo Saari I-08 Pharmacokinetics of free hydromorphone concentrations in patients after cardiac surgery

Teijo I Saari (1), Harald Ihmsen (1), Jan Mell (1) , Katharina Fröhlich (1) , Jörg Fechner (1), Jürgen Schüttler (1), Christian Jeleazcov (1)
Department of Anesthesiology, University of Erlangen-Nuremberg, Germany

Objectives: Hydromorphone (HM) is an opioid analgesic used to relieve moderate-to-severe pain. The pharmacokinetic models published so far [1] consider young healthy volunteers but not postoperative patients. On the other hand, as the drug effect is dependent on the unbound plasma drug concentrations, an alteration in the protein binding during postoperative care may result in clinically significant changes in the pharmacokinetics. Therefore, we investigated the pharmacokinetics of free HM in cardiac surgery patients during postoperative pain therapy.

Methods: After IRB approval, written informed consent was obtained from 50 patients with ASA physical status class 3 undergoing coronary artery bypass surgery. HM was administered postoperatively on the ICU as target controlled infusion (TCI) with the pharmacokinetic model described by Westerling et al. [1] and plasma target concentrations of HM between 0.8 and 10 ng/ml. Arterial blood samples were drawn in each patient during and up to 12 h after TCI. The plasma concentrations of free HM were measured after ultrafiltration by LC/MS/MS [2]. A pharmacokinetic model was determined by non-linear mixed-effects modelling (FOCEI) in NONMEM 7.2 using linear multicompartment models. The influence of demographic and clinical characteristics on the elimination clearance and volumes of distribution were tested.

Results: 49 patients (40-81 yrs) received HM and data from 44 patients were analysed. Median free fraction was 0.90 with a range of 0.37 - 0.98. The

pharmacokinetics of free HM were best described by a three compartment model (median PE=-4.5%). The elimination clearance CL1 and the central volume of distribution V1 decreased with age: CL1 = 16.2*(1 - 0.012*(age - 67)) mL/kg/min, V1 = 0.056*(1 - 0.0172*(age - 67)) L/kg. The intercompartmental clearances and the peripheral volumes of distribution were linearly related to body weight: CL2=20.1 mL/kg/min, V2=0.21 L/kg, CL3=22.6 mL/kg/min, V3=2.12 L/kg. The terminal half-life of HM was 186 min. No gender effect could be observed.

Conclusions: The pharmacokinetics of free HM in patients after cardiac surgery show age and weight dependent clearance and volume of distribution. Protein binding of HM in cardiac surgery patients was similar to the values reported in the literature.

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Tarjinder Sahota I-09 Real data comparisons of NONMEM 7.2 estimation methods with parallel processing on target-mediated drug disposition models

Tarjinder Sahota (1), Enrica Mezzalana (1), Alienor Berges (1), Duncan Richards (2), Alex Macdonald (1), Daren Austin (1), Stefano Zamuner (1)
(1) Clinical Pharmacology Modelling and Simulation, GSK, UK. (2) Academic DPU, GSK, UK

Objectives: Target-mediated drug disposition (TMDD) models are increasingly used to describe drug-target interactions. In practice, however, their use can come with long running times and convergence problems in NONMEM. Gibiansky et al., have previously used simulated data to investigate the accuracy and parallel processing efficiency of TMDD models with NONMEM 7.2.0 estimation methods1. They found all methods except BAYES gave accurate parameter estimates, standard error estimates, and high (85-95%) parallel processing efficiency. Importance sampling (IMP) was found to be the fastest exact likelihood method in terms of run time.
Here we detail our modelling experience of clinical studies using FOCE and IMP with parallelisation on two separate compounds exhibiting TMDD. We evaluate the methods for model stability and parallel processing efficiency.

Methods: *Compound 1:* CPHPC, a small molecule targeting serum amyloid P component (SAP), a soluble target. CPHPC was administered to patients and plasma CPHPC and SAP sampling were collected from baseline (day -1) to follow up (day 28). Only total concentrations (free + bound fractions of CPHPC-SAP) in plasma were available. Limited SAP recovery information was available.
Compound 2: Otelixizumab, a monoclonal antibody which is directed against human CD3ε on T lymphocytes4. Free drug in serum and free, bound and total receptors on T cells were measured using immunoassay and flow

cytometry, respectively. However ~70% of free drug concentrations were below the limitation of quantification (BLQ).
Estimation method evaluation was via comparison of OFV with exact likelihood OFV (ISAMPLE=20000), run time, minimisation success criteria and parallel efficiency. Parallelisation was performed using MPI on up to four cores.

Results: FOCE linearisation was found to heavily bias the OFV in some instances. Model convergence can also fail with FOCE when datasets are associated with limitations in sampling schedule and bioanalytical assay (e.g. measurements limited to total concentrations or significant proportions of BLQ data). In contrast, both models performed well with IMP. Diagnostic performance was good and key parameters were in line with previously published values. Moreover, IMP gave significant run time improvements over FOCE. Use of parallel processing with MPI efficiently reduced run time further to levels where model development and exploration were feasible.

Conclusions: IMP is recommended over FOCE for TMDD models.

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Maria Luisa Sardu I-10 Tumour Growth Inhibition In Preclinical Animal Studies: Steady-State Analysis Of Biomarker-Driven Models.

M.L. Sardu (1), A. Russu (2), I. Poggesi (2), G. De Nicolao (1)
(1) Department of Industrial and Information Engineering, University of Pavia, Italy (2) Model-based Drug Development, Janssen Research & Development, Beerse, Belgium

Objectives: Three different models describing tumour growth inhibition (TGI) dynamics in xenografted mice are considered, two of which are biomarker-driven. The main objective is finding whether and under which conditions the tumour is eradicated or its volume tends to an asymptote. A further objective is to assess the explanatory capability of the models through their application to experimental preclinical data as well as their identifiability through simulated population data.

Methods: A comparison is carried out between the drug-driven Simeoni's TGI model [1,2] and two recent biomarker-driven TGI models, called B1-Simeoni and B2-Simeoni [3]. These two models assume that the biomarker modulation, described by a type I indirect PK-PD model, is causal for tumour growth inhibition.
To investigate the steady-state behaviours of the models, possible equilibrium values of the tumour volume have been analytically derived assuming that mice are exposed to constant plasma concentrations of a drug. For the B1- and B2-Simeoni models, the type I indirect model is used to obtain the corresponding steady-state biomarker inhibition, to be plugged into the biomarker-driven TGI model. A visual comparison between steady-state behaviours is obtained by plotting the output (equilibrium tumour volumes) against the input (constant drug concentrations).
Models are fitted to literature data [4]. Estimated parameters are used to

simulate different steady-state conditions. The models are also assessed in a population context by analysing simulated TGI data. In particular, the issue of model mismatch is considered by fitting data using a model different from the one used for generating them.

Results: The stability analysis of the three models highlights two distinct behaviours. Both the standard Simeoni and B2-Simeoni models present a threshold concentration above which tumour eradication is asymptotically achieved. Conversely, in the B1-Simeoni model, the existence of a threshold drug concentration ensuring tumour eradication depends on the values of some parameters. All models explain well the experimental data.

Conclusions: The aim of this work is to further investigate two biomarker-driven TGI models, comparing their steady-state behaviours with those of the standard Simeoni model. This analysis highlights the equivalence between standard Simeoni and B2-Simeoni models, whereas achievement of tumour eradication in the B1-Simeoni model depends on the parameters values.

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Emilie Schindler I-11 PKPD-Modeling of VEGF, sVEGFR-1, sVEGFR-2, sVEGFR-3 and tumor size following axitinib treatment in metastatic renal cell carcinoma (mRCC) patients

Emilie Schindler (1), Michael Amantea (2), Peter A. Milligan (2), Mats O. Karlsson (1), Lena E. Friberg (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (2) Pfizer Global Research and Development

Objectives: Axitinib (Inlyta®) is a multi-targeted tyrosine kinase inhibitor with anti-angiogenic properties, approved for the treatment of metastatic renal cell carcinoma (mRCC). Axitinib inhibits vascular endothelial growth factor (VEGF) receptors 1, 2 and 3. This study aims to characterize the time-course of candidate biomarkers (VEGF and its circulating receptors sVEGFR-1, sVEGFR-2, sVEGFR-3 as well as sKIT) and to investigate potential longitudinal relationships between axitinib dose, AUC, biomarkers and tumor size in patients with metastatic renal cell carcinoma using PKPD models previously developed for sunitinib in patients with gastro-intestinal stromal tumors (GIST) [1].

Methods: VEGF, VEGFR-1,2,3, sKIT and tumor size (sum of the longest diameters, SLD) measurements were available from 64 Japanese cytokine-refractory mRCC patients treated with axitinib administered orally at a starting dose of 5 mg BID continuously. Biomarker and SLD data were collected for up to 89 and 104 weeks, respectively. Axitinib PK was characterized by individual parameter estimates from a previously developed PK model. Indirect response models were fitted to log-transformed biomarker data. Models for each biomarker were developed separately and finally combined into a joint model to explore correlations. Dose, daily AUC and model-predicted relative change from baseline in the biomarkers were

evaluated as drivers for the change in SLD with a longitudinal tumor growth inhibition model [1,2].

Results: Indirect response models adequately described the time-course of VEGF, sVEGFR-1, 2 and 3. Axitinib inhibited the production of sVEGFR-1, 2 and 3 and the degradation of VEGF. A linear disease progression was included in the VEGF model. Axitinib AUC50 values were 348, 1400, 722 and 722 µg/L.h, for VEGF, sVEGFR-1, 2 and 3, respectively. A common typical AUC50 could be estimated for sVEGFR-2 and 3. Individual AUC50 for sVEGFR-1, 2 and 3 were highly correlated (80-99%). No drug effect was identified for sKIT. Longitudinal SLD data were well characterized by a tumor growth inhibition model. The relative change in sVEGFR-3 was found to be the best predictor for SLD time-course, and inclusion of AUC did not result in a further improvement of the model fit.

Conclusions: The time-courses of VEGF, sVEGFR-1, 2 and 3 following axitinib treatment in mRCC patients were successfully characterized by indirect response models. sVEGFR-3 baseline value was lower in mRCC than in GIST (19700 vs 63900 pg/mL), and the mean turnover times were shorter in mRCC; 0.55, 19 and 6.1 days vs 3.8, 23 and 17 days, for VEGF, sVEGFR-2 and sVEGFR-3, respectively. The soluble biomarkers were highly correlated. As for sunitinib in GIST, sVEGFR-3 was the best predictor of change in tumor size in mRCC following axitinib treatment. In a next step, the relationship of biomarkers and SLD to overall survival will be investigated.

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Alessandro Schipani I-12 Population pharmacokinetic of rifampicine in Malawian children.

Alessandro Schipani (1), Henry Pertinez (1), Rachel Mlota (2), Nuria Lopez (2), Paul Tembo (2), Steve Ward (3), Saye Khoo (1), Gerry Davies (1)
(1) Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK. (2) Department of Paediatrics, College of Medicine, Blantyre, Malawi. (3) Liverpool school of tropical medicine, Liverpool, UK

Objectives: Rifampicine (RIF) is considered a key drug for the treatment of pulmonary infections caused by M. tuberculosis. It rapidly kills the majority of bacilli in tuberculosis lesions, prevents relapse and thus enables 6-month short-course chemotherapy.
Low RIF plasma exposure can lead to a delayed, incomplete response to treatment or to increased risk of developing drug resistance. RIF has known high variability in reaching the therapeutic range with standard doses and for this reason the World Health Organization (WHO) recently increased the recommended oral dosage from 10 to 15 mg/kg body weight. However in most parts of Africa patients still receive the 10mg/kg dosage, particularly affecting children, who typically show lower levels of RIF than in adults, for a given dose.
The objectives of this study were to:

- Evaluate the PK of RIF in Malawian children with tuberculosis
- Assess the new WHO dosing recommendation for the use of currently available fixed dose combination tuberculosis medicines in children
- Investigate the use of surrogates for weight (age and height), as indicators of body size for dosing bands

Methods: A total of 151 RIF concentrations from 55 patients, aged 0.58 to 17 years and weighing 4.8 to 45kg, were included to build a population pharmacokinetic model using non-linear mixed effects modelling (NONMEM7).

Results: A one-compartment model with first-order absorption best described the data. The typical population estimate of oral clearance was 6.80L/h, while the volume of distribution was estimated to be 179L. Interindividual variability was estimated to be 36% for clearance and 134% for volume of distribution. Body weight was included as a covariate in the final model using allometric scaling. Models with the inclusion of age and height covariates were evaluated separately. Simulations of the dosing bands using age and height as surrogates for weight showed similar results. Simulations for the new WHO doses generate a better exposure especially for younger children compared with the present weight band dosage in Malawi.

Conclusion: The final model successfully described RIF PK in the population studied and is suitable for simulation in this context. The data have shown that children have low plasma concentrations, indicating a need for new formulations. Simulations from dosing bands based on height and age show these can be used as alternatives to weight to set doses in clinical settings where weight may be hard to assess.

Henning Schmidt I-13 The "SBPOP Package": Efficient Support for Model Based Drug Development – From Mechanistic Models to Complex Trial Simulation

Henning Schmidt
Novartis Pharma AG

Objectives: Model-based drug development (MBDD) emphasizes the quantitative integration of relationships among diseases and disease targets, drug characteristics, and individual variability across studies and development phases for rational and scientifically based decision making [1]. MBDD deals with a large model space, consisting of, e.g., Systems Biology, PBPK/PD, dose-concentration-response, and mechanism based disease models. Fast turnaround of modeling and simulation activities is crucial in order to influence the decision making process in drug development projects. Such a fast turnaround, however, requires that workflows are efficiently supported by powerful and user-friendly tools.

Methods: The "SBPOP Package" has been developed as a toolbox for MATLAB [2], supporting MBDD from mechanistic modeling to complex trial simulations. An important focus has been on user friendliness, documentation, training material, and extensibility.

Results: It consists of three parts: SBTOOLBOX2 [3], SBPD, and SBPOP. The first two parts are widely used in the area of Systems Biology, implementing functionality for general representation of dynamic models, simulation, analysis, and parameter estimation. While these parts are ideal for support of data and information integration in research and preclinical phases of drug discovery and development, the third part (SBPOP) adds powerful functionality for PBPK, population PK/PD modeling via a seamless interface to MONOLIX [4], and clinical trial simulation. The "SBPOP Package" is

continuously developed to include additional analyzes and industrializations of standard modeling approaches, such as dose-concentration and concentration-response relationship characterizations. The development is driven by real needs in drug development projects at Novartis, with the goal to increase Modeling&Simulation efficiency, allowing for timely feedback of insights to the decision making process.

Conclusions: The “SBPOP Package” efficiently supports the process of drug discovery and development, providing powerful and user-friendly functionality, from mechanistic modeling to complex clinical trial simulations. Additionally, due to its level of documentation and robustness, it is extraordinarily well suited for educational purposes. The “SBPOP Package” is published as open source under a GNU General Public License and available upon request.

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Stephan Schmidt I-14 Mechanistic Prediction of Acetaminophen Metabolism and Pharmacokinetics in Children using a Physiologically-Based Pharmacokinetic (PBPK) Modeling Approach

Xi-Ling Jiang (1, 2), Ping Zhao (2), Lawrence J. Lesko (1), Stephan Schmidt (1)
(1) Center for Pharmacometrics & Systems Pharmacology, Department of Pharmaceutics, University of Florida, Orlando, FL (2) Immediate Office, Office of Clinical Pharmacology, Office of Translational Sciences, CDER, FDA, Silver Spring, MD

Objectives: Acetaminophen (APAP) is available in more than 200 OTC and Rx products [1]. APAP poisoning is common in children because of accidental ingestion or overdosing [2]. Prediction of APAP pharmacokinetics (PK) in children is challenging, because the expression of enzymes involved in APAP elimination and bioactivation undergoes developmental changes [3,4]. The aim of this project was to develop a physiologically-based PK (PBPK) model for APAP that uses available information on the underlying enzymatic system and its maturation towards a mechanistic understanding of APAP metabolism and PP in children.

Methods: An APAP PBPK model was developed using Simcyp V12 with special emphasis on characterizing the contribution of all phase I (CYP1A2, 2E1, 3A4, etc.) and phase II (UGT1A1, 1A9, 2B15 and sulfotransferases) enzymes to APAP metabolism. This bottom-up approach was merged with a top-down approach to determine respective model parameters from published adult PK and pharmacogenetic data. The model was then qualified by predicitng adult PK data from independent studies using different dosing regimens in healthy subjects and cirrhosis patients. The model was subsequently used to predict APAP PK and metabolism in children across the entire age spectrum

(neonates: 0-28 days to adolescents: 12-16 years) by accounting for age-dependent physiological differences.

Results: The PBPK model that was developed and qualified based on adult data was able to characterize i.v. and oral dosed APAP plasma PK profiles as well as changes in the urinary recovered APAP-glucuronide to APAP-sulfate ratio, which reflects the impact of enzyme ontogeny on APAP metabolism. The model-predicted changes in APAP clearance in children of different age groups were comparable to those estimated from an independent population PK analysis in children aged 37 weeks to 14 years [5].

Conclusions: A PBPK model containing detailed information on each enzyme known to substantially contribute to APAP metabolism successfully predicted APAP PK and metabolism in children after single and multiple dosing. This strategy of merging top-down and bottom-up approaches demonstrated the clinical utility of PBPK models for predicting PK in understudied populations, such as children, using *in vitro* data and PK data from adults. The model also may be used to identify subgroups and age ranges of children who are most susceptible to APAP-induced liver injury.

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Rik Schoemaker I-15 Scaling brivaracetam pharmacokinetic parameters from adult to pediatric epilepsy patients

Rik Schoemaker (1), Armel Stockis (2)
(1) SGS Exprimo, (2) UCB Pharma

Objectives: To investigate the adequacy of allometric scaling of adult brivaracetam population pharmacokinetic parameters to a pediatric patient population using either body weight (WT) or lean body weight (LBW).

Methods: A population pharmacokinetic model for brivaracetam (single-compartment, first order absorption and elimination, V and Cl allometrically scaled using WT or LBW with theoretical exponents) was previously developed, using data from 1188 subjects from 2 Phase II and 3 Phase III clinical trials in adult subjects suffering from partial epilepsy and localization-related or generalized epilepsy. A currently on-going trial in pediatric patients (1 month-<2 years, n=30; 2-11 years, n=52; 12-<16 years, n=18) allows a comparison of clearance and volume predictions based on allometric scaling of the adult population parameters with those obtained in the actual pediatric patient population (estimated using NONMEM V7.2.0 with FOCE-I), using the adult structural model restricted to the pediatric patient data.

Results: Empirical Bayes estimates for Cl from the pediatric model were virtually identical whether WT or LBW was used. Individual pediatric Cl estimates were predicted adequately and without bias using the adult parameters with LBW scaling. LBW scaling was superior to WT scaling.

Conclusions: Allometric scaling from adults to pediatric patients using LBW provide superior predictions of pediatric Cl, but pediatric patients on their own are equally well described using WT or LBW scaling. This means pediatric dosing adaptations can be WT-based and do not require the more complex

LBW-scaling, and allometric principles can be used to scale brivaracetam pharmacokinetics from adults to children.

Yoon Seonghae I-16 Population pharmacokinetic analysis of two different formulations of tacrolimus in stable pediatric kidney transplant recipients

Seonghae Yoon (1), Jongtae Lee (1), Sang-il Min (2), Jongwon Ha (2), In-jin Jang (1)

(1) Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea, (2) Department of Surgery, Seoul National University College of Medicine and Hospital, Seoul, Korea

Objectives: Tacrolimus is an immunosuppressive agent, largely used in kidney transplantation. The objectives of this study were to develop the population pharmacokinetic (PK) model of once-daily tacrolimus formulation (Advagraf®) and twice-daily tacrolimus formulation (Prograf®) in stable pediatric kidney transplant recipients and to identify significant covariates that influence on tacrolimus PK.

Methods: Thirty-four stable pediatric kidney transplant recipients were enrolled in open-label, parallel study. Enrolled patients received twice-daily tacrolimus formulation for 7 days. On the morning of day 8, the regimen was converted to once-daily tacrolimus formulation on a 1:1 for their total daily dose and was remained for the last of the study. Blood samples were collected on study day 7, 14, 21(trough concentration) and 28 (after dosing adjustment). Nonlinear Mixed-effects modeling (NONMEM, ver. 7.2) was used to determine the typical population PK parameters and their inter-individual and intra-individual variability. The first-order conditional estimation (FOCE) with interaction method was used to fit the plasma concentration-time data. Basic goodness-of-fit diagnostics and visual predictive checks were used to evaluate the adequacy of the model fit and prediction.

Results: The PK of tacrolimus was best described by a two-compartment model with first-order absorption. In the final pharmacokinetic model, centered hematocrit and cytochrome P450 3A5 were significant covariates on apparent clearance (CL/F). For apparent central volume (V2/F), centered age was a significant covariate. Diurnal variation in absorption kinetics of tacrolimus was described by the difference of absorption rate constant.

Conclusions: Once-daily tacrolimus formulation and twice-daily tacrolimus formulation showed different PK characteristics. The final PK parameter estimates and covariates (hematocrit, CYP3A5, age) can be applied to determine the optimal dosage regimens of tacrolimus in pediatric kidney transplantation patients.

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Catherine Sherwin I-17 Dense Data - Methods to Handle Massive Data Sets without Compromise

C.M.T. Sherwin (1), B.L. Jones (2, 3, 4), J.S, Leeder (2, 3), K.A. Neville (2,3), G.L. Kerns (2,3) and Spigarelli MG (1)

(1)Division of Clinical Pharmacology & Clinical Trials Office, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah, USA (2)Divisions of Pediatric Pharmacology and Medical Toxicology, Departments of Pediatrics University of Missouri, Kansas City, Missouri, USA (3)Section of Allergy, Asthma and Clinical Immunology, Departments of Pediatrics University of Missouri, Kansas City, Missouri, USA (4)Children's Mercy Hospitals and Clinics, Departments of Pediatrics University of Missouri, Kansas City, Missouri, USA

Objectives: Histamine iontophoresis with laser Doppler monitoring (HILD) is a robust and dynamic surrogate for histamine microvasculature response. We characterized histamine pharmacodynamics in adult participants using HILD, although some distinct challenges were seen that needed to be solved in order to allow subsequent data modelling to occur. This type of data collection produces a rare situation for pharmacometricians in which they have an abundance of data that needs to be appropriately (maintaining variability) pared down to a useful and usable size.

Methods: HILD data was obtained in 16 adults as previously described (1) in a convenience sample for the evaluation of HILD. The data was aligned based upon application of a second derivative function to determine rise from baseline, maximal effect and when possible, return to baseline. A non-compartmental analysis and non-linear mixed-effects model with a linked effect PK/PD model was used to provide estimates for area under the effect curve (AUEC), maximal response over baseline (EffmaxNT), and time of EffmaxNT (Tmax) using Phoenix® WinNonlin version 6.2 (Pharsight, Mountain

View, CA). ANOVA and regression analyses were used for sub-group comparisons using R statistical software.

Results: Distinct histamine response phenotypes were identified among the adult participants after data sampling. The need for this method of data handling arises as a result of the HILD technique itself that generates data at 40 Hz producing nearly 30,000 measurement/time data parings as a result of a run of 2 hours in duration. In addition, as the data is generated from the start of the data recorder as opposed to being directly timed, aligning multiple subject data produces some rarely seen logistical challenges. Reduction of data revealed no change in time to peak response after data was aligned and intra-individual variability was preserved.

Conclusions: Data quality and integrity remain the most important consideration when assessing large dataset although current modelling software programs have difficulty with very large data sets as they were designed to handle far fewer samples per individual than techniques such as HILD. Automated processes that will allow adequate sampling and subsequent modelling is clearly needed.

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Giovanni Smania I-18 Identifying the translational gap in the evaluation of drug-induced QTc interval prolongation

Giovanni Smania1, Ramona Graf1, Massimo Cella1, Vincent Dubois2, Oscar Della Pasqua1,2
1 Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Stockley Park, UK. 2 Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden, The Netherlands

Objectives: Assessment of the propensity of new drugs in prolonging QT/QTc interval is critical for the progression of compounds into clinical development. Given the similarities in QTc response between dogs and humans, dogs are often used in pre-clinical CV safety studies [1]. However, it is unclear how the changes in QTc interval in dogs can be translated into risk of QTc prolongation in humans. The objective of our investigation was to characterise the PKPD relationships of three new compounds in order to assess the interspecies differences in drug-induced QTc prolongation.

Methods: Pharmacokinetic and pharmacodynamic data from typical cardiovascular safety study experiments in conscious dogs and first time in human trials in healthy subjects were used to evaluate the effects of GSK945237, SB237376 and GSK618334, three new compounds in development. First, drug concentrations at the time of each QT measurement were derived. Concentration-QT interval data were then analysed using a hierarchical PKPD model previously implemented and tested with positive controls, namely moxifloxacin, sotalol and cisapride [2]. A threshold of 10msec was used to explore the probability of QTc interval prolongation at the relevant therapeutic range. Results were compared using model-derived PC_{50} estimates, i.e., the concentration associated with a probability of 50% increase in QTc interval. Modelling was performed using WinBUGS v1.4.3, whilst R was used for data manipulation, graphical and statistical summaries.

Results: Our analysis showed that GSK945237 does not prolong QTc interval neither in humans nor in dogs, whilst SB237376 shows a weak effect in both species, but does not reach 10ms QTc prolongation at the expected therapeutic range. In contrast to the other two compounds, GSK618334 was found to cause QTc-interval prolongation $\geq$ 10 msec since the range of concentration needed to achieve it contains the observed Cmax. These findings differed from typically reported results in telemetered dogs, which are often based on nonparametric methods and statistical summaries of the data.

Conclusions: Although no QTc-prolonging effects were observed for GSK945237, the results from the analysis of SB237376 and GSK618334 illustrate the value of a quantitative approach to characterise drug effects in early drug development. Furthermore, our analysis shows that accurate interpretation of pre-clinical findings requires suitable pharmacokinetic sampling and some understanding of expected therapeutic exposure. Based on the data analysed so far, including previously published results, dogs appear to be a suitable, but less sensitive species to the drug-induced QTc-prolonging effects, as compared to humans.

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Alexander Solms I-19 Translating physiologically based Parameterization and Inter-Individual Variability into the Analysis of Population Pharmacokinetics

A. Solms (1,2), A. Schäftlein (1,3), M. Zeitlinger (4), C. Kloft (3), W. Huisinga (2)
(1) Graduate Research Training Program PharMetrX: Pharmacometrics & Computational Disease Modeling, Freie Universität Berlin and Universität Potsdam; (2) Computational Physiology Group, Institute of Mathematics, Universität Potsdam, Potsdam, Germany; (3) Department of Clinical Pharmacy and Biochemistry, Freie Universität Berlin, Berlin, Germany; (4) Department of Clinical Pharmacology, Medical University Vienna, Vienna, Austria;

Objectives: Physiologically based pharmacokinetics (PBPK) is a useful tool for predicting the PK of a drug. The physiological and anatomical parameterization allows to easily integrate patient characteristics and information about population specific variability. So far, there is no systematic approach how PBPK models can be used to analyze population PK data. Hence, the objective was to develop an approach integrating prior knowledge of the mechanism of (i) drug distribution and (ii) inter-individual variability (IIV), and estimate relevant drug- and physiology related parameters and the unexplained variability. The approach was exemplified on levofloxacin (Lev).

Methods: Lev plasma and interstitial fluid (ISF) microdialysis (µD) data was collected in [1,2,3]. PK was modeled based on a 13 compartment PBPK model with tissue distribution according to [4]. Individualization of the anatomy and physiology (e.g. tissue volumes) was done via the lean body mass scaling approach [5]. The data analysis was performed in R using an EM algorithm similar to [6] for nonlinear mixed effects modeling. Predicted PK, the target

site of Lev, were compared to ISF μD measurements in adipose and muscle tissue.

Results: Drug transfer was realised by regional tissue blood flows; represented by the surrogate parameter cardiac output (Co). A random effect on Co was considered with a fixed distribution based on literature [7]. We found that tissue distribution strongly depended on Lev lipophilicity and its affinity to acidic phospholipids (AP). Lipophilicity was represented by the surrogate parameters logP, which was considered as a fixed effects parameter. Affinity to AP was represented by the surrogate parameter BP where additionally a random effect was assumed. The estimated parameter values well corresponded with published values. Model diagnostics, based on various tools, indicated excellent agreement between model predictions and plasma data. So far no established reference method is available to determine ISF kinetics; the comparison of model prediction and μD data revealed further insight in both techniques, e.g. their assumptions and limitations.

Conclusions: The new parameterization will lead to a different allocation of variabilities, offering a mechanism based interpretation. This gives a new perspective on parameter correlations, explained and unexplained variability in population PBPK modeling, as well as in the purely data based approach.

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Hankil Son I-20 A conditional repeated time-to-event analysis of onset and retention times of sildenafil erectile response

Hankil Son1,2, Hyerang Roh1,2, Donghwan Lee1,2, and Kyungsoo Park1,2
1Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea. 2Brain Korea 21 Project for Medical Science, Yonsei University, Seoul, Korea

Objectives: Sildenafil has been commonly used for the treatment of erectile dysfunction [1]. A previous research explored sildenafil's effectiveness based on qualitative indices [2], but there has been no report on the quantitative aspect of erectile response of sildenafil. Based on this background, using a conditional repeated time-to-event (CRTTE) model, this study aimed to assess onset and retention times of erectile response as the direct measure of drug effects in conjunction with sildenafil pharmacokinetics (PK).

Methods: Data were taken from 58 healthy Korean volunteers who received a sildenafil 100mg tablet. Plasma samples for PK analyses were obtained up to 24 hours after dosing, and onset and retention times of erectile response were recorded over12 hours after dosing. A CRTTE model was developed by using an ordinary hazard function for the onset time and a secondary hazard function for the retention time, where the retention hazard function was modeled with its time shifted by the onset time on the assumption that its occurrence was conditioned on the onset event. The hazard function was modeled under various distributional assumptions including exponential, Gompertz and Weibull distributions. The influence of drug effect was incorporated by scaling the baseline hazard by the exponential of the predicted drug effect. The final models were further tested for covariate effects and evaluated by VPC. All analyses were performed using NONMEM 7.2

Results: Sildenafil concentrations were best described by a two-compartment model with first-order absorption and the model appropriateness was well confirmed by VPC. For a CRTTE model, onset times were best described by Gompertz hazard with scale and shape parameters of 0.70/hr and -1.35/hr, respectively, and retention times by Weibull hazard with scale and shape parameters of 0.66/hr and 1.39/hr, respectively, yielding the estimated median onset and retention times of about 0.45hr and 0.40hr, respectively. Overall, the observed onset and retention times were well included within the 90% predicted intervals by VPC. When plasma concentrations included, the model performance improved. No significant relationship was found between covariates and hazard parameters.

Conclusion: This work has demonstrated the feasibility of applying a CRTTE model to quantitatively understanding the drug response in general clinical situations, with an application to the erectile response of sildenafil.

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Heiner Speth I-21 Referenced Visual Predictive Check (rVPC)

Heiner Speth, Martin Burschka, Ruediger Port

Objectives: The prediction-corrected VPC (pcVPC) [1] reduces the variance in the observed data and in the model distributions by normalizing to an "identically distributed" situation for all individuals. The computation of the prediction correction factor for each bin separately, limits this method to situations of balanced data within each bin. The goal is to extend the prediction-corrected VPC to situations of sparse and unbalanced data by avoiding binning on the independent variable (idv) scale and to show:
1. The equivalence of the new rVPC method to the pcVPC in cases of balanced data.
2. The robustness of the rVPC in cases of sparse and unbalanced data.
In addition to model evaluation, the rVPC is to provide a base for discussion with clinicians on dosing adequacy in untypical individuals.

Methods: For every observation, the model is requested to give a normalized prediction, based on a data tuple of normalized covariate values (reference) and the same random effects from the fit for this observation. The implementation is particularly simple in NONMEM.

Results: The rVPC is independent from binning and calculates the correct reference factor in any observed/ simulated data-point.

Conclusions: The rVPC implements the idea of covariate adjusting to any kind of data and allows an arbitrary choice of referenced covariate values.

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Michael Spigarelli I-22 Title: Rapid Repeat Dosing of Zolpidem - Apparent Kinetic Change Between Doses

M.G. Spigarelli (1, 2), D. Healy (3, 4), W. Buterbaugh (3), M. Gottschlich (4), R.J. Kagan (4, 5) and C.M.T. Sherwin (1, 2)

(1)Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah, USA (2) Clinical Trials Office, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA, (3) James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati, Ohio, USA (4)The Shriners Hospitals for Children®, Cincinnati, Ohio, USA (5)Department of Surgery, University of Cincinnati, Cincinnati, Ohio, USA

Objectives: Zolpidem, a common sleep inducing imidazopyridine, that has been the subject of recent regulatory dosing adjustments. This project sought to evaluate rapid repeat (single dose followed by second equal dose four hours later) zolpidem dosing in pediatric burn patients.

Methods: Zolpidem was administered to paediatric patients (2 controls and 9 cases) at a mean dose of 0.22+0.1 mg/kg in either tablet or suspension as tolerated by the patient under an IRB approved protocol. Each participant was taking the drug for clinical purposes, informed consent and assent obtained and the drug was given in either 1 episode per day (control) or twice separated by a period of four hours. PK samples were obtained at 0, 1, 2, 4, 5, 6 and 8 hours after the first dose. Analysis of the resulting concentration time curves was performed utilizing NONMEM 7.2 and Prism Graph 6.0b.

Results: First order elimination modeling was obtained for the 1, 2 and 4 hour time points and residual concentration of drug were estimated and subtracted from the combined, overlying curves to produce two distinct

concentration time curves for each dose administered. This technique was used to estimate the concentrations from the later time points for the control subjects which were strongly in agreement. In six of nine cases, the algorithm was able to fit the individual data and produce clearance equation with an r2 > 0.951 and in each case the calculated half-life for the second curve was significantly shorter than the first curve and demonstrated an appropriately increase in k.

Conclusions: Rapid repeat zolpidem dosing, on the order of four hours, is associated with a predictable change in elimination phase kinetics for the second dose as compared to the first. This technique has application to other similar situation in which a second dose is given while there is still residual from previous dosing to determine the relative concentration by dose.

Christine Staatz I-23 Dosage individulisation of tacroliums in adult kidney transplant recipients

Christine E. Staatz (1), Troels K. Bergmann (1,2), Katherine A. Barraclough (3), Nicole M. Isbel (3), Stefanie Hennig (1).
(1) School of Pharmacy, University of Queensland, Brisbane, Australia; (2) Department of Medicine, Aabenraa Hospital, Aabenraa, Denmark; (3) Department of Nephrology, University of Queensland at the Princess Alexandra Hospital, Brisbane, Australia

Objectives: 1) To develop a population pharmacokinetic model of tacrolimus in adult kidney transplant recipients; 2) to use this model to compare cytochrome P450 3A5 (CYP3A5) genotype based initial dosing to standard per-kilogram based initial dosing of tacrolimus; and 3) to predict the best starting regimen of tacrolimus based on patient genotype to achieve a trough concentration between 6 and10 ug/L by day 5 post-transplant.

Methods: Data from 173 adult kidney transplant recipients at the Princess Alexandra Hospital in Brisbane, Australia were analysed. In total, 1554 tacrolimus concentration-time measurements taken on 338 occasions were available along with patient covariate information. Population pharmacokinetic modelling was performed using NONMEM 7.2 and the FOCE+I estimation method. Starting dose regimens were compared by simulating tacrolimus trough concentrations in all patients using the final model with population parameters fixed at final estimates.

Results: A 2-compartment model with first order absorption after a lag time and first order elimination described the data well. Patient *CYP3A5* genotype (rs776746), weight, haematocrit and post-operative day were identified as significant covariates effecting tacrolimus apparent clearance (CL/F). Higher CL/F was identified in *CYP3A5 *1* allele carriers, heavier patients, patients

with low haematocrit and those in the immediate post-transplant period. Typical population estimates for tacrolimus CL/F in *CYP3A5 *1* allele carriers and non-carriers were 42.7 L/h and 24.8 L/h respectively. In patients carrying the *CYP3A5*1* allele, standard 0.075 mg/kg twice daily initial dosing of tacrolimus was too low with approximately 65% of simulated subjects achieving trough concentrations below 6 µg/L at day 5 post-transplant.

Conclusions: To reduce the risk of under immunosuppression in the immediate post-transplant period carriers of a *CYP3A5*1* allele are likely to benefit from a tacrolimus starting regimen of 0.115 mg/kg twice daily.

Gabriel Stillemans I-24 A generic population pharmacokinetic model for tacrolimus in pediatric and adult kidney and liver allograft recipients

G Stillemans (1), R Verbeeck (1), P Wallemacq (2), FT Musuamba (1,2)
(1) Louvain Drug Research Institute, Université Catholique de Louvain, Belgium, (2) Louvain centre for Toxicology and Applied Pharmacology, Université Catholique de Louvain, Belgium

Objectives: To date, several pharmacokinetic (PK) models have been proposed for tacrolimus (TAC) in pediatric and adult patients after liver and kidney transplantation. They are different and lack consistence in their structure and in the covariates included. There is a need for more generic and robust models that could serve for dose individualisation in different settings and situations. This meta-analysis, using data from 9 trials, aimed to propose a library of mechanism-based models for tacrolimus in hepatic and renal transplantation - pediatrics and adults.

Methods: TAC doses and routine TDM trough levels from 289 pediatric and adult liver and kidney allograft recipients during the first year post-transplantation were used to develop a population PK model using NONMEM VII. Patients' demographic and physiological characteristics, type of transplantation and biochemical test results were tested as covariates to explain interindividual variability in tacrolimus distribution and elimination. The model was then internally and externally validated using graphical and numerical tools.

Results: A two-compartment model with first-order elimination best described the TAC PK. Apparent volumes of distribution of central and peripheral compartments estimates were 30L and 200L, and intercompartmental clearance and blood clearance estimates were 11L/h

and 45L/h. The absorption rate was fixed to 4.5h-1. Bodyweight was imputed on apparent clearance and volumes of distribution using an allometric function with the exponent estimated as part of the modelling process. Bias and precision of estimates were within acceptable limits in the model validation. Different models were proposed, using different combinations of covariates.

Conclusions: We developed and validated tacrolimus PK models covering the first year after pediatric and adult liver and kidney transplantation. After implementation in PK software with Bayesian prediction, these models could therefore constitute tools to help clinicians in tacrolimus dose individualisation.

Elisabet Størset I-25 Predicting tacrolimus doses early after kidney transplantation - superiority of theory based models

Elisabet Størset (1, 3), Christine Staatz (2), Stefanie Hennig (2), Troels K. Bergmann (2, 4), Anders Åsberg (1), Stein Bergan (1, 3), Sara Bremer (3), Karsten Midtvedt (3), Nick Holford (5)
(1) School of Pharmacy, University of Oslo, Norway, (2) School of Pharmacy, University of Queensland, Australia, (3) Oslo University Hospital, Rikshospitalet, Norway, (4) Department of Pharmacology, Aarhus University, Denmark, (5) Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

Objectives: Two independent population pharmacokinetic models have been developed for tacrolimus in kidney transplant recipients in Brisbane [1] and Oslo [2]. Both included "time after transplantation" as an empirical covariate. The objectives of this study were to develop a new population pharmacokinetic model based on combined data from Brisbane and Oslo, using a theory based approach to covariate recognition and to evaluate the models' abilities to predict internal and external tacrolimus concentrations.

Methods: Model building and Bayesian forecasting was performed using NONMEM 7.2. A total of 3100 tacrolimus whole blood concentrations were obtained from 242 patients. Tacrolimus whole blood concentrations were predicted using literature values of maximum binding capacity to erythrocytes (Bmax), binding affinity (Kd) [3] and hematocrit. Body size metrics (total body weight, normal fat mass, fat free mass) were evaluated using allometric scaling. CYP3A5 expression was included as a covariate on both bioavailability and clearance. External evaluation was performed by retrospective Bayesian forecasting of observed concentrations in 30 new patients the first two weeks after kidney transplantation.

Results: Relating pharmacokinetics to implicit plasma concentrations rather than whole blood concentrations improved the model markedly (ΔOFV -193). Bioavailability decreased as a function of prednisolone dose, best described by an Emax model (Predmax=-61 %, Pred50=19 mg), theoretically resulting from induction of intestinal CYP3A/P-gp [4]. Fat free mass was the best body size metric using theory based allometry. In CYP3A5 expressers, as predicted from theory, clearance was higher (32 %) and bioavailability was lower (15 %). The combined model showed superior predictive performance of external concentrations compared with the two previous empirically based models.

Conclusions: Theory based population pharmacokinetic modeling of tacrolimus improves predictive performance in external patients.

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Fran Stringer I-26 A Semi-Mechanistic Modeling approach to support Phase III dose selection for TAK-875 Integrating Glucose and HbA1c Data in Japanese Type 2 Diabetes Patients

Fran Stringer (1), Kumi Matsuno (1), Nelleke Snelder (2) and Masashi Hirayama (1)
(1) Clinical Pharmacology Dept, Takeda Pharmaceutical Company, Osaka, Japan; (2) LAP&P Consultants BV, Leiden, The Netherlands;

Objective: TAK-875 is a selective agonist of G protein-coupled receptor 40, and has a different mechanism of action for type 2 diabetes (T2DM) by improving glucose-dependent insulin secretion. This analysis integrated fasting plasma glucose (FPG) and HbA1c to evaluate the drug action of TAK-875 in Japanese T2DM patients. The comprehensive model incorporated placebo effects and was developed to be utilised in the design of the subsequent Phase III clinical trials.

Methods: The efficacy and safety of TAK-875 in T2DM patients were assessed in a Phase II randomized, double-blind study at doses of 6.25, 12.5, 25, 50, 100, and 200mg[1]. PK and PD data for FPG and HbA1c were collected throughout the trial. The individual PK parameters were estimated in addition to a covariate analysis to explore the influence of different patient characteristics on the exposure of the drug. The relationship between exposure, time, FPG and HbA1c was explored using a simultaneous cascading indirect response model with the measures for individual PK exposure utilised. A number of models were explored to describe the placebo effect.

Results: The observed TAK-875 plasma concentrations were adequately described by a one-compartment model with first order absorption and elimination. Body weight was identified as a covariate on volume. An Emax type exposure-response relationship could be identified for the TAK-875

reductive effect on FPG, with an Emax of 24% and an EC50 of 0.61mg/L, the FPG baseline was estimated as 167mg/dL. The placebo effect was described using a separate Tmax model on the production rate of FPG, capturing both the intervention due to diet and lifestyle in addition to the loss of function due to the washout of previous treatment. Integrating FPG with HbA1c was found to result a lower residual error for HbA1c compared to a model using HbA1c alone, 2.3% vs. 2.49% respectively.

Conclusion: Phase III doses of 25mg and 50mg were selected with the aid of this approach. Combining the description of FPG and HbA1c improved the understanding of the drug effect of TAK-875. Congruent with glucose homeostasis, the drug effect is not on HbA1c, but on glucose regulation mechanisms. However the incorporation of the drug effect on FPG does not fully explain the HbA1c level during treatment with TAK-875. A combined model with FPG and postprandial glucose could further increase the understanding of the novel mechanism of action of TAK-875.

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Eric Strömberg I-27 FIM approximation, spreading of optimal sampling times and their effect on parameter bias and precision.

Eric A. Strömberg, Joakim Nyberg, Andrew C. Hooker.
Department of Pharmaceutical Biosciences Uppsala University,

Objectives: Optimizing potentially different designs for multiple individuals with the first order (FO) linearized Fisher Information Matrix (FIM) will produce the same optimal design (with potentially repeated samples) for all individuals given the same input and a rich enough individual design. However, it is natural to think that a first order conditional estimation (FOCE) approximation of the FIM potentially will spread the optimal sampling times for each individual due to the fact that the individual responses are different and these differences are acknowledged in the FOCE linearization. The purpose of this project is to investigate how the optimal design is affected by the FIM approximation and to investigate the bias and precision of parameter estimates in these designs. Moreover, the optimal designs performances are compared to designs that are randomly spread from the optimal design points.

Methods: A sampling schedule with 5 samples (in some situations more), t_i (0,50), was optimized in PopED [1-2] for an EMAX model with exponential inter individual variability IIV on Emax and EC50 amongst 100 individuals placed in one design group. The optimizations were performed using the determinant of the FO-FIM, FOCE-FIM and Monte-Carlo (MC) FIM with various residual error structures. Three random designs were also applied to the optimal designs: for each individual, each optimal sample was uniformly spread ±2% (RN2), ±6% (RN6) of the design space and completely random (RN). The parameters for all designs were re-estimated (FOCEI) with NONMEM 7.2 [3] using MC simulations in PsN [4-5] (SSE).

Results: The OD differed between approximation methods and residual error models. The FO design showed clustering of individual samples and had 3 support points. The FOCE designs had no clustering of sampling points and showed at least 6 support points. MC-OD gave similar designs as FOCE-OD. For proportional residual error SSE studies revealed the best design was the FOCE based designs. The FO design gave poorer bias and precision than the FO-RN2 and FO-RN6 designs while the FOCE design had higher precision and lower bias than FOCE-RN2 and FOCE-RN6. The completely random design had the lowest parameter bias, but the worst precision.

Conclusions: Using the FOCE approximation of the FIM increases the number of support points in a design and gives better estimation properties than FO. When using FO a random spread from the OD support points can be beneficial.

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Herbert Struemper I-28 Population pharmacokinetics of belimumab in systemic lupus erythematosus: insights for monoclonal antibody covariate modeling from a large data set

Herbert Struemper (1), Wendy Cai (2)
(1) Clinical Pharmacology Modeling & Simulation, GlaxoSmithKline, RTP, NC, USA; (2) Human Genome Sciences, Inc., Rockville, MD, USA

Objectives: Belimumab is a recombinant, human immunoglobulin (Ig)-G1λ monoclonal antibody (mAb) that targets B-lymphocyte stimulator (BLyS), a cytokine that promotes B-cell selection, survival, and differentiation[1]. Belimumab currently is indicated for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy. The objective of this analysis was to characterize the population pharmacokinetics of belimumab following intravenous infusion in patients with SLE.

Methods: Data from 1 Phase I, 1 Phase II and 2 Phase III studies (1603 subjects total, doses ranging from 1-20 mg/kg) were analyzed with a non-linear mixed effects modeling approach using NONMEM. A structural model was developed by exploring compartmental behavior, interindividual and residual variability, and other model features. Available covariates included standard demographics and laboratory values, markers of SLE disease activity, and a wide range of SLE-specific and more general classes of comedications. For stepwise covariate model building a 0.001 α-level was chosen as the significance threshold for forward addition and backward elimination.

Results: The final population PK model described belimumab PK in the form of a linear 2-compartment model with clearance from the central compartment (CL). The population estimates were 0.22 L/day for CL and 5.3 L for Vss with a corresponding terminal half life of 19 days. The model included a total of 16 covariate effects of which 9 were related to patient characteristics. The effect of proteinuria on CL was best represented by a linear relationship with a slope of 18.7 mL/g.

Conclusion: The PK parameters were consistent with results for other IgG1 mAbs without marked target-mediated disposition[2]. The large number of SLE subjects allowed to characterize covariate effects typically not identified in mAb PK analyses. Interestingly, proteinuria and estimated creatine clearance were identified as effects on CL, although renal clearance of mAb is typically deemed negligible. Based on the slope of the proteinuria effect a marked decrease in exposure would be predicted in populations with higher proteinuria levels. Other covariates supported by physiological mechanisms incuded effects of IgG on CL and haemoglobin on central volume. However, none of the covariate effects on belimumab PK were found to alter exposure in a manner requiring dose adjustment in the SLE population[3].

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Elin Svensson I-29 Individualization of fixed-dose combination (FDC) regimens - methodology and application to pediatric tuberculosis

Elin M Svensson, Martin Näsström, Maria C Kjellsson, Mats O Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: To develop a model based methodology to guide design of FDCs and selection of an exposure based dosing regimen with the application to pediatric anti-tuberculosis (TB) drugs, individualized based on weight.

Methods: A rational approach for selection of optimal covariate-based dosing for single drugs has previously been developed [1]. Here, this methodology was expanded to accommodate several drugs simultaneously and a fixed tablet content. Further, the relationship between estimation stability and choice of equation mimicking the discontinuous step between dose-levels was investigated. Weights for children with a uniform distribution between 2-10 years were simulated based on the WHO growth standards [2] assuming log-normal distribution. Individual clearances for standard anti-TB drugs were simulated using published models [3-6] and allometric scaling. Estimation of optimal drug content per tablet and break points for change of dose were based on minimizing deviation between the logarithm of individual exposure (AUC) and a PK target, calculated from dosing recommendations.

Results: A function including exponentials with weight and break points as coefficients and a sigmoidicity factor was successfully used to mimic the step between dose-levels. However, using FOCE in NONMEM 7.2, estimation was unstable and dependent on initial estimates for high sigmoidicity factors. This could be overcome by sequential estimation of models with increasing steepness of the step function and successive update of initial estimates. The

definition of optimization criteria should be carefully considered and depends on clinical considerations for the drugs. Optimization on overall target attainment can lead to systematic differences between groups. The benefit of increasing number of dose levels depends on the covariate relationship and the inter-individual variability (IIV) in the drug's PK. For example, relative RMSE of the exposure decreased from 30 to 23% for pyrazinamide (low IIV) and 75 to 69% for rifampicin (high IIV), when changing from one to three dose levels.

Conclusions: An easy to employ and flexible methodology for design of FDCs was successfully developed. Anti-TB drugs were used as an example, but current results should not be interpreted as recommendations for FDC development. For such a proposal, the methodology should be applied with pediatric models, clinically valid targets and practical constraints such as co-formulation aspects.

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Eva Sverrisdóttir I-30 Modelling analgesia-concentration relationships for morphine in an experimental pain setting

Eva Sverrisdóttir (1), Richard Upton (2), Anne Estrup Olesen (3), David Foster (2), Mads Kreilgaard (1)
(1) Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; (2) Australian Centre for Pharmacometrics, School of Pharm and Med Sci, UniSA, Adelaide, SA; (3) Mech-Sense, Department of Gastroenterology & Hepatology, Aalborg University Hospital, Denmark

Objectives: To develop a population pharmacokinetic-pharmacodynamic (PK-PD) model describing the concentration-effect relationships for morphine on experimental pain caused by skin heat and muscle pressure.

Methods: Data were analysed from a study in 39 healthy volunteers who received 30 mg oral morphine or placebo. Blood samples were collected up to 150 min post dose, while experimental skin heat and muscle pressure pain was induced at time 0, 15, 30, 45, 60, and 150 min. Nociceptive input was increased until the subjects reported a pain score of 7 on a 0-10 visual analogue scale, where 5 is the pain detection threshold. The PK-PD relationships of morphine, M6G, and M3G were analysed with non-linear mixed effects modelling (NONMEM v. 7.2, ICON Plc) using a sequential approach. One- and two-compartment models were fitted to morphine, M6G, and M3G plasma concentration-time data. First order and transit compartment absorption models were tested. The placebo-response of both pain metrics was fitted to slope 0, linear, and quadratic effect versus time models. The drug effect was tested as proportional or additive to the placebo-response. Drug effect was fitted to slope 0, linear, and Emax models of effect versus plasma or effect compartment concentration. Morphine, M6G, or M3G were tested as the concentration driving analgesia. The

influence of the covariates sex, height, weight, body mass index (BMI), and age was also tested. Model selection criteria included Akaike Information Criterion (AIC) and diagnostic plots.

Results: The plasma concentration-time profiles of morphine, M6G, and M3G were best described with a one-compartment distribution, and the absorption of morphine was best described with a six transit compartment model with a combined additive and proportional residual error model. The placebo-response for skin heat was best described by a linear model with between-occasion variability (BOV) on baseline, and additive residual error model. For muscle pressure, a slope 0 model with BOV on baseline and proportional error model best described the placebo response. Morphine's effect on both skin heat and muscle pressure was proportional to the placebo-response and described by a linear model with between subject variability (BSV) on drug effect slope and an effect compartment for muscle pressure. Drug slopes were 0.000406 °C/ng/ml for skin heat and 0.0156 kPa/ng/ml for muscle pressure. The inclusion of covariates did not improve the models.

Conclusions: The data were characterised by high inter and intra individual variability. In contrast to previous studies, the placebo-response showed minimal change with time. A linear concentration-effect relationship of morphine was identified for both pain metrics. However, drug effect slopes were marginal in relation to clinical relevance.

Maciej Swat I-31 PharmML – An Exchange Standard for Models in Pharmacometrics

Maciej Swat (1), Stuart Moodie (1), Niels Rode Kristensen (2), Nicolas Le Novère (3) on behalf of DDMoRe WP4 contributors.
(1) EMBL-EBI, Hinxton UK, (2) Novo Nordisk, Denmark, (3) Babraham Institute, UK

Objectives: A long-standing problem in Pharmacometrics is the lack of a common standard allowing for exchangeability of models between existing software tools, such as Bugs, Monolix, NONMEM and others. PharmML, as part of the DDMoRe interoperability platform [1], presented here in its 1st specification tries to fill this gap. The modelling framework is that of Nonlinear Mixed Effects Models, NLME, which allows for nonlinear models with random and fixed effects. This new standard provides encoding platform for approaches currently in use but also attempts to create support for novel elements.

Methods: The development of PharmML is based on requirements provided by the DDMoRe community, including numerous academic and EFPIA partners, use cases for various estimation and simulations tasks encoded in languages such as NMTRAN and MLXTRAN and mathematical documents outlining the statistical background prepared within DDMoRe ([2],[3]). The methodology included analysis of use cases and their implementation in Matlab, abstraction of the information necessary to encode a particular type of model, creating an XML schema and testing its performance and functionality. We reuse where possible existing standards, such as SBML to encode the structural model.

Results: The current specification supports the exchange of continuous models, in the form of algebraic equations or systems of ODEs. The

parameter model offers a very flexible structure allowing for the use of most common parameters. It is linear in the transformed parameter, and the resulting additive structure allows for easy interpretation and implementation of its components, such as continuous and discrete covariates, correlation structure of the random effects and virtually any level of variability as nested hierarchy. The clinical trial model provides the modeller with almost unlimited possibilities to construct arbitrary study designs using only few basic building blocks, such as Treatment, Treatment Epoch and Group. PharmML is providing a means to annotate an arbitrary element of the model, making effective searching and reasoning on models in a repository possible. Models encoded in this way can be used not only for the standard tasks, such as simulation and estimation but also modelling and exploration.

Conclusions: This specification provides a solid basis for further development of PharmML in future. Subsequent releases will support discrete models, Bayesian inference framework, stochastic differential equations and Hidden Markov Models etc.

This work is presented on behalf of the DDMoRe project.

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Amit Taneja I-32 From Behaviour to Target: Evaluating the putative correlation between clinical pain scales and biomarkers.

Taneja A(1),Danhof M(1), Della Pasqua OE(1,2)
(1) Division of Pharmacology Leiden Academic Centre for Drug Research Leiden University The Netherlands (2) Clinical Pharmacology Modelling & Simulation GlaxoSmithKline Stockley Park UK.

Objectives: Pain response in clinical trials relies on the use of clinical scales of pain intensity and relief. In contrast to current practice, here we show how a model-based approach can be used to determine the most appropriate dose range in a Phase III trial in patients with rheumatoid arthritis. Using a new selective COX-2 inhibitor as paradigm compound we illustrate how prostaglandin inhibition can be correlated to pain relief (core set measures of rheumatoid arthritis).

Methods: Data from a phase IIb clinical study in 540 patients was available for the analysis. Nonlinear mixed effects modelling was used to characterise the pain response, as defined by the ACRN scale. Model development included the evaluation of placebo and drug effect terms. The use of a Weibull function in conjunction with an I_{max} model was found to describe the placebo and drug effects appropriately. To enable identification of patient subgroups during model building and evaluate a putative correlation between target inhibition and pain relief, patients were categorised into responders and non-responders, based on the magnitude of changes from baseline (i.e., >25% decrease in pain). These data were then linked to a previously published model of prostaglandin (PG) inhibition using a non-parametric smoothing function. Modelling and simulation was performed in NONMEM v7.2, whilst data manipulation, graphical and statistical summaries were performed in R.

Results: The longitudinal response model described the data adequately, with the number of responders increasing from 54 to 69% with ascending dose levels (i.e., from 0, 10, 35 to 50mg). Different potency (IC_{50}) estimates were obtained for each subgroup, i.e. responders and non-responders). Target (>80%) inhibition was predicted to be reached at doses greater than 250mg, whilst the median ACRN drop >50% occurred at a dose >100mg.

Conclusions: The assumption of an underlying exposure-response model for the clinical changes in ACRN allowed us to describe the time course of pain response in rheumatoid arthritis patients and make inferences about the heterogeneity in response. Despite the challenges in sampling and analysing biomarkers in Phase III studies, our exercise illustrates how a model-based approach can be used to better substantiate the dose rationale of compounds for the treatment of chronic pain.

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Joel Tarning I-33 The population pharmacokinetic and pharmacodynamic properties of intramuscular artesunate and quinine in Tanzanian children with severe falciparum malaria; implications for a practical dosing regimen.

Joel Tarning (1,2), Ilse C E Hendriksen (1,2), Deogratius Maiga (3), Martha M Lemnge (3), George Mtove (4), Samwel Gesase (5), Hugh Reyburn (6), Niklas Lindegardh (1,2), Nicholas P J Day (1,2), Lorenz von Seidlein (7), Arjen M Dondorp (1,2), Nicholas J White (1,2)

1) Mahidol-Oxford Tropical Research Unit, Faculty of Tropical Medicine, Bangkok, Thailand. 2) Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK. 3) National Institute for Medical Research, Tanga Medical Research Centre, Tanga, Tanzania. 4) National Institute for Medical Research, Amani Centre, Tanga, Tanzania. 5) National Institute for Medical Research, Korogwe Research Station, Tanga, Tanzania. 6) London School of Tropical Medicine and Hygiene, London, United Kingdom. 7) Menzies School of Health Research, Casuarina, NT, Australia.

Objectives: Parenteral artesunate is the drug of choice for treatment of severe malaria. The pharmacokinetic properties of intramuscular artesunate have not been studied in the main treatment group who carry the highest mortality; critically ill children with severe malaria. Although artesunate is superior, parenteral quinine is still widely used. The objectives were to characterize the pharmacokinetic-pharmacodynamic properties of quinine, artesunate and dihydroartemisinin (the active metabolite of artesunate) in children with severe malaria in Tanzania and recommend practical dosing regimens.

Methods: A nested population pharmacokinetic study was conducted, as part of a large outcome trial [1], in Tanzanian children aged 4 months to 11 years.

They received a standard body weight-based dose of quinine (n=75) [2] or artesunate (n=70) [3]. Sparse capillary data were characterized using nonlinear mixed-effects modeling and outcome modeled with a time-to-event approach. The final population pharmacokinetic models were used for Monte-Carlo simulations and dose optimization.

Results: Observed mortality was 12.9% [CI.6.05-23.0%] and 17.3% [CI.9.57-27.8%] after artesunate and quinine dosing, respectively; relative reduction of 25.8% for artesunate treatment compared with quinine treatment. A zero-order absorption model with one-compartment disposition pharmacokinetics described all the drugs adequately. Body weight as an allometric function was a significant covariate in all models. An exposure-effect relationship was established for quinine with cumulative AUC modulating the hazard of mortality. No exposure-effect relationship could be established for artesunate/dihydroartemisinin in the pharmacokinetic cohort. Simulations using the final population pharmacokinetic models indicated a reduced quinine, artesunate and dihydroartemisinin exposure at lower body weights after a standard weight-based dosing.

Conclusions: Artesunate/dihydroartemisinin and quinine pharmacokinetics were adequately described. A loading dose of quinine is recommended and resulted in adequate drug levels for all body weights with no evidence of dose related drug toxicity. Children at lower body weights had reduced artesunate/dihydroartemisinin exposure and the final model was used to develop a practical dosing table for intramuscular artesunate in the treatment of severe malaria.

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David Ternant I-34 Adalimumab pharmacokinetics and concentration-effect relationship in rheumatoid arthritis

David Ternant (1), Piera Fuzibet (2), Emilie Ducourau (2), Olivier Vittecoq (3), Thierry Lequerre (3), Philippe Goupille (1), Denis Mulleman (1), Gilles Paintaud (1)
(1) CNRS UMR 7292 GICC, (2) Department of Rheumatology, Tours, France, (3) Department of Rheumatology, Rouen, France.

Objectives: Adalimumab, an anti-TNF-α monoclonal antibody, is effective in active rheumatoid arthritis (RA). Subcutaneous injections of adalimumab lead to highly variable concentrations between patients and this pharmacokinetic (PK) variability partly explains the variability of clinical effect. However, adalimumab PK after subcutaneous injection has never been reported. The goal of this study is to build a simplified PK model for therapeutic drug monitoring (TDM) of adalimumab in CD patients and to describe the concentration-effect relationship of adalimumab in these patients using PK-PD modeling.

Methods: Adalimumab PK data were taken from a multicentric observational study. Adalimumab 40 mg was administered subcutaneously every other week. Trough adalimumab concentrations, CRP levels and RA disease activity score (DAS28) were measured at inclusion visit, then at weeks 6, 12, 24 and 52. Adalimumab PK was decribed using a one compartment model with first-order absorption and elimination rates. The relationship between adalimumab concentrations and CRP levels was described using using an indirect response model with inhibition of CRP input, whereas the relationship between adalimumab concentrations and DAS28 was described using a direct inhibitory model. A population approach was used and models were run simultaneously. Sex, age and body weight were tested as covariates on each pharmacokinetic and PK-PD parameter.

Results: Thirty patients were included, and 131 adalimumab trough concentrations, CRP levels and DAS28 measurements were available. The following PK and PK-PD parameters were estimated (interidividual coefficient of variation): apparent volume of distribution (Vd/F) = 12.4 L (75%), apparent clearance (CL/F) = 0.31 L/day (17%), first-order absorption constant (ka) = 0.41 day-1, zero-order CRP input rate (kin) = 129 mg/L/day (47%), first-order CRP output rate (kout) = 8.3 day-1 and adalimumab concentration leading to 50% decrease of kin (C50) = 5.7 mg/L (102%), initial DAS28 (DAS0) = 5.5 mg/L (11%) and adalimumab concentration leading to 50% decrease of DAS0 (IC50) = 11.8 mg/L (66%). Apparent clearance was higher for increasing body weight and for men.

Conclusions: This is the first study describing the pharmacokinetics and concentration-effect relationship of adalimumab in rheumatoid arthritis. This model allows therapeutic drug monitoring of adalimumab in RA patients.

Adrien Tessier I-35 High-throughput genetic screening and pharmacokinetic population modeling in drug development

Tessier A (1, 2), Bertrand J (3), Fouliard S (2), Comets E (1), Chenel M (2)
(1) Univ Paris Diderot, Sorbonne Paris Cité, UMR 738, F-75018 Paris, France and INSERM, UMR 738, F-75018 Paris, France; (2) Clinical Pharmacokinetic Department, Institut de Recherches Internationales Servier, Suresnes, France; (3) University College London, Genetics Institute, London, UK

Objectives: To develop a population PK model and integrate a large number of SNPs, genotyped in clinical studies, as covariates in this model.

Methods: The dataset included 78 subjects receiving molecule S (Servier laboratories) in Phase I studies (60 as single dose, 18 as repeated doses daily over 21 days). Subjects were sampled extensively on Day 1 and 21 (for repeated doses) along with additional trough samples. They were genotyped for 176 Single Nucleotide Polymorphisms (SNPs) using a DNA microarray. Forty genes corresponding to markers of metabolic enzymes, carriers and nuclear receptors were screened for their influence on PK parameters. A population PK model was developed to describe the evolution of concentrations data, and the parameters were estimated using NONMEM 7.2 [1], FOCE-I. Here the number of observations (PK profiles) is less than the number of covariates to explore (SNPs). Thus the analysis requires reducing the number of covariates to include. We used the algorithm proposed by Lehr et al. [2] based on a preliminary screening using univariate ANOVA on the individual Bayesian estimates (EBE).

Results: The pharmacokinetics of drug S followed a two-compartment model with zero order absorption (D1) and a lag time (Tlag). Non-linearity in the PK with dose was modeled through a variable bioavailability (F). The PK profile showed a rebound at approximately 24h, which was described assuming a

gallbladder compartment with an emptying time-window, corresponding to enterohepatic circulation (EHC). Inter-individual variability was estimated for F, D1, Tlag, the intercompartmental clearances between central and peripheral compartment (Q) and between central and gallbladder compartment (QGB), and the oral clearance (CL). Three genotypic models (additive, dominant and recessive) were tested for SNPs on EBE. One SNP was associated additively with CL on the gene coding for metabolism enzyme NAT1 and another recessively with QGB on the gene coding for nuclear receptor VDR.

Conclusions: Using NLME modeling rather than observed AUC to study the impact of many genetic variants during the development of drug S (nonlinearity, EHC) enabled identifying how the genetic markers impact the different phase of ADME (Absorption, Distribution, Metabolism, Excretion) process. Effects of SNPs revealed by this work will be explored through focused in vitro studies.

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Iñaki F. Trocóniz I-36 Modelling and simulation applied to personalised medicine

Álvaro Janda1, Zinnia Para-Guillén1, Julian Gorrochategui2, Joan Ballesteros2 , and Iñaki F. Trocóniz1
1, Department of Pharmacy and Pharmaceutical Technology; School of Pharmacy; University of Navarra; Pamplona; Spain

Objectives: To describe the methodology followed to characterize the subject's specific type of pharmacodynamic (PD) drug interactions in leukemic patients.

Methods: Data obtained from ex vivo response vs concentration studies were used. Two studies including combination of two of drugs have been tested. Response was expressed as the absolute number of malignant cells alive (MCA). Data analysis was performed using the population approach using NONMEM 7.2. The modelling exercise involved the following steps: (i) population PD modelling of the ex vivo response vs concentration data in monotherapy, (ii) establishing for each patient the 95% prediction intervals (PI) of the isobologram based on the variance-covariance matrix from each individual parameter, (iii) computation of the combination index [1] using raw data descriptors from combination experiments, and (iv) finally characterization of the type of interaction calculating the distance between CI and the lower limit of the PI, and visualization of the results using colour maps.

Results: The inhibitory I_{MAX} model was the selected model for all the drugs tested in this analysis. Inter-patient variability was included in all model parameters and in the residual part of the population model as well. For each patient and drug tested one thousand concentrations values corresponding to a 20, 40, 60 and 80% decrease in MAC with respect to baseline were

simulated, allowing to generate for each patient and drug combination the individual isobologram with uncertainty. The type of interaction and its frequency found in the two studies, correlated well to which was previously known.

Conclusions: The proposed procedure can be largely automated to be used efficiently in personalized medicine programs. It avoids the need of modelling drug combination data, which it is not trivial and can lead to limitations at the time of estimating variability in the interaction parameters, making patient stratification difficult.

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Nikolaos Tsamandouras I-37 A mechanistic population pharmacokinetic model for simvastatin and its active metabolite simvastatin acid

Nikolaos Tsamandouras (1), Aleksandra Galetin (1), Gemma Dickinson (2), Stephen Hall (2), Amin Rostami-Hodjegan (1,3) and Leon Aarons (1)
(1) Centre for Applied Pharmacokinetic Research, University of Manchester, UK, (2) Eli Lilly and Company, Indianapolis, IN, USA, (3) Simcyp Ltd, Sheffield, UK

Objectives: Simvastatin (SV), a commonly used HMG-CoA reductase inhibitor, is a prodrug with complex pharmacokinetics due to the interconversion between the parent drug and its main active metabolite, simvastatin acid (SVA) [1]. In addition both SV and SVA are subject to drug-drug interactions and are affected differentially by genetic variation in enzyme/transporter proteins relevant for their disposition [2,3]. An operating model that mechanistically describes the disposition of both these forms can have many applications. Therefore, this study aims to develop a mechanistic joint pharmacokinetic model for both SV and SVA.

Methods: SV and SVA plasma concentrations from 34 healthy volunteers derived from two clinical studies with intensive sampling were analysed. Population pharmacokinetic modelling was performed using nonlinear mixed effects software (NONMEM 7.2) and the prior functionality [4]. A mechanistic model was implemented with a physiologically based compartmental structure that allows interconversion between the lactone and acid form of the drug. Prior information for model parameters and (when available) their variability was extracted from physiology literature, *in vitro* experiments and *in silico* methods. An independent dataset was used for the external validation of the mechanistic model. The developed model was finally

employed to simulate concentration profiles in plasma, liver and muscle and investigate the impact of different scenarios.

Results: The mechanistic model provided a good fit to the plasma concentration data for both SV and SVA, while the model predictions were also in close agreement with the observed data used for external validation. Additionally, the model provides a mechanistic basis for the interconversion between the two forms in different tissues and quantifies this process. Simulations with the developed model using reduced hepatic uptake of SVA (representing the scenario of a *SLCO1B1* polymorphism) recovered the reported increase in exposure of SVA in plasma [5]; comparable increased fold-exposure was simulated in the muscle, consistent with the risk of toxicity in this tissue; whereas impact on liver exposure was minimal.

Conclusion: The developed mechanistic model successfully describes the pharmacokinetics of both SV and SVA. Its main advantage is that it allows extrapolation and predictions of different scenarios, such as the impact of genetic polymorphisms or potential drug-drug interactions.

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Sebastian Ueckert I-38 AD i.d.e.a. – Alzheimer's Disease integrated dynamic electronic assessment of Cognition

Sebastian Ueckert (1), Elodie L. Plan (1), Kaori Ito (2), Mats O. Karlsson (1), Brian Corrigan (2), Andrew C. Hooker (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (2) Global Clinical Pharmacology, Pfizer Inc, Groton, CT, USA

Objectives: Assessing a persons cognitive ability is a challenging and time consuming process, yet essential for the diagnosis and monitoring of patients with Alzheimer's disease (AD). Existing cognitive tests are either quick, e.g., mini-mental state examination (MMSE) [1], or precise, e.g., ADAS-cog [2], but fail to be both. The objective of this project was to develop a procedure that achieves both, by combining pharmacometric methods with the capabilities of a modern Web application, and creating an integrated dynamic electronic assessment of cognition in Alzheimer's disease.

Methods:
IRT model: The work was based on an item response theory (IRT) model, which links the response of each test in the ADAS-cog and MMSE assessments to the hidden variable cognitive disability using a binary, binomial, or ordered categorical probability model [3].

Adaptive Test Algorithm: The procedure consists of 3-step iterations: I) an approximate posterior is determined from previous patient responses, the population prior for disability, and the IRT model, II) the expected Fisher information for all cognitive tests in the database is calculated using the posterior, III) the most informative test is selected, presented to the patient, whose response is recorded to obtain refined estimates in the next iteration.

Web Application: Adaptive test selection and storing of patient responses are handled on the server-side through a Ruby on Rails based web application with connection to a SQLite database. On the client-side, the user interface is implemented using HTML5 and JavaScript in a responsive design paradigm to optimize usability for wide a range of devices (from smartphone to desktop).

Results: The AD i.d.e.a. application was created and the adaptive testing algorithm was compared to the MMSE assessment via simulations (n=1000). In all 3 simulated patient populations (mild cognitively impaired, mild AD, and AD) the adaptive algorithm had a lower root mean squared error (Δ=-15.7% on average) and was 33% shorter than the MMSE.

Conclusions: The adaptive algorithm used in the AD i.d.e.a. application improves cognitive testing in AD patients by making it quicker and more precise than existing tests. This project exemplifies how pharmacometric methods can be combined with modern Web technology to be integrated into the clinic and directly affect patient care.

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Wanchana Ungphakorn I-39 Development of a Physiologically Based Pharmacokinetic Model for Children with Severe Malnutrition

Wanchana Ungphakorn (1), Alison H. Thomson (1,2)
(1) Strathclyde Institute of Pharmacy & Biomedical Sciences, University of Strathclyde, Glasgow, UK, (2) Pharmacy Department, Western Infirmary, Glasgow, UK

Objectives: Severe malnutrition in children remains a global health problem. The pharmacokinetics of drugs are affected by several physiological changes associated with malnutrition. A physiologically based pharmacokinetic (PBPK) models have advantages in relating pharmacokinetic parameters to such physiological changes. The aims of this work were to develop a PBPK model for predicting drug disposition in children with severe malnutrition, using ciprofloxacin as a model drug and (2) to investigate the impact of tissue:plasma partition coefficients (Kp) predicted with different methods on the predictions.

Methods: The WBPBPK model was initially developed for healthy adults and then scaled to healthy and malnourished children. The model comprises 13 physiologically realistic compartments namely artery, venous, lungs, liver, kidneys, gut, adipose, skin, muscle, heart, brain, bone, and spleen. A rest compartment was included in the model to compensate for unaccounted mass of drug. The dynamic processes of drug in each organ/tissue were described using linear ordinary differential equations written in the MATLAB program. Physiological parameters for healthy adults and children were compiled from the literature. Kp(s) were calculated using Poulin models [1], Rodgers' models [2] and the empirical methods [3]. For malnourished children, body weights were predicted using age, height, gender and Z-score taken from the WHO database. Organ/tissue weights were scaled from

normal values using scaling factors for each organ. Cardiac output was estimated using body surface area and cardiac index and was subsequently used to calculate organ blood flows. Predictions of pharmacokinetic profiles were compared with observed data taken from the literature.

Results: For healthy adults and children, the predicted versus observed concentration-time profiles were well described with intravenous (IV bolus and short infusion) models. Oral predictions were also in good agreement with literature data but peak concentrations were more rapidly achieved with a higher dose. Unlike the Poulin model, the concentration-time profiles predicted using Kp from the Rodgers models and the empirical methods were similar, and closely resembled the observed data. When models were scaled for malnutrition, inter-individual variability was higher, especially during the absorption phase. However, pharmacokinetic profiles were still adequately described.

Conclusion: A PBPK model was developed successfully for malnourished children. The Rodgers models and the empirical methods are suitable to predict Kp values for ciprofloxacin.

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Elodie Valade I-40 Population Pharmacokinetics of Emtricitabine in HIV-1-infected Patients

Elodie Valade (1) (2), Saïk Urien (1) (2), Floris Fauchet (1) (2), Naïm Bouazza (2), Frantz Foissac (2), Sihem Benaboud (3), Déborah Hirt (1) (2) (3), Jean-Marc Tréluyer (1) (2) (3)
(1) Université Paris Descartes, Sorbonne Paris Cité, EA 3620 (2) Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France (3) Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, Paris, France

Objectives: The aim of this study was to describe the pharmacokinetics of emtricitabine (FTC) in a large population of HIV-1-infected adults, and to assess patient characteristics influencing the pharmacokinetics of emtricitabine.

Methods: Ambulatory HIV-1 positive patients taking a FTC-containing regimen were included. The data were analyzed using the nonlinear mixed-effect modeling software program Monolix version 4.1.3. The influence of covariates (sexe, body weight, age, cotreatments) on the pharmacokinetic parameters of FTC was explored.Thanks to Bayesian estimation of the parameters, drug exposure (AUC), maximal and minimal FTC concentrations were obtained for each individual.

Results: From 282 patients, 366 plasma FTC concentrations were available. The FTC pharmacokinetics was best described by a two-compartment model with linear absorption and elimination. The mean population parameter estimates (inter-patient variability) were 1.0 h-1 for the absorption rate constant; 14.3 L/h (18.3%) and 3.6 L/h for the apparent elimination and intercompartmental clearances; 60.2 L and 54.6 L for the apparent central and peripheral volumes of distribution. FTC apparent elimination clearance increased significantly with body weight. The median population AUC and the

maximal and minimal FTC concentrations were respectively 13.5mg.h/L, 2.06 and 0.086 mg/L.

Conclusions: This is the first population-model describing the FTC pharmacokinetic profile in HIV-infected adults. The influence of body weight on the clearance explains a part of the inter-patient variability.

Georgia Valsami I-41 Population exchangeability in Bayesian dose individualization of oral Busulfan

Efthtymios Neroutsos, Georgia Valsami, Aris Dokoumetzidis
Laboratory of Biopharmaceutics & Paharmacokinetics, Faculty of Pharmacy, National & Kapodistrian University of Athens, Panepistimiopolos, Zographou, 15771, Greece

Objectives: To investigate the usage of a popPK model for Bayesian individualization of oral Busulfan dosing in patients from a different hospital. This was done by simulating patients using a popPK model taken from literature and adjusting the dose by applying a different popPK model also taken from literature.

Methods: A total of 1000 children were simulated in NONMEM for three different blood sampling schemes, according to a PopPK model taken from literature (model A) [1]. Based on the posthoc estimates of clearance for these patients using the same model (model A), we calculated the AUC and individualized the dose targeting AUC=1125 μM*min (therapeutic range of Busulfan 900-1350 μM*min). The AUC of the second day of administration was recorded by simulating again using the adjusted dose. Patients that fall outside the therapeutic range were counted before and after the dose adjustment (day 1 vs day 2 of treatment). The dose of the same simulated patients was also adjusted by applying a different model from literature (model B) [2] using the same procedure.

Results: For a blood sampling scheme at 2, 4, 6 hours, the patients' AUC that fall within the therapeutic range were 40.3%. After the individualization with model A (the same as the one used for simulation) patients within the range increased to 62% while with model B (a different model to the one used to simulate the patients) increased to 52.8%. As expected better performance is

achieved with an in-house model while the overall performance even of the in-house model is moderate. Richer sampling schemes, namely at 2, 3, 4, 5, 6 h and 1.5, 3.5, 5, 6, 8, 12 h, performed similarly without offering significant improvement.

Conclusions: In the present study we observed that Bayesian individualization of oral Busulfan dosing offers some improvement while the development of an in-house model rather than the use of a literature model is deemed necessary.

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Sven van Dijkman I-42 Predicting antiepileptic drug concentrations for combination therapy in children with epilepsy.

Sven van Dijkman (1), Meindert Danhof (1), Oscar Della Pasqua (1,2)
(1) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, The Netherlands; (2) Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Uxbridge, UK

Objectives: Despite the wide number of publications on the pharmacokinetics of antiepileptic drug combinations, drug-drug interactions have not been accurately characterised in children, resulting in unclear dose rationale. In this study, we aim to use a model-based approach to characterise AED concentrations following a variety of regimens with Valproic Acid (VPA), Carbamazepine (CBZ) and Phenytoin (PHT) and explore the impact of developmental growth on systemic exposure. The resulting models will later be used to simulate concentrations for patients in another dataset with outcome data where only dose was recorded, to be able to more accurately quantify the concentration-effect relationships for these drugs.

Methods: Population pharmacokinetic models [1, 2, 3] from published literature were used as basis for the simulation of plasma concentration of individual drugs as well as combined therapy [4, 5]. PK profiles were generated for a cohort of children from 03 months to 16 years of age to assess the magnitude of the interaction between developmental growth and drug-induced changes in metabolic clearance on the resulting systemic exposure. AUC, Cmax and Cmin and their ratios in combination therapy were derived as parameters of interest. Results were then compared to drug levels in adults. Simulations were performed in NONMEM v7.2. R was used for data manipulation, graphical and statistical summaries.

Results: Allometric models were implemented to describe the effects of body weight and metabolic maturation on clearance and volume of distribution. In contrast to current practice, simulated profiles clearly show that drug-drug interactions must be taken into account to ensure comparable exposure in children and adults. Significant differences were found for the ratio of AUC, Cmax and Cmin in adult and paediatric population. Our results indicate that currently recommended dosing algorithms and titration procedures do not warrant maintenance of the appropriate therapeutic levels of AEDs in children.

Conclusions: Phenytoin when combined with carbamazepine or valproic acid significantly alters the average plasma concentrations of these drugs. Dosing regimen and titration in children need therefore to account for such interactions. A model-based algorithm can provide the basis for improved dosing regimen, especially in very young children.

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Coen van Hasselt I-43 Design and analysis of studies investigating the pharmacokinetics of anti-cancer agents during pregnancy

JGC van Hasselt(1,2), K van Calsteren(3), ADR Huitema(2), L Heyns(3), S Han(3), M Mhallem(3), JHM Schellens(1,4), JH Beijnen(2,4), F Amant(3)
(1) Department of Clinical Pharmacology, Netherlands Cancer Institute, Netherlands; (2) Department of Pharmacy & Pharmacology, Slotervaart Hospital, Netherlands; (3) Obstetrics and Gynecology, University Hospitals Leuven, Leuven; (4) Faculty of Science, Department of Pharmaceutical Sciences, Utrecht University, Netherlands.

Introduction: Physiological changes during pregnancy may affect pharmacokinetics (PK) [1]. Studies investigating changes in PK may therefore be needed to assess if dose adjustments are necessary. The evaluation of changes in PK of anti-cancer (AC) agents during pregnancy is of specific relevance, as the narrow therapeutic window of such agents may have severe consequences, either due to increased toxicity or decreased efficacy. However, the conduct of PK studies during pregnancy is constrained by practical and ethical limitations such as low numbers of available subjects, therefore requiring informative trials that are analyzed in an efficient fashion. The aims of this project were to: i) estimate changes in PK for four AC agents and the impact on current dosing guidelines; ii) evaluate if a semi-physiological approach could be used to predict expected changes in PK.

Methods: A nonlinear mixed effect modelling approach was used to estimate gestational effects. Subsequently, we simulated the impact of estimated changes on dosing regimens. Limited D-optimal sampling designs were derived for all treatments that could be expected. Designs were optimized taking into account that each treatment could consist of multiple drugs of

interest, and, expected changes in PK were leveraged in a semi-physiological fashion including renal function [2] and body composition [3].

Results: For doxorubicin, we estimated increases of 23% (RSE 24%) and 32% (RSE 15%) for the initial (V1) and terminal (V3) volumes of distribution respectively, with no identifiable change in clearance (CL). For epirubicin we estimated 10% (RSE 9%) increase in CL, 55% (RSE 13%) increase in V1 and 208% (RSE 25%) increase in V2. For docetaxel we estimated 19% increase (RSE 7%) in CL, while V1, V2 and V3 changed by 7% (RSE 12%), 37% (RSE 18%) and -9.7% (RSE 15%) respectively. For paclitaxel we estimated 30% (RSE 41%) increase in CL, , while V1, V2 and V3 changed by -15.4% (RSE 70%), 48% (RSE 34%) and 28% (RSE 29%) respectively.
Limited optimal sampling designs were successfully developed for all expected AC treatments, with a minimum of 4-5 samples required to obtain adequate PK parameter estimates.

Conclusion: Gestational effects of pregnancy on PK parameters of doxorubicin, epirubicin, docetaxel and paclitaxel were quantified, and associated dose adjustments were computed. Moreover we demonstrated how physiological data can be leveraged into a PK model in order to obtain informative clinical study designs.

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Anne van Rongen I-44 Population pharmacokinetic model characterising the influence of circadian rhythm on the pharmacokinetics of oral and intravenous midazolam in healthy volunteers

A. van Rongen (1), F. van Oosterhout (2), M.J. Brill (1,3), J.H. Meijer (2), J. Burggraaf (3,4), C.A.J. Knibbe (1,3)
(1) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands; (2) Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands, (3) Division of Pharmacology, Leiden/ Amsterdam Academic Center for Drug Research, Leiden University, Leiden, The Netherlands, (4) Centre for Human Drug Research, Leiden, The Netherlands

Objectives: Chronopharmacology studies have revealed circadian variability in pharmacokinetics and pharmacodynamics of different drugs. Time-dependent changes may occur for absorption, distribution, metabolism and/or excretion processes. The aim of this study is to evaluate the influence of circadian rhythm on the pharmacokinetic parameters of midazolam after oral and intravenous administration in a semi-simultaneous way.

Methods: The study was an open-label, 6 way crossover study in 12 healthy volunteers, in which at each of the 3 study visits the subjects received oral (2 mg) and iv (1 mg) midazolam (separated by 150 min) twice a day at a 12 hour interval. The clock times of midazolam dosage differed for each study occasion with a 4 hour interval and as a result data were collected at 6 time points to construct a 24 hour profile of midazolam pharmacokinetic parameters. Twenty samples were collected per patient per 12 hour interval. Population PK modelling and covariate modelling was performed using NONMEM VI.

Results: A two compartment pharmacokinetic model with an oral absorption transit compartment with k_{tr} equal to k_a best described the data with values of 0.38 L/min (CV of 7.5%), 21.8 L (4.3%), 0.35 (7.3%) and 0.06 min^{-1} (5.1%) for clearance, volume of distribution of the central compartment, oral bioavailability and k_a, respectively. For oral bioavailability, a circadian night dip was identified which was parameterized as half a cycle of a sinus function. The amplitude representing the magnitude of the circadian variability was 0.08 (34.9%). Circadian rhythm was not found to influence any of the other pharmacokinetic parameters ($p>0.05$).

Conclusions: In this chronopharmacology study in 12 healthy volunteers, an influence of circadian rhythm was identified for oral bioavailability of midazolam representing a maximum reduction of 23% at night. Further research using physiologically-based modelling should elucidate which subprocess contributes to this circadian variability in bioavailability.

Marc Vandemeulebroecke I-45 Literature databases: integrating information on diseases and their treatments.

Vandemeulebroecke M, Demin I, Luttringer O, McDevitt H, Ramakrishna R, Sander O
Novartis

Objectives: Quantitative knowledge about the clinical efficacy of approved drugs makes it possible to interpret the efficacy of a candidate drug in light of the competitive landscape. This can be used when setting the desired efficacy profile of a new drug candidate, for example in proof of concept, dose finding or inlicensing. In this context, our objective is to build comprehensive literature-based databases on selected indications and their major treatments, containing longitudinal data and covariates to facilitate dynamic modeling.

Methods: Motivated by a case example in Rheumatoid Arthritis, we present the range of applications to date, and a new generic database infrastructure that was developed to further ramp up these efforts.

Results: Eight drug-disease databases have been built, and two are in development. The range of successful applications spans from dose selection to supporting Go/Nogo milestones. The generic database solution has an easy-to-use front end and allows quick extraction of relevant information, while still retaining the full complexity of a relational database in the background.

Conclusions: Great value can be derived from investing time and effort into building literature-based drug-disease databases.

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Nieves Velez de Mendizabal I-46 A Population PK Model For Citalopram And Its Major Metabolite, N-desmethyl Citalopram, In Rats

Nieves Velez de Mendizabal (1, 2), Kimberley Jackson (3), Brian Eastwood (4), Steven Swanson (5), David M. Bender (5), Stephen Lowe (6), Robert R. Bies (1, 2)

(1) Indiana Clinical and Translational Sciences Institute (CTSI), Indianapolis, IN, USA; (2) Department of Medicine, Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, USA; (3) Global PK/PD/Trial Simulation, Eli Lilly and Company, Windlesham UK; (4) Global Statistical Sciences, Eli Lilly and Company, Windlesham UK; (5) Lilly Corporate Center, Eli Lilly and Company, Indianapolis, Indiana, USA; (6) Lilly-NUS Centre for Clinical Pharmacology, Eli Lilly and Company, Singapore, Singapore

Objectives: To develop a population PK model able to simultaneously describe citalopram and N-desmethyl citalopram plasma concentrations in rats after IV and PO administration of citalopram.

Methods: Citalopram was administered intravenously (IV) and orally (PO) to Sprague-Dawley rats (mean weight: 285 grams) at different doses: 0.3, 1, 3, and 10-mg/kg IV and 10-mg/kg PO. Plasma samples were collected for citalopram and N-desmethyl citalopram. Data below the limit of quantification BLQ were reported for both compounds at 0.1 ng/mL. All analyses were performed by using NONMEM 7.2 software. BLQ values were included in the analyses and treated as censored information using the M3 method [1]. The Laplacian numerical estimation method was used for parameter estimation. Citalopram and its metabolite were simultaneously modeled for all doses and administration routes. The model was then extended to Wistar rats (mean weight: 497 grams) at different oral doses: 0.3, 1, 3, 10, 30 and 60-mg/kg. Several absorption models were explored (e.g.

first, zero order and combined absorptions, Michaelis-Menten, lag time) in combination with dose and/or time covariate effects.

Results: Disposition of citalopram and of its major metabolite was described by a 5-compartment model: a 3-compartment model for citalopram and a 2-compartment for the metabolite. Citalopram clearance and metabolite formation rate were adequately described as linear processes. Metabolite clearance was best described using a Michaelis-Menten clearance. When the Wistar data were included (over a large range of oral doses), the absorption process revealed its complexity.

Conclusions: As far as we are aware, this is the first combined citalopram and metabolite population PK model to describe IV as well as oral data in rats in the literature. A complex absorption model was required to adequately describe the disposition of citalopram and N-desmethyl citalopram over the large dose range studied herein.

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An Vermeulen I-47 Population Pharmacokinetic Analysis of Canagliflozin, an Orally Active Inhibitor of Sodium-Glucose Co-Transporter 2 (SGLT2) for the Treatment of Patients With Type 2 Diabetes Mellitus (T2DM)

E. Hoeben (1), W. De Winter (1), M. Neyens (1), A. Vermeulen (1) and D. Devineni (2)
(1) Janssen Research and Development, Model Based Drug Development, Turnhoutseweg 30, B-2340 Beerse, Belgium; (2) Janssen Research and Development, Clinical Pharmacology, 920 Route 202, Raritan, New Jersey, USA

Objectives: Canagliflozin, an orally active inhibitor of SGLT2, is currently in development for the treatment of patients with T2DM. The objective of this analysis was to develop a population pharmacokinetic (PK) model, including relevant covariates as source of inter-individual variability (IIV), with the aim to describe Phase 1, 2 and 3 PK data of canagliflozin in healthy subjects and in patients with T2DM.

Methods: Data were obtained from 1616 subjects enrolled in 9 Phase 1, 2 Phase 2 and 3 Phase 3 trials. Nonlinear mixed effects modeling of pooled data was conducted using NONMEM®[1.2]. IIV was evaluated using an exponential error model and residual error described using an additive model in the log domain. The FOCE method with interaction was applied and the model was parameterized in terms of rate constants. Covariate effects were explored graphically on empirical Bayes estimates of PK parameters, as shrinkage was low. Clinical relevance of statistically significant covariates on model parameters was evaluated. The model was evaluated internally (visual and numerical predictive check) and externally (bias and precision)[3].

Results: The population PK model was first developed using richly sampled Phase 1 data. Gender, age and WT on V_c/F, BMI on k_a and BMI and over-encapsulation on T_{lag} were identified as the most significant covariates affecting the absorption and distribution characteristics of canagliflozin. The absorption and distribution parameters from the final Phase 1 model, including their covariate and random effects, were fixed and the model was re-run on a combined Phase 1, 2 and 3 dataset. A two-compartment PK model with lag-time and sequential zero- and first order absorption was found to provide an adequate description of the observed study data. Further covariate evaluation on k_e, estimated in the final model, demonstrated that eGFR, dose and genetic polymorphism (carriers of UGT1A9*3 allele) were statistically significant. The model passed internal and external evaluation and was considered valid from an accuracy and precision point of view.

Conclusions: The developed population model successfully described the PK of canagliflozin in healthy subjects and in patients with T2DM. Although the effects of gender, age and WT on V_c/F and eGFR, dose and genetic polymorphism on k_e were statistically significant, given the small magnitude of these effects, they were considered not to be of clinical relevance.

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Marie Vigan I-48 Modelling the evolution of two biomarkers in Gaucher patients receiving enzyme replacement therapy.

M. Vigan(1), J. Stirnemann(2,3), C. Caillaud (2,4), R. Froissart (5), A. Boutten (6), B. Fantin (7), N. Belmatoug (2,7), F. Mentré(1)
(1) INSERM, UMR 738, Univ Paris Diderot, Sorbonne Paris Cité, Paris, France; (2) Referral Center for Lysosomal Diseases, Paris, France; (3) Division of General Internal Medicine, Faculty of Medicine, Geneva University Hospital, Geneva, Switzerland; (4) Laboratoire de Biochimie, Hôpital Cochin, Paris, France; (5) Laboratory of Inborn Errors of Metabolism, Hospices Civils de Lyon, Bron, France; (6) Laboratoire de Biochimie A, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, 46 rue Henri Huchard, 75018 Paris, France; (7) Service de Médecine Interne, Hôpital Beaujon, AP–HP, Clichy, France.

Objectives: Gaucher disease (GD) [1] is a rare recessively inherited disorder due to the deficiency of lysosomal enzyme glucocerebrosidase. Several biomarkers are significantly increased during this disease, such as ferritin and chitotriosidase. GD can be treated by enzyme replacement therapy (ERT), imi/al-glucerase, but no physiological model was proposed to analyse the evolution of biomarkers during ERT [2,3]. The aim of this study was to develop a drug-disease model explaining the response of biomarkers to ERT and to analyse the influence of several covariates.

Methods: We analysed patients from the French Registry of GD [4] who were treated by ERT (N=238). The accumulation of glucosylceramide in their macrophages leads to an increased production of ferritin and chitotriosidase. Therefore, we modelled that ERT participates in the decrease of these biomarkers and, neglecting their half-life, the turnover models were simplified to exponential drug-disease models. We analysed separately the evolution of both biomarkers using all measurements since initiation of ERT to stop of ERT (more than 6 months) or end of follow-up. Several covariates

were tested including age at initiation of ERT, splenectomy and sex. Estimations were performed with MONOLIX 4.2.0 [5].

Results: Median time of follow-up during ERT was 9 [1-19] years. Median age at the initiation of ERT was 22 [1-67] years (18%<0.001).

Conclusions: This is the first study of the evolution of biomarkers in GD by a dynamic model. It will be further extended by modelling jointly the two biomarkers and by studying the link with repeated bone events [4].

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Paul Vigneaux I-49 Extending Monolix to use models with Partial Differential Equations

Paul Vigneaux (1), Violaine Louvet (2), Emmanuel Grenier (1)
(1)ENS de LYON & INRIA Numed ; (2) Université de LYON & INRIA Numed

Objectives: To develop a methodology able to include models made of Partial Differential Equations (PDE), instead of Ordinary Differential Equations (ODE), in SAEM algorithms like the one used by the Monolix Software[1].

Methods: We design a general methodology to make parameters estimation within the Monolix software, for models involving PDE (see [2]). Indeed, Monolix is known to be a very efficient tool but, up to now, it is only able to work with models made of ODE (see e.g. [3]). In particular, this means that spatial effects can not be included in the associated dynamical models (only the time is included). The idea is (i) to translate to PDE model in terms of times series, by spatial integration and (ii) to build a computational time decreasing algorithm. This can be applied generically to a broad range of PDEs. As a specific illustration, we here present the application of our method to the Kolmogorov-Petrovsky-Piskounov (KPP) PDE which is the canonical model for reaction-diffusion phenomena[4]. We build a noisy population of individuals in silico. Monolix was used to estimate the population and individual parameters. Namely, these parameters were : the reaction and diffusion coefficients and the location of the initial condition of the model.

Results: The method correctly predicted the individual parameters, including the initial condition locations, a parameter typically associated with the spatial effects of the underlying model (KPP). Furthermore the total computational cost of the Monolix run to make the parameters estimation is of the same order as for an ODE model, namely in less than 30 minutes. This

is a significant achievement since without our time deacreasing algorithm this total computational time is around 23 days.

Conclusions: To our knowledge, this is the first time that parameters estimation with a population approach, a Stochastic Approximation Expectation Maximization algorithm as used in Monolix, is performed with a PDE model. The method is precise and computationally efficient: it can open the path to the use of numerous new types of models and applications in population approaches.

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Winnie Vogt I-50 Paediatric PBPK drug-disease modelling and simulation towards optimisation of drug therapy: an example of milrinone for the treatment and prevention of low cardiac output syndrome in paediatric patients after open heart surgery

Winnie Vogt
Dept. of Clinical Pharmacy and Pharmacotherapy, Heinrich-Heine-Universität Düsseldorf, Germany

Objectives: There is an undisputable need for improving paediatrics' access to safe and effective drug therapy. Thus, regulatory agencies have fostered the increased use of modelling and simulation to minimise the burden of clinical trials and maximise the use of existing information [1,2]. In this scope, physiology-based pharmacokinetic (PBPK) modelling and simulation could be an appropriate tool, especially for treatment indications where bridging of pharmacokinetics from adults to paediatrics is limited due to differences in disease and outcome. This is the case for low cardiac output syndrome (LCOS), which determines morbidity and mortality after open heart surgery for congenital cardiac lesion in paediatric patients [3]. Although drugs are an essential component to treat and prevent paediatric LCOS, limited prescribing guidance hampers the appropriate use of drugs with the inherent risk of increased patient harm and/or lack of efficacy. This also applies to milrinone, the drug of choice for paediatric LCOS treatment and prevention across Europe [4,5].
Therefore, the objective of the study was to employ a PBPK drug-disease modelling and simulation approach towards the evaluation and optimisation of current milrinone dosing for LCOS treatment and prevention in paediatric patients after open heart surgery. This approach should provide insight into

the capabilities of system-biology modelling as exploratory tool for improving paediatric drug dosing.

Methods: Model development was based on existing workflows for PBPK drug-disease modelling in adults [6–9] and retrograde drug clearance scaling from healthy adults to paediatrics [10–13] but extended by a link between them. This was necessary because retrograde drug clearance scaling from adult to paediatric patients is limited when age- and disease related differences in drug exposure exist. Thus, a bridge was established to link healthy adult volunteers with aged adult patients and paediatric patients by quantifying and attributing the impact of the normal age-related decline of renal and hepatic clearance pathways and disease on drug exposure. Model development and evaluation was done in PK-Sim® and Mobi®, respectively. The first step of model building involved the development of the adult PBPK drug model for intravenously administered milrinone by incorporating physico-chemical input parameters (logP, fu, Mw, pKA/B) as well as hepatic and renal clearance values for milrinone from healthy male adult volunteers taken from literature. In addition, urinary excretion data of milrinone in patients with renal impairment and healthy adult volunteers were merged to quantify the effect of renal impairment on milrinone's fraction excreted unchanged in urine. This regulator component was also introduced into the model together with a dose-response relationship of milrinone on blood flow. The second step of model development proceeded with a literature search on pre- and postoperative organ function values in adult patients with (treatment) or without (prevention) LCOS after open heart surgery, which were integrated in a disease model as factorial changes from the reference values in young healthy adults. The disease model was integrated in the drug model to describe the altered pharmacokinetics in diseased adults. At last, the PBPK drug-disease model for adult patients was adapted to paediatric patients and primarily based on clinical and experimental disease data in paediatrics. Each step of model development was evaluated against historical datasets for which 1000 virtual individuals were replicated to reflect (patho-)physiological variability of the study cohorts but also to incorporate variability of the physico-chemical input parameters. Model robustness was assessed by parametric sensitivity analysis.
Following successful model evaluation, the PBPK drug-disease model was used to evaluate current milrinone dosing for LCOS treatment [14] and

prevention [4,15] in paediatrics towards achieving the therapeutic target range of 100-300 ng/ml milrinone in plasma. For this, virtual paediatric patient populations were created each with 1000 subjects and reflecting the average paediatric patient characteristics with regard to gender and degree of malnutrition from neonatal to adolescent age. The populations were integrated in Mobi and used to run the PBPK drug-disease model. Optimised dosing regimens were subsequently developed.

Results: A population based PBPK drug model for milrinone was developed and linked with a LCOS disease model for adult and paediatric patients, which constituted disease characteristic key parameter changes, such as haematocrit, albumin abundance, cardiac output and organ blood flows as well as hepatic and renal drug clearances. The model accurately described the pharmacokinetics of milrinone for healthy and diseased, different dosing regimens, ethnicities and age groups: observed versus predicted plasma concentration profiles of milrinone were compared with an average fold error of 1.1±0.1 (mean±SD) and mean relative deviation of 1.5±0.3 as measures of bias and precision, respectively. In addition, observed versus predicted total plasma clearance and volume of distribution deviated by 1.1±0.1 and 1.2±0.2 fold errors, respectively. Normalised maximum sensitivity coefficients for model input parameters ranged from -0.84 to 0.71 indicating the robustness of the model.
The evaluation of milrinone dosing across different paediatric age groups showed that none of the currently used dosing regimens for milrinone achieved the therapeutic target range across all paediatric age groups. Optimised dosing regimens were subsequently developed that considered the age-dependent and (patho-)physiological differences.

Conclusions: The herein presented approach demonstrates the feasibility and transferability of paediatric PBPK drug-disease modelling and provides evidence on its capabilities as exploratory tool for improving paediatric drug dosing. The selected disease, LCOS, presents an example with marked differences in drug exposure due to age and disease, which is also commonly observed for other cardiovascular, hepatic and renal diseases. PBPK drug-disease modelling helped attributing these differences and optimising dosing strategies for paediatric patients. Nonetheless, model development also highlighted current weaknesses of PBPK drug-disease modelling, driven by

the incomplete understanding of disease on body function and drug exposure. Future research needs to narrow these gaps, which may ultimately lead to improved *a-priori* prediction of drug exposure in paediatric patients and limit the burden of clinical trials.

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Max von Kleist I-51 Systems Pharmacology of Chain-Terminating Nucleoside Analogs

Sulav Duwal (1), Kaveh Pouran Yousef (1), Roland Marquet (2), Max von Kleist (1)

(1) Dep. of Mathematics and Computer Science, Freie Universität Berlin, Germany, (2) Architecture et Réactivité de l'ARN, Université de Strasbourg, CNRS, IBMC, Strasbourg, France

Objectives: Nucleoside analogs (NAs) are an important drug class for the treatment of viral infections (HBV, HCV, HSV and HIV) and cancer. They are administered as pro-drugs, which, after intracellular phosphorylation, compete with endogenous nucleotides (dNTP/NTP) for incorporation into nascent DNA/RNA. Incorporated NAs prevent subsequent primer extension by chain termination, which ultimately inhibits replication/proliferation. Plasma- and effect-site pharmacokinetics are usually asynchronous and cell-specific for this inhibitor class, which is also true for the pharmaco-/toxicodynamics, due to their mechanism of action [1,2]. Within this project, we elucidated pharmacokinetic- as well as pharmacodynamic limitations through an integrative systems' pharmacology modelling approach, which we validated by HIV-1 enzyme kinetics, drug resistance mechanisms and in vivo dynamics following drug application.

Methods: We formulated the underlying dose-response relation of NAs in terms of a mean first-hitting-time model, which could be solved analytically to derive a mechanistic expression for the IC50 value, revealing kinetic, as well as cell-specific parameters of drug efficacy [3]. We used reverse transcriptase kinetic data from known drug resistance patterns in HIV-1 to elucidate the validity of the model. Pharmacokinetic models for prototypic HIV-1 NA inhibitors (NRTIs) were derived to predict clinical effects for this inhibitor class [4].

Results: Our derived model of NA inhibition revealed kinetic, as well as cell-specific parameters of drug efficacy [3]. Kinetic changes induced by drug resistance mutations in HIV-1 made perfect sense in the light of the developed model, which considered their interaction in distinct cellular environments. The pharmacodynamic model revealed that drug inhibition by NAs depended on endogeneous substrate concentrations, as well as concentrations of co-substrates, leading to heterogeneous inhibition and toxicodynamics in distinct target cells/cellular activation states. Plasma- and cellular pharmacokinetics of prototypic HIV-1 inhibitors were then used to predict viral dynamics following drug application in agreement with clinical [4] and ex vivo data [5].

Conclusions: The presented approach allows combining bottom-up and top-down approaches to quantify and elucidate mechanisms of NA drug efficacy. This allows for a more complete picture of drug-interference on the molecular, cellular and whole body level that can be highly useful for drug design.

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Camille Vong I-52 Semi-mechanistic PKPD model of thrombocytopenia characterizing the effect of a new histone deacetylase inhibitor (HDACi) in development, in co-administration with doxorubicin.

C. Vong (1,2), Q. Chalret du Rieu (2), S. Fouliard (2), E. Roger (3), I. Kloos (3), S. Depil (3), M. Chenel (2), LE. Friberg (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (2) Clinical Pharmacokinetic department and (3) Oncology business Unit, Institut de Recherches Internationales Servier, Suresnes, France

Objectives: Recent studies [1, 2] demonstrated that the combination of an HDAC inhibitor and DNA-damaging agents has synergistic effects to induce apoptosis. This observation is of potential clinical applicability although several dose-limiting toxicities need to be pre-assessed before dose optimization. The aim was to develop a PKPD model of thrombocytopenia to assess the combined effects of an HDACi in development and the cytotoxic agent doxorubicin on circulating platelets.

Methods: 8 patients suffering from solid tumors received six 4-week cycles administration of oral twice-daily doses of HDACi given 4 hours apart and a fixed 15 minutes IV-infusion dose of doxorubicin, in a 3 out of 4 week regimen in an ongoing phase I dose-escalation study. 230 and 160 PK samples for HDACi and doxorubicin respectively, and 202 platelet counts were analyzed with FOCE-I in NONMEM 7.2. A PK model previously developed using internal data to describe HDACi's disposition and a literature PK model [3] characterizing the time course of doxorubin and its metabolite doxorubicinol were used in a sequential modeling approach, where individual Bayesian estimates of PK parameters were fixed in subsequent PD modeling. A semi-physiological model incorporating stem cell proliferation inhibition

drug effect from HDACi [4] and structurally similar to the myelosuppression model described by Friberg et al. [5, 6] was further refined and the effect of doxorubicin was added. Patient baseline characteristics were modeled using the B2 method [7].

Results: An Emax and a power models describing respectively HDACi and doxorubicin for the drug effect on the proliferative cells were found to best characterize the platelet data. Incorporation of an interaction between the two drugs (INT), implemented in the concentration-effect model as Eff(HDACi) + Eff(DOXO) + INT x Eff(HDACi) x Eff(DOXO) was found not significant. A mean transit time through the chain of non-proliferative cells of 104 hours, a feedback parameter of 0.239 and a platelet baseline value of 277×10^9 /L were estimated. Model evaluation using Visual Prediction checks showed that the resulting PKPD model adequately described the 80% PI of the data.

Conclusions: A PKPD model was developed that integrated the PK of HDACi and doxorubicin to describe their combined effects on the time-course of platelets. The thrombocytopenic effects were adequately predicted assuming an additive effect between the two drugs on the proliferative cells. Future refinements of the model are expected with additional dosing regimen data.

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Katarina Vučićević I-53 Total plasma protein and haematocrit influence on tacrolimus clearance in kidney transplant patients - population pharmacokinetic approach

B. Golubović (1), K. Vučićević (1), D. Radivojević (2), S. Vezmar Kovačević (1), M. Prostran (3), B. Miljković (1)
(1) Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade, Serbia; (2) Nephrology Clinic, Clinical Centre of Serbia, University of Belgrade, Serbia; (3) Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Serbia

Objectives: Tacrolimus is a low-clearance drug extensively bound to erythrocytes and highly protein bound. The aim of the study was to investigate the influence of haematocrit and total plasma protein on tacrolimus (TAC) clearance (CL/F).

Methods: A total of 1999 measured trough concentration were obtained from routine therapeutic monitoring of 105 kidney transplant patients. TAC was administered two times daily as part of triple immunosuppressive therapy. Pharmacokinetic analysis was performed using a non-linear mixed-effects modelling program NONMEM® (version 7 level 2) and Perl speaks NONMEM (version 3.5.3). An one-compartment model with first-order absorption and first-order elimination as implemented in ADVAN2/TRANS2 subroutine was used to fit the concentration-time data. Based on literature data volume of distribution and absorption rate constants were fixed at 0.68 l/kg and 1.3 h-1, respectively. FOCEI was used for parameter estimation. Internal validation was performed.

Results: Interindividual variability of TAC CL/F was best described by the exponential error model, while an additive error model most adequately

characterized residual variability in TAC concentrations. In the final model, mean interindividual coefficient of variability for CL/F was 15.2% and residual variability was 4.07 ng/ml. The estimate of CL/F for a typical patient was 10.02 l/h. TAC CL/F was significantly ($p < 0.001$) influenced by haematocrit and total protein. In the forward modelling building step inclusion of haematocrit and total protein produced decrease in OFV by 275.3 and 26.68, since omission of these covariates in the backward modelling building step induce increment in OFV by 76.93 and 15.35. According to our model, CL/F decreased with haematocrit. This study demonstrated incensement for 10.4% in tacrolimus CL/F with alteration of patients' minimal measured total protein levels to upper normal range.

Conclusions: The study described and quantified the effect of haematocrit and plasma proteins on tacrolimus clearance. The final model demonstrates the feasibility of estimation of individual tacrolimus clearance based on sparse TDM data.

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Bing Wang I-54 Population pharmacokinetics and pharmacodynamics of benralizumab in healthy volunteers and asthma patients

B. Wang(1), Z. Yao(1), L. Yan(1), W. White(2), H. Kawai(3), C. Ward(4), D. Raible(5), L. Roskos(2)
(1) Clinical Pharmacology & DMPK, MedImmune, Hayward, CA, USA;(2) Clinical Pharmacology & DMPK, MedImmune, Gaithersburg, MD, USA;(3) Clinical Science Department, Kyowa Hakko Kirin Co.,LTD., Tokyo, Japan;(4) Translational Sciences, MedImmune, Gaithersburg, MD, USA; (5) Clinical Development, MedImmune, Gaithersburg, MD, USA

Objectives: To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of benralizumab, an afucosylated human IgG_1 monoclonal antibody direct against interleukin-5 receptor, in healthy volunteers and asthma patients using a population approach.

Methods: Pharmacokinetic and blood eosinophil count data from two healthy volunteer studies (n=48, Japan) and four studies in asthma patients (n=141, North America) were pooled and simultaneously modeled in this meta-analysis. To reduce the parameter estimation bias the PHI subroutine implemented in NONMEM 7 was used to censor the zero observations. The final model was evaluated using posterior visual predictive check and bootstrapping.

Results: Benralizumab PK was adequately described by a two-compartment model with first-order elimination from the central compartment, and first-order absorption from the dosing site for subcutaneously administered benralizumab. The estimated systemic clearance and volume of distribution were typical for human IgG not subject to the target-mediated clearance (antigen-sink). Only body weight was identified as a relevant PK demographic

covariate. The depletion of blood eosinophil counts was depicted by a modified transit model in which benralizumab induced destruction of eosinophils in each age compartment. A tissue compartment was also incorporated in the model to account for the extravascular eosinophils. Stochastic simulations demonstrated comparable PK exposure and eosinophil suppression in adolescence and adult subjects.

Conclusions: The mechanistic model appropriately described the PK of benralizumab and the depletion of blood eosinophil counts. Results from the meta-analysis facilitated the exposure-response relationship assessment and the selection of appropriate dose and dosing schedule for late-stage clinical studies.

Jixian Wang I-55 Design and analysis of randomized concentration controlled

Jixian Wang and Kai Grosch
Novartis Pharma AG, Basel, Switzerland

Objectives: To examine confounding biases in the estimation of dose-PK and PKPD relationships in randomized concentration controlled (RCC) trials with different design and analysis approaches using.

Methods: We propose using instrumental variables (IV) [1, 2, 3] for estimation of parameters in PKPD and dose-exposure models to eliminate or reduce confounding biases for RCC trials. Performance of a number of approaches including the IV approach with different designs for RCC trials were examined from theoretical aspects and via simulations. An approach to detect confounding bias based the IV approach in combination with bootstrap was also proposed.

Results: Simulations showed that in general the IV approach can eliminate confounding bias for both RCC trials but it is less robust to confounded treatment heterogeneity. A good trial design of is the key to ensure high performance of the IV approach. With the bootstrap approach, confounding bias can also be detected even when the number of exposure ranges is very low (e.g. 2). The IV approach is less efficient than the simultaneous modeling approach but it is based on much weaker assumptions, hence provides a robust alternative to it. The IV estimate for the dose-proportionality parameter had almost no bias when the trial is well designed.

Conclusion: Using randomized exposure range as IV can eliminate the confounding bias for a well-designed RCC trial. Issues and approaches for causal effect determination with response dependent dose adjustment [4]

should be examined carefully when using RCC trials to analyze PKPD relationships.

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Franziska Weber I-56 A linear mixed effect model describing the expression of peroxisomal ABCD transporters in CD34+ stem cell-derived immune cells of X-linked Adrenoleukodystrophy and control populations

Franziska Weber, Sonja Forss-Petter, Johannes Berger, Willi Weber
Center for Brain Research, Medical University of Vienna, Austria

Objectives: X-linked Adrenoleukodystrophy (X-ALD) is a fatal neurodegenerative disorder with inflammatory demyelination of the brain caused by mutations in the *ABCD1* gene, a member of the peroxisomal ABCD transporter family. Currently, the only curative therapies are transplantations of either allogeneic hematopoietic cells or genetically corrected autologous CD34+ stem cells, implicating the importance of CD34+ stem cell-derived immune cells in the arrest of brain inflammation. We compared mRNA levels of peroxisomal ABCD transporters between these immune cells of 5 X-ALD patients and 5 controls.

Methods: Immune cells from blood samples were isolated by magnetic activated cell sorting. Quantitative PCR was used to determine mRNA levels of the ABCD transporters. RNA was reverse transcribed into cDNA. A DNA-binding dye, SYBRgreen, intercalates into double-stranded DNA, emitting fluorescence. The fluorescence intensity increases proportionally to the cDNA copies produced during each PCR cycle. The slope of the fluorescence curve mirrors the growth rate of the cDNA copies. The proportionality factor is determined by measuring DNA standards of known copy numbers, allowing cDNA concentrations to be quantified [1]. A linear mixed effect (lme) model was used with the mRNA copies as dependent variable and two predictor variables, a gene factor (HPRT, ABCD1/2/3) and a population factor (X-ALD, control). Using the lme function from the nlme R-package [2] with the

treatment option, we obtained mean values of ABCD1/2/3 mRNA normalized to the housekeeping gene HPRT of the control population and their difference to the X-ALD population.

Results: The three ABCD transporters were differentially expressed in CD34+ derived cells of controls: ABCD1 and ABCD2 mRNA were inversely expressed in all cell types, whereas ABCD3 was equally distributed. Monocytes show high levels of ABCD1, the ABCD2 mRNA is barely detectable. In contrast, T cells express high levels of ABCD2 and moderate levels of ABCD1. ABCD2, closest homolog of ABCD1 could be expected to compensate for the ABCD1 deficiency in X-ALD. However, no differences were found in the expression pattern of ABCD2 in X-ALD.

Conclusions: We propose that the beneficial effect of the transplantations may rely on the replacement of those cells lacking sufficient ABCD2 expression in ABCD1 deficiency. Mixed effect modelling was an effective tool to compare mRNA expression between different cells of a target and a control population.

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Sebastian Weber I-57 Nephrotoxicity of tacrolimus in liver transplantation

Sebastian Weber, Michael Looby, Thomas Dumortier
Modeling & Simulation, Novartis Pharma

Objectives*:* The immunosuppresive drug tacrolimus (TAC) is key to prevent organ rejection in patients post liver transplantation. However, a severe side effect of TAC is nephrotoxicity. Clinically it is known that the impairment of the renal function is both acute and chronic [1,2]. The main objectives of this work are to establish (i) a model describing kidney degradation and (ii) evaluate acute and chronic progression.

Methods*:* From the study [3] a total of N=695 patients were included in the analysis data set out of which 454 were monitored the first 30 days post transplantation and the remaining 241 patients up to 2 years. Due to the high variability of TAC trough concentrations, bid oral dosing was continuously monitored and adapted by physicians. The target regimen was 8-12 ng/mL for the first 4 months and was reduced to 6-10 ng/mL thereafter. Glomerular filtration rate (GFR) based on creatinine clearance was used as a surrogate for kidney function. The PK/PD model was developed using FOCE in NONMEM 7.2.

Results*:* The PK was adequately described by a one-compartment model (similar to [4]) with linear elimination and included a dose-adjusted relative bioavailability. The link between the PK and the PD was modeled with an effect compartment (EC). Kidney degradation (GFR) was modeled by a four parametric logistic function with dependence on the EC concentration. The PK and PD data showed large between subject variability, i.e. a CV of 38.5% for TAC trough and 39.8% for GFR on day 30 post transplant. The model for acute impairment used the log-concentration of the EC to drive GFR

response. Overall the model described the data adequately, but most parameter estimates showed considerable uncertainty, i.e. a CV of 30%. To account for a chronic TAC effect on kidney degradation, the logarithm of the AUC of the EC concentration was added to the acute model. This combined model of acute and chronic effects provided a minor improvement in the objective function value (p-value of 1% for a LRT), but uncertainty in model parameter estimates was increased.

Conclusions*:* We have implemented a PK/PD model, which describes the time-course of TAC effect on GFR. Given the extensive noise present in these measurements, a discrimination between acute and chronic contributions to nephrotoxic kidney degradation was not possible. While the large uncertainties can limit the applicability of the model, the established PK/PD model will be valuable to plan future studies with TAC treatment as reference therapy.

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Mélanie Wilbaux I-58 A drug-independent model predicting Progression-Free Survival to support early drug development in recurrent ovarian cancer

Mélanie Wilbaux (1), Emilie Hénin (1), Olivier Colomban (1), Amit Oza (2), Eric Pujade-Lauraine (3), Gilles Freyer (1,4), Benoit You (1,4) , Michel Tod (1)
(1) EMR 3738, Ciblage Thérapeutique en Oncologie, Faculté de Médecine et de Maïeutique Lyon-Sud Charles Mérieux, Université Claude Bernard, Oullins, France ; Université de Lyon, Lyon, France, (2) Department of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, Toronto, Ontario, Canada, (3) Hôpital Hôtel Dieu, Place du Parvis Notre-Dame, 75004 Paris, France, (4) Service d'Oncologie Médicale, Investigational Center for Treatments in Oncology and Hematology of Lyon, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, F-69310, Pierre-Bénite, France

Objectives: Early prediction of the expected benefit, based on change in CA125 change, in treated patient with recurrent ovarian cancer (ROC) may help for early selection of the best drug candidates during drug development. The aim of the present study was to quantify and to validate the links between CA125 kinetics and Progression-Free Survival (PFS) in ROC patients.

Methods: Patients from the CALYPSO randomized phase III trial, comparing 2 platinum-based regimens in ROC patients were considered. The cohort was randomly split into a "learning dataset" (N=356) to estimate model parameters and a "validation dataset" (N=178) to validate model performances. Screening for consistent significant factors was performed using Kaplan-Meier plots and semi-parametric Cox regression analyses. A K-PD semi-mechanistic joint model for tumor size and CA125 [1] was used to estimate their values at week 6. Fractional changes in CA125 (ΔCA125) and in tumor size (ΔTS) from baseline at week 6 were then calculated. A full

parametric survival model was developed to quantify the links between ΔCA125, ΔTS, significant prognostic factors and PFS. This model was reduced in 2 separate models to compare the predictive ability of ΔTS versus ΔCA125 on PFS. The respective predictive performances were evaluated through simulations on the validation dataset.

Results: PFS from 534 ROC patients were properly characterized by a parametric model with log-logistic distribution. The factors significantly linked to PFS in the full parametric model were ΔCA125, ΔTS, baseline CA125 ($CA125_{BL}$) and therapy-free interval. By reducing this model, according to the Akaike criterion, $\Delta CA125+CA125_{BL}$ was a better predictor of PFS than ΔTS. Simulations confirmed the predictive performance of this model. Patients should achieve at least 49% ΔCA125 decline during the first 6 weeks of treatment to observe 50% PFS improvement. This effect was independent of treatment arm. On the basis of individual ΔCA125, patients could be categorized across 2 groups: responder and non-responder.

Conclusion: This is the first drug-independent parametric survival model quantifying links between PFS and CA125 kinetics in ROC. The modeled CA125 decline required to observe a 50% improvement in PFS in treated ROC patients was defined. It may be a surrogate marker of the expected gain in PFS, and may embody an early predictive tool for go/no go drug development decisions.

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Dan Wright I-59 Bayesian dose individualisation provides good control of warfarin dosing.

Daniel F.B. Wright (1), Stephen B. Duffull (1)
(1) School of Pharmacy, University of Otago, Dunedin, New Zealand

Objectives: Warfarin is a difficult drug to dose accurately and safely due to large inter-individual variability in dose requirements. Current dosing strategies achieve INRs within the therapeutic range only 40-65% of the time [1,2]. Bayesian forecasting methods have the potential to improve INR control. The aims of this study were (1) to assess the predictive performance of a Bayesian dosing method for warfarin implemented in TCIWorks, and, (2) to determine the expected 'time in the therapeutic range' (TTR) of INRs predicted using TCIWorks.

Methods: Patients who were initiating warfarin therapy were prospectively recruited from Dunedin Hospital, Dunedin, New Zealand. Warfarin doses were entered into TCIWorks from the first day of therapy until a stable steady-state INR was achieved. The KPD model developed by Hamburg et al was used as the prior model [3]. The Bayesian method was used to predict steady-state INRs (INRss); (1) under the prior model, .i.e. without using any observed INR values to individualise parameters, then, (2) by incorporating the first measured INR value, i.e. the posterior prediction of INRss based on 1 INR value, then, (3) by incorporating the first and second measured INR values, i.e. the posterior prediction of INRss based on the first 2 INR values (4) and then by sequentially including additional measured INR values. Observed and predicted INRss values were compared using measures of bias (mean prediction error [MPE]) and imprecision (root mean square error [RMSE]) [4]. The TTR was determined by calculating the percentage of predicted INRss values between 2 and 3

Results: A total of 55 patients completed the study. The prior model was positively biased (MPE 0.52 [95% CI 0.30, 0.73]) with an RMSE of 0.96. The bias became non-significant (MPE -0.09 [95% CI -0.23, 0.05]) and imprecision improved (RMSE <0.54) once 3 or more INR values were entered into TCIWorks. Based on the level of imprecision in the prediction of INRss, the Bayesian dosing method was able to predict the INRss within the therapeutic range 65% of the time when 3 INR values were included and 70-80% of the time with 4-6 INR values.

Conclusions: The Bayesian warfarin dosing method produced accurate and precise steady-state INR predictions after the inclusion of 3 or more INR values. The expected TTR of 65-80% is a substantial improvement in INR control compared to current dosing methods. Further evaluation of this method in the clinic is warranted.

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Klintean Wunnapuk I-60 Population analysis of paraquat toxicokinetics in poisoning patients

Klintean Wunnapuk (1,2) , Fahim Mohammed (3,4,5), Indika Gawarammana (3,4,5), Xin Liu (1), Roger K. Verbeeck (6,7), Nicholas A. Buckley (5,8,9), Michael S. Roberts (1,10), Flora T. Musuamba (6)
(1) Therapeutics Research Centre, School of Medicine, University of Queensland, Brisbane, QLD, Australia (2) Department of Forensic Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (3) Department of Pharmacology, Faculty of Medicine, University of Ruhuna, Sri Lanka. (4) Department of Medicine, Faculty of Medicine, University of Peradeniya, Sri Lanka (5) South Asian Clinical Toxicology Research Collaboration, Faculty of Medicine, University of Peradeniya, Sri Lanka (6) Louvain Drug Research Institute, Louvain Centre for Toxicology and Applied Pharmacology, Catholic University of Louvain, Brussels, Belgium (7) Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa (8) Australian National University, Canberra, Australia (9) Professorial Medicine Unit, University of New South Wales, NSW, Australia (10) School of Pharmacy & Medical Science, University of South Australia, Adelaide, SA, Australia

Objectives: Paraquat (PQ) is a commonly used herbicide that has caused many accidental or intentional deaths. Only a few studies have been done on PQ toxicokinetics (TK) in humans (1, 2). In this study a population TK analysis was performed to estimate the typical TK parameters and interindividual variability of PQ distribution in intoxicated patients. Potential covariates were explored as well.

Methods: A TK model for PQ was developed using Phoenix NLME version 1.2. PQ plasma concentrations from 78 poisoning patients were used in the analysis. A two-compartmental TK model with first-order absorption and first-order elimination was fit to the data when choosing the basic structural

model. The model was parameterized with apparent oral clearance (CLPQ/F), apparent volume of distribution of central compartment (V1/F), apparent volume of distribution of peripheral compartment (V2/F), inter-compartmental clearance (Q/F), absorption rate constant (Ka) and bioavailability factor (XF). Stepwise approach was used for TK covariate model building with forward inclusion followed by backward exclusion. The following covariates were assessed for their effects on PQ disposition: body weight (BW, kg), amount of ingestion (g) and renal function markers: serum creatinine concentration (sCr, mg/dL) and estimated creatinine clearance (eCLcr, L/h).

Results: As the ingested dose was estimated from volume of ingestion, the varying doses were imputed as covariates on the bioavailability factor and the median dose of PQ (10 g) was given as the amount administered to each patient. The typical value of Ka and V2/F were fixed to 1/h and 86 L, respectively. The typical CLPQ/F was 0.15 L/h (31%CV) and V1/F was 13.63 L (16%CV). The proportional and additive residual errors were 48% (39%) and 0.89 µg/L, respectively. The visual predictive check showed that approximately 95% of the observed data appear to fall within the 95% confidence interval indicating the accuracy of the model. Bayesian estimations of CLPQ/F and V1/F were 1.17 L/h and 0.33 L, respectively.

Conclusions: This TK model was well characterised PQ plasma concentration-time profile in patient with renal alteration. Future study are planned to incorporate PD data using renal function as an outcome.

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Rujia Xie I-61 Population PK-QT analysis across Phase I studies for a p38 mitogen activated protein kinase inhibitor – PH-797804

Rujia Xie (1), Jakob Ribbing (2), Peter Milligan (3), Lutz Harnisch (3), Grant Langdon (4)
(1) Clinical Pharmacology & Pharmacometrics, Pfizer (China) R&D, China, (2) Pharmacometrics, Pfizer, Sweden, (3) Pharmacometrics, Pfizer Inc, UK, (4) PTx Solution Ltd. UK

Objectives: The purpose of this analysis was to develop a PK-QT model describing the time-course of QTc interval prolongation following dosing with PH-797804 in healthy volunteers, and aid in dose selection for a thorough QT study.

Methods: Six Phase I studies were included in the analysis with a total of 129 subjects receiving single or multiple oral doses of PH-797804 (range 0.3-60 mg) or placebo. Generally, 3 replicate 12-lead ECG were recorded at each time point. PK-QT analysis was conducted in four steps: 1) nonparametric PK modeling, 2) PK-RR interval analysis; 3) evaluating correction methods using baseline QT data; 4) PK-QTc analysis. QT-triplicate correlation was accounted in residual by using the L2 option in NONMEM. The final PK-QTc model was utilized for trial simulations.

Results: PH-797804 concentrations at QT time points were well predicted by the linear interpolation method. In the RR interval modeling, a negative linear concentration-effect relation was found but 95%CI based on bootstrap included a zero slope; indicating that there was no significant effect on the RR interval.

Five correction methods were evaluated: QTcB, QTcF, QTcP (population), QTcS (study) and QTcI (individual). A model with individual correction and an extra study correction factor for two studies was the best (QTcIS), minimizing any trend between QT and RR interval. All QT data including active treatment and placebo were sufficiently corrected using this method and QTcIS was therefore selected as the dependent variable in developing the concentration effect model.

A step log-linear concentration effect model was the final drug effect model for QTcIS, which consisted of: one cosine circadian term; log-linear concentration effect on QTcIS; and gender effect on baseline. The slope was 1.44 [95%CI: 0.93-1.91] and cut-off concentration was 1.27 [95%CI: 0.22-4.36] ng/ml. Female baseline QTcIS was 7.36 ms longer. There were large replicate variability (within replicate ε correlation r=0.32). Trial simulations indicated that the maximum mean double DQTcI would not be greater than 8.5 ms and the upper 95% CI for the mean would not exceed 10 ms at most of time across a range of supratherapeutic doses up to 24mg.

Conclusions: A modified individual correction method was the best approach. The PK-QTcIS model described QTcIS data well and supported dose selection for the planned TQT study.

Shuying Yang I-62 First-order longitudinal population model of FEV1 data: single-trial modeling and meta-analysis

E. Marostica(1), S. Yang(2), A. Russu(1)*, G. De Nicolao(1), S. Zamuner(2), M. Beerahee(2)

*(1) Department of Industrial and Information Engineering, University of Pavia, Pavia, Italy, (2) Clinical Pharmacology Modeling & Simulation, GlaxoSmithKline, Stockley Park, UK, * Current address: Model Based Drug Development, Janssen Research & Development, Beerse, Belgium*

Objectives: Asthma is a complex and multi-factorial disease and the underlying physiopathological mechanism is not completely known. Therefore, empirical models are usually adopted to describe the evolution of the patient's health state. The first objective of this work is to develop a parsimonious population model to describe the time course of placebo response. The clinical response is measured by the Forced Expiratory Volume in the first second (FEV1). The second objective is to perform a model-based meta-analysis, in order to assess differences among studies and to estimate the inter-trial variability.

Methods: Placebo FEV1 longitudinal data from 11 clinical trials in subjects with mild-to-moderate asthma were available. All studies lasted 12 weeks. A parametric first-order response model was developed and identified on each dataset. Based on a single-trial analysis, the proposed model was compared to the linear, polynomial, Inverse Bateman and Weibull-and-Linear models. All the models were implemented in WinBUGS 1.4.3 [1] and compared through the Deviance Information Criterion (DIC). The best model was then adopted to perform a meta-analysis on the 11 datasets together. In the meta-analysis model, each individual parameter was defined as the sum of a term relative to the subject and one relative to the study. For both the single-

trial analysis and the meta-analysis, log-normal distribution was assumed for all the parameters. Graphical outputs were obtained through R 2.13.1 [2].

Results: In the single-trial analysis, the first-order parametric model here proposed yielded the best performance in terms of DIC in most cases. Good individual fittings and Visual Predictive Checks were obtained for all the 11 trials. Hence, meta-analysis was performed. The proposed model yielded good performances also when applied in a meta-analysis context. Moreover, it was found that the inter-individual variability in each study is higher than the inter-trial one (baseline: 24% vs 6%; maximal response: 148% vs 28%; time constant: 906% vs 71%).

Conclusion: A parsimonious parametric model able to describe FEV1 data from different studies in mild-to-moderate asthma was developed. The proposed model performs well both in the single-trial analysis and meta-analysis context. Moreover, the model can be extended by including clinically relevant covariates which may affect the patient's health state. A further work is to assess the model capabilities in predicting long-term outcomes from short-term trials in placebo group.

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Jiansong Yang I-63 Practical diagnostic plots in aiding model selection among the general model for target-mediated drug disposition (TMDD) and its approximations

Jiansong Yang & Peiming Ma
Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline R&D China

Objectives: To develop diagnostic plots to aid model selection among the general model for target-mediated drug disposition [1] and its approximations, such as the quasi-equilibrium (QE, or rapid binding), quasi-steady-state (QSS) and Michaelis-Menten (MM) models[2,3].

Methods & Results:

Diagnostic plots for QSS/QE approximation

The QSS approximation assumes: $kon \cdot R \cdot C-(koff+kmet) \cdot M=0$ (1)
thus $kon \cdot R \cdot C-(koff+kmet) \cdot M$ should be close to 0, and it should not lead to trends in the distribution in a plot of $kon \cdot R \cdot C-(koff+kmet) \cdot M$ vs. time.
Eq. 1 is equivalent to Eq. 2 and Eq. 3.

$M=R_{tot} \cdot C/(Km+C)$ (2)

$R=R_{tot} \cdot Km/(Km+C)$ (3)

where $Km=(koff+kmet)/kon$ is the Michaelis-Menten constant. Plotting observed M (or R) against predicted M (or R) should be around the line of identity, otherwise it suggests the assumption for QSS (i.e. Eq 1) is not valid.
Similarly, the QE approximation assumes: $kon \cdot R \cdot C-koff \cdot M=0$ (4)
thus $kon \cdot R \cdot C-kmet \cdot M$ should be close to 0 and it should not lead to trends in the distribution in a plot of $kon \cdot R \cdot C-koff \cdot M$ vs. time.

Diagnostic plot for the assumption that R_{tot} is constant

If R_{tot} is constant, QSS and QE models can be further simplified. The validity of the assumption needs to be checked by the R_{tot} vs. time plot. However, if R_{tot} is not measured, or it is measured but the data are quite noisy, a plot of

observed R_{free}% vs. predicted values from Eq. 5 (derived from Eq. 3) can help judging if the assumption of R_{tot} being constant is valid.

$$R_{free}\%=Km/(Km+C) \quad (5)$$

Conclusions: The proposed diagnostic plots, together with conventional model diagnostic tools, should aid the model selection for drugs exhibiting TMDD.

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Rui Zhu I-64 Population-Based Efficacy Modeling of Omalizumab in Patients with Severe Allergic Asthma Inadequately Controlled with Standard Therapy

R. Zhu*(1), Y. Zheng*(1), W. Putnam(1), J. Visich(1), T. Lu(1), J. Jin(1), M. Eisner(2), K. Rosén (3), J. Matthews(3), D.Z.D'Argenio(4), *These authors contributed equally to this work.

(1) Department of Clinical Pharmacology, Genentech, Inc. South San Francisco, CA, USA; (2) Department of Clinical Science Immunology, Genentech, Inc. South San Francisco, CA, USA; (3) Department of Clinical Science Respiratory, Genentech, Inc. South San Francisco, CA, USA; (4) Biomedical Simulations Resource (BMSR), University of Southern California, Los Angeles, CA, USA.

Objectives: Omalizumab, a recombinant humanized monoclonal antibody, is the first approved anti-IgE agent indicated in the US for adults and adolescents (≥ 12 years of age) with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids (ICS). The objective of this study was to use population-based efficacy modeling to quantitatively characterize the relationship between serum free IgE and pulmonary function (as measured by FEV1, forced expiratory volume in 1 sec) following treatment with omalizumab in asthma patients.

Methods: A population-based efficacy model linking serum free IgE level to FEV1 was developed to describe FEV1 responses. The model utilizes a single differential equation to describe FEV1 responses in both placebo and omalizumab groups. The model was developed using data from the EXTRA trial [1] in which severe allergic asthma patients received omalizumab or placebo (in addition to high-dose ICS and long-acting beta agonists (LABA), with or without additional controller medications) for 48 weeks [2]. The

dosing was based on baseline IgE and body weight according to the omalizumab dosing table. Numerous covariates, including demographics, disease status, and baseline pharmacodynamic biomarkers, were evaluated in the modeling to explain the variability in the FEV1 response. The model was expanded to incorporate the effect of ICS on FEV1 using a direct-response model, and fitted to data from omalizumab Phase III pivotal trials [3,4] in asthma with time-varying ICS doses.

Results: Results from the IgE-FEV1 model confirmed the current omalizumab dosing rationale in asthma based on the mean target serum free IgE level of 25 ng/mL [5] and quantified the variability for the target. None of the covariates evaluated were significant in explaining the variability in the FEV1 response. The expanded model incorporating the ICS effects on FEV1 adequately described the data from omalizumab Phase III pivotal trials in asthma and confirmed the estimated target free IgE level from the original IgE-FEV1 model.

Conclusions: The population-based efficacy model presented provided useful insights into the relationships between serum free IgE level and pulmonary function (as measured by FEV1) in asthma patients. The modeling results provided a quantitative confirmation for the mean target free IgE level (25 ng/mL) for omalizumab treatment.

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Thomas Dorlo II-01 Miltefosine treatment failure in visceral leishmaniasis in Nepal is associated with low drug exposure

Thomas P. C. Dorlo (1,2,3), Suman Rijal (4), Bart Ostyn (5), Peter J. de Vries (3), Rupa Singh (4), Narayan Bhattarai (4), Surendra Uranw (4), Jean-Claude Dujardin (5), Marleen Boelaert (5), Jos H. Beijnen (1,2), Alwin D.R. Huitema (1)

(1) Department of Pharmacy & Pharmacology, Slotervaart Hospital / the Netherlands Cancer Institute, Amsterdam, the Netherlands, (2) Division of Pharmacoepidemiology & Clinical Pharmacology, UIPS, Utrecht University, Utrecht, the Netherlands, (3) Div. Infectious Diseases, Academic Medical Center, Amsterdam, the Netherlands, (4) B.P. Koirala Institute for Health Sciences, Dharan, Nepal, (5) Institute of Tropical Medicine, Antwerp, Belgium

Objectives: Recent reports indicated high miltefosine treatment failure rates for the neglected tropical disease visceral leishmaniasis (VL) on the Indian subcontinent [1]. To further explore the pharmacological factors associated with these treatment failures, a population pharmacokinetic-pharmacodynamic (PK-PD) study was performed to examine the relationship between miltefosine drug exposure and treatment failure in a cohort of Nepalese VL patients treated with miltefosine monotherapy according to standard treatment protocols.

Methods: Sparse blood samples were collected nominally at the end of treatment (EOT) and the miltefosine steady-state concentrations in these samples were analyzed using liquid chromatography coupled to tandem mass spectrometry. A population PK-PD analysis was performed in a sequential manner using non-linear mixed-effects modeling (NONMEM 7.2) and a logistic regression model for the binary treatment outcome (failure vs. cure). A population pharmacokinetic model for miltefosine was developed [2,3] and

used to derive several measures of individual drug exposure, linked to in vitro drug susceptibility of clinical *Leishmania* isolates from this Nepalese cohort (C_{EOT}, $AUC_{0\text{-}EOT}$, $AUC_{0\text{-}\infty}$, $Time>EC_{50}$, $Time>10xEC_{50}$).

Results: The overall probability of treatment failure was 21%. The time the plasma concentration exceeded 10x the EC50 of miltefosine (median 30.2 days) was significantly associated with treatment success and failure: the odds ratio for treatment failure increased with 1.08 (95% CI 1.01-1.17) for every day that the EOT blood concentration did not exceed 10xEC50.

Conclusions: We here established that achieving sufficient miltefosine exposure is a significant and critical factor for VL treatment success, which urges the evaluation of the recently proposed optimal allometric miltefosine dosing regimen [3]. This study constitutes a first step towards the definition of PK-PD targets to be attained for miltefosine in the treatment of VL.

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Anne Dubois II-02 Using Optimal Design Methods to Help the Design of a Paediatric Pharmacokinetic Study

Anne Dubois and Marylore Chenel
Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Suresnes, France

Objectives: When performing a pharmacokinetic (PK) study, it is important to define an appropriate design, which has an important impact on the precision of parameter estimates and the power of tests. This is of most interest, especially when the number of PK samples is limited as in paediatric studies. To optimise such designs, methods based on the Fisher information matrix in nonlinear mixed effects modelling (NLMEM) can be used [1]. A development plan for the use of a Servier drug S in the paediatric population is underway. Our objective was to propose a design for the future paediatric PK study based on the population PK modelling developed on adult data and using optimal design methods. This study design should allow detecting a minimal clinically relevant age effect.

Methods: Adult PK data were modelled using NLMEM by a two-compartment model with first-order absorption and elimination. This model was implemented in the optimal design software PopDes [2]. Considering several clinical constraints, as the number of age groups and a reasonable number of children per group (no more than 30), we optimised the number of sampling times and the allocation of the time. Then, we assumed an effect of age on the PK of drug S. Again, we optimised the sampling times assuming that we should be able to demonstrate this age effect. A sensitivity analysis was then performed to evaluate the impact of the effect size (*i.e.* we considered several age effects). At last, considering the precision of the age effect estimate, we computed the minimal number of subjects required to detect the minimal clinically relevant age effect.

Results: We were able to optimise the PK sampling design of the paediatric study and to compute the number of subjects needed in order to detect any potential clinically relevant age effect on the drug S clearance. Conclusions: Optimal design trough Fisher information matrix approach is a powerful tool to help planning paediatric PK studies.

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Cyrielle Dumont II-03 Influence of the ratio of the sample sizes between the two stages of an adaptive design: application for a population pharmacokinetic study in children

Cyrielle Dumont (1,2), Marylore Chenel (2), France Mentré (1)
(1) UMR 738, INSERM, University Paris Diderot, Paris, France; (2) Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Suresnes, France

Objectives: Nonlinear mixed-effect models are used to analyse pharmacokinetic (PK) data during drug development, notably in pediatric studies[1,2]. To optimise their design, adaptive designs[3], among which two-stage designs, allow to provide flexibility and could be more efficient than fully adaptive design[4]. We investigated, with a simulation approach, the impact of a two-stage design on the precision of parameter estimation, by varying sample size ratio of each stage, when the 'true' and the a priori PK parameters are different.

Methods: A two-stage design for a population PK study proceeds as follows. At the 1st stage, from a model and a priori population parameters Ψ_0, data for N_1 children are collected based on design ξ_1, optimised with Ψ_0. The same design is assumed for all children. At the 2nd stage, ξ_2 for the remaining N_2 children is optimised using a combined information matrix with the estimated Ψ_1 after 1st stage. At the end, Ψ_2 parameters are estimated using data of $N=N_1+N_2$ children. We evaluated this approach and the influence of the ratio between N_1 and N_2 by a clinical trial simulation in R. The PK model was a 2-compartment model with 1st-order absorption. Optimal one- and two-stage designs were derived using PFIM[5], assuming N=60 children with the same design (5 sampling times) at each stage. We assumed different

'true' Ψ^* and a priori Ψ_0 parameters. From Ψ_0, we optimised ξ_1. From 10 simulated data sets, 10 vectors Ψ_1 were estimated with SAEMIX[6]. ξ_2 was then optimised for each Ψ_1. 10 simulations were performed with each of the 10 ξ_2 designs. We obtained 100 data sets. Relative root mean square errors (RRMSE) for the 100 estimated Ψ_2 were compared for the extremum designs 60-0 (ξ_1) and 0-60 (ξ^*, optimal design), and two-stage designs: 50-10 ($\xi_{50\text{-}10}$), 30-30 ($\xi_{30\text{-}30}$), 10-50 ($\xi_{10\text{-}50}$). The standardized RRMSE was calculated for each parameter and each design as the RRMSE divided by the RRMSE of ξ^*. For each design, mean standardized RRMSE was then computed.

Results: The mean standardized RRMSE equalled 2.48 for ξ_1 optimised with the wrong Ψ_0. Hopefully, the mean standardized RRMSE of the two-stage designs were very close to the one for ξ^*, and equalled 1.15, 1.06, 1.07 for $\xi_{10\text{-}50}$, $\xi_{30\text{-}30}$ and $\xi_{50\text{-}10}$, respectively.

Conclusions: The two-stage designs allowed to compensate from the unsatisfactory result obtained for ξ_1. When the size of the 1st cohort was small, the result was slightly worse. The design with $N_1=N_2$ appears to be a good compromise.

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Thomas Dumortier II-04 Using a model-based approach to address FDA's midcycle review concerns by demonstrating the contribution of everolimus to the efficacy of its combination with low exposure tacrolimus in liver transplantation

Thomas Dumortier, Michael Looby, Olivier Luttringer
Modeling & Simulation, Novartis Pharma

Objectives: At the mid cycle review meeting, the FDA challenged the seemingly favorable results of everolimus (EVR) in combination with tacrolimus at low exposure (low TAC) from a registration study in liver transplantation, on the grounds that there was insufficient information to determine whether EVR has a significant contribution to the efficacy of the combination. This regulatory challenge was justified. Not addressing it would have jeopardized the registration. A dose-exposure-response analysis was conducted to assess the contribution of EVR to the efficacy of the combination.

Methods: In this study where the combination (EVR + low TAC) was compared with TAC alone at high exposure (high TAC alone), the absence of a putative placebo group (low TAC alone) prevented a direct comparison with the combination and thus an easy way to assess the contribution of EVR to the efficacy of the combination. We proposed to (1) establish the relationship between TAC exposure and the occurrence of rejection, (2) predict the efficacy of low TAC alone from this relationship, and finally (3) estimate the contribution of EVR to the efficacy of the combination, using a Cox proportional hazard model adjusted for time-varying TAC exposure. In the context of sparse PK samples (

Results: Using this model-based approach, the probability of rejection over a 12 month period in an hypothetical subject treated with low TAC alone was estimated equal to 27%, which is much higher than the 10% and 6% with high TAC alone and the combination, respectively. The hazard ratio for the comparison between low TAC alone and the combination was equal to 5.1 (95% CI=[2,3,11.4]), indicating that the instantaneous risk of rejection is decreased 5 times when EVR is added to low TAC.

Conclusion: By combining dose and concentration histories in a model-based approach, it was possible to account for the frequent changes in dose strength and to provide an accurate estimate of the TAC exposure which serves as precise basis for the subsequent exposure-response analysis. Using this model-based methodology, the contribution of EVR to the efficacy of the combination was successfully characterized, addressing the FDA's challenge; as a result the FDA approved the combination.

Mike Dunlavey II-05 Support in PML for Absorption Time Lag via Transit Compartments

Michael R. Dunlavey, Robert H. Leary
Certara/Pharsight Corp.

Objectives: Savic et al [1] give a closed-form computation to model absorptive delay through multiple transit compartments, where the number of compartments is a parameter to be estimated. It works for single delta-function inputs sufficiently separated in time. It is desirable to be able to model such absorption in a way that easily handles arbitrary dosing sequences and steady-state determination.

Methods: A statement is included in the Pharsight Modeling Language (PML) that models a delay of time MTT (Mean Transit Time, estimated) as a discrete sequence of N+1 compartments, where N (non-negative) is estimated and is the number of transitions, all of equal rate. N need not be integer, as log-domain interpolation between integer numbers of compartments can be used. The underlying model implemented by the statement consists of a system of ordinary differential equations. When the interpolation is performed in the log-domain, the error fraction between the interpolated and closed-form solution depends only on the number of transitions, not on time, and it can be exactly corrected.

Results: Absorption models are compared between a PML statement implementation, an implementation using explicit ODEs written in PML, and ,where applicable, the Savic model using a closed form absorption delay function.

Conclusions: The discrete method with interpolation compares well with the closed form method, and is not limited to delta-function inputs well separated in time.

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Charles Ernest II-06 Optimal design of a dichotomous Markov-chain mixed-effect sleep model

CS Ernest II (1,2), J Nyberg(1), MO Karlsson (1), AC Hooker(1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden; (2) Eli Lilly and Company, Indianapolis, IN, USA.

Objectives: Optimal design (OD) for discrete-type responses have been derived using generalized linear mixed models [1] and simulation based methods for computing the Fisher information matrix (FIM) of nonlinear mixed effect models (NLMEM) [2]. In this work, OD using a closed form approximation of the FIM for dichotomous, non-homogeneous, Markov-chain sleep NLMEM was investigated.

Methods: NLMEM OD was performed by determining the FIM for each Markov component (previously awake, FIM1, or previously asleep, FIM0) and weighted to the average probability of response being awake, p(1), or asleep, (1-p(1)), over the night to derive the total FIM (FIMtotal) using PopED [3]. FIMtotal,i for a design group i was computed as the sum of the two FIMs: FIMtotal,i=pi(1)*FIM1,i+(1-pi(1))*FIM0,i. The NLMEM consisted of transition probabilities (TP) of dichotomous sleep data estimated as logistic functions. Dose effects were added to the TP to modify the probability of being in either sleep stage. The reference designs (RD) were placebo, 1-, 6-, and 10-mg dosing for a 1- to 4-way crossover study in 4 dosing groups. Optimized design variables (ODV) were dosage and number of subjects in each dosage group and a D-optimal design criterion was used. The designs were validated using stochastic simulation/re-estimation (SSE).

Results: The predicted parameter estimates obtained via the FIM were less precise than parameter estimates computed by SSE; likely due to the weighting scheme, small contribution of the awake Markov component, or

lack of correlation between population means and variances in the FIM as opposed to SSE. The ODV improved the precision of parameter estimates leading to more efficient designs compared to the RD. The increased efficiency was more pronounced for SSE than predicted via FIM optimization.

Conclusion: Using an approximate analytic solution of parts of the FIM (FIM1, FIM0), the FIMtotal could be calculate without extensive Monte Carlo simulations. The optimized designs provided increased efficiency for the crossover study designs examined and provided more robust parameter estimation.

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Christine Falcoz II-07 PKPD Modeling of Imeglimin Phase IIa Monotherapy Studies in Type 2 Diabetes Mellitus (T2DM)

C. Falcoz (2), M. Marchand (2), P. Chanu (2), S. Bolze (1)
(1) Poxel SA, Lyon, France; (2) Pharsight Consulting Services™, a division of Certara™, St Louis, MO, USA

Objectives: To set up early on a PK and PKPD framework based on clinical endpoints (fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c)) in T2DM for imeglimin, the first in a new, tetrahydrotriazine-containing class of oral antidiabetic agents, the Glimins.

Methods: Phase IIa study 1 (39 subjects; 1000 mg BID or 2000 mg OD for 4 weeks) and study 2 (92 subjects; placebo, 500, or 1500 mg BID for 8 weeks) were used for the population (Pop) PK model of imeglimin (99 subjects). Study 2 was selected for the Pop PKPD indirect response (IR) models for FPG with imeglimin inhibiting glucose production, and for HbA1c production from FPG [1,2]. Models developed in NONMEM 7.2 were qualified through Visual and Posterior predictive checks (Trial Simulator v.2.2.1).

Results: *PopPK.* The model selected for PKPD purposes was a 3-compartment model with zero-order absorption, dose influence on bioavailability F and inter-individual variability (IIV) on CL/F, V1/F and V2/F. Concentrations were well described and parameters well estimated with standard errors (RSE) <= 34%. *Pop PKPD.* HbA1c data were few (baseline, end of treatment (EoT)) and a joint FPG-HbA1c model was therefore not selected. Parameters of the FPG model were well estimated (RSE <=27%); individual profiles were reasonably well captured considering day-to-day IIV, including the one week washout. In the HbA1c model, HbA1c degradation rate was fixed to a value estimated with denser data [1]; other parameters were well estimated (RSE <= 20%). *Model qualification.* Predictive checks indicated adequate performance of all

models. Observations were within the 90% prediction intervals. Median change from baseline at EoT in the placebo, 500 mg BID and 1500 mg BID groups was predicted respectively at: (i) 0.76, 0.03 and -0.71 mmol/L for FPG (vs. observed 0.55, 0.20 and -0.90 medians); and (ii) 0.5, 0.2 and -0.1 % for HbA1c (vs. observed 0.2, 0.1 and -0.1 medians).

Conclusions: PK data from two Phase IIa monotherapy studies were combined. Data from study 1 were essential for PK model development. IR models could be used to characterize changes in FPG and HbA1c over 8 weeks of treatment. Model development with early limited data should already prove useful in guiding biopharmaceutical development and the design of future imeglimin studies.

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Floris Fauchet II-08 Population pharmacokinetics of Zidovudine and its metabolite in HIV-1 infected children: Evaluation doses recommended

Floris Fauchet (1) (2), Jean-Marc Tréluyer (1) (2) (3) (4), Saïk Urien (1) (2) (4), Déborah Hirt (1) (2) (3) (4)
(1) EA 3620 Université Paris Descartes, Sorbonne Paris Cité, France, (2) Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France, (3) Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, France, (4) CIC-0901 Inserm, Cochin-Necker, Paris, France

Objectives: To describe Zidovudine (ZDV) pharmacokinetics (PK) and its biotransformation to its metabolite (G-ZDV) in HIV-infected children, to identify factors that influence the ZDV pharmacokinetics, to compare and evaluate doses recommended by the World Health Organization (WHO)[1] and by the Food and Drug Administration (FDA)[2]

Methods: In 247 children aged from 6 months to 18 years, ZDV and G-ZDV concentrations were collected. A total of 782 and 554 samples for the ZDV and G-ZDV were retrospectively measured on a routine basis. The data were analyzed using the nonlinear mixed-effect modeling software NONMEM (version 6.2) [3]

Results: A one-compartment model, with first-order absorption and elimination, was used to describe plasma ZDV concentrations. An additional compartment for G-ZDV was added, which was linked to the ZDV compartment with a first order rate constant. A combined variability and a proportional variability models were used to describe accurately the residual errors. The effect of bodyweight was significant on the apparent elimination clearance and on the apparent volume of distribution. The mean population parameter estimates (between-subject variability) were as follows: the

apparent elimination clearance, 89.7 liters h^{-1} (0.701); the apparent volume of distribution, 229 liters (0.807); the apparent metabolic clearance, 12.6 h^{-1}.$liters^{-1}$ (0.352) and the elimination rate constant of G-ZDV, 2.27 h^{-1}. Based on simulations of FDA and WHO dosing recommendations, the probabilities of observing exposure described as efficient (around 3 to 5 mg.L.h^{-1})[4-6] with lower adverse event (below 8.4 mg.L.h^{-1})[7] are higher following the FDA recommendations than the WHO recommendations. But, risks of toxicity are more important in children weighing from 20 to 40 kg, 20 % of their exposures were higher than the safety target.

Conclusions: Modelling and simulation of ZDV PK suggest that the FDA recommendations are more appropriate but lower doses should be considered for the weight band 20-40 kg. These results seem according to another study [8] which has suggested that the neonatal doses recommended by the WHO produced very high exposure of ZDV.

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Eric Fernandez II-09 drugCARD: a database of anti-cancer treatment regimens and drug combinations

Eric Fernandez, Jianxiong Pang, Chris Snell, Cheryl Turner, Cathy Derow, Frances Brightman, Christophe Chassagnole and Robert Jackson
Physiomics plc, The Oxford Science Park, Oxford OX4 4GA and Pharmacometrics Ltd, Southend-on-Sea SS2 6HZ

Objectives: Physiomics and Pharmacometrics have collaborated to design a new database of anti-cancer drugs and therapeutic treatment information. The objective is to provide PKPD data, regimens and combinations for use by clinicians and researchers in oncology.

Methods: The drugCARD database, accessible through the web, offers data on more than 130 anti-cancer drugs (small molecules and biologics) used in research and in the clinic. It contains information on drug combinations as well as several hundreds of cancer chemotherapy regimens used routinely in the clinic. The data are classified according to tumour type, species and experimental system (in vitro or in vivo). A new search engine, based on Apache Solr™ [1], has been integrated, allowing users to perform powerful reliable and faceted search on any term and fields of the database.

Results: Individual drug information contained within the database comprises PK profiles, mechanisms of action and resistance, dose-response effect, dosing limits, therapeutic index and immunosuppression data. Drug combinations where the level of synergy is dependent upon the drug schedule, drug sequence or administration timing are also referenced and thoroughly discussed. The database covers synergy or antagonism, and includes the combination therapeutic index and cross-resistance information. The user can browse and compare chemotherapeutic regimens, and analyse the overall drug dose over a course of treatment, by tumour type, in animal

and clinical models. Data can be exported for analysis in spreadsheets, modelling software or simulation packages.

Conclusions: The database enables users to design new combinations and regimens that obey dosing constraints (such as MLD and MTD), and can be used to determine drug candidates that could be combined with a new chemical or biological entity, given the respective mechanisms of action and other PK/PD data. Also, the database allows the expression and nomenclature of chemotherapy regimens to be standardized, which is of paramount importance in improving efficacy, as well as reducing medication errors [2].

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Martin Fink II-10 Animal Health Modeling & Simulation Society (AHM&S): A new society promoting model-based approaches for a better integration and understanding of quantitative pharmacology in Veterinary Sciences

Martin Fink (1), Jonathan P. Mochel (1,2), Johan Gabrielsson (3), Wendy Collard (4), RonetteGehring (5), Celine Laffont-Rousset (6), Yahong Liu (7), Tomas Martin-Jimenez (8), LudovicPelligand (9), Jean-Louis Steimer (1), Pierre-Louis Toutain (6), Ted Whittem (10), and Jim Riviere (5)
(1) Department of Modeling and Simulation, Novartis Campus St. Johann, 4002 Basel, Switzerland. (2) Department of Pharmacology, Leiden-Academic Centre for Drug Research, 2300 Leiden, The Netherlands. (3) Division of Pharmacology and Toxicology, Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences, Uppsala, Sweden. (4) Veterinary Medicine Research and Development, Zoetis Inc, Kalamazoo, MI 49007, USA. (5) Institute of Computational Comparative Medicine, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66502, USA. (6) INRA, UMR 1331, Toxalim, F-31027 Toulouse, France. (7) Department of Veterinary Pharmacology and Toxicology, College of Veterinary Medicine, South China Agricultural University, Guangzhou 510642, China. (8) Department of Comparative Medicine, University of Tennessee, College of Veterinary Medicine, Knoxville, TN 37996, USA. (9) Department of Veterinary Basic Sciences, Royal Veterinary College, Hatfield, Herts, UK. (10) Faculty of Veterinary Science, University of Melbourne, Werribee, Victoria, Australia

The **Animal Health Modeling & Simulation Society (AHM&S)** is a newly founded association (2012) that aims at promoting the development, application, and dissemination of modeling and simulation techniques in the field of Veterinary Pharmacology and Toxicology. The association is co-

chaired by Pr. Johan Gabrielsson (Europe) and Pr. Jim Riviere (USA), and currently counts about 15 founding core members from both academia and industry.

Our objectives The primary objective of the society is to maximize the value of available pharmacokinetic/pharmacodynamics datasets to identify physiological and pathological factors that account for differences in drug safety and efficacy in animals. Examples (not exhaustive) of data analyses of interest to our group include:

- **Quantitative pharmacology** Pharmacokinetics and pharmacodynamics comprise traditionally distinct disciplines within pharmacology, the study of the interaction of drugs with the body. It is our intention to show that by deliberately, closely and systematically integrating these disciplines our understanding of drugs and the efficiency and effectiveness of drug discovery and development may be greatly enhanced.
- **Dosing regimen determination** Conduct of dose/exposure/response modeling to estimate an efficacious and safe dose for a new or already existing molecule to be used in companion animals (individual treatment), and food producing animals (collective treatment).
- **Withdrawal time determination** In food animal medicine the veterinarian must be sure an effective dose of drug is given but also that the edible products from the treated animals do not contain residues of the drug at or above the permitted concentrations when processed for marketing.
- **Trial design and analysis** Optimization of trial design through simulation of scenarios; provide support to trial analysis, interpretation, and decision making. This goal includes but is not limited to: adaptive designs, dose finding, compliance modeling, and evaluation of endpoints.
- **Disease modeling** Quantitative characterization of the disease progress as a function of time and other predictors; to determine relationships among prognostic factors, biomarkers, and clinical outcomes in available data.

Conclusion The AHM&S offers a new scientific platform promoting cross-fertilization among basic, translational, and clinical research between species, using model-based approaches.

Sylvain Fouliard II-11 Semi-mechanistic population PKPD modelling of a surrogate biomarker

Sylvain Fouliard and Marylore Chenel
Department of Clinical Pharmacokinetics, Servier, Suresnes, France

Objectives: To develop through a sequential approach a single PKPD model of a surrogate biomarker SB as a function of two independent variables (time=IDV1 and IDV2) after the administration of drug S, describing the effect of drug S and its active metabolite M, consistently with *in vitro* activity assays and drug mechanism knowledge.

Methods: A combined PK model of drug S and its active metabolite M was first developed using PK data from 25 healthy volunteers being administered drug S as a slow-release formulation. Individual PK parameters for S and M were obtained from the final PK model through Bayesian approach, and used as an input in a PKPD dataset along with PD measurements in order to fit SB as a function of IDV1 (time) and IDV2. A drug/receptor binding kon/koff model was implemented including the influence of S and M on SB. An identifiability analysis was performed using design evaluation software POPDES in order to assess the data's and model's ability to estimate both S and M activities. Comparison was also performed between sequential approach (fit of SB(IDV1), then fit of SB(IDV1, IDV2)) and simultaneous approach (direct fit of SB(IDV1, IDV2)) [1].

Results: The PK model of S and M concentration-time profile after administration of S as an extended-release formulation consisted in a mono-compartmental model for S and M, with a complex absorption (2 depot compartments and a time-dependent absorption rate) and first order elimination for both drugs. Inter-individual and inter-occasion variabilities were estimated on several parameters. A drug/receptor binding modelled

the dependence of SB on IDV1 and a direct model described SB variation with IDV2. The identifiability analysis showed that it was not possible to estimate the effect of both S and M on SB thus their relative activity was fixed to a value from an *in vitro* assay. The sequential approach and the simultaneous approach showed similar results and allowed a satisfactory description of SB(IDV1, IDV2).

Conclusion: A PKPD model successfully described the effect of drug S and its metabolite M on SB with respect to two independent variables and will be used for further PKPD simulations providing a powerful tool in the context of model-based drug development.

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Nicolas Frances II-12 A semi-physiologic mathematical model describing pharmacokinetic profile of an IgG monoclonal antibody mAbX after IV and SC administration in human FcRn transgenic mice.

Frances N. (1), Richter W. F. (1), Grimm H. P. (1), Walz A. (1), Roopenian D. (2)
(1) F. Hoffmann-La Roche AG, pRED, Pharma Research & Early Development, Non-clinical Safety, CH-4070 Basel, Switzerland, (2) The Jackson Laboratory, Bar Harbor, ME 04609, USA.

Objectives: To characterize the observed PK profiles of mAbX after IV and SC administration in variants of human FcRn transgenic mice in a mathematical model incorporating physiological elements of FcRn salvage.

Methods: Transgenic mice deficient of mouse FcRn and expressing human FcRn (hFcRn) were provided by Jackson Laboratory in Bar Harbor, Maine (USA) where also all in vivo PK studies were performed (presented at AAPS Annual Meeting in October 2012 [1]). In short, the PK of mAb X, a humanized IgG1 antibody, not cross reactive with the murine target, was investigated after administration of 10 mg/kg iv and sc administration. Mice expressing human FcRn either in somatic cells, in bone-marrow derived cells, in both cell types or none (4 groups, 8 animals per group and per route of administration) were prepared as described elsewhere for wild-type mice [2].
Compartmental PK models were developed to describe the PK in in all groups and route of administration simultaneously. Model parameters were estimated using Monolix and simulations performed with Matlab. Model comparisons were based on the Akaike criterion.

Results: Observed IV PK profiles were adequately described by a model involving plasma, extravascular compartments and two endosomal

compartments representing somatic and bone marrow-derived cells. In this model, antibodies are eliminated uniquely from the endosomal compartments. FcRn knock-in variants were modeled by permitting recycling from the corresponding endosomal compartment and thereby salvaging them from degradation. Similarly, observed SC PK profiles were adequately described by transferring the drug from a compartment representing the SC administration site to compartments of the IV model structure.

Conclusions: Contribution of both somatic and bone marrow derived cells in FcRn salvage from catabolism [3] is adequately described in the presented novel mathematical model, which reflects the various localizations of FcRn and associated salvage processes. It is an alternative to other models incorporating similar mechanism [4, 5, 6].

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Chris Franklin II-13 : Introducing DDMoRe's framework within an existing enterprise modelling and simulation environment.

Chris Franklin (1), Lorenzo Ridolfi (1), Oscar Della Pasqua (1)
Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT

Objectives: Among the various objectives of the DDMoRe consortium, the development of a simplified modelling language is envisaged which will allow users to specify the mathematical structure of models. This will be defined in a general manner, allowing the use of different modelling tools. Here we show how the proposed modelling framework can be embedded within an existing modelling and simulation environment and identify how such concepts can benefit model-based drug development activities in R&D.

Methods: Using GlaxoSmithKline's current computer architecture and modelling environment as basis for a change impact analysis, we delineate how hardware, software, workflow, computing capacity and systems interconnectivity will be affected by the availability of a modelling language. In addition to the traceability and dependency of requirements and specifications, our analysis also evaluates how the proposed changes will affect operations and user community.

Results: Our change impact analysis reveals that the modifications required to incorporate DDMoRe concepts into a new environment are limited. These changes represent however potentially major challenges to standard business process and workflow. A change management programme needs to be considered to ensure that new process is taken up in an effective manner.

Conclusions: The acceptability of a new environment within an established business community has been appraised. The impact on business efficiency

depends on the availability of translators and connectors suitable for the current software and on the implementation of an early change management program.

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Ludivine Fronton II-14 A Novel PBPK Approach for mAbs and its Implications in the Interpretation of Classical Compartment Models

Ludivine Fronton (1,3) and Wilhelm Huisinga (1,2)
(1) Institute of Biochemistry and Biology, Universitaet Potsdam, Germany; (2) Institute of Mathematics, Universitaet Potsdam, Germany; (3) Graduate Research Training Program PharMetrX: Pharmacometrics & Computational Disease Modeling, Freie Universitaet Berlin and Universitaet Potsdam, Germany

Objectives: Classical compartment models are successfully used to characterize the pharmacokinetics (PK) of therapeutic monoclonal antibodies (mAbs). These models, however, still lack a theoretically sound interpretation of their PK parameters. Physiologically-based pharmacokinetic (PBPK) models are an alternative approach because they allow one to integrate in-vitro data (e.g. the neonatal Fc Receptor (FcRn) affinity, KD), physiological data (e.g. endogenous IgG (IgGendo) concentration, plasma and lymph flows, plasma, residual blood and tissue volumes) and in-vivo data (e.g. plasma and tissue concentrations). Existing PBPK models are very complex and parameter identifiability is a major issue as documented by the high parameter sensitivity reported by several authors [1, 2, 3]. The objectives were (i) to develop a novel PBPK model for mAbs which complexity is adapted to the available experimental data, in mice, in absence of target and (ii) to establish its link to classical compartment models.

Methods: We used the physiological parameters reported in [1] and [4]. The experimental venous plasma and tissue data of the mAb (7E3), administered intravenously at 8 mg/kg, were extracted from [2] for wild-type mice using the software DigitizeIt, version 1.5.8a. The residual blood volumes were reported in [5]. MATLAB R2010a was used for modeling (lsqcurvefit) and

simulation (ode15s solver). The unknown parameters, i.e. tissue-to-plasma partition coefficients and tissue extraction ratios, were estimated for wild-type mice data.

Results: Because of their large molecular mass ($\sim$ 150 KDa), mAbs exhibit a poor extravasation into tissues. Based on the detailed PBPK model published in [2] and previous insights into mAbs- and IgGendo-binding to FcRn [6], we derived a PBPK model which implicitly considers IgGendo and FcRn-mediated salvage. In short, the characteristics of the resulting PBPK model are similar to those of a PBPK model for small molecule drugs showing a low volume of distribution, permeability-limited tissue distribution and a linear clearance in various tissues. The PBPK model allowed estimating reliably a minimum number of parameters: tissue-to-plasma partition coefficients and tissue extraction ratios. We extended the lumping methodology described in [7] to mAbs. The resulting minimal lumped model can be related to a simple 2-compartment model with a linear clearance from the peripheral compartment that comprises the eliminating tissues.

Conclusions: Our PBPK model suggests a new interpretation of classical compartment models. A very recent article by Shah and Betts [8] supports the generalization of our approach to non-target expressing tissues for rat, monkey and human.

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Aline Fuchs II-15 Population pharmacokinetic study of gentamicin: a retrospective analysis in a large cohort of neonate patients

Aline Fuchs (1), Monia Guidi (1, 2), Eric Giannoni (3), Thierry Buclin (1), Nicolas Widmer (1), Chantal Csajka (1, 2)
(1) Division of Clinical Pharmacology, Service of Biomedicine, Department of Laboratory, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland, (2) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland, (3) Service of Neonatology, Department of Pediatrics, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

Objectives: Gentamicin is one of the most commonly prescribed antibiotics for suspected or proven infection in newborns. Because of age-associated (pre- and post- natal) changes in body composition and organ function, large interindividual variability in gentamicin drug levels exists, thus requiring a close monitoring of this drug due to its narrow therapeutic index [1]. We aimed to investigate clinical and demographic factors influencing gentamicin pharmacokinetics (PK) in a large cohort of unselected newborns and to explore optimal regimen based on simulation.

Methods: All gentamicin concentration data from newborns treated at the University Hospital Center of Lausanne between December 2006 and October 2011 were retrieved. Gentamicin concentrations were measured within the frame of a routine therapeutic drug monitoring program, in which 2 concentrations (at 1h and 12h) are systematically collected after the first administered dose, and a few additional concentrations are sampled along the treatment course. A population PK analysis was performed by comparing various structural models, and the effect of clinical and demographic factors on gentamicin disposition was explored using NONMEM®.

Results: A total of 3039 concentrations collected in 994 preterm (median gestational age 32.3 weeks, range 24.2-36.5 weeks) and 455 term newborns were used in the analysis. Most of the data (86%) were sampled after the first dose (C1 h and C12 h). A two-compartment model best characterized gentamicin PK. Average clearance (CL) was 0.044 L/h/kg (CV 25%), central volume of distribution (V_c) 0.442 L/kg (CV 18%), intercompartmental clearance (Q) 0.040 L/h/kg and peripheral volume of distribution (V_p) 0.122 L/kg. Body weight, gestational age and postnatal age positively influenced CL. The use of both gestational age and postnatal age better predicted CL than postmenstrual age alone. CL was affected slightly by dopamine administration and non-significantly by indometacin and furosemide. Body weight and gestational age significantly influenced V_c. Model based simulation confirms that preterm infants need higher dose, superior to 4 mg/kg, and extended interval dosage regimen to achieve adequate concentration[2].

Conclusions: This study, performed on a very large cohort of neonates, identified important factors influencing gentamicin PK. The model will serve to elaborate a Bayesian tool for dosage individualization based on a single measurement.

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Aurelie Gautier II-16 Pharmacokinetics of Canakinumab and pharmacodynamics of IL-1β binding in cryopyrin associated periodic fever, a step towards personalized medicine

Aurélie Gautier, Andrej Skerjanec, Olivier Luttringer, Phil McKernan, Philip Lowe
Novartis Pharma AG, Basel, Switzerland

Objectives: Canakinumab is a high-affinity fully human monoclonal antibody of the IgG1/k isotype, designed to bind and functionally neutralize the bioactivity of IL-1B, which is recognized as one of the principal pro-inflammatory cytokines in cryopyrin associated periodic syndromes (CAPS). The objectives of the study were to describe the kinetics of canakinumab and dynamics of binding IL-1B in CAPS patients; to determine if these are different in 2- and 3-year-old children versus older children and adults; and to explore the impact of CAPS phenotype (Muckle-Wells Syndrome [MWS], Familial Cold Autoinflammatory Syndrome [FCAS], Neonatal-Onset Multisystem Inflammatory Disease [NOMID]) on the kinetics of canakinumab and dynamics of binding to IL-1B.

Methods: A pharmacokinetics (PK)-binding model was used to describe the kinetic and binding parameters of canakinumab and IL-1B in CAPS patients, and in other populations relative to CAPS. The subgroup of 7 CAPS patients who were 2 and 3 years of age at baseline was also compared to the overall CAPS population.

Results: The 7 CAPS patients did not show any difference in terms of PK. However, they showed a higher IL-1B turnover including IL-1B clearance and production. IL-1B levels were linked with the severity of the CAPS phenotype. In the pediatric population, MWS and especially NOMID patients had higher concentrations of the inert canakinumab/IL-1B complexes after

administration of canakinumab, indicating more cytokine in the body to be captured.

Conclusions: Correlation with clinical responses suggested that these increased levels of IL-1B may explain why younger and NOMID phenotype patients require higher doses or escalation to higher doses.

Ronette Gehring II-17 A dynamically integrative PKPD model to predict the efficacy of marbofloxacin treatment regimens for bovine Mannheimia hemolytica infection

Ronette Gehring (1), Michael D Apley (1), Jim E Riviere (1)
(1) Institute of Computational Comparative Medicine, Kansas State University

Objectives: To develop a PKPD model that dynamically integrates in vitro and in vivo data, specifically the pharmacokinetics of marbofloxacin in cattle with the in vitro effect of varying concentrations of marbofloxacin on Mannheimia hemolytica, to predict the efficacy of different clinically feasible dosage regimens.

Methods: A Hill equation was fit to published time-kill data for marbofloxacin and bovine isolates of Mannheimia hemolytica [1] [2]. Marbofloxacin plasma concentrations were predicted using a published three compartment model in calves [3]. The predicted concentration served as input for the Hill equation to predict fluctuations in bacterial growth as a result of exposure to changing marbolfoxacin concentrations over time. The sensitivity of the bacterial population to marbofloxacin was varied to an MIC that was 8 fold higher than was used to initially parameterize the Hill equation. Simulations for 5 different clinically feasible dosing regimens were done using ACSLXtreme (Aegis Technologies, Huntsville, AL). Bacterial population sizes at 24 hours after the final dose were compared.

Results: All dosage regimens were equally effective in decreasing populations of highly sensitivie bacteria. Those that administered higher doses less frequently remained effective as the bacteria became more resistant, whereas dosage regimens that administered lower doses more frequently became less effective. None of the dosage regimens were effective once

sensitivity of the bacteria to marbofloxacin had decrease to a six fold higher MIC from the original population used to parameterize the Hill equation.

Conclusions: This integrative PKPD model offers an economical tool to predict to effective dosage regimens that may then be validated with carefully designed clinical trials. Variability of the drug's pharmacokinetics within the target population can easily be incorporated into the simulations using this model. This has the potential to decrease the cost of drug development, as well as identifying breakpoints for resistant isolates.

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Peter Gennemark II-18 Incorporating model structure uncertainty in model-based drug discovery

Peter Gennemark
CVGI iMED DMPK AstraZeneca R&D, Sweden

Objectives: Drug discovery is characterized by relatively small pharmacokinetic and pharmacodynamic (PKPD) data sets for lead compounds that are routinely screened in an animal model. The turn-over time of pre-clinical PKPD analysis is usually short and in depth model selection is seldom executed. In addition, selection of the best model structure for one compound is hard due to sparse data. The objective of this study is to improve standard model-based predictions from preclinical data sets by incorporating model structure uncertainty, and not only parameter uncertainty, in an approach that is useful in practice.

Methods: The time constraint of model selection was addressed by automatization of time consuming modeling steps. Uncertainty in model structure was considered by evaluating several models from a model space using a model selection criterion. In this study we have used AIC. Model based predictions were generated from all models in the model space, and weighted using the posterior model probabilities from the calculated Akaike weights. Our approach was developed and tested using compound exposure and compound targeted receptor occupancy data from mice.

Results: Two main obstacles for proper model selection in drug discovery are time constraints and sparse data. Using PKPD data from a drug discovery project, we addressed both issues. To incorporate structure uncertainty we defined a large model space including a reasonable space of both PK and the PD structural models, and weighed the set of feasible models based on their posterior probability. Concerning the time constraint, we accelerated model

selection by implementing a user-friendly computational process with input data in form of an Excel file and output in form of a PowerPoint presentation file. Taken together, we could rapidly obtain robust estimation with uncertainty of, e.g., compound potency, by sampling from the inferred model distribution.

Conclusions: Model structure uncertainty, and not only parameter uncertainty for one single model structure, can be incorporated in drug discovery practice. This implies improved robustness in model selection, which is particularly important when data is sparse. A more realistic estimation of model prediction uncertainty can then be expected, which is pivotal in decision making such as compound selection.

Eva Germovsek II-19 Age-Corrected Creatinine is a Significant Covariate for Gentamicin Clearance in Neonates

Eva Germovsek (1), Alison Kent (2), Nigel Klein (1), Paul Heath (2), Elisabet I Nielsen (3), Joseph F Standing (1)
(1) UCL Institute of Child Heath, Infectious Diseases and Microbiology Unit, London, UK; (2) St George's, University of London, London, UK; (3) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Gentamicin is an antibiotic with a narrow therapeutic window, making therapeutic drug monitoring (TDM) vital. However, currently there is no consensus on how best to perform gentamicin TDM in neonates. Previous studies have not found a relationship between serum creatinine concentration (SECR) and gentamicin clearance (CL), but these have often not accounted for the rapid changes in expected creatinine levels over the first weeks of life. This study aims to improve gentamicin TDM in neonates by firstly building a population PK (popPK) model and then using it to create a Bayesian computer tool, which will predict trough levels from levels taken at earlier and more convenient times.

Methods: The concentration-time data used for modelling were from two published studies [1, 2] and included 174 neonates and 1163 serum levels. Their gestational age ranged from 23.3-42.1 weeks, and postnatal age (PNA) from 0-65 days. To establish PK parameters NONMEM VII with FOCE-I method was used. In order to define the basic PK model several structural models and different error models were tested. The effect of different covariates (age, body weight, SECR) on the PK parameters was evaluated. SECR was incorporated into the model through organ function, which corrected measured SECR for age by using a SECR typical for that age from

the literature [3, 4]. Inter-occasion variability (IOV) was tested for each parameter.

Results: A 3-compartment structural model described the data best. The final covariate model included allometric weight scaling of PK parameters, a hyperbolic sigmoid maturation function (with parameters fixed to values from a previous study [5]) and also a logistic function to explain the changes in CL with PNA. Age-corrected SECR was found to further significantly improve the model (the OFV decreased by 35.6 units). Final estimates for PK parameters were: CL=6.85 L/h/70kg, Vc=27.6 L/70kg, Q1=0.30 L/h/70kg, Vp1=253.4 L/70kg, Q2=2.24 L/h/70kg, Vp2=22.4 L/70kg. Between-subject variability (%CV) was: 30.0, 9.25, 71.5, 12.2 and 19.3 for CL, Vc, Vp1, Q2 and Vp, respectively. IOV on CL was 15.6%. GOF and VPC plots showed a good fit of the model to the data and good predictive properties.

Conclusion: A popPK model for gentamicin in neonates that provided the best fit to the observed data was a 3-comparment model. We have shown that correcting SECR for age is necessary in neonatal studies.

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TJ Carrothers II-20 Comparison of Analysis Methods for Population Exposure-Response in Thorough QT Studies

Parviz Ghahramani (1), Tatiana Khariton (1), Timothy J Carrothers (1)
(1) Forest Research Institute, Jersey City, NJ, USA

Objectives: To compare two approaches for evaluating the relationship between drug concentrations and QTc interval.

Methods: Data from two dedicated thorough QT (TQT) studies were used to compare two common approaches [1,2] used in evaluating concentration-QTc relationships for both escitalopram (ESC, n=107 subjects) and citalopram (CIT, n=119 subjects). The first approach (delta-delta) specified baseline-and-placebo-adjusted QTc as the dependent variable and considered linear mixed-effects models based on observed drug plasma concentrations, with or without log-transformation. The second approach (covariate model) utilized nonlinear mixed-effects models with QTc as the dependent variable, and with terms for baseline, placebo effect, and drug effect (used an Emax model, with intersubject variability on baseline and Emax as a function of individual predicted concentrations). Comparison of the two approaches was made via simulation of the QTc change at steady state Cmax.

Results: For both studies, the delta-delta analysis approach yielded models with population median intercepts that excluded zero (e.g., -19.6 ms for CIT), which would be physiologically unlikely (i.e., indicate QTc shortening at low concentrations). For the CIT study, both approaches gave similar mean predictions of drug-related prolongation, but with different confidence intervals:

CIT Dose	Mean QTc Prolongation (ms, 90% CI)

	Delta-delta	Covariate model
20 mg	7.8 (6.2, 9.3)	8.2 (6.5, 10.4)
40 mg	12.6 (10.9, 14.3)	12.5 (10.1, 15.6)
60 mg	16.0 (14.0, 18.1)	15.5 (12.2, 19.7)

For the ESC study, the two approaches gave different predictions (mean and 90 CI) of drug-related QTc prolongation. At 20 mg dose, the delta-delta approach estimated a mean (90% CI) QTc change of 6.6 ms (5.3, 7.9), but the covariate approach estimated 8.3 ms (7.3, 9.2).

Conclusions: Modeling QTc directly using the covariate approach may provide a more physiologically relevant model for predictions across the full concentration range. On the other hand, the delta-delta approach may be computationally less intensive. While both approaches examined above avoid the multiple comparison bias and inefficiency of the Intersection Union Test commonly used in E14-standard TQT studies [3], they may provide different results. Additional validation work is recommended in comparing the relative merits of each C-QT approach.

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Parviz Ghahramani II-21 Population PKPD Modeling of Milnacipran Effect on Blood Pressure and Heart Rate Over 24-Hour Period Using Ambulatory Blood Pressure Monitoring in Normotensive and Hypertensive Patients With Fibromyalgia

Parviz Ghahramani (1), Tatiana Khariton (1), Antonia Periclou (1)
(1) Forest Research Institute, Jersey City, NJ, USA

Objectives: To develop population PKPD models describing the relationship between milnacipran (MLN) and ambulatory blood pressure (BP) and heart rate (HR).

Methods: A double-blind, placebo-controlled study assessed the effects of MLN on ambulatory BP and HR in fibromyalgia (FM) patients, normotensive or with stable hypertension, measured at baseline, Week 4 (steady state for 100 mg/d), and Week 7 (steady state for 200 mg/d). The population PK model [1] was updated and used to predict exposures at time points matching BP or HR readings. The relationships between diastolic (DBP), systolic BP (SBP) or HR and the predicted exposures were assessed using a nonlinear mixed-effects (NLME) modeling in NONMEM. Models for SBP, DBP, and HR were fit separately and consisted of 4 sequentially fitted additive terms: baseline, placebo, drug effect, and residual error. Demographics, hypertensive status, and diurnal variation (using Fourier approach) were evaluated.

Results: The PD population included 49,792 observations from 269 patients. Piece-wise linear relationships between exposure and SBP, DBP, or HR described the data best. Additive inter-individual variability terms were estimated on baseline, placebo and drug effects. No evidence of hysteresis was found. PKPD models suggest that the drug effect on SBP, DBP and HR was near plateau by Week 4. Although the dose and exposure at Week 7 (200

mg/d) was twice those at Week 4 (100 mg/d), the increase in the estimated drug effect was small: the mean increases in DBP, SBP and HR for 100 mg/day were estimated to be 5.0 mmHg, 5.1 mmHg and 12.8 bpm, respectively (Table 1); the additional effects at 200 mg/d dose were not statistically significant compared to 100 mg/day dose. Patients identified as hypertensive had higher estimated SBP and DBP values (but not HR) at baseline; however, the magnitude of increase in DBP and SBP drug effect in hypertensives was not significantly different.

Table 1	DBP, mmHg*	SBP, mmHg*	HR, bpm*
Drug effect for 100 mg/d	5.0 (3.8, 6.2)	5.1 (3.5, 6.7)	12.8 (11.3, 14.3)
Additional drug effect for 200 mg/d	0.7 (-0.4, 1.8)	1.2 (-0.5, 3.0)	1.2 (-0.2, 2.7)
*mean (95% CI)			

Conclusions: Although exposure to MLN is associated with an increase in SBP, DBP and HR in FM patients, 200 mg/d does not lead to significant additional increases in BP and HR compared to 100 mg/d. Furthermore, hypertensive patients do not appear to have greater increase in BP and HR with increase in MLN exposure as compared to normotensive patients

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Ekaterina Gibiansky II-22 Immunogenicity in PK of Monoclonal Antibodies: Detection and Unbiased Estimation of Model Parameters

Leonid Gibiansky, Ekaterina Gibiansky
QuantPharm LLC, North Potomac, MD, US

Objectives: To propose and evaluate methods for immunogenicity detection and unbiased estimation of model parameters in the presence of immunogenicity.

Methods: A two-compartment model typical for monoclonal antibodies was used to simulate six-month study with monthly dosing. Sampling included the rich data following the first and the last doses, and trough and peak values for all other doses. Immunogenicity (in 30% of subjects) was simulated as increase in clearance: (a) 5-fold after 2-6 months of dosing; (b) according to a Hill function of time with inter-individual variability in E_{max} and T_{50} parameters. Two methods of accounting for immunogenicity were tested.

The first method introduced the random effect ETA_{err} on the magnitude of the residual error, hypothesizing that subjects with immunogenicity would have higher ETA_{err}. The model was then fitted to the datasets where increasing fractions of subjects with the highest ETA_{err} were removed.

The second method used Nonmem mixture model routine. For the data set (a) it was assumed that the study population consisted of several subpopulations. Subpopulation 1 did not have immunogenicity while the other subpopulations were allowed to have an increase in clearance following i^{th} dose (i=2 to 6). For the data set (b) 2 subpopulations represented

non-immunogenic and immunogenic subjects with increase in clearance modeled by Hill function of time.

Results: The parameter estimates of the model that did not account for immunogenic increase of clearance were significantly biased. Introduction of ETA_{err} reduced, but not eliminated bias. High ETA_{err} identified immunogenic subjects. When subjects with high ETA_{err} were removed from the data, bias due to unaccounted immunogenic increase of clearance was eliminated. The mixture models provided the unbiased estimates of the model parameters in both cases (a) and (b). The simulated immunogenic subjects were correctly assigned to the appropriate subpopulations.

Conclusions: For the simulated datasets with rich sampling, the proposed methods identified subjects with immunogenic increase of clearance, provided unbiased individual estimates of onset time and magnitude of immunogenicity, and unbiased estimates of the population parameters. Application to the real data will likely face more difficulties. However, the proposed methods may provide useful tools for detection and evaluation of changes in the PK parameters related to immunogenicity.

Leonid Gibiansky II-23 Monoclonal Antibody-Drug Conjugates (ADC): Simplification of Equations and Model-Independent Assessment of Deconjugation Rate

Leonid Gibiansky, Ekaterina Gibiansky
QuantPharm LLC, North Potomac, MD, USA

Objectives: To simplify equations that describe distribution, deconjugation, elimination and interaction with the target of antibody-drug conjugates (ADC) under specific assumptions; to propose model-independent method to assess deconjugation.

Methods: This work continues investigation of ADC equations started in [1]. It was assumed that ADC parameters are independent of drug-to-antibody ratio (DAR), deconjugation rate is proportional to DAR, and internalization rate is high. Under these assumptions, the system of equations for ADC species with different DARs was simplified to describe two observed quantities: total antibody concentration (tAB) and concentration of the antibody-conjugated toxin (acT). Unobserved concentration-time courses of each of the ADC species could then be predicted using the parameters of this system.

Results: Under the described assumptions, the system of equations for all ADC species with different DARs was reduced to two coupled two-compartment models with the combined linear and Michaelis-Menten elimination terms for two observed quantities (tAB and acT). Equations for acT differed from those for tAB by an additional term k_{dec}*acT (elimination due to deconjugation) and by the denominator of the Michaelis-Menten term that was expressed as (K_{SS}+tAB) instead of the expected (K_{SS}+acT). Here k_{dec} and K_{SS} are deconjugation rate constant and quasi-steady-state constant, respectively. If the non-linear part of elimination is negligible, equations de-

couple allowing for a separate fit. In this case k_{dec} can be computed as $k_{dec}V = D_{acT}/AUC_{acT} - D_{tAB}/AUC_{tAB}$, where V is volume of the central compartment, D_{tAB} is dose of total antibody, $D_{acT} = D_{tAB}$* mDAR (mDAR is mean DAR of the dosing solution), and AUC_{acT} and AUC_{tAB} are the observed areas under acT and tAB concentration-time curves. If deconjugation rate is small relative to total antibody clearance, then tAB = acT/mDAR.

Conclusions: Under certain assumptions the pharmacokinetics of ADCs can be described by two coupled two-compartment systems with parallel linear and Michaelis-Menten elimination. In linear case, equations decouple allowing for independent fit and ADC deconjugation rate constant can be computed using known doses and observed AUC data. Simultaneous fit of tAB and acT data should allow for more precise identification of model parameters.

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Pascal Girard II-24 Tumor size model and survival analysis of cetuximab and various cytotoxics in patients treated for metastatic colorectal cancer

P. Girard (1), A. Kovar (2), B. Brockhaus (2), M Zuehlsdorf (2), M Schlichting (2), A. Munafo (1).
(1) Merck Serono S.A., Geneva, Switzerland; (2) Merck KGaA, Darmstadt, Germany

Objectives Cetuximab (CET) is a monoclonal antibody targeting the epidermal growth factor receptor which is prescribed for different solid tumor cancers, in association with cytotoxics (CTX). The treatment has been shown to reduce tumor size (TS) and improve overall survival (OS) [1]. We developed an exposure-TS-OS model to explore potential differences between weekly (QW) and every-2-week (Q2W) CET regimen in metastatic colorectal cancer patients.

Methods Patients from 3 studies, receiving CET weekly (400 mg/m² wk1 then 250 mg/m2/wk) or Q2W (400 or 500 mg/m2 every 2 wk) and one CTX regimen (FOLFIRI, FOLFOX4 or irinotecan) were analyzed. A simplified 2-compartment PK model with linear elimination was used to estimate individual AUC. PK was missing in one study and AUC fixed to population value adjusted by body weight. TS was described by differential equation:
$dTS/dt=[Kf - PCET \bullet AUCb \bullet PCTX \bullet \exp(-Kr \bullet t)] \bullet TS$
where t is time; Kf and Kr rate constants of TS formation and resistance; PCET and PCTX the CET and CTX treatment effect parameters; AUCb the AUC in biophase compartment [2]. From this model, predictions of early tumor shrinkage at week 8 (ETS) and time to nadir (TN time at which individual predicted TS is minimal) were estimated [3]. For both TS and OS models, KRAS mutation, health status, dosage regimen and study were tested as

potential covariates. For OS model only, ETS and TN were tested separately. All modeling was performed with NONMEM7.2 (FOCEI) and R.

Results 369 patients contributed to 3821 PK, 2053 TS and 233 death observations. For TS model, 3 significant covariates were identified: KRAS mutation decreased treatment effect PCET by 63% and CTX increased it by 50%. Q2W regimen decreased significantly and only Kr, but this effect disappeared after excluding 2nd-line treatment resistant patient data. TS model provided excellent prediction and was qualified by stratified visual predictive check. For OS model, TN was found as the best predictor of survival, better than ETS, followed by baseline TS, health status and KRAS mutation.

Conclusion This exposure-TS model is the first one developed for cetuximab. It confirmed that KRAS wild-type is a predictive marker for OS. No difference between the treatment regimens was observed on any parameter, including the development of resistance, in first-line setting patients. For overall survival, increase in time to TS nadir was found as the best predictive covariate, as suggested by a previous analysis [4].

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Sophie Gisbert II-25 Is it possible to use the plasma and urine pharmacokinetics of a monoclonal antibody (mAb) as an early marker of efficacy in membranous nephropathy (MN)?

Sophie Gisbert, Guy Meno-Tetang, Herbert Struemper, Christine Barrett, Daren Austin
GSK Stockley Park, UK

Objectives: Renal clearance is typically not considered to be a major pathway of elimination of monoclonal antibody (mAb) due to their large molecular size [1]. However it becomes a major pathway of clearance of mAb in membranous nephropathy (MN) because of "leaky kidneys". The purpose of this work is to show that urine and plasma PK may be used as early markers of clinical efficacy in MN as IgG-specific leakage in urine might be a more sensitive endpoint than non-specific proteinuria [2].

Methods: Historical Pharmacokinetics (PK) data of a typical IgG mAb were used to perform the following simulations for different multiple dosing regimen (every 4 weeks with or without a loading dose at week 2): (1) plasma PK of mAb in healthy and MN patients with different degrees of disease severity: renal clearance (CLR) equals to 0, 20, 40, 60, 80 and 100% of renal blood flow (2) amount excreted of mAb in urine for each disease severity and dosing regimen during the course of the treatment and for different urine collection intervals . Data from literature that described proteinuria as a function of glomerular filtration rate (GFR) were compared to the simulated amount of mAb excreted in urine.

Results: Simulation show that: (1) Involvement of kidneys in the elimination of the mAb leads to a proportional increase of its total clearance (2) Amount of mAb excreted in urine varies as a function of disease severity (3)

Correlations were observed between both proteinuria and the amount of mAb excreted in urine and GFR.

Conclusions: Urine PK of mAb could be followed in MN patients to assess treatment effect.

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Timothy Goggin II-26 Population pharmacokinetics and pharmacodynamics of BYL719, a phosphoinositide 3-kinase antagonist, in adult patients with advanced solid malignancies.

Stefan S.S. De Buck, Annamaria Jakab, Douglas Bootle, Markus Boehm, Cornelia Quadt and Timothy K Goggin
Oncology Clinical Pharmacology, Novartis, Basel

Objectives: To characterized the dose concentration effect relationship of BYL719, a phosphoinositide 3-kinase (PI3K) antagonist, in patients with advance solid malignancies.

Methods: The scope of this study was to develop a population pharmacokinetic and pharmacodynamic (PK/PD) model using the data from an ascending multiple dose, "proof of concept study", phase 1 clinical study. The model was used to assess the between-subject (BSV) and between-occasion (BOV) variability in drug exposure. The relationship between drug exposure and tumour response was also explored and schedule dependence assessed. Serial PK plasma samples and longitudinal tumour size measurements were collected from 60 patients with advanced solid malignancies who received oral BYL719 once daily (30 - 450 mg) or twice daily (120-200 mg). BYL719 was measured in plasma using an HPLC-MS/MS method and the sum of the longest diameter of target lesions was measured using CT or MRI scans. Goodness of fit was assessed by; classical diagnostic plots, visual predictive checks, bootstrap procedure, and precision of parameters throughout the model building process.

Results: The PK of BYL719 was best described by an open one-compartment disposition model with transit compartments accounting for the lag in

absorption. The apparent clearance and volume of distribution of BYL719 in the population were 10 L/h and 108 L, with BSV of 26% and 28 % respectively. The estimated optimal number of transit compartment was 8.1, with mean transit time (MTT) to the absorption compartment of 1.28 h (BSV 32%). Considerable BOV in the rate (MTT) and relative extent of absorption (Frel) was found (46% and 26% respectively). Tumour growth was modeled using a turnover model with a zero order growth rate (Kgrowth, 0.581 cm/week) and a first order death rate (Kdeg, 0.0123 1/week).
BYL719 inhibited growth with an IC50 of 100 ng/mL (BSV, 154%). Based on stochastic simulation of fully adherent patients, administered 400 mg once daily (the defined MTD based on an adaptive Bayesian logistic regression model with overdose control), the fraction of patients experiencing stable disease or a partial response at 20 weeks, according to the RECIST criteria was 78% and 9 % respectively. Assessment of schedule dependence indicated only a very limited difference between once or twice daily administrations of a total daily dose of 400 mg but there was an advantage of twice daily administration of the same total dose at lower doses. A considerable loss of benefit was seen already at a dosing rate of 800 mg every other day.

Conclusions: The good pharmacokinetic properties and evidence of a concentration effect relationship supports the further development of this potential therapeutic. The MTD of 400 mg given once daily seems to be an appropiate starting dose. In patients in whom mechanism based tolerability appears upon chronic dosing, a twice daily dosing rate should be considered. For example, based on the results of simulations, the administration of 100 mg given twice daily, resulted in a typical response 51 % greater than 200 mg given once daily.

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Roberto Gomeni II-27 Implementing adaptive study design in clinical trials for psychiatric disorders using band-pass filtering approach

Navin Goyal (1) and Roberto Gomeni (2)
(1) Clinical Pharmacology-Modeling and Simulation, GlaxoSmithKline, PA, USA, (2) Pharmacometrica, Longcol, La Fouillade, France

Objective: Multicenter randomized clinical trials (RCTs) in depression are relatively inefficient, and fail to differentiate known effective antidepressant drug treatments from placebo in ~50% of trials. The main reason for this failure is thought to be uncontrolled placebo response. The aim of this work was to develop an adaptive approach for conducting RCTs in depression with the objective to increase the signal-to noise ratio at study-end using the band-pass filter approach.

Methods: The band-pass filter methodology has been recently proposed as a strategy for maximizing the signal to be detected in RCTs by filtering out noise occurring in form of responses outside the low and high cutoff limits of the filter [1]. In this framework, the adaptive strategy is used to identify the non-plausible placebo response trajectories generated in a given center in a clinical trial. Blinded and unblinded approaches were evaluated to classify each recruitment center on an ongoing basis as informative or non-informative. A methodology is proposed for discontinuing the enrollment in un-informative centers and to increase the patient enrollment in informative centers.

Results: Clinical trial simulation was used to demonstrate the benefit of the proposed approach as compared to the traditional study design and study conduct. The proposed adaptive approach demonstrated that the expected drug related treatment effect in a placebo-controlled RCTs can be

significantly improved when data from informative recruitment centers are considered.

Conclusions: With this novel approach, the overall placebo response rate can be reduced and the signal-to-noise ratio substantially increased. Overall, such adaptive approach could markedly facilitate the process of clinical development of new compounds for the treatment of psychiatric disorders.

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JoseDavid Gomez Mantilla II-28 Tailor-made dissolution profile comparisons using in vitro-in vivo correlation models.

J. D. Gómez-Mantilla(1), U. F. Schäfer(1), T. Lehr(2) ,V. G. Casabó(3), C. M. Lehr(4)

(1) Biopharmaceutics and Pharmaceutical Technology, Saarland University, Saarbruecken, Germany; (2) Clinical Pharmacy, Saarland University, Saarbruecken, Germany; (3)Department of Technological Pharmacy, University of Valencia, Burjassot, Spain; (4) Helmholtz-Institute for Pharmaceutical Research (HIPS), Helmholtz Center for Infection Research (HZI), Saarbruecken, Germany

Objectives: Current alternatives for performing dissolution profile comparisons are limited to mathematical distances in which limits for declaring similarity or non-similarity are fixed, drug-unspecific and not based in any biopharmaceutical criteria. This study is aimed to develop drug-specific Dissolution Profile Comparisons able to detect the differences in release profiles between different formulations that can lead to differences in the in-vivo performance (Bioequivalence) of the formulations, using IVIVc models, computer simulated bioequivalence trials and permutation tests.

Methods: Extended release formulations of Metformin, Diltiazem and Pramipaxole were included in the study [1,2]. Available published differential equations based IVIVc models were employed using one (Metformin and Diltiazem) or two (Pramipaxole) compartment models. Release profiles were modelled using Hill and Weibull equations; Bio-relevant limits in the dissolution profiles were detected identifying the change in Hill or Weibull parameters necessary to produce non-bioequivalent formulations. Bioequivalence cross over studies were simulated with 12 healthy volunteers and Intra Individual Variability was described to fit available population data. Customization of dissolution profiles comparisons was made by adjusting the

delta of a recently described Tolerated Difference Test (TDT)[3], this delta value was tailored for each formulation to detect the differences in release profiles identified as bio-relevant limits with the IVIVc models. Effect of Number of patients, Number of time points and drug properties (ka, kel) were studied in these customizations.

Results: Bio-relevant limits in release profiles differences were identified for all three formulations. Delta values for TDT were tailored for each formulation as follows: 3.8 for Metformin, 5.8 for Diltiazem and 3.5 for pramipaxole, this value represents the average tolerated difference (in Percentage) between two formulations at any time point to produce bio-equivalent formulations under both criteria AUC and Cmax. Total overlap of zones was not possible, but safe zones (Bioequivalent formulations under Cmax or AUC criteria) were totally identified. The studied variables had a greater impact in the bioequivalence decisions made by Cmax than by AUC, especially Ka and kel.

Conclusion: TDT test allows customization of formulation-specific dissolution profile comparisons of extended released formulations with bio-relevant limits.

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Ignacio Gonzalez II-29 Simultaneous Modelling Of Fexofenadine In In Vitro Cell Culture And In Situ Experiments

Gonzalez-García, I. (1), Mangas-Sanjuan,V.(2), Bermejo, M.(2), Casabo, VG.(1)
(1) Departamento de Farmacia y Tecnología Farmacéutica, Universidad de Valencia;(2) Departmento de Ingeniería, Universidad Miguel Hernández de Elche.

Introduction: Fexofenadine HCl (FEX), a second generation non-sedating histamine H1 receptor antagonist, is an active metabolite of terfenadine. Permeability of FEX was determined in an in vitro cell model and in situ experiment at different donor concentrations, and the effect of sodium dodecyl sulfate (SDS) at two concentration levels (10 and 50 µM) on FEX permeability was evaluated simultaneously.

Objective: The aim of this work is to model simultaneously in vitro and in situ data to obtain common parameters of the absorption and distribution of Fexofenadine in both biological systems.

Materials and Methods: The in vitro transport studies were developed in Caco-2 cell in apical-to-basolateral (AB) and basolateral-to-apical (BA) direction. The in situ experiments were performed in Wistar rats. Permeability values were estimated by non-linear regression of cumulative amounts in the receptor chamber, and remaining amounts in donor chamber versus time and by non-linear regression of decreasing concentrations in lumen. The fitting procedures were performed using NONMEM 7.2 with FOCE+I for objective function estimation and ADVAN9 subroutine. Several kinetic models were fitted to the data, functional and mechanistic models, selecting the best model with lowest objective function value. The inter-individual and residual variabilities of the kinetic parameters were described

with exponential models. Goodness of fit plots and visual predictive check were generated to confirm the final model.

Results: The simultaneous analysis of in vitro and in situ experiments are well modeled using a common permeability for all concentrations without surfactant and a different permeability in the presence of surfactant. An active transport is observed in cells and in rats which was included in the final model. The presence of high concentration of surfactant (50 mM) affects to the passive diffusion of FEX in cells systems. Nevertheless, the presence of surfactant does not affect in vivo, but changes the function of the transport. Permeability as a function of time and lag time parameters were used to account for the intercept of the cumulative fractions permeated versus time that was different from 0.

Conclusions: Fexofenadine has a low intestinal permeability in vitro in Caco-2 cells and in situ rats experiments and the transport of the drug is concentration-dependent. The simultaneous analysis allows to estimate parameters that are present in both systems and to be able to establish similarities or differences between the cell line and rats.

Sathej Gopalakrishnan II-30 Towards assessing therapy failure in HIV disease: estimating in vivo fitness characteristics of viral mutants by an integrated statistical-mechanistic approach

Sathej Gopalakrishnan (1,2), Hesam Montazeri (3), Stephan Menz (4), Niko Beerenwinkel (3), Wilhelm Huisinga (4)
(1) Institute of Biochemistry and Biology, Universitaet Potsdam, Potsdam, Germany, (2) PharMetrX Graduate Research Training Program, Freie Universitaet Berlin and Universitaet Potsdam, Germany, (3) ETH Zurich, Department of Biosystems Science and Engineering (D-BSSE), Basel, Switzerland, (4) Institute of Mathematics, Universitaet Potsdam, Potsdam, Germany

Objectives: Mechanistic viral infection models have long been used to investigate in vivo HIV-1 dynamics [1], while statistical models [2] have been applied to learn mutational schemes from sparse clinical data. While the former approach generally uses highly simplified mutation schemes, the latter methods limit mechanistic understanding. Combining the two approaches would prove valuable to estimate viral fitness characteristics and to assess causes of therapy failure. The objective of this work was to link the two modelling strategies and to evaluate the integrated approach by comparing estimated in vivo fitness characteristics of various mutants arising under monotherapy with Zidovudine (AZT) and Indinavir (IDV) to values in literature.

Methods: We used a two-stage mechanistic HIV infection model [3] to predict in vivo viral dynamics. We utilized continuous time conjunctive Bayesian networks [4] to learn mutational schemes, resistances and average waiting times to mutations from clinical data (the Stanford HIV Database) [5].

Simulations and estimation procedures were carried out with MATLAB R2010b.

Results: We translated phenotypic IC50 values from in vitro assays to an in vivo setting that we use in our mechanistic model. We then developed an approach to compare the average statistical waiting times and mechanistically predicted waiting times to observe various mutations. Estimating in vivo fitness costs of different mutants arising under AZT (a reverse transcriptase inhibitor), we recovered the well-known TAM-1 and TAM-2 mutation pathways and observed excellent agreement with existing knowledge. We also reproduced the interesting observation that the rebound of the wild-type strain, in case of insufficient drug efficacy, contributes significantly to the initial rebound in the total viral load and the wild-type is out-competed by the mutants only after about 60-70 days. We finally estimated fitness costs of mutants arising under IDV (a protease inhibitor) therapy to demonstrate the generality of our approach.

Conclusions: Our scheme relies only on clinical data that is typically censored and is usually the most commonly available form of data. Such integrated mechanistic-statistical approaches provide a first step towards analysis of HAART regimens.

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Verena Gotta II-31 Simulation-based systematic review of imatinib population pharmacokinetics and PK-PD relationships in chronic myeloid leukemia (CML) patients

Verena Gotta(1,2), Thierry Buclin(1), Nicolas Widmer(1), Chantal Csajka(1,2)
(1)Division of Clinical Pharmacology, Department of Laboratories, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; (2)School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

Objectives: Several population pharmacokinetic (PPK) and pharmacokinetic-pharmacodynamic (PK-PD) analyses have been performed with the anticancer drug imatinib. Inspired by the approach of meta-analysis, we aimed to compare and combine results from published studies in a useful way - in particular for improving the clinical interpretation of imatinib concentration measurements in the scope of therapeutic drug monitoring (TDM).

Methods: Original PPK analyses and PK-PD studies (PK surrogate: trough concentration C_{min}; PD outcomes: optimal early response and specific adverse events) were searched systematically on MEDLINE. From each identified PPK model, a predicted concentration distribution under standard dosage was derived through 1000 simulations (NONMEM), after standardizing model parameters to common covariates. A "reference range" was calculated from pooled simulated concentrations in a semi-quantitative approach (without specific weighting) over the whole dosing interval. Meta-regression summarized relationships between C_{min} and optimal/suboptimal early treatment response.

Results: 9 PPK models and 6 relevant PK-PD reports in CML patients were identified. Model-based predicted median C_{min} ranged from 555 to

1388 ng/ml (grand median: 870 ng/ml and inter-quartile range: 520-1390 ng/ml). The probability to achieve optimal early response was predicted to increase from 60 to 85% from 520 to 1390 ng/ml across PK-PD studies (odds ratio for doubling C_{min}: 2.7). Reporting of specific adverse events was too heterogeneous to perform a regression analysis. The general frequency of anemia, rash and fluid retention increased however consistently with C_{min}, but less than response probability.

Conclusions: Predicted drug exposure may differ substantially between various PPK analyses. In this review, heterogeneity was mainly attributed to 2 "outlying" models. The established reference range seems to cover the range where both good efficacy and acceptable tolerance are expected for most patients. TDM guided dose adjustment appears therefore justified for imatinib in CML patients. Its usefulness remains now to be prospectively validated in a randomized trial.

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Bruce Green II-32 Clinical Application of a K-PD Warfarin Model for Bayesian Dose Individualisation in Primary Care

Bruce Green (1,2) and Robert McLeay (1)
(1) DoseMe Pty Ltd, Brisbane, Australia, (2) Model Answers Pty Ltd, Brisbane, Australia

Objectives: To compare the probability of successful INR attainment using individualised dosing for warfarin via Bayesian forecasting (DoseMe) or nomogram-based dosing methods.

Methods: A pre-existing K-PD model for warfarin [1] was used to simulate INR over 6 weeks using 2 nomograms and a Bayesian forecasting program (DoseMe) [2]. The first nomogram adjusted dose based upon genotype and INR [3], whereas the second nomogram adjusted dose based upon INR alone [4,5]. DoseMe was also used to adjust dose with and without genotype information.

Results: At day 20 and 60, 40% [24 - 46%] and 78% [67 - 86%] (median, 95%CI) of subjects were expected to have an INR in range using the genotype nomogram-based dosing. At day 20 and 60, 26% [16 - 36%] and 26% [16 - 38%] of subjects were expected to have an INR in range using the non-genotype nomogram-based dosing. Comparative genotype Bayesian-based dosing was expected to have 64% [49.0 - 76%] and 72% [59 - 82%] of subjects in the range at day 20 and 60, respectively, whilst non-genotype Bayesian-dosing was expected to have 63% [48 - 72%] and 74% [60 - 84%] of subjects in the range. The observed clinical trial result for the genotype nomogram-based dosing was 66.7% [3], which was captured by the simulation model.

Conclusions: Non-genotype Bayesian dosing resulted in quicker and more accurate attainment of therapeutic INR when compared to non-genotype

nomogram-based dosing. Genotype-based Bayesian dosing also resulted in quicker attainment of therapeutic INR compared to genotype nomogram-based dosing. As genotype is rarely available in clinical practice, Bayesian methods such as DoseMe provide an easy to use practical solution that should be used in clinical practice to optimise patient outcomes.

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Zheng Guan II-33 The influence of variability in serum prednisolone pharmacokinetics on clinical outcome in children with nephrotic syndrome, based on salivary sampling combined with translational modeling and simulation approaches from healthy adult volunteers

Zheng Guan(1,2), Nynke Teeninga(3), Jeroen Nauta(3), Joana E. Kist-van Holthe(4), Mariëtte T. Ackermans(5), Ron H.N. van Schaik(6), Teun van Gelder(7), Jasper Stevens(1), Jan Freijer(1)

(1) Centre for Human Drug Research, Leiden, the Netherlands; (2) Leiden university medical centre, Leiden, the Netherlands; (3) Department of Pediatrics, division of Nephrology Erasmus University Medical Centre – Sophia Children's Hospital, Rotterdam, the Netherlands; (4) Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands; (5) Department of Clinical Chemistry, Laboratory of Endocrinology, Academic Medical Center, Amsterdam, the Netherlands; (6) Department of Clinical Chemistry, Erasmus University Medical Centre, Rotterdam, the Netherlands; (7) Departments of Internal Medicine and Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, the Netherlands

Background: Prednisolone (PLN) represents the cornerstone for the treatment of childhood nephrotic syndrome (NS) since 1950's. However, pediatric patients show considerable variability in therapeutic response and side-effects to standard, empirically based dosing regimens [1, 2, 3, 4, 5]. The question arises whether variability in PK can explain, as driving force for the PD, the differences in therapeutic response between individuals. Concentrations in saliva may represent free PLN levels in blood, as only free fraction of PLN can diffuse into target tissues and cells, and can therefore be considered clinically more relevant than total PLN concentrations [1, 2, 6, 7,

8]. Salivary sampling can also help to avoid burdensome in pediatric patients caused by blood sampling. In present study, we tested the influence of variability in PLN on clinical outcome in children with NS, based on only salivary sampling combined with translational modeling and simulation approaches from healthy adult model.

Methods: 385 salivary PLN measurements were obtained from 104 Dutch children with NS. The children received 40 mg/m2 oral PLN after induction dosing period of six weeks. Parents collected salivary samples at home with Salivette. We adapted the developed adult population PK model [9] to our current pediatric population using body weight-dependent exponent model [10]. Based on the individual parameters estimated and the actual PLN dose administered, individual post hoc curves of free serum PLN were simulated and then were used to derive area under the curve of free concentration of PLN in serum (AUCfree). Differences in the AUCfree between categories of clinical outcomes were assessed with either a Student's T-test or ANOVA.

Results: Clearance and distribution volume were estimated to be 18.7 L/hr and 74.4 L with relatively small RSE values (23.0% and 10.4%). AUCfree was then calculated to be 859 (inter quartile range: 806-943) ng.hr/ml based on simulated individual free serum concentration-time profiles. AUCfree showed no significant correlation with therapeutic effect and adverse effects.

Conclusions: Using translational modeling and simulation, the model described in the present study supports the use of salivary PLN concentrations as a reliable predictor of free levels in serum. However, we conclude that it is unlikely that variability in PLN exposure in the therapeutic dose range studied is a major determinant of clinical outcome in children with NS.

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Monia Guidi II-34 Impacts of environmental, clinical and genetic factors on the response to vitamin D supplementation in HIV-positive patients

M. Guidi (1) (2), G. Foletti (3), A. Panchaud (1), P. Tarr (4), B. Sonderegger (5), M. Cavassini (6), A. Telenti (3), M. Rotger (3), C. Csajka (1) (2) and the Swiss HIV Cohort Study

(1) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva Switzerland; (2) Division of Clinical Pharmacology, Department of Laboratories, University Hospital Lausanne, Lausanne, Switzerland; (3) Institute of Microbiology, University Hospital Lausanne, Lausanne, Switzerland; (4) Medizinische Universitätsklinik, Kantonsspital Bruderholz, Basel, Switzerland; (5) Infectious Diseases Service, Inselspital, Berne, Switzerland; (6) Infectious Diseases Service, University Hospital Lausanne, Lausanne, Switzerland.

Objectives: Vitamin D deficiency is highly prevalent in HIV-infected individuals and has been associated to the progression of the disease and/or to antiretroviral therapy [1,2]. Vitamin D supplementation in patients with plasma levels of 25-hydroxy-vitamine D (25-OHD) < 30 mcg/l has become standard of care. The aim of this analysis was to characterize the time profile of 25-OHD in HIV patients before and after vitamin D supplementation and to test the influence of genetic polymorphisms along with antiretroviral treatment (ART) and non-genetic factors on vitamin D levels. The model served for the simulation of different vitamin D regimens that will help establishing the appropriate dose and time interval for vitamin D supplementation.

Methods: A one-compartment model with first-order absorption and elimination was used to describe 25-OHD concentrations, including a steady-state production rate for the estimation of the endogenous 25-OHD

(NONMEM®). Co-administered ART drugs, demographic, environmental variables and seven genetic variants (located on GC, CYP2R1, DHCR7/NADSYN1, CYP24A1) known to influence vitamin D levels according to two genome wide association studies (GWAS) were tested as covariates [3,4].

Results: A total of 1285 25-OHD concentrations, either basal or after a single vitamin D dose supplementation, were collected from 618 patients in three different Swiss hospitals. Average oral clearance was 2.77 L/day, volume of distribution 258 L and endogenous production rate 0.14 micromol/day (CV 39%). Among all the tested covariates, season effect had the most salient impact on vitamin D production rate (maximal increase of 27% ($CI_{95\%}$: 23-30%) at day 228 (220-235 day), i.e. August). Body mass index, smoking status and SNP rs2282679 located on the GC gene, responsible for the vitamin D binding protein transcription, reduced 25-OHD production rate respectively by 39% ($CI_{95\%}$: 24-54 %), 13% (8-19 %) and 20% (7-33 %); while co-administration of darunavir increased it by 16% (5-27 %). An effect of the study center was also observed. The significant covariates explained altogether 12% of the interpatient variability associated to the vitamin D endogenous production rate.

Conclusion: This analysis of 25-OHD plasma levels in HIV infected patients allowed identifying genetic and other risk factors associated with vitamin D deficiency in this population. Improvement of dosage regimen and timing of vitamin D supplementation is proposed based on those results.

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Vanessa Guy-Viterbo II-35 Tacrolimus in pediatric liver recipients: population pharmacokinetic analysis during the first year post transplantation

Vanessa Guy-Viterbo (1), Anaïs Scohy (1), Raymond Reding (2), Roger Verbeeck (3), Pierre Wallamacq (1), Flora Tshinanu Musuamba (1, 3)
(1) Louvain Center for Toxicology and Applied Pharmacology, Université catholique de Louvain, Brussels, Belgium (2) Pediatric Surgery and Liver transplant Unit, Cliniques Universitaires St-Luc, Université catholique de Louvain, Brussels, Belgium (3) Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium.

Objectives: Different tacrolimus pharmacokinetics (PK) models have been proposed to characterize the tacrolimus PK variability observed in pediatric liver transplantation. They mainly focused on the early post transplantation period. However, as acute rejection may occur up to the end of the first year, the objective of this study was to describe tacrolimus PK during the first year post liver transplantation in a pediatric cohort.

Methods: TAC doses and routine TDM trough levels from 82 pediatric liver allograft recipients during the first year post transplantation were used to develop a population PK model using mixed effects modelling. Patient's demographics, biochemical test results and physiological characteristics were tested as covariates to explain interindividual variability. Data from 42and 40 patients were used for model building and model validation, respectively.

Results: A two-compartment model with first-order elimination best described the TAC PK. Apparent volumes of central and peripheral compartments, intercompartmental clearance and blood clearance estimates were 85L, 100L, 11.3L/h and 4.96L/h, respectively. The absorption first order rate fixed to $4.5h^{-1}$. Bodyweight was the only covariate found to have a

significant effect on volumes of distribution whilst hematocrit levels, time after transplantation and bodyweight all influenced the TAC clearance. Bias and precision of estimates were within acceptable limits after model validation.

Conclusions: We developed and validated a tacrolimus PK model covering the first year after pediatric liver transplantation. After implementation in PK software with Bayesian prediction, this model could therefore constitute a unique tool to help clinicians for tacrolimus posology adaptation.

Chihiro Hasegawa II-36 Modeling & simulation of ONO-4641, a sphingosine 1-phosphate receptor modulator, to support dose selection with phase 1 data

Chihiro Hasegawa (1), Susumu Nakade (2), Tomoya Ohno (1), Junji Komaba (2), and Mikio Ogawa (1)
(1) Pharmacokinetic Research Laboratories, Ono Pharmaceutical Co., Ltd, Japan, (2) Drug Development, Ono Pharma USA, Inc., U.S.A.

Objectives: ONO-4641 is an orally administered sphingosine 1-phosphate (S1P) receptor modulator that is currently under clinical evaluation for multiple sclerosis (MS). The pharmacokinetic (PK) and pharmacodynamic (PD) properties of ONO-4641 in MS patients were assessed in order to support dose selection for the future trial in terms of efficacy and safety.

Methods: The population PK-PD modeling was performed using NONMEM based on plasma concentrations of ONO-4641 and absolute lymphocyte counts (ALC) obtained in phase 1 trials. With the use of the developed model, a clinical trial simulation was conducted based on the study design planned for phase 2 trial.

Results: The population PK-PD model was developed using data from 83 subjects. The relationship between ALCs and plasma concentrations of ONO-4641 was described by an indirect-response model [1-3]. The indirect-response model had an Imax value of 0.991 and an IC50 value of 2.12 ng/ml for MS patients. Based on the ALC-endpoint relationship in phase 2 trial of another MS drug, the ALC suppression of >60% from baseline was believed to show the efficacy on the endpoint (number of lesions obtained with magnetic resonance imaging) [4]. The simulation results using the developed model indicated that ONO-4641 dose more than 0.1 mg produced the decrease. The suppression with lower doses was mild to moderate (30-45%), but the

efficacy on the number of lesions was unknown. Further, the simulation results indicated the mean drop-out rate due to the lymphopenia of at most 3% of total patients in phase 2 trial.

Conclusions: The clinical trial simulation of ALC based on the developed population PK-PD model led to the acquisition of useful information for selecting doses in the future trial.

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Michael Heathman II-37 The Application of Drug-Disease and Clinical Utility Models in the Design of an Adaptive Seamless Phase 2/3 Study

Michael Heathman(1), Zachary Skrivanek(1), Brenda Gaydos(1), Mary Jane Geiger(2), Jenny Chien(1)
(1)Eli Lilly and Company, Indianapolis, IN, USA; (2)Relypsa, Inc, Redwood City, CA, USA

Objectives: A two-stage, adaptive dose-finding, inferentially seamless Phase 2/3 study was designed to optimize the development of dulaglutide (dula), a new therapeutic for the treatment of type 2 diabetes mellitus. Integrated models of dula pharmacokinetics and pharmacodynamics (PD) of key clinical and safety measures were developed, leveraging early phase clinical data and literature data of marketed comparators. These models were used to simulate virtual patients and to evaluate the operating characteristics and probability of success of the trial.

Methods: Data from early phase studies were used to develop models of prospectively selected clinical endpoints for dose determination: a linked model of glucose-HbA1c, a weight loss model with placebo response and circadian rhythm models of blood pressure and heart rate. Published comparator's longitudinal data were used to inform the timecourses of PD endpoints. Virtual patient populations (N=10,000) were simulated to match baseline demographic and disease characteristics of a typical Phase 3 study population for up to a year. A Bayesian theoretical framework was used to adaptively randomize virtual patients sampled from the dataset in Stage 1 to one of seven dula doses. At each interim analysis, a multi-attribute clinical utility function was applied to predefined dose selection criteria to support either stopping for futility or selecting up to 2 dula doses to advance to Stage 2.

Results: Dula drug-disease models predicted the most likely doses to demonstrate optimal and competitive glycemic efficacy and safety profiles. In simulated studies, the adaptive algorithm identified the correct dose 88% of the time, compared to as low as 6% for a fixed-dose design using frequentist decision rules.

Conclusions: Drug-disease models developed using limited Phase 1 and literature data are efficient tools to support the optimization of drug development. Model-based trial simulations allow systematic and robust evaluation of trial design and assessment of probability of trial success.

Emilie Hénin II-38 Optimization of sorafenib dosing regimen using the concept of utility

Emilie Hénin, Michel Tod
EMR HCL/UCBL 3738 CTO, Faculté de Médecine Lyon-Sud, Université de Lyon

Objectives: The utility function allows finding a compromise between drug efficacy and toxicity, balancing the probability of benefit and the probability of risks [1, 2]. Sorafenib is an oral non-specific multi-kinase inhibitor, approved for the treatment of renal and hepatic carcinoma, blocking cell proliferation and angiogenesis by targeting Raf/ERK pathway. Hand-foot Syndrome (HFS) is one of the major dose-limiting toxicity. This work aimed at applying the concept of utility function to determine the optimal regimen of sorafenib, integrating models for efficacy and toxicity.

Methods: Sorafenib-induced efficacy and toxicity in 100 replicates of 100 patients were simulated under various dosing regimen: daily dose ranging between 200 and 2000 mg, fractionated as 1, 2, 3 or 4 occasions.
The pharmacokinetics were described by a one-compartment model with first-order elimination and saturable absorption [3]. The efficacy on tumor growth inhibition (TGI) was sigmoidally linked to the area under the unbound concentration curve at steady state [4]. The risk of HFS was characterized by a latent variable model whose kinetics is impacted by sorafenib accumulated plasma concentration and whose levels are translated into HFS probability [5].
The utility was defined as a weighted sum of the probability of benefit and the probability of non-risk, the weights adding to 1. It aimed at maximizing the percentage of patients showing at least 20% TGI (responders) and minimizing the risk for grade 2 or 3 HFS. The sensitivity to the relative contribution of efficacy and toxicity to the utility was also evaluated.

Results: The usual regimen of sorafenib is 400mg twice daily (800mg per day). The non-linear pharmacokinetics of sorafenib result in greater exposure the more the daily dose is fractionated.
Considering a 60% efficacy-40% toxicity balance, a maximal plateau in utility is obtained for 200mg to 400mg twice daily. Increasing the contribution of efficacy (or the expected TGI for responders) tends to favor the fractionation of the daily dose: e.g. if the efficacy criterion is the % of responders with TGI > 40% or greater, the utility function favors the four times daily regimen.

Conclusion: The utility is a comprehensible concept for the optimization of dosing regimen, allowing the balance between the required response and acceptable risks. This approach relies on the combination of several PK-PD models, and can be extended to multi-scale models.

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Eef Hoeben II-39 Prediction of Serotonin 2A Receptor (5-HT2AR) Occupancy in Man From Nonclinical Pharmacology Data. Exposure vs. 5-HT2AR Occupancy Modeling Used to Help Design a Positron Emission Tomography (PET) Study in Healthy Male Subjects.

E. Hoeben (1), V. Sinha (2), P. de Boer (3), K. Wuyts (4), H. Bohets (5), E. Scheers (5), X. Langlois (6), P. Te Riele (6), and H. Lavreysen (6)
Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse Belgium

Objectives: JNJ-mGluR2 PAM, a positive allosteric modulator of the metabotropic glutamate receptor-2 and 5-HT_{2A}R antagonist, is currently in development for the treatment of disorders of the central nervous system [1,2]. To understand the pharmacological profile of JNJ-mGluR2 PAM and to define exposure *vs.* 5-HT_{2A}R occupancy relationship in man, a PET study was performed in healthy male subjects [3]. To help in designing a PET study, 5-HT_{2A}R occupancies in man were predicted based on *in vitro* and *in vivo* nonclinical pharmacology data in the rat.

Methods: *In vitro* functional and radioligand binding experiments were performed to investigate the *in vitro* activity and binding of JNJ-mGluR2 PAM and its major metabolite (M47) to human 5-HT_{2A}R. Receptor occupancy assays were conducted in rats to evaluate JNJ-mGluR2 PAM occupancy to 5-HT_{2A}R *in vivo*. Plasma concentrations *vs.* 5-HT_{2A}R modeling was performed in rat and used to predict the 5-HT_{2A}R occupancy in man. The relationship between predicted 5-HT_{2A}R occupancy and simulated plasma concentrations in man was used to predict 5-HT_{2A}R occupancy in man at clinical doses of 50 to 700 mg.

Results: *In vitro* preclinical experiments showed that JNJ-mGluR2 PAM is a weak 5-HT_{2A}R antagonist. In rats, JNJ-mGluR2 PAM is rapidly metabolized to M47 which is a relatively potent and selective 5-HT_{2A}R antagonist. Modeling experiments suggested that M47 significantly contributes to the 5-HT_{2A}R binding in the rat but in humans only limited metabolism to M47 has been observed. Accounting for the different contributions of parent and metabolite and the differences in free fraction in rat *vs.* man, 5-HT_{2A}R occupancy could be predicted in man based on exposure *vs.* 5-HT_{2A}R modeling in the rat. At clinical doses of 50 to 700 mg, predicted 5-HT_{2A}R occupancy in man ranged between 5% and 25%. The human PET data confirmed minimal 5-HT_{2A}R occupancy by JNJ-mGluR2 PAM in man, which is not expected to be clinically relevant.

Conclusions: 5-HT_{2A}R occupancy could be predicted in man based on nonclinical pharmacology data in the rat, taking into account the difference in free fraction and the different contributions of parent and metabolite in rat *vs.* man. At clinical doses, predicted 5-HT_{2A}R occupancy in man was low and in good agreement with observed 5-HT_{2A}R occupancy in man. This modeling work illustrated the "translatability" of *in vitro* and *in vivo* preclinical information to 5-HT_{2A}R occupancy in man.

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Taegon Hong II-40 Usefulness of Weibull-Type Absorption Model for the Population Pharmacokinetic Analysis of Pregabalin

Taegon Hong (1,2), Seunghoon Han (1,2), Jongtae Lee (1,2), Sangil Jeon (1,2), Jeongki Paek (1,2), Dong-Seok Yim (1,2)
(1) Department of Pharmacology, College of Medicine, The Catholic University of Korea, (2) Department of Clinical Pharmacology and Therapeutics, Seoul St.Mary's Hospital

Objectives: Pregabalin is an anticonvulsant used for the treatment of neuropathic pain and partial seizure in adults. The aim of this study was to develop a population pharmacokinetic (PK) model to describe the absorption characteristics of pregabalin given fasting or after meals.

Methods: Data from 5 healthy subject PK studies (n = 88) of single or multiple dose pregabalin (150 mg) were used. Pregabalin was administered twice daily, without meals or 30 min after a meal (regular diet or high fat diet) in the morning and 30 min or 4 h after a meal (regular diet) in the evening. Serial plasma samples were collected up to 24 h after the last dose for PK analysis. To find the model that best describes the absorption process, first-order, transit compartment, and Weibull-type absorption models were compared using the non-linear mixed effect method (NONMEM, ver. 7.2).

Results: A two-compartment linear PK model with Weibull-type absorption using its cumulative distribution function was better than the first-order absorption model with lag time. The conditional weighted residuals at T_{max} and visual predictive check plots obtained from the Weibull-type absorption model were less biased than those from the first-order absorption model.

Conclusions: We found that the Weibull-type absorption model best described the absorption characteristics of pregabalin regardless of meal status and the absorption model should be carefully chosen based upon the principle of model development and validation, not by following a conventional model for its popularity and simplicity, especially when the PK dataset includes densely sampled data.

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Andrew Hooker II-41 Platform for adaptive optimal design of nonlinear mixed effect models.

Andrew C. Hooker (1), J. G. Coen van Hasselt (2)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (2) Department of Clinical Pharmacology, Netherlands Cancer Institute, Amsterdam, Netherlands.

Introduction: Recent years have seen an increasing interest in adaptive trial design methodologies. With the growing use of nonlinear mixed effect (NLME) models to support clinical development, adaptive optimal design (AOD) approaches have also become increasingly
relevant. A recent survey indicated that out of 10 major European pharmaceutical companies, the importance of AOD for NLMEM was ranked, 4 on a scale of 5, on average [1]. The usefulness of AOD approaches for NLME models has been previously demonstrated for PET occupancy studies [2], bridging studies [3] and pediatric PK studies [4].

Aims: To develop a general computational platform for adaptive optimal study design in the context of NLME models.

Methods: A general algorithm for implementing AOD methodology was created using the optimal design software package PopED [5,6] which links to NONMEM [7] and Perl speaks NONMEM [8] for the estimation steps. The proposed AOD methodology consisted of the following steps:
i) definition of prior NLME model(s);
ii) study design optimization of an initial cohort of subjects based on the prior NLME model(s);
iii) collection and estimation of a cohort of data using the optimized study design (alternatively, stochastic simulation and re-estimation);
iv) updating of the prior NLME model(s) from the estimation step.

Steps ii-iv are repeated (and might change between each iteration) until a predefined stopping criteria has been reached.

Results: An initial implementation of the AOD platform was successfully implemented, allowing the evaluation of feasibility and the identification of technical challenges. The AOD platform has a modular setup and a generalized and flexible design, allowing modifications for specific study design characteristics. As proof-of-concept, an application of adaptive optimal design of a pediatric PK bridging study supported by a maturation model [9] was implemented, in which study designs were optimized for age-cohorts and sampling times.

Conclusion: We successfully developed an initial implementation of an AOD computational platform, which will be available as freeware when released.

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Daniel Hovdal II-42 PKPD modelling of drug induced changes in thyroxine turnover in rat

D. Hovdal (1)
(1) Modelling & Simulation, iMed DMPK CVGI, AstraZeneca R&D Mölndal, Sweden

Objectives: To determine the *in vivo* potency of drug induced reduction in plasma thyroxine, T4, levels for three different drugs in rat and to explore how *in vivo* potency correlates with *in vitro* data.

Methods: A three day toxicological study with a two days washout period in rat was performed. Vehicle and three different compounds were tested at two or three dose levels. The study was designed to monitor the onset and extent of T4 reduction, as well as the return of T4 levels to baseline during washout. In all blood samples collected, the drug exposure and T4 levels were measured. A pharmacokinetic model was developed for each compound. Since all treatment groups share the systems parameters related to the turnover of T4, one PD model in form of a standard turnover model was applied to all T4 data. To identify the effects of the different compounds, the drug induced changes in T4 levels were driven by the individual pharmacokinetic profiles and unique *in vivo* potency of T4 reduction (*IC50*) was used for each compound. All analysis was performed using the NMLE module in Phoenix.

Results: The pharmacokinetics of the three drugs could be described by oral one or two compartment models with modified absorption. A drift in the baseline levels of T4 was observed and accounted for in the turnover model. The drug induced changes in T4 levels were successfully modeled by applying an I_{max} function on the production rate of T4. In contrast to consider one compound at a time, the simultaneous fit of the model to all T4 data allowed

determination of the systems parameters of T4 turnover. As a result the potency of the different compound could be determined; despite administration of insufficient dose ranges to appropriately define the full inhibitory function of each compound. The derived *in vivo* potencies confirmed the ranking the compounds obtained by *in vitro* data.

Conclusions: Population PKPD modeling of preclinical data allows generation of more robust models (takes into account all available information) and allows conclusions to be drawn when the available information of each data set is insufficient for individual analysis.

Yun Hwi-yeol II-43 Evaluation of FREM and FFEM including use of model linearization

Hwi-yeol (Thomas) Yun, Ronald Niebecker, Elin M. Svensson, Mats O. Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: In full model approaches, covariate relations are predefined [1]. Attaching covariate relations selectively to only some of the model parameters can lead to selection bias [2,3]. By allowing all covariates of interest to affect all parameters, this risk of selection bias is mitigated. In the present work we evaluate and compare two full model approaches that both allow estimation of all parameter-covariate relations: a full random effects model (FREM [3,4]) and a full fixed effects model (FFEM) saturated with respect to parameter-covariate relations.

Methods: A semi-mechanistic myelosuppression model with four structural parameters and a dataset containing 636 individuals and 3549 observations was used [5]. In addition, two dummy covariates having correlations of 0.5 and 0.75 respectively with a clinically relevant covariate were generated to investigate the performances of correlated covariates in both models. Linearization to decrease run times during model development and evaluation was assessed for both methods [6,7]. The performance was evaluated in terms of model run times, estimates and precision of parameters and ability to identify clinically relevant covariates. Precision was derived from variance-covariance matrix and bootstraps. FOCE-I with NONMEM 7.2 assisted by PsN was used.

Results: Both FREM and FFEM were successfully implemented, also as linearized models with good agreement and several magnitudes shorter run

times. FFEM and FREM were found to be similarly precise. Run times for FREM and FFEM were similar. Both methods identified the same parameter-covariate relationships to be clinically relevant. However, in the case of correlated covariates, only FREM was able to identify all clinically relevant parameter-covariate relations. Furthermore, the coefficients were more precisely estimated compared to FFEM.

Conclusions: Although FREM and FFEM performed equally well in this case with an informative dataset and predominantly uncorrelated covariates, FREM has advantages in comparison with FFEM when investigating correlated covariates. This first combination of linearization and FREM/saturated FFEM appears to be promising and should be further evaluated.

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

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Ibrahim Ince II-44 Oral bioavailability of the CYP3A substrate midazolam across the human age range from preterm neonates to adults

I. Ince (1,2), S.N. de Wildt (1), M.Y.M. Peeters (3), K. Burggraaf (4), E. Jacqz-Aigrain (5), J.S. Barrett (6), M. Danhof (2), C.A.J. Knibbe (1,2,3)
1.Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands; 2.Leiden/Amsterdam Center For Drug Research, Leiden, The Netherlands; 3.St. Antonius Hospital, Nieuwegein, The Netherlands; 4.Centre for Human Drug Research, Leiden, The Netherlands; 5.University Diderot, Paris, France; 6.Children's Hospital of Philadelphia, Philadelphia, PA, USA

Objectives: A maturation model for midazolam clearance from preterm neonates to adults has been previously developed, analyzing data that were obtained after IV dosing of midazolam across the entire human age range.[1] The aim of this study was to investigate changes in oral bioavailability and absorption rate of midazolam across the pediatric age range upon oral dosing of midazolam. The results can be used for the development of evidence-based dosing of oral midazolam in children.

Methods: Pharmacokinetic (PK) data were obtained from a combined dataset of 7 previously reported studies in 52 preterm infants (26-37 weeks GA, PNA 2-13 days), 305 children (3 months-18 years) and 20 adults, who received IV and/or PO midazolam. Population PK modeling was performed using NONMEM v6.2, and the influence of postnatal age (PNA), bodyweight (BW) and study population was investigated in a systematic covariate analysis.

Results: Oral bioavailability of midazolam with a population estimate of 24% (CV of 7.5%) was negatively influenced by BW in an allometric function, resulting in a value of 67% in a preterm neonate of 0.77 kg to 17% in an adult (70 kg). Previous results on the influence of BW on midazolam CL,

characterized using an allometric function with a BW dependent exponent (BDE),[1] were confirmed.

Conclusions: Oral bioavailability of midazolam decreases from preterm neonates to adults, leading to higher systemic availability of midazolam in preterm neonates (67%) compared to older children or adults (17%). While this information may aid for the development of evidence-based dosages of oral midazolam for children of different ages, further physiologically-based modeling should elucidate the exact subprocesses that contribute to the reported age related changes in oral bioavailability of midazolam.

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Lorenzo Ridolfi II-45 Predictive Modelling Environment - Infrastructure and functionality for pharmacometric activities in R&D

Lorenzo Ridolfi (1), Chris Franklin (1), Oscar Della Pasqua (1)
(1) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT

Objectives: The Predictive Modelling Environment (PME) supports Clinical Pharmacology Modelling & Simulation, enabling the implementation of M&S activities which are used to facilitate decision making within GSK. The system's architecture has been developed taking into account a pre-defined workflow and the interaction between software packages such as R and NONMEM 7.2. Here we describe how a server-based tool has been implemented within the regulated R&D environment. Moreover, we show how workflow and software functionalities are integrated to meet the needs of a continuously growing pharmacometric community.

Methods: Architecture and system requirements to integrate hardware (platforms), software and user interface functionality have been summarised and reviewed against user requirements and workflows for data manipulation, model building, validation and reporting. An overview of system performance is provided, which includes a GAP analysis and a summary of modelling outputs and typical computation times.

Results: The current environment provides access to NONMEM 7.2 as executable software in the web and command line (Linux shell), which are linked to a grid engine with PsN, RStudio and R as ancillary tools supporting the pre-defined M&S workflow. Integrated modules have been identified to provide functionality for project management, data warehouse (DCP), data set creation (DEP) as well for analysis and reporting (DMP). In addition,

structured user interface features allow efficient access to previously generated files and templates (e.g. reports). Gaps remain in terms of data reuse, as analysis-ready datasets include software- and model-specific syntax. Likewise, workflows may not always be fully transferred across analyses in an automatic manner due to differences in model selection criteria and data set structure.

Conclusions: PME 2.5 is the result of years of internal and external development where the users' needs have been balanced with the industry standards, taking into account the requirements for an integrated workflow. Many of the technical challenges arising from the development and upgrade of modelling and simulation environment are due to differences in the expectation and expertise within the user community, which impose flexibility and consensus on workflows. System modularity, standard processes and grid computing are essential to ensure M&S tools can be upgraded in a rapidly evolving field.

Masoud Jamei II-46 Accounting for sex effect on QT prolongation by quinidine: A simulation study using PBPK linked with PD

Manoranjenni Chetty1, Sebastian Polak1, Pavan Vajjah1,3, Masoud Jamei1, Amin Rostami 1,2

(1) Simcyp Ltd (a Certara Company), Blades Enterprise Centre, John St, Sheffield, S2 4SU; School of Pharmacy and Pharmaceutical Sciences, Manchester University, Manchester; (3) Current affiliation: UCB Celltech, 208, Bath road, Slough, SL13WE; UK

Objectives: To evaluate the sex effects on the potential risk of significant QT prolongation using a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model.

Methods: The Simcyp Population Based Simulator (version 12 release 1) was used to simulate the concentration-time profiles of quinidine in virtual male and female Caucasian healthy volunteers with a full PBPK model and a systemic clearance of quinidine of 20.59 (CV 38%) L/h1. Clinically observed changes in QT prolongation corrected for heart rate (QTc)2 were used to develop the Emax models with differences in baseline QTc values between males and females obtained from the literature2. Parameter estimation was used to determine the ΔEmax (the maximum value of ΔQTc) and the concentration of quinidine required to produce 50% of the maximum response (EC50). Following evaluation of the developed models to predict clinically observed data, the models were used to simulate PD profiles in 500 males and females respectively. The proportion of subjects of each sex who showed QTc >500ms and hence probably carried a greater risk of experiencing torsade de pointes3, were then estimated.

Results: Visual predictive checks suggested that the PBPK model recovered the clinical PK profiles adequately and there was no significant difference between the PK profiles in males and females. The estimated parameters for the Emax models were not significantly different with respect to the Δ Emax values in males and females (128.9 ms and 130.8 ms respectively) but differed in the values for EC50 (6.28 μM for females and 7.01 μM for males), suggesting a greater sensitivity to change in QT in females. The PBPK/PD model recovered the clinical data adequately. Simulation of QTc in the sexes showed that 56% of females were likely to show maximum QTc > 500ms while the corresponding value for males was 43%.

Conclusions: This PBPK/PD model effectively recovered the higher rate of QT prolongation reported in females and predicted a 1.3 times higher risk of significant QT prolongation in females on quinidine. The estimated sensitivity parameter (EC50) of the PD model suggests a female/male ratio of 0.89. Clinical support for a lower EC50 in Caucasian females comes from the study by Benton and coworkers who reported that at a 'therapeutic' concentration of 3μg/mL women are likely to show a 38ms greater increase in QT change than men4. Future PBPK/PD models should include 3-hydroxyquinidine.

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Alvaro Janda II-47 Application of optimal control methods to achieve multiple therapeutic objectives: Optimization of drug delivery in a mechanistic PK/PD system

A. Janda (1,2), S. Ardanza-Trevijano (2), E. Romero (1), N. Vélez de Mendizábal (3), I.F. Trocóniz (1)
(1) Department of Pharmacy and Pharmaceutical Technology and (2) Department of Physics and Applied Mathematics; University of Navarra, Pamplona, Spain. (3) Indiana University School of Medicine; Indianapolis, IN, USA.

Objectives: Optimizing delivery systems targeting constant drug concentration levels in plasma represents always a challenge, especially for long periods of treatment, and in case of complex non-linear pharmacokinetics/pharmacodynamics (PKPD) systems. Recently we have developed a mechanistic PKPD model for the testosterone (TST) effects of triptoreline (TRP) in prostate cancer patients using data from five different sustained formulations [1]. TST profiles are characterised by an undesired initial flare-up, following by a profound receptor-down regulation eliciting castration (TST

Methods: The analysis has been performed in three steps. First, a population of individual set of disposition PK, PD, and system-related paremeters is generated [1]. Second, using this set of parameters, the optimal drug absorption and TST profiles for each patient are derived by means of optimal control methods implemented by the softwares PSOPT and GPOPS [2,3]. Finally, and to summarize the absorption properties the optimal (non-parametric) absorption profiles are described using standard absorption models considering several simultaneous absorption processes based on zero and first order kinetics. The individual model parameters are estimated by

the R package DEoptim which performs global optimization by differential evolution [4].

Results: The optimal TST profiles obtained reveal that the time to castration can be minimized to 21 days (13 – 36) while the increase of TST levels at the flare is only 30% (0,1% – 50%) with respect to baseline (95% interval confidence between parenthesis). The castration time has been evaluated for different doses of TRP and the administration of 20 mg achieve the castration time longer than 9 months for 95% of patients. Additionally, the therapeutic objectives obtained have been compared to those from the formulations reported in [1] showing an important improvement, especially on the flare-up and the castration time.

Conclusions: The application of optimal control methods profiles are useful techniques for the optimization PK/PD profiles. They are more relevant in physiological systems with complex dynamics where simple simulation exercises tuning parameters are not effective. Moreover, the flexibility of the method allows to deal with multiple and tight therapeutic objectives performing real optimization.

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Nerea Jauregizar II-48 Pharmacokinetic/Pharmacodynamic modeling of time-kill curves for echinocandins against Candida.

Sandra Gil-Alonso (1), Nerea Jauregizar (1), Ignacio Ortega (2), Elena Eraso (3) and Guillermo Quindós (3)
(1) Department of Pharmacology, Faculty of Medicine, University of the Basque Country (UPV/EHU), Spain. UFI11/25 "Microbios y Salud". (2) Research Development and Innovation Department, Faes Farma S.A. Leioa. Spain. (3) Department of Immunology, Microbiology and Parasitology, Faculty of Medicine, University of the Basque Country (UPV/EHU), Spain. UFI11/25 "Microbios y Salud"

Objectives: In vitro time-kill studies are commonly used in the assessment of efficacy of antimicrobial agents. The aim of the present study was to develop a general semi-mechanistic pharmacokinetic/pharmacodynamic mathematical model that fits three echinocandins time-kill data against *Candida* isolates in vitro.

Methods: Time-kill curve data from static in vitro experiments with *Candida albicans*, *Candida glabrata* and other emerging species exposed to constant concentrations of three echinocandins (caspofungin, micafungin and anidulafungin) were used for model development. The concentrations ranged from 0.06 to 2 µg/mL and samples for viable counts were taken at time points 0, 2, 4, 6, 24 and 48 h after start of experiments. Data was modeled using NONMEM V7.2.0 [1] with first order conditional estimation method. Diagnostic plots and precision of parameter estimates were evaluated to assess model performance.

Results: Time-kill data were best fit by using an adapted sigmoidal Emax model that corrected for delay in the growth of *Candida* and the onset of the

three drugs activity, steepness of the concentration-response curve, and saturation of the cell number of *Candida*. Time-kill curves of all investigated strains, drugs and concentrations were well predicted by the model.

Conclusions: The activity of the three echinocandins against *Candida* isolates can be accurately described using this semi-mechanistic mathematical model. The developed model allowed the estimation of pharmacodynamic parameters (EC50: concentration of echinocandin necessary to produce 50% of maximum effect; Kmax: maximum killing rate constant and delay in the onset of killing) for the comparison of the three echinocandins.

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Roger Jelliffe II-49 Multiple Model Optimal Experimental Design for Pharmacokinetic Applications

David Bayard and Roger Jelliffe
Laboratory of Applied Pharmacokinetics, USC School of Medicine, Los Angeles CA USA

Objective: To develop an experiment design approach for multiple model problems where the population model associated with the Bayesian prior is specified as a finite discrete probability distribution. Such population models are generated routinely by nonparametric population modeling programs such as NPEM and NPAG.

Methods: The multiple model estimation process can be interpreted as a classification problem. As a classification problem, estimator performance can be scored in terms of how well it minimizes the Bayes risk, i.e., the probability of a misclassification. The use of Bayes risk as an experiment design criteria provides an alternative to D-optimality and other criteria based on the asymptotic Fisher Information matrix. Unfortunately, the Bayes risk is difficult to compute. However, a theoretical upper bound on the Bayes risk has recently appeared in the literature (cf., Blackmore, Rajamanoharan and Williams 2008). Because of its clear computational advantages, this poster proposes experiment designs for pharmacokinetic applications based on minimizing the Bayes risk upper bound.

Results: In a simulated example, sampling times were discretized to every 15 minutes rather than continuously. An additive assay error of 0.1 units was assumed. It is not necessary to get one sample for each model parameter. For a 1 compartment model with parameters V and Kel, and a 1 hour infusion IV, the 1 sample strategy was best at 4.25 hrs, with a cost of 1.6457. The 2 sample strategy was best at 1 hr and 9.5 hrs, with cost of 0.7946. The 3

sample strategy was best at 1, 1, and 10.5 hrs, with cost of 0.5988. The 4 sample strategy was best at 1, 1, 1, and 10.75 hrs, with cost of 0.5062.

Conclusions: Multiple Model Optimal Design (MMOpt) can potentially improve on D-optimal design, as it is based on a true MM formulation of the problem (classification theory), and is optimal with respect to a Bayesian prior. It is applicable to the full assay error polynomial: Sigma_noise=c0 + c1*y + c2*y^2 + c3*y^3. It is based on a recent theoretical overbound on Bayes Risk. In contrast to D-optimal designs, MMOpt discriminates models by using global differences in model response curves rather than local sensitivity to small parameter variations. Also, MMopt experiment designs can handle populations of heterogeneous model types, for example, models having different numbers of compartments. MMOpt will soon be included in the USC *RightDose* software.

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Sangil Jeon II-50 Population Pharmacokinetics of Piperacillin in Burn Patients

Sangil Jeon (1), Heungjeong Woo (2), Seunghoon Han (1), Jongtae Lee (1), Taegon Hong (1), Jeongki Paek (1), Hyeongsik Hwang (2), Dong-Seok Yim (1)
(1) Department of Clinical Pharmacology and Therapeutics, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea, (2) Department of Internal Medicine, Hangang Sacred Heart Hospital, Hallym University Medical Center, Seoul, Korea

Objectives: Piperacillin-tazobactam is a parenterally administered combination of β-lactam antibiotic/β-lactamase inhibitor. It shows broad antibacterial activity against *Pseudomonas aeruginosa* and other pathogens. This combination has been frequently used for the empirical treatment of infection in intensive care patients including burn patients. The purpose of this study was to develop a population pharmacokinetic (PK) model for piperacillin in burn patients.

Methods: Fifty patients with burns ranging from 1% to 81% of total body surface area treated with piperacillin-tazobactam were enrolled. Piperacillin-tazobactam was administered via infusion for about 30 minutes at a dose of 4.5 g every 8 h. Blood samples were collected right before and at 1, 2, 3, 4 and 6 h after more than 5 infusions. The population PK model of piperacillin was developed using a nonlinear mixed effect method (NONMEM, ver 7.2).

Results: The final model was a two-compartment model with first-order elimination. Covariates included in the final model were creatinine clearance (CL_{CR}) on the clearance and sepsis on the central volume of piperacillin. The mean population PK parameters were; clearance (L/h) = 15 × CL_{CR} (mL/min) / 132, V1 (central volume) = 24.6 + 16.3 × presence of sepsis L, V2 (peripheral volume) = 14.6 L, and Q (intercompartmental clearance) = 0.645 L/h with

interindividual variability (CV%) of 36.0%, 38.3%, 0%(not estimated) and 93.7%, respectively.

Conclusions: The population PK of piperacillin have been characterized in burn patients after infusion. These results are to be used for further pharmacodynamic modeling and simulation in burn patients.

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Guedj Jeremie II-51 Modeling Early Viral Kinetics with Alisporivir: Interferon-free Treatment and SVR Predictions in HCV G2/3 patients

Jeremie Guedj, Jing Yu, Micha Levi, Bin Li, Steven Kern, Nikolai V. Naoumov, Alan S. Perelson
1INSERM UMR 738, University Paris Diderot, F-75018 Paris

Objectives: Alisporivir (ALV) is a cyclophilin inhibitor with pan-genotypic activity against hepatitis C virus (HCV). We characterized viral kinetics (VK) in 249 patients infected with HCV genotypes 2 or 3 during treatment with ALV interferon-free regimens for six weeks ±800 mg ribavirin (RBV) daily.

Methods: We used a VK model that integrated pharmacokinetic (PK) and pharmacodynamic effects to analyze patient data as well as to predict the effect of different doses of ALV twice a day with RBV on the sustained virologic response (SVR) rate.

Results: The VK model was able to fit the individual viral load profiles of 214 (86%) patients by assuming that ALV blocked viral production. A mean antiviral effectiveness of 0.93, 0.86 and 0.75 in patients treated with 1000, 800 and 600 mg ALV QD, respectively was estimated. Patients receiving RBV had a significantly faster rate of viral decline, which was attributed in our model to an effect of RBV in increasing the loss rate of infected cells, δ (mean δ=0.35 d-1 vs 0.21 d-1 in patients +/- RBV, respectively, P=0.0001). The remaining 35 patients (14%) had a suboptimal response (i.e. flat or increasing levels of HCV RNA after week 1), and their viral kinetic profile was not described using the model. The occurrence of this suboptimal response was higher in patients that received ALV monotherapy than those receiving ALV+RBV (21.5 vs 10.5%, P=0.02). Moreover, high body weight and low RBV levels were associated with suboptimal response (in patients receiving RBV).

There was a trend for low exposure to ALV to be associated with suboptimal response as well, suggesting that high RBV and ALV exposures are important in reducing the suboptimal response rate. The model predicts 71.5% SVR following 400 mg ALV BID + 400 mg RBV BID for 24 weeks. The predicted SVR rate following response-guided therapy was 79%.

Conclusions: Alisporivir 400 mg BID plus RBV may represent an effective IFN-free treatment that is predicted to achieve high SVR rates in genotypes 2 or 3 patients. Response-guided therapy would further increase SVR. In addition, weight-based RBV dosing should be considered to prevent suboptimal exposure.

Claire Johnston II-52 A population approach to investigating hepatic intrinsic clearance in old age: Pharmacokinetics of paracetamol and its metabolites

Claire Johnston (1,2), Andrew J McLachlan (3,4), Carl M Kirkpatrick (5) and Sarah N Hilmer (1,2)

1. Sydney Medical School, University of Sydney, Sydney, Australia; 2. Department of Clinical Pharmacology, Royal North Shore Hospital, Sydney, Australia; 3. Centre for Education and Research on Ageing, Concord RG Hospital, Sydney, Australia; 4. Faculty of Pharmacy, University of Sydney, Sydney, Australia; 5. Centre for Medicine Use and Safety, Monash University, Melbourne, Australia.

Objectives: The aims of this study were to investigate the pharmacokinetics of paracetamol and its sulfide and glucuronide metabolites in older people. Paracetamol can be used as a marker of hepatic intrinsic clearance and Phase 2 metabolism. This is due to its capacity limited clearance and low protein binding [1]. There is large variability in drug response in older people that is often not explained by chronological age. The investigation of important covariates to pharmacokinetic and pharmacodynamic responses in this population is vital as they are frequently excluded from clinical trials and dosing recommendations may not be appropriate. The concept of frailty as a determining factor of health outcomes in older people is an increasing trend in geriatric medicine [2]. There are only a handful of papers that have investigated the use of frailty in explaining pharmacokinetic changes in old age. To our knowledge this is one of the only studies to use frailty as a covariate in population modeling. We aim to determine the important covariates that can describe the variability seen in paracetamol pharmacokinetics in pain patients aged over 70 years.

Methods: Data from two studies of oral paracetamol were pooled. The first was a study of steady state paracetamol in healthy volunteers with intensive plasma sampling over 6 hours post dose [3]. The second was a large observational study of inpatients over 70 years old, admitted for pain. These patients had residual blood taken from routine blood tests, with 1-25 samples per patient. Frailty was measured using the Reported Edmonton Frailty Scale (REFS), with a score of more then or equal to 8 out of a possible 18 being considered frail [4]. Both the categorical and continuous frailty score will be included in the model. The paracetamol glucuronide and sulfide metabolites were measured for each sample along with the parent drug concentration using HPLC. Population pharmacokinetic analysis was undertaken using NONMEM (version 7.2) and Pirana software. Missing data for weight and height was imputed [5].

Results: The total study population was 219; 20 healthy volunteers and 199 inpatients. The average age of the volunteers was 35.7 years and the inpatients was 84.7 years. There were 139 frail patients and 61 non-frail. The best model was a one-compartment linear model for parent drug and one compartment models for each of the metabolites. There was high variability in both populations.

Conclusions: Decreasing variability in the model will allow for more predictable therapeutic outcomes in older people. Frailty may be an important measure for predicting drug responses in older people.

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Niclas Jonsson II-53 Population PKPD analysis of weekly pain scores after intravenously administered tanezumab, based on pooled Phase 3 data in patients with osteoarthritis of the knee or hip

E. Niclas Jonsson (1,2), Rosalin Arends (3), Rujia Xie (3) and Scott Marshall (3)
(1) Exprimo NV (2) now Pharmetheus AB, (3) Pfizer

Objectives: To characterize the relationship between tanezumab concentrations and weekly pain scores (WPS) over time (measured daily on a 0-10 numerical rating scale) after IV administration in patients with OA of the knee or hip, including covariate relationships and probability of dropout.

Methods: Data were available from four Phase 3 studies (n=2449) for which a population PK model previously had been developed. Separate models for the response and dropout probability after placebo and active treatment were developed. The final PKPD model described the WPS response as the sum of the tanezumab and the placebo effects. The impact of covariates was characterized for all models and simulations, integrated with the PK model, were used to quantify their impact on the clinically relevant endpoint - the baseline and placebo corrected WPS response at week 16, both with and without BOCF imputation.

Results: A set of exponential functions was used to describe the onset of placebo response after the first and subsequent doses. The higher placebo effect with higher baseline pain score and the higher placebo effect in knee compared to hip patients were only evident over the first dosing interval. The rate of placebo onset was faster in two studies investigating patients with more severe osteoarthritis (population not appropriate for NSAID use).
The placebo dropout pattern as well as the tanezumab dropout pattern was

characterized for the first 3 doses separately using a parametric survival model.
An indirect response model was used to link the PK to WPS. The maximal achievable decrease in WPS by tanezumab was higher in females compared to males, higher in patients with OA of the hip and higher in patients with more severe pain at baseline. The potency of tanezumab was lower with higher baseline pain score and higher with higher body weight.
The simulations indicated the site of OA (knee or hip) to be the most potentially clinically relevant covariate for the clinical endpoint, followed by weight, baseline pain score and sex.

Conclusions: The established population PKPD model adequately describes the relationship between tanezumab concentration and WPS after IV administration in patients with OA. The most potentially clinically relevant covariate in terms of the endpoint is the site of OA. While other covariates predict additional small differences in the endpoint, all characterized groups gain benefit from treatment with tanezumab.

Marija Jovanovic II-54 Effect of Carbamazepine Daily Dose on Topiramate Clearance - Population Modelling Approach

M. Jovanovic (1), D. Sokic (2) I. Grabnar (3), T.Vovk (3), M. Prostran (4), K. Vucicevic (1), B. Miljkovic (1)
(1) Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade, Serbia; (2) Clinic of Neurology, Clinical Centre of Serbia, Belgrade; (3) Department of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, University of Ljubljana, Slovenia; (4) Departmant of Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade, Serbia.

Objectives: The aim of the study was to investigate influence of carbamazepine (CBZ) on topiramate (TPM) oral clearance (CL/F) in adult patients with epilepsy.

Methods: Data were collected from 78 adult epilepsy patients on mono- or co-therapy of TPM and other antiepileptic drug(s). Daily doses of TPM were in range from 50 - 1200 mg and dosage regimens were once, twice or three times a day. One to two blood samples were taken per patients in steady-state. Patients co-treated with CBZ administered doses in range from 300 - 1600 mg. The population pharmacokinetic (PK) analysis was performed using NONMEM® software (version 7.2).

Results: A one-compartment model with first-order absorption and elimination was used as a structural model. The interindividual variability was evaluated by an exponential model while residual variability was best described by proportional model. Volume of distribution was estimated at 0.575 (0.499 - 0.651) l/kg. TPM CL/F was significantly ($p < 0.001$) influenced by CBZ daily dose. The estimate of CL/F for a typical patient was 1.534 (1.448 - 1.612) l/h while the interindividual variability in studied population was

16.514% (11.780 - 20.166%). Mean TPM CL/F during CBZ co-therapy was higher for 60.78% than in patients not co-treated with CBZ. The stability of the model was confirmed by bootstrap resampling technique.

Conclusions: Final population PK model quantifies influence of CBZ daily dose on TPM CL/F. The results from the study allow individualization of TPM dosing in routine patient care, especially useful for patients on different CBZ dosing regimens.

Rasmus Juul II-55 Pharmacokinetic modelling as a tool to assess transporter involvement in vigabatrin absorption

Rasmus Vestergaard Juul (1), Martha Kampp Nøhr (2), Carsten Uhd Nielsen (2), Rene Holm (3) and Mads Kreilgaard (1)
(1) Department of Drug Design and Pharmacology and (2) Department of Pharmacy, University of Copenhagen, Denmark, (3) Biologics and Pharmaceutical Science, H. Lundbeck A/S, Valby, Denmark

Objectives: Vigabatrin is an anti-epileptic drug used for the treatment of infantile spams. Vigabatrin has been identified as a substrate of the human proton-coupled amino acid transporter, hPAT1 [1], and *in vitro* studies suggest that PAT1 mediates the transepithelial transport [2]. The aim of this study was to develop a population-based pharmacokinetic (PK) model of the oral absorption of vigabatrin and to assess the potential involvement of PAT1.

Methods: Vigabatrin plasma concentration-time profiles were obtained from 78 rats dosed either orally (0.3mg/kg, 1mg/kg, 3mg/kg or 30mg/kg) or intravenously (i.v.) (1mg/kg). The involvement of PAT1 was investigated by co-administration of the hPAT1 substrate and inhibitor, proline (100mg/kg) and tryptophan (100mg/kg). PK models were fitted to data using non-linear mixed-effects modelling implemented in NONMEM (V7.2.0.). One to three compartment models with 1st order elimination were investigated to describe disposition of vigabatrin. Oral absorption of vigabatrin was investigated among zero-order, 1st order and saturable (Michaelis-Menten) absorption models encompassing lag-time or transit compartments [2,3]. Models were selected and evaluated based on objective function value, visual goodness of fit, parameter precision, visual predictive checks and bootstraps.

Results: A two-compartment model best described the disposition of vigabatrin after oral and i.v. administration. A transit compartment model with estimated 1.4 compartments and a population mean transit time (MTT) of 4.5 min best described the oral absorption of vigabatrin. An apparent dose dependent absorption was observed, as the MTT of 0.3mg/kg doses were lower (3.0 min) than for other doses. Administration of proline and tryptophan resulted in significantly prolonged MTT of 9.2 min.

Conclusions: The oral absorption of vigabatrin in rat was successfully described by a population PK model with dose-dependent transit that could be prolonged by the PAT1 inhibitors proline/tryptophan. These findings are the first *in vivo* evidence suggesting that PAT1 could be involved in intestinal vigabatrin absorption.

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Matts Kågedal II-56 A modelling approach allowing different nonspecific uptake in the reference region and regions of interest – Opening up the possibility to use white matter as a reference region in PET occupancy studies.

M. Kågedal(1), MO Karlsson(2) AC Hooker(2)
(1) AstraZeneca R&D Södertälje, Sweden (2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Analyses of receptor occupancy studies are often performed using the concentration in a reference region in the brain as input function. These analyses assume identical non-specific binding in the reference region and in the region of interest (ROI). In the present work it is investigated if an apparent difference in occupancy between regions could be explained by different non-specific uptake. In addition it is investigated whether the use of white matter as reference region is possible by estimation of non-specific uptake in the ROI relative to reference. The analysis is based on data from a study published previously (Varnäs et al 2011) [1].

Methods: Nonlinear mixed effects modelling of data from PET scans with the 5-HT1B radioligand [^{11}C] AZ10419369 was applied. Data from all PET-scans and several brain regions of interest were included simultaneously in the analysis. The simplified reference tissue model with cerebellum as reference region was applied as described previously (Zamuner et al) [2] but modified to allow nonspecific uptake to differ between regions. The use of white matter as reference region was also explored. A simulation experiment was performed to assess the ability of the model to pick up a difference in non-specific uptake and the consequence of not accounting for this difference. The study included six healthy subjects with PET-scans at baseline and after different oral doses of the 5-HT1B antagonist AZD3783.

Results: Based on the likelihood ratio test, regional difference in occupancy was more likely than differences in non-specific uptake. Using white matter as reference region resulted in a similar affinity estimate as that obtained with cerebellum as reference region if the difference in non-specific uptake was accounted for. The simulation experiment, showed a bias in occupancy when differences in non-specific uptake were not accounted for.

Conclusions: In the present case, difference in occupancy rather than in non-specific uptake between regions was concluded. This evaluation was possible by a simultaneous analysis of several regions of interest and all PET-measurements. Estimation of occupancy by the use of white matter is possible by accounting for any difference in non-specific uptake. Results presented show that differences in non-specific binding between the reference region and the regions of interest can markedly bias the occupancy estimate if not accounted for.

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Ana Kalezic II-57 Application of Item Response Theory to EDSS Modeling in Multiple Sclerosis

Ana Kalezic (1), Radojka Savic (2), Alain Munafo (3), Mats O Karlsson (1)
(1) Dept of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Traditional approaches to measurement scales generally disregard the underlying nature of the subcomponent data. In contrast, item response theory (IRT) refers to a set of mathematical models that describe, in probabilistic terms, the relationship between a person's response to a survey question and its level of the "latent variable" being measured by the scale [1]. In the area of clinical pharmacology, IRT modeling has previously been applied to ADAS-cog assessments [2].
The objective of this analysis was to apply IRT methodology to the Expanded Disability Status Score (EDSS) [3], a widely used measure of disease disability in multiple sclerosis (MS).

Methods: Data were collected from a 96-week Phase III clinical study with relapsing-remitting MS. For this analysis, 41664 EDSS observations from 1319 patients at baseline or treated with placebo were used.
The assumption is that the outcome of each item constituting EDSS depends on an unobserved variable "disability."
Unlike most measurement scales, EDSS total score does not result from simple addition of individual items, but instead results from individual components via a decision tree.
For each EDSS item, a model was developed in accordance with the nature of data, describing the probability of a given score as a function of disability variable. Sets of parameters characterizing each item were modeled as fixed effects, while the MS disability was modeled as subject-specific random effect with or without time components. All models were fitted using

NONMEM 7.2; simulation-based diagnostics for model evaluation also used PsN and R/Xpose4 software.

Results: The final model contained 8 ordered categorical submodels for a total of 54 parameters. Simulations from the IRT model were in good agreement with the observed EDSS and item-level data. The disability variable showed a significant increase ($p<0.01$) over time in the typical individual, but with considerable variability across patients.

Conclusions: This is the first time that the IRT methodology has been applied to the MS area and to a score that is not a summation of items. For the latter type, IRT models have been shown to increase precision in predictions and power to predict drug effects and linkage to biomarkers [4, 5]. The developed model can be used to explore potential benefits of the IRT methodology for characterizing MS disability.

Acknowledgement: This work was supported by the DDMoRe project.

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Takayuki Katsube II-58 Pharmacokinetic/pharmacodynamic modeling and simulation for concentration-dependent bactericidal activity of a bicyclolide, modithromycin

Takayuki Katsube (1), Toshihiro Wajima (1), Yoshinori Yamano (2), Yoshitaka Yano (3)

(1) Clinical Research Department, Shionogi & Co., Ltd., Japan, (2) Medicinal Research Laboratories, Shionogi & Co., Ltd., Japan, (3) Education and Research Center for Clinical Pharmacy, Kyoto Pharmaceutical University, Japan

Objectives: The aim of this study was to develop a pharmacokinetic/pharmacodynamic (PK/PD) model of a bicyclolide, modithromycin, to explain its concentration-dependent bactericidal activity against *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus pneumoniae* based on the drug-bacterium interaction model [1].

Methods: We have already developed a PK/PD model to explain the time-dependent bactericidal activity of β-lactams [1-4]. In this study, the model is extended to explain the concentration-dependent bactericidal activity and was applied to *in vitro* time-kill data of modithromycin, telithromycin and clarithromycin. An effect compartment model was incorporated into our original model [1] to explain the time delay between pharmacokinetics and pharmacodynamics. A turnover model for reversible reduction of drug efficacy was also incorporated to explain the re-growth.

Results: The model adequately described the time-kill profiles for each drug-bacterium combination. The estimated model parameters related to drug efficacy strongly correlated with MIC, and the simulated bacterial counts at 24 hours strongly correlated with both ratios of area under concentration-time curve to MIC (AUC/MIC) and ratios of maximum drug concentration to

MIC (Cmax/MIC). Based on the results, simulations of bactericidal activity of modithromycin in patients could be performed.

Conclusions: These results suggested that the proposed drug-bacterium interaction model can be applied to both concentration-dependent and time-dependent bactericidal kinetics, and would be useful for predicting the bactericidal activity of modithromycin.

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Irene-Ariadne Kechagia II-59 Population pharmacokinetic analysis of colistin after administration of inhaled colistin methanesulfonate.

Irene-Ariadne Kechagia, Zoe Athanassa, Sophia Markantonis, Aris Dokoumetzidis
School of Pharmacy, University of Athens, Greece

Objectives: Colistin is an antimicrobial agent administered to treat multidrug-resistant gram-negative bacterial infections [1]. The aim of the present study was to develop a population PK model of colistin after inhalation of colistin methanesulfonate (CMS), an inactive prodrug of colistin. Nebulized CMS was administered via a vibrating-mesh nebulizer to critically ill patients suffering from ventilator-associated tracheobronchitis (VAT).

Methods: Pharmacokinetic data were obtained from a previous study [2] and included concentrations of colistin in serum and in lung epithelial lining fluid (ELF) after the first inhalation of CMS. Population pharmacokinetic analysis was performed using the FOCE method with interaction in NONMEM (version 7.2). Model parameters clearance (CL/F), volume (V/F), Weibull scale (a) and shape parameters (b) together with OMEGAs for CL/F, V/F and b were estimated. Diagnostic graphs were generated by the Xpose program (version 4). Demographical and biochemical data were tested as covariates for the pharmacokinetic parameters. Visual predictive check and a nonparametric bootstrap resampling method were performed to evaluate the model. Also, a monoexponential model was used to fit each patient's ELF data to obtain the elimination rate constant of colistin from ELF ($k_{e,ELF}$) which was tested as a covariate on absorption parameters.

Results: Colistin pharmacokinetics was best described by a one compartment model with first order elimination and absorption being modeled by the

weibull distribution function. Residual variability was modeled by a time dependent error model to account for higher residual error during the absorption phase. Furthermore, due to unusually high Cmax values attributed to suspected hydrolysis of CMS to colistin during sample analysis, a systematic bias was introduced to the residual error. Creatinine clearance was a significant covariate for CL/F and $k_{e,ELF}$ for the shape parameter of weibull distribution, b. The population mean estimates for apparent clearance (CL/F) and apparent volume of distribution (V/F) were 6.76 liters/h (CV 28%) and 37.2 liters (CV 19%), respectively.

Conclusions: A population PK model for colistin was developed. A residual error including systematic bias allows interpretation of unusually high Cmax values suspected to be erroneous.

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Ron Keizer II-60 cPirana: command-line user interface for NONMEM and PsN

Keizer, Ron J
UCSF / Pirana Software & Consulting BV

Objectives: Develop a "lite" version of Pirana for use on the UNIX command-line.

Background: Graphical user interfaces (GUIs) for NONMEM and PsN like Pirana[1], provide a convenient and powerful tool to perform modeling & simulation (M&S). However, the use of GUIs may be impeded for various reasons:
- when working on a remote cluster and only simple tasks are involved, it may be faster or more convenient to work from the command line (through ssh).
- more experienced modelers often prefer to work from the command line
- no GUI is currently available for mobile platforms (iOS / Android) to perform M&S on clusters

To address the points above, development of a command line-based interface to NONMEM and PsN was initiated ("cPirana").

Methods: cPirana was written in Perl, using the NCurses::UI [2] module (which builds upon the ncurses library for user-interfaces on the UNIX command line). Where possible, routines previously developed for Pirana were re-used. For the layout of the interface, the "orthodox file manager"-style such as in Norton Commander[3] was chosen. cPirana was developed and debugged on linux and OSX. It was evaluated whether all functionality worked over remote ssh connections as well as locally, and whether cPirana could be used effectively from iOS devices (iPad, using the ssh-app "Prompt" to connect to a cluster over ssh).

Results: The Curses::UI library provided a stable GUI, and most of Pirana's core functionality could be re-used with only minor code changes. Limited testing showed that cPirana provides a faster alternative to Pirana when working over slow cluster connections. Through ssh connections, all functionality could be accessed from iPad as well. Compared to Pirana, cPirana is less feature-rich, however the aim of this tool is different and there is no intention to implement all Pirana features in cPirana.

Conclusions: cPirana provides a comprehensive interface to NONMEM and PsN on the UNIX command line, allowing fast and easy access to core M&S tools. It also allows M&S on clusters from mobile devices.

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Frank Kloprogge II-61 Population pharmacokinetics and pharmacodynamics of lumefantrine in pregnant women with uncomplicated P. falciparum malaria.

Frank Kloprogge (1,2), Rose McGready (1,2,3), Warunee Hanpithakpong (2), Siribha Apinan (2), Nicholas P.J. Day (1,2), Nicholas J. White (1,2) , François Nosten (1,2,3), Joel Tarning (1,2)
(1) Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom, (2) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, (3) Shoklo Malaria Research Unit, Mae Sot, Thailand

Objectives: Artemether-lumefantrine is the most widely used ACT in the world, but its efficacy in the treatment of malaria in pregnancy in a low transmission setting along the Thailand-Myanmar border has been disappointing. Lumefantrine plasma concentrations on day 7 are a commonly used pharmacokinetic endpoint to assess therapeutic responses however recent studies suggested that the main active metabolite, desbutyl-lumefantrine, might be correlated better to efficacy. The objective of the current analysis was to evaluate the pharmacokinetic and pharmacodynamic properties of lumefantrine and desbutyl-lumefantrine in pregnant women in Thailand with uncomplicated *Plasmodium falciparum* malaria.

Methods: Dense venous [1] and sparse capillary [2] lumefantrine and desbutyl-lumefantrine plasma concentration samples from 116 patients were evaluated simultaneously in a drug-metabolite model using NONMEM v7.2. Different absorption, distribution, variability, covariate and error models were assessed using the FOCE-I estimation method. Laplacian-I was used to model the time to recrudescent infection with an interval-censored time-to-event approach.

Results: A first-order absorption model with lag-time followed by two distribution compartments for lumefantrine and desbutyl-lumefantrine fitted the data adequately. A correction factor, at a population level, was implemented for the differences between the capillary and venous blood samples. Time to recrudescent malaria infections was best described using a Gompertz hazard model. Lumefantrine and desbutyl-lumefantrine realised a similar improvement in model fit when added as a traditional maximum effect function on the exponential baseline hazard. However, lumefantrine showed better predictive power compared to desbutyl-lumefantrine. A simultaneous lumefantrine and desbutyl-lumefantrine drug effect did not further improve the model.

Conclusions: The developed model described the pharmacokinetic and pharmacodynamic data well. Lumefantrine and desbutyl-lumefantrine concentrations were highly correlated and could be used interchangeably to predict the time to recrudescent malaria but lumefantrine realised a better predictive power. This model will be highly useful in informing the selection of new artemether-lumefantrine dose strategies in pregnant patients with malaria.

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Gilbert Koch II-62 Solution and implementation of distributed lifespan models

Gilbert Koch (1) and Johannes Schropp (2)
(1) The State University of New York at Buffalo, Pharmaceutical Sciences, Buffalo NY 14214, USA (2) Department of Mathematics and Statistics, University of Konstanz, Germany

Objectives: A realistic assumption for a (cell) population is that every individual has its own and unique lifespan. Krzyzanski, Woo and Jusko [1] developed PKPD models where these lifespans are described by a continuous distribution, e.g. Lognormal or Weibull. In these models, the rate of change of the population is formulated based on the mathematical convolution operator. Unfortunately, standard PKPD software is not able to handle this convolution operator. Even in MATLAB the implementation is complex. The objective of this work is to derive and implement a new and handy solution representation of such distributed lifespan models (DLSM).

Methods: We implemented the solution representation of DLSMs, given in an integral form, by the Riemann sum in NONMEM and ADAPT. In MATLAB we present several approaches to solve this integral form and perform a run-time comparison.

Results: We calculated the solution representation of DLSMs. In the rate of change formulation these models use the convolution operator. It turns out that this operator vanishes in the solution representation. Instead the cumulative distribution function (CDF) of the distribution appears. Note that in case of the realistic Weibull distribution for lifespans, the CDF is an explicitly known function.

Conclusions: The solution representation of a DLSM does not contain the convolution operator and therefore could be easily implemented in standard PKPD software, e.g. in NONMEM or ADAPT.

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Kanji Komatsu II-63 Modelling of incretin effect on C-Peptide secretion in healthy and type 2 diabetes subjects.

K.Komatsu(1), J.I. Bagger(2), F.K.Knopp(2), T. Vilsböll(2), M.C.Kjellsson(1), M.O.Karlsson(1)

(1) Department of Pharmaceutical Bioscience, Uppsala University, Sweden. (2) Department of Internal Medicine F, Gentofte Hospital, University of Copenhagen, Denmark.

Objectives: The aim of this project was to model the secretion profile of C-peptide. As C-peptide is co-secreted with insulin in equimolar amounts but does not undergoing hepatic extraction, it is useful for evaluating beta cell function in healthy subjects and type 2 diabetes mellitus (T2DM) patients. In this study, all subjects were subjected to both oral glucose tolerance test (OGTT) and isoglycemic intravenous glucose infusion (IIGI) in order to evaluate the effect of the incretin hormones GLP-1 & GIP on C-peptide secretion. GLP-1 and GIP are small peptides, released in the intestine, contributing to the incretin effect; a stronger insulin response when glucose is ingested as opposed to injected.

Methods: Previously published clinical data [1] was used for population analysis. Healthy subjects (n=8) and T2DM patients (n=8) were administered 3 doses of glucose orally (25, 75 and 125 g) on three separate occasions after a 10 hours fasting. Therafter, three IIGI studies were conducted to mimic the plasma glucose-time profile from the OGTTs. Observations of frequently sampled plasma C-peptide, glucose, GLP-1 and GIP were used for modelling. Previously published models for insulin secretion in healthy subjects after IV glucose tests were initially applied to the C-peptide data of the healthy subjects [2, 3]. On the most suitable structural model, effects of GLP-1 and GIP were investigated and incorporated into the model using data from the OGTT experiments in healthy subjects. After finishing the structural model for

healthy subjects with both IV and oral experiments, the models was applied to T2DM patients. All modelling was performed using NONMEM 7.2. and Xpose4 was used for model diagnostics.

Results: Among the investigated models, the mathematical beta cell model[2] showed the best performance in goodness of fit, individual fit and OFV. GLP-1 effect was incorporated on provision rate of C-peptide and change of provision fraction to readily releasable pool compartment with respect to plasma glucose concentration. In addition to GLP-1, GIP was also included in model. The same structural model of incretin effect was successfully implemented also for T2DM patients with re-estimation of parameters.

Conclusions: It was possible to model C-peptide secretion profile in healthy subjects and T2DM patients using the mathematical beta cell model with modifications for the incretin effect.

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

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Julia Korell II-64 Gaining insight into red blood cell destruction mechanisms using a previously developed semi-mechanistic model

Julia Korell (1,2), Stephen Duffull (1)
(1) School of Pharmacy, University of Otago, Dunedin, New Zealand, (2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Modelling the survival time of various haematological cell populations, including red blood cells (RBCs), has recently gained interest within the area of pharmacometrics. Most of the proposed models follow the principle of parsimony. For RBCs, these models mainly focus on the predominant destruction mechanism of age-related cell death (senescence) and do not account for within subject variability in the RBC lifespan. Assessment of the underlying physiological destruction mechanisms can be of interest in pathological conditions that affect RBC survival, for example sickle cell anaemia or anaemia of chronic kidney disease. We have previously proposed a semi-mechanistic RBC survival model which accounts for four different types of RBC destruction mechanisms [1]. Here, it is shown that the proposed model in combination with informative RBC survival data obtained using the biotin labelling technique is able to provide a deeper insight into RBC destruction mechanisms.

Methods: The data used for this analysis was digitally extracted from Cohen et al. [2]. It had been obtained from six diabetic subjects and six healthy controls using age-independent random (i.e. population) labelling of RBCs with biotin. Non-linear mixed effect modelling was conducted in MATLAB R2012a using an implementation of the SAEM algorithm used in MONOLIX 1.1 [3].

Results: Three RBC destruction mechanisms were estimable based on the available data: random destruction, senescence and destruction due to delayed failure. Large between subject variability in the individual mean RBC lifespan was seen (50 to 90 days, median 76.7 days). It was possible to identify three subjects with a decreased RBC survival in the study population (mean RBC lifespan less than 60 days). These three subjects all showed differences in the contribution of the estimated destruction mechanisms: an increased random destruction, versus an accelerated senescence, versus a combination of both. Diabetes mellitus was not a significant covariate on RBC survival.

Conclusions: The proposed RBC survival model is able to provide a deeper insight into the underlying RBC destruction mechanisms when it is used to analyse informative RBC survival data. In contrast to parsimonious RBC survival models, it allows for variability in the underlying RBC lifespan distribution and the mean RBC lifespan on the individual as well as the population level.

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Stefanie Kraff III-01 Excel®-Based Tools for Pharmacokinetically Guided Dose Adjustment of Paclitaxel and Docetaxel

Stefanie Kraff (1), Andreas Lindauer (1), Markus Joerger (2), Salvatore Salamone (3), Ulrich Jaehde (1)

(1) Institute of Pharmacy, Clinical Pharmacy, University of Bonn, Germany, (2) Department of Oncology & Hematology, Cantonal Hospital, St. Gallen, Switzerland, (3) Saladax Biomedical Inc., Bethlehem, PA, USA

Objectives: In prospective clinical trials pharmacokinetically guided dose adjustment was performed for paclitaxel and docetaxel [1, 2]. As target parameters for dose adaptation the time above a paclitaxel threshold concentration of 0.05 µmol/L ($T_{c>0.05}$) is used for paclitaxel and the area under the curve (AUC) for docetaxel. Individual $T_{c>0.05}$ and AUC values are estimated based on previously published pharmacokinetic (PK) models of paclitaxel and docetaxel [3, 4] by using the software NONMEM®. Since many clinicians are not familiar with the use of NONMEM® we developed Excel®-based dosing tools performing comparable parameter estimations like NONMEM®.

Methods: Typical population PK parameters and interindividual variability were taken from published models [3, 4]. An Alglib VBA code was implemented in Excel® to compute differential equations for the paclitaxel PK model [5]. Bayesian estimates of the PK parameters (EBE) were determined by the Excel® solver using individual drug concentrations and in addition for the paclitaxel PK model bilirubin concentrations, BSA, gender and age as covariates. For paclitaxel, concentrations from 50 patients were simulated receiving 6 cycles of chemotherapy. The paclitaxel dose was adapted according to a previously published algorithm [6]. For docetaxel, concentrations from 300 patients were simulated receiving one cycle of

chemotherapy. Predictions of the Excel® tool were compared with those of NONMEM®, where EBEs were obtained using the POSTHOC function.

Results: The results suggested that there was no major difference in the predictive performance between Excel® and NONMEM® regarding drug concentrations and $T_{c>0.05}$ or AUC values. Bias (median prediction error) for $T_{c>0.05}$ of paclitaxel was 0.07% with NONMEM® and 2.81% with Excel®, for the AUC of docetaxel 0.84% and 2.91%, respectively. Precision (median error) for $T_{c>0.05}$ was 10.14% and 11.44%, for the AUC 14.27% and 14.75%, respectively. The mean deviation of the estimated paclitaxel $T_{c>0.05}$ values between both programs was about 8 minutes. In 11% of the dose calculations, diverging $T_{c>0.05}$ values between the Excel® and NONMEM® Bayesian estimations resulted in different doses. The mean deviation of the estimated docetaxel AUC values was 0.158 mg·h/L.

Conclusions: The PK models of paclitaxel and docetaxel could be adequately implemented in Excel® with a predictive performance comparable to that of NONMEM. The developed dosing tools are self-explanatory and easy-to-use with acceptable computation times.

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Andreas Krause III-02 Modeling the two peak phenomenon in pharmacokinetics using a gut passage model with two absorption sites

Andreas Krause(1), Marc Lavielle(2), Kaelig Chatel(2), Christopher Kohl(3), Ruben de Kanter(3), Stephane de la Haye(3), Alison Mackie(1), Jochen Zisowsky(1), Jasper Dingemanse(1)
(1) Actelion Pharmaceuticals Ltd, Department of Clinical Pharmacology, Gewerbestr. 16, 4123 Allschwil, Switzerland, (2) Lixoft - Incuballiance, 84 rue de Paris, 91400 Orsay, France, (3) Actelion Pharmaceuticals Ltd, Drug Metabolism and Pharmacokinetics, Gewerbestr. 16, 4123 Allschwil, Switzerland

Objectives: Characterization of the pharmacokinetic (PK) two peak phenomenon with pronounced second peak in higher doses by a gut passage model with two absorption sites and an absorption limit on the first site of absorption.

Methods: The first study with a new compound in humans showed PK characteristics that can be characterized by single compartment models. Higher doses though exhibited a two peak phenomenon: after the drug concentration had almost returned to 0, a second peak occurred that became more pronounced with higher doses. Preclinical data suggested that the underlying mechanism could be a gut passage with two absorption sites, in the upper and lower intestinal tract, respectively.
A PK model with the desired properties was implemented in Monolix. It comprises two separate dose administration compartments with direct first order absorption and a set of transit compartments (with the number of transit compartments estimated). The last transit compartment transfers into the central compartment, thus causing a second peak in systemic

concentration. The amount of drug absorbed from the first absorption compartment is limited, and the absorption limit is estimated.

Results: The gut passage model with two absorption sites with an absorption limit on the first captures the two peak PK phenomenon very well. It can capture very different shapes of concentration-time profiles, including large differences between subjects in the magnitude of the second peak relative to the first peak.

Conclusions: The gut passage model represents a viable alternative to enterohepatic recycling models for the PK two peak phenomenon ([1], [2], [3]).

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Elke Krekels III-03 Item response theory for the analysis of the placebo effect in Phase 3 studies of schizophrenia

Elke H.J. Krekels (1), Lena E. Friberg (1), An M. Vermeulen (2), Mats O. Karlsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (2) Janssen Research & Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium

Objectives: Disease severity in schizophrenia is quantified using the PANSS scale, a composite psychological and functional scale divided into 7 positive, 7 negative, and 16 general items, all scored from 1 to 7. We investigated a new approach based on item response theory (IRT) to simultaneously analyze the scores of all individual items, instead of analyzing the single composite score [1].

Methods: 102,481 records of item-level data were available from 3 Phase 3 studies. Data of each item were modeled as ordered categorical data. The parameters describing the probability curves of each score of each item were estimated as fixed effect. The underlying disease state of individuals at baseline was modeled as a random effect with a fixed variance of 1. Baseline data were used to establish a reference for the probability curves, which were fixed when modeling the longitudinal placebo data. Linear, power, asymptotic and Weibull functions were tested to describe the changes in the disease state as a function of time.

Results: At baseline, the correlations between the disease states on the positive, negative
and general subscales were low; -0.119 for pos-neg, 0.368 for pos-gen, and 0.125
for neg-gen. On all three subscales there was a relatively fast initial

improvement rate in disease state for placebo treated patients that slowed down
later. This was best described by asymptotic functions, with half-lives of 14.4, 15.4, and 11.1 days for the positive, negative and general subscale and disease
states asymptoting to mean variance values of 0.839, 0.419, and 1.49 respectively. This time-course means that at the end of the study (42 days), 64%
of the patients on placebo treatment had a disease state on the positive subscale that was better than the disease state of the typical individual at baseline. For the negative and general subscales this was 59% and 71% respectively.

Conclusions: IRT modeling allows for the analysis of PANSS scores on both the individual item level as well as on the composite scores. The low correlations between the disease states estimated for each individual at baseline on the positive, negative and general subscale suggest that schizophrenia influences the three subscales differently for individual patients. The time-course of the placebo effect does however appear to be rather similar on all three subscales.

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Anders Kristoffersson III-04 Inter Occasion Variability (IOV) in Individual Optimal Design (OD)

Anders N. Kristoffersson (1), Lena E. Friberg (1), Joakim Nyberg (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: IOV may adversely affect the precision of maximum a posteriori (MAP) estimated individual parameters and have long been recognized to impact the potential of feedback individualization of dosing regimens [1], yet the inclusion of IOV in OD for estimation of individual parameters has not been previously investigated. This work aims to explore methods for including IOV in individual OD.

Methods: The individual FIM maximum a posteriori (FIM_{MAP}) was calculated as previously described [2] and three strategies were investigated to include IOV in the optimization: i) Inflate - The prior covariance matrix was inflated (re-estimated) to include IOV ii) POP_{occ} - IOV was included in the individual FIM as a population occasion random effect . iii) MAP_{occ} - IOV was added to the individual FIM as a fixed effect occasion deviation sampled per individual occasion from the prior IOV distribution. As reference the designs were optimized without inclusion of IOV, termed Ignore.

Two test models were used; a Colistin-PK model [3] as well as a constructed 1-compartment IV-bolus model (1-CIV). The individual deviation parameters, (η_{CL}, η_Q, η_{RE}) for Colistin-PK and (η_{CL}, η_V) for 1-CIV were set as interesting in the PopED [4] ED_s criteria. The designs were evaluated by stochastic simulations and MAP re-estimations in NONMEM7 [5] with the expected standard deviation (SD) and the observed Root Mean Squared Error (RMSE) of the Empirical Bayes Estimates (EBE) compared with the expected SD from the PopED inverse FIM_{MAP}.

Results: Inflate and ignore provided identical designs, sampling the first and last occasion for 1-CIV and all occasions for Colistin-PK. POP_{occ} and MAP_{occ} sampled all occasions for 1-CIV and the first occasion for Colistin-PK.

The mean PopED predicted SD of η_{CL} and η_V of model 1-CIV for Ignore, Inflate, MAP_{occ} and POP_{occ} were 13, 13, 55 and 52 % of the prior while the observed RMSE were 64, 64, 56 and 54 % of the prior. The same trend was found for the Colistin-PK model with MAP_{occ} and POP_{occ} providing in general better or equal RMSE compared to method Ignore.

The runtime for one PopED FIM calculation with 1-CIV for Inflate, MAP_{occ} and POP_{occ} were 1.0, 4.0 and 46 times slower relative to Ignore.

Conclusions: Not including IOV in the FIM_{MAP} was detrimental to the design performance and provided overly optimistic PopED SD. Based on EBE RMSE as well as run times we would recommend method MAP_{occ} for individual OD for models including IOV.

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Cédric Laouenan III-05 Modelling early viral hepatitis C kinetics in compensated cirrhotic treatment-experienced patients treated with triple therapy including telaprevir or boceprevir

C. Laouénan (1,2), J. Guedj (1), M. Lapalus (3), F. Khelifa-Mouri (4), M. Martinot-Peignoux (3), N. Boyer (4), L. Serfaty (5), JP. Bronowicki (6), F. Zoulim (7), P. Marcellin (3,4), F. Mentré (1,2) and MODCUPIC ANRS-CO20 study group

(1) INSERM UMR 738, University Paris Diderot, Sorbonne Paris Cité, Paris, France; (2) AP-HP, Hosp Bichat, Service de Biostatistique, Paris, France; (3) INSERM U773-CRB3, University Paris Diderot, Sorbonne Paris Cité, Clichy, France; (4) AP-HP, Hosp Beaujon, Service d'Hépatologie, Clichy, France; (5) AP-HP, Hosp Saint-Antoine, Service d'Hépatologie, Paris, France; (6) CHU Nancy, Service d'hépato-gastroentérologie, Vandoeuvre-les-Nancy, France; (7) Hospices Civils de Lyon, Lyon, France and INSERM U1052, Université de Lyon, Lyon, France

Objectives: ANRS MODCUPIC is a clinical study designed to provide a precise description of the early hepatitis C viral kinetics during triple therapy involving a protease inhibitors (PI) in compensated cirrhotic treatment-experienced patients in real-life setting.

Methods: Patients were prospectively included to receive tripe therapy containing either telaprevir (TVR)/PEG-IFN/RBV or boceprevir (BOC)/PEG-IFN/RBV). Viral load (VL) was frequently assessed during the first week following treatment initiation at days 0, 0.33, 1, 2, 3, 7 and then at weeks 2, 3, 4, 6, 8, 12. The viral kinetic model was the standard biphasic model and data up to VL rebounds (if any) were fitted [1]. In this model, the rates of the first and second phase of viral decline are roughly equal to the clearance rate

of virus (c) and the loss rate of infected cells (δ), respectively. The magnitude of the first phase of viral decline, ε, reflects therapy's effectiveness in blocking viral production. Parameters and their variability were estimated using the SAEM algorithm in MONOLIX V4.2 [2]. The Wald test was performed to detect a difference in parameters between treatment groups.

Results: Fifteen patients were included (9 TVR, 6 BOC), 9 patients (60%) had undetectable VL at week 4 and VL rebounded in two patients (at week 3 and 8). The biphasic model described adequately VL decline in all patients. The clearance rate of virus and the loss rate of infected cells were not significantly different between treatment groups (mean values: c = 4.5 day-1 and δ = 0.20 day-1). However the antiviral effectiveness was significantly larger with TVR than with BOC (εTVR vs εBOC: 0.998 vs 0.989, P = 0.004). Permutation test should be performed to confirm the difference between TVR and BOC [3], also it should be noted that this is not a randomized trial.

Conclusion: For both PIs, the two phases of viral decline were about four times smaller than what had been observed in non-cirrhotic naive patients during TVR monotherapy [4,5] and close to typical values observed during PEG-IFN/RBV therapy. This discrepancy could be due to impaired pharmacokinetics and lower penetration capacity of PIs in hepatocytes of cirrhotic patients. Consequently cirrhotic treatment-experienced patients may need longer time to achieve viral eradication than other patients [4]. Pharmacokinetic data of PI, PEG-IFN and RBV will be available and should allow to better understand the origin of this impaired virologic response.

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Anna Largajolli III-06 An integrated glucose-insulin minimal model for IVGTT

A. Largajolli (1), A. Bertoldo (1), C. Cobelli (1), P. Denti (2)
(1) Department of Information Engineering, University of Padova, Italy (2) Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa

Objectives: The glucose and insulin regulatory system following an intravenous glucose injection (IVGTT) can be investigated through the so-called minimal models (MM) [1,2], quantifying insulin sensitivity and release. However, these approaches suffer from the limitation of analysing the two signals separately, by using one as known input to predict the other, and vice versa. Although this procedure has been shown to have a small impact on parameter estimation [3], it limits the simulation capabilities of the models and may not be as robust with sparse data. We propose an integration of the glucose and insulin MM by using nonlinear mixed effect modelling.

Methods: The dataset is composed of 204 healthy subjects [4] (118 M /86 F, mean age 55.53 ± 21.66, mean BMI 26.62 ± 3.39 kg/m^2) that underwent an insulin-modified IVGTT. The model building strategy (NONMEM using FOCE with INTERACTION) focused first on the two subsystems separately, to then proceed to the integration and simultaneous fit. Allometric scaling was used for CL and V terms and correlations were investigated between the model parameters.

Results: The original glucose minimal model (GMM) was revised with the use of a two compartment model as in [1] and by adding transit compartment input [5] to cater for the glucose kinetic in the first minutes of the experiment, previously customarily discarded. The original insulin minimal model (IMM) [2] was modified with the addition of a transit model to capture

the delay in the onset of insulin release and a second compartment to better describe the kinetics. The model adequately fits both glucose and insulin and the VPC shows a better description when compared to the VPCs obtained from the separate models, with tighter simulated CIs around the observed data percentiles. The fixed effects estimates have an average normalized discrepancy value of 15% from the estimates obtained on the separated models. The size of BSV in the parameter estimates is reduced and strong correlations were detected between the insulin sensitivity and action (79%), and insulin and glucose delay (67%).

Conclusions: This integrated model, while providing parameter estimates compatible with the traditional MM approaches, allows the simultaneous characterization of the glucose-insulin regulation system. Unlike the GMM and IMM this integrated model provides full simulation capabilities and can be used as a framework to explore disease and drug effects. The model could be further improved by integrating C-peptide kinetics.

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Robert Leary III-07 A Fast Bootstrap Method Using EM Posteriors

Robert H. Leary, Michael R. Dunlavey, and Jason Chittenden
Pharsight Corporation

Objectives: In the most usual form of NLME bootstrapping for parameter uncertainty estimation, each replicate data set is constructed by pooling *Nsub* (=total number of subjects) random selections of individual data sets with equal probability 1/*Nsub* on each individual. In effect, the bootstrap replicates are the concatenation of *Nsub* samples from a mixture distribution of individual data sets with equal probabilities on each such set. An intriguing analogy occurs in the optimal NLME estimation solution via EM methods – the fixed effects parameters in the optimal solution are the means, and the random effect parameters the variance/covariances, of the mixture distribution of posteriors with equal probabilities 1/*Nsub*. This suggests a very fast method for bootstrapping – rather than construct a large number of bootstrap data sets and solve the estimation problem separately for each one, simply solve the base case problem with each individual represented exactly once, and then bootstrap the resulting posteriors. All that is required is to save the means and variance/covariance matrices of each posterior from the base case, and then perform a rather small amount of very fast linear algebra to get parameter estimates for each bootstrap replicate.

Methods: The posterior EM bootstrap methodology was implemented within the Pharsight Phoenix NLME parametric QRPEM method for 1000 simulated data sets from a simple IV bolus model. For each data set, fixed and random effect parameter values were computed for 10000 bootstrap replicates in less than 3 seconds total time using the EM posterior method. Coverage analyses were performed for the posterior estimates relative to the known

true values used to simulate the data to evaluate the quality of confidence limits.

Results: Coverage was remarkably accurate for essentially all confidence probability levels for fixed effects estimates, somewhat less so for random effect estimates.

Conclusions: EM posterior bootstrapping appears a viable methodology for computing confidence limits and standard errors, particularly for fixed effects.

Donghwan Lee III-08 Development of a Disease Progression Model in Korean Patients with Type 2 Diabetes Mellitus(T2DM)

Donghwan Lee (1,2) , Bongsoo Cha (3), and Kyungsoo Park (1,2)
(1) Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea. (2) Brain Korea 21 Project for Medical Science, Yonsei University, Seoul, Korea (3) Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

Objectives: T2DM is a progressive disease. Decreasing β-cell function, increasing insulin resistance and increasing fasting plasma glucose levels are the natural sequels of T2DM. The purpose of this work is (i) to develop a disease progression model for Korean patients with T2DM and (ii) apply the developed model as a supportive tool to designing an optimal treatment regimen in this clinical population.

Methods: Data were obtained from medical records from 330 (121 new and 209 established) patients who were diagnosed of T2DM and visited outpatient clinics at Severance Hospital (Seoul, Korea) during the period from 2006 to 2012. The primary endpoints of disease progression were fasting plasma glucose (FPG, mmol/L) and glycated hemoglobin (HbA1c, %) observed for up to two years after the treatment began. Disease progression was modeled as the natural history of progress, denoted by the baseline and progress rate [1], and drug effect influencing the baseline ("offset") or the progress rate ("slope") or both [2]. A linear or Emax model was used for drug effect, which was related to the effect-site "dose rate" via a K-PD model [3] as no concentration information was available. All analyses were performed using NONMEM 7.2.

Results : Patients consisted of 69 men and 52 women, with the median age of 60 years. They were prescribed 1 to 3 classes of oral hypoglycemic agents(OHAs) at the first visit. When new patients' FPG data were separately analyzed using an offset model for disease progression and a linear model for drug effect, parameter estimates were 7.71 mmol/L for the baseline, 0.311 mmol/L/year for the progress rate (individual variability 107%), and 11.6 days for the equilibrium half-life (individual variability 157%). The latter results indicated that inter-individual variation in our study population was similarly large as compared to previous results in western population [1], but disease progression rate was slower, with the effect-site equilibrium rate being faster. Analyses with other model types, influences of classes of OHAs and other covariates, characteristic differences between new and established patients as well as causal relationship between FPG and HbA1c are currently underway.

Conclusions: These preliminary results have demonstrated that Korean T2DM patients have the slower disease progression rate and the faster effect-site equilibrium rate as compared to western population. More work will be needed to complete the model and generalize the results.

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Joomi Lee III-09 Population pharmacokinetics of prothionamide in Korean tuberculosis patients

Joomi Lee1,2, Sung Min Park1,2, Sook-Jin Seong1,2, Jong Gwang Park1,Jeong Ju Seo1,2, Mi-Ri Gwon1,2, Hae Won Lee1, Young-Ran Yoon1,2
1 Clinical Trial Center, Kyungpook National University Hospital, Daegu, Korea.
2 Department of Biomedical Science, Kyungpook National University Graduate School, Daegu, Korea

Objectives: Prothionamide (PTH) is a thioamide drug that has been used for multidrug-resistant tuberculosis (MDR-TB). It is bactericidal and is prescribed as second-line anti-TB medications. The population pharmacokinetic (PK) modeling of PTH has not been developed. The aim of this study was to investigate the population PK of PTH in Korean patients with MDR-TB.

Methods: Seventeen Korean patients with MDR-TB participated in this study. All patients had received multiple oral doses of PTH for at least 2 weeks, with other second-line anti-TB drugs. Plasma samples were collected before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after dosing. The concentration of plasma PTH was analyzed with high performance liquid chromatography. The population PK data were analyzed using NONMEM (Ver. 6.2).

Results: A 1-compartment model with Weibull-type absorption described the best fit to a total 221 concentrations of PTH from TB patients. The major population parameter estimates were as follows; k_a, 0.509 h^{-1}; V_c *(volume of central compartment),* 104 L; and CL, 34 L/h. The 1-compartment structural model was validated through visual predictive check (VPC) with no serious model misspecification.

Conclusions: A population PK model was developed and reasonable parameters were obtained from the data of Korean pulmonary TB patients. Further study will be required to develop a final PK model through comparison with other compartment PK models and to evaluate the usefulness of dose-response relationship using bootstrap simulation.

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Junghoon Lee III-10 Modeling Targeted Therapies in Oncology: Incorporation of Cell-cycle into a Tumor Growth Inhibition Model

Junghoon Lee (1), Konstantinos Biliouris (2), Jeremy Hing (1) , Stuart Shumway (1), Dinesh De Alwis (1)
(1) Merck Research Laboratories, Merck & Co. Inc., Rahway, NJ 07065, U.S.A.
(2) Chemical Engineering Department, University of Minnesota, Twin Cities, Minneapolis, MN 55455, U.S.A.

Objectives: The tumor-growth model by Simeoni et al. [1] has been widely used to understand and characterize the drug effect observed in xenograft models. Two improvements to the Simeoni model are proposed to model the effects of targeted therapeutics.

Methods: Phase-specificity of targeted therapeutics is modeled by introducing four additional compartments, representing gap 1 (G1), synthesis (S), gap 2 (G2), and mitosis (M) phases of the cell cycle. The relative transition rates among the four compartments are fixed and adopted from the literature, whereas the cell-death rates from the compartments are empirically determined to closely recapitulate the exponential-to-linear growth characteristics of the Simeoni model. Finally, the drug effect on cell death from the S-phase compartment is modeled with a sigmoidal function instead of a proportional one.

Results: The model is validated against data from xenograft bearing mice treated with gemcitabine and drug X known to be targeted. The transition from the proportional to the Emax model for the drug effect on cell death successfully captures both the non-proportional effect of drug X on tumor growth and the proportional effect of gemcitabine during the first 30 days of treatment. In a 60-day simulation, the proposed model, unlike Simeoni

model, predicts that tumor regression is affected not only by the total amount of administered drug but also by the treatment schedule.

Conclusions: Our model suggests that the efficacy of targeted therapeutics may exhibit treatment-schedule dependency due to their phase-specificity; a characteristic that Simeoni model fails to capture. In addition, validation using drug-X data shows that the drug effect on cell death is non-linear for some drugs and the Simeoni model needs to be adjusted. The use of literature (and possibly in-vitro) values for some model parameters can help limit the number of additional estimated parameters to two, keeping the proposed model practical for drug development settings. Further validation of the proposed model with longer-term data is needed to confirm the predicted dependency on treatment schedule.

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Tarek Leil III-11 PK-PD Modeling using 4β-Hydroxycholesterol to Predict CYP3A Mediated Drug Interactions

Tarek Leil , Sreeneeranj Kasichayanula, David Boulton, Frank LaCreta
Bristol-Myers Squibb, Princeton, NJ USA

Objectives: Develop a semi-mechanistic PK-PD model for the effects of rifampin and ketoconazole on CYP3A mediated formation of plasma 4b-hydroxycholesterol.

Methods: PK and PD data from a clinical study of the effects of rifampin and ketoconazole on the metabolism of endogenous markers of CYP3A4 activity, and on midazolam PK in healthy subjects was used in the analysis. The data included midazolam PK, plasma total cholesterol, plasma 4b-hydroxycholesterol, and 4a-hydroxycholesterol. Model development was conducted via a Markov Chain Monte Carlo (MCMC) Bayesian estimation approach with informative priors (Figure 1), helping to overcome the lack of availability of PK data for ketoconazole and rifampin. Convergence of the model parameters and objective function was evaluated by visual inspection of the "caterpillar" plots for three independent MCMC chains and by examination of the Gelman & Rubin statistics. Thirty thousand iterations of each MCMC chain were used during the burn-in phase, and one thousand for the stationary phase. Additional model evaluation was conducted by visual inspection of the predictions with the observed data, and comparison of predicted vs. observed summary PK measures.

Results: The three MCMC chains appeared to converge to the same objective function value and parameter estimates based on the Gelman & Rubin statistics and visual inspection of the "caterpillar" plots. The upper bound of the 95% confidence interval for the Gelman & Rubin shrink factor for the objective function value was 1.33, while for the fixed effect parameters it was

1.11. Separate parameters were required for induction of CYP3A in the gut (~ 30-fold) relative to liver (~ 3.4-fold), and for ketoconazole's Ki for midazolam (~ 0.14 nM) vs. 4b-hydroxycholesterol (~ 50 nM). The PK-PD model was effective in predicting the time course of plasma midazolam and 4b-hydroxycholesterol levels under conditions of CYP3A inhibition and induction (Figure 2). The model was also effective in estimating the change in oral and IV midazolam AUC in the presence of ketoconazole, and the change in oral midazolam AUC in the presence of rifampin. However, the effect of rifampin on the AUC of IV midazolam was under-predicted.

Conclusions: A semi-mechanistic PK-PD model was developed to describe the effect of ketoconazole and rifampin on midazolam PK and plasma 4b-hydroxycholesterol levels. This model will facilitate incorporation of 4b-hydroxycholesterol as a biomarker of CYP3A modulation in future clinical studies.

Annabelle Lemenuel-Diot III-12 How to improve the prediction of Sustained Virologic Response (SVR) for Hepatitis C patients using early Viral Load (VL) Information

Annabelle Lemenuel-Diot (1), Nicolas Frey (1)
(1) Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: In clinical drug development of Chronic Hepatitis C treatments, early VL information between week 2 and week 8 (e.g.: magnitude of VL drop or VL below the detection limit), are generally used to predict SVR, the primary clinical endpoint defined as undetectable VL 24 weeks after end of treatment. The objective of this work is to investigate if an integration of the early VL profile using a viral kinetic (VK) model would allow improving the SVR prediction. The impact of using VL information from the relapse that may occurred following treatment interruption was also investigated.

Methods: Using the Hepatitis C viral kinetic model previously developed [1], the analysis plan was defined as follow:

1. Simulation of different treatment durations: 2, 4, 8 weeks, with or without treatment interruption, for a set of 1000 patients using the individual VK parameters from the original model.
2. Estimation of the population/individual VK parameters with Monolix 3.2 using the available VL information for each simulated treatment.
3. Simulation of full treatment duration (48 weeks) with the estimated individual parameters to predict SVR.
4. Assessment of the SVR predictive performance for the different predictors: Early Viral Response, Early VL drop, Early VL time course w/wo treatment interruption.

Results: The main results are summarized in the table below with: Predicted SVR (the true being 55%), Sensitivity (True SVR among predicted SVR) and Specificity (True noSVR among predicted noSVR).

	Predicted SVR (%)	Sensitivity (%)	Specificity (%)
3 log VL drop w2	22	89	55
2 log VL drop w8	81	66	89
VR w4	15	97	52
VR w8	41	89	68
VL Time Course 4w	74	68	81
VL Time Course 4w + relapse	55	90	86

Among the different predictors, the full integration of the VL information with a treatment interruption, to use the relapse information, is the best way to accurately predict SVR combining both high sensitivity and high specificity.

Conclusions: Different strategies using early VL drop criteria are generally implemented in clinical drug development to predict SVR. From the simulation, it can be shown the limitation of such approaches. Actually, the best predictive performances of SVR are obtained using full information of VL time course from a short treatment including a treatment interruption. However, the issue related to a treatment interruption would be the potential higher risk of development of resistance.

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Joanna Lewis III-13 A homeostatic model for CD4 count recovery in HIV-infected children

J. Lewis (1,2), J. F. Standing (1), A. S. Walker (3), N. Klein (1) and R. Callard (1,2)
(1) UCL Institute of Child Health, (2) UCL CoMPLEX, (3) MRC Clinical Trials Unit

Objectives: A two-compartment model of CD4 memory T-cell homeostasis has already provided a compelling explanation of the slow decline in CD4 count during chronic HIV infection, as a set-point modified by changing population dynamics[1]. We aimed to use a similar model to investigate recovery of CD4 count in HIV-infected children starting antiretroviral therapy (ART), and to understand mechanisms and determinants of long-term reconstitution.

Methods: We studied 9166 CD4 counts collected over 2 years in 914 HIV-infected children (median(IQR) age 5.6(2.3,8.9) years; pre-ART CD4 count 342(165,643) cells/uL) showing typical, asymptotic CD4 recovery following ART initiation[2]. Using NONMEM[3] and nonlinear mixed-effects models based on ordinary differential equations, we fitted fixed and random effects for thymic activity, stimulation of T-cells to divide and death of resting T-cells.

Results: Diagnostic plots and simulated datasets demonstrated the model's fit to the data and good predictive properties. Examining estimated child-specific parameters we found that children with poor recovery had low thymic output, faster stimulation of T-cells to divide and increased death of resting cells (all p

Conclusions: A homeostatic model of T-cell dynamics can be used to understand CD4 T-cell dynamics and recovery in HIV-infected children starting ART. Faster T-cell death, faster activation to divide and lower thymic

output are all candidate causes for incomplete T-cell reconstitution in children. Children starting ART at older ages have higher thymic output, relative to expected level in a healthy child. We found correlations between random effects and markers of T-cell activation and division, suggesting that between-child differences in recovery are related to altered T-cell homeostasis.

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Yan Li III-14 Modeling and Simulation to Probe the Likely Difference in Pharmacokinetic Disposition of R- and S-Enantiomers Justifying the Development of Racemate Pomalidomide

Yan Li, Simon Zhou*, Matthew Hoffmann, Gondi Kumar and Maria Palmisano
Celgene Cooperation, Summit, NJ, USA

Introduction: Pomalidomide is a immunomodulatory drug with pleiotropic actions of cytotoxity against multiple myeloma cells, immunomodulatory and anti-angiogenic activity, that has been approved for the treatment of multiple myeloma. Pomalidomide has an asymmetric carbon center and exists as the optically active forms S (-) and R (+), and has been developed as a racemate. The aim of this analysis was to explore the pharmacokinetic (PK) disposition of two pomalidomide enantiomers based on racemate PK profile in humans, and enantiomer PK profiles in animals, and to evaluate the interaction of distinct enantiomer PK dispositions and their in vivo interconversion on plasma exposure to the two enantiomers.

Material and methods: PK Modeling were performed in NONMEM 7.2 to describe the observed PK data of S- and R-isomers in humans and monkeys accounting for respective species difference in enantiomer PK disposition and enantiomer interconversion on two enantiomer plasma exposure in humans and monkeys. Subsequent simulations were conducted to assess the interaction between isomer interconversion and distinct isomer elimination on plasma exposure to two isomers. Key measure of isomer interconversion rate relative to racemate elimination rate were derived and calibrated in determining potential difference to individual isomer plasma exposure.

Results: PK modeling based on a physiological plausible model with distinct PK dispositional parameters for two enantiomers and concurrent isomer intercoversion provided adequate fit for the S- and R-isomer observations in humans and monkeys. Modeling results showed that the in vivo elimination rate is 0.09 hr-1 which was lower than the R-/S- inter-conversion rate of 0.353 hr-1 in human. However, the in vivo elimination rate is 0.55 hr-1, and comparable/higher than the R-/S- inter-conversion rate of 0.223 hr-1 in monkeys. Simulation results demonstrated that the higher the ratio of the in vivo elimination to the inter-conversion, the larger the difference of PK exposures between R- and S- enantiomers.

Conclusions: This PK analysis demonstrated the utility and power of M&S in elucidating experimentally challenging and technically difficult issues, providing scientific rationale and eliminating the need for uninterruptable and costly studies.

Lia Liefaard III-15 Predicting levels of pharmacological response in long-term patient trials based on short-term dosing PK and biomarker data from healthy subjects

Lia Liefaard (1), John Grundy (2), Nicola Williams (1), Andrew Shenker (3), Chao Chen (1)
(1) GlaxoSmithKline, UK (2) Isis Pharmaceuticals, Carlsbad, US (3) GlaxoSmithKline, US

Objectives: To develop a population PK/PD model using short-term dosing PK and biomarker data from healthy subjects; to apply this model to predict levels of pharmacological response, along with their uncertainty, in long-term treatment trials in patients.

Methods: PK and biomarker data from a short-term study in healthy subjects, in which a compound was administered at several dose levels, were analysed by means of population PK/PD modelling using NONMEM 7. Because of the expected long half life of the compound steady state was not reached in this study. The resulting PK/PD model was then used to predict the individual steady state biomarker levels in patients at the proposed clinical dose and administration frequency as well as sample size, taking into account inter-subject variability. For the simulations, the drug response was assumed to be generally comparable between healthy volunteers and patients, and the system part of the model was adapted for the patient population based on literature data. 300 replicates of the simulation were obtained, allowing for the uncertainty in the parameter estimates using the TNPRI subroutine of NONMEM [1]. The distribution of the proportion of patients reaching various specified levels of pharmacological response were calculated using the results of the 300 simulation replicates.

Results: A 2-compartment model with 1st-order absorption described the plasma PK adequately. The PK/PD model consisted of an indirect response model, in which the production of the biomarker is inhibited by the compound. An effect compartment accounted for the time differences between plasma PK and effect on biomarker levels. Using this model, including the parameter estimates and their uncertainty, the median and its 90% certainty of the proportion of patients meeting different levels of pharmacological response at steady-state could be predicted.

Conclusions: With this approach, the median proportion of patients in a long-term clinical trial meeting a desired level of pharmacological response and the certainty around this median can be predicted. In situations where certain levels of pharmacological response of a biomarker may be anticipated or known to correlate to a clinically meaningful effect, this approach allows for prediction of the probability of meeting such pharmacological response levels in a long-term clinical trial. This could then be used to justify dose selection or determine criteria for a futility analysis.

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Karl-Heinz Liesenfeld III-16 Pharmacometric Characterization of the Elimination of Dabigatran by Haemodialysis

Karl-Heinz Liesenfeld (1), Alexander Staab (1), Sebastian Härtter (1), Stephan Formella (2), Andreas Clemens (2,3), Thorsten Lehr (1,4)
(1) Translational Medicine, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany, (2) Clinical Development and Medical Affairs, Boehringer Ingelheim GmbH & Co KG, Ingelheim, Germany, (3) Center for Thrombosis and Hemostasis, Johannes Gutenberg University, Medical Center, Mainz, Germany, (4) Saarland University, Saarbruecken, Germany

Objectives: To characterize the effect of haemodialysis at different blood flow rates on the pharmacokinetics (PK) of dabigatran by pharmacometric approaches and to evaluate the effects of different clinically relevant haemodialysis settings in order to assess their potential impact on elimination of dabigatran.

Methods: Data analysis was based on a population PK model originally developed to optimize the design of the haemodialysis study in end-stage renal disease (ESRD) patients [1]. Data from 7 patients with 28 dialysis and 308 plasma samples were available. The model was developed to fit the data and then used for various simulations. Data analyses were performed using NONMEM® and SAS.

Results: A 2-compartment model with first-order absorption and a lag time best described the PK of dabigatran. The apparent total body dabigatran clearance in subjects with ESRD was estimated at 12.4 L/h. An apparent dialysis clearance was implemented in parallel to describe the accelerated drug clearance caused by haemodialysis (> 0 during haemodialysis; 0 during the interdialytic periods). The effect of blood flow rate was best described using the Michaels equation. It demonstrated that, by doubling the blood

flow from 200 to 400 mL/min, the dialysis clearance increases by 30%, resulting in additional reduction of the dabigatran plasma concentration by about 8%. Simulations of various haemodialysis settings (eg, type of filter, dialysis flow rate and blood flow rate), variations in renal function and duration of dialysis showed that dialysis duration had the strongest impact on dabigatran concentration. Plasma concentrations are roughly halved every 4 hours under dialysis. The observations for dabigatran also showed that the average redistribution effect after dialysis was low when plasma concentrations were similar to those usually observed in nonvalvular atrial fibrillation patients. The final model successfully predicted the plasma dabigatran concentrations described in a published case report of a patient undergoing dialysis.

Conclusions: This analysis allows a detailed description of the effect of dialysis on the plasma dabigatran concentrations in ESRD patients with a normal exposure to dabigatran. Dialysis duration was identified as having the strongest impact on the reduction of plasma dabigatran concentrations and redistribution effects were consistently found to be low. The developed model might serve as a useful tool to provide guidance for optimizing the use of haemodialysis in patients where dabigatran elimination is needed.

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Otilia Lillin III-17 Model-based QTc interval risk assessment in Phase 1 studies and its impact on the drug development trajectory

O. Lillin, W. Comisar, J. Stone, D. Tatosian, R. de Greef
MSD

Objectives: Population C-QTc analysis is useful tool to leverage QTc data from Phase I studies. We present the results of three Ph1 C-QTc analyses and discuss 1) the impact on the drug development trajectories of each of these compounds and 2) what type of ECG data are required for a reliable estimate of the drug effect.

Methods: Mixed effects models with circadian rhythm as covariate on the intercept QTc and direct linear drug effect[4] (Drug A and B) and a linear mixed effects model (Drug C) were developed based on concentrations and QTc data from Phase 1 studies. Three examples of novel compound candidates are included.

Results:

All compounds were weak to moderate hERG inhibitors.

Drug A: establish safety margin of therapeutic window, predict TQT, negotiate ECG strategy in Ph2/3

- - Ph1 C-QTc modeling predicted high likelihood of <10 ms QTc prolongation at doses ≤ 3.5-fold the therapeutic dose

- - The predicted QTc prolongation (mean and upper CI) at supra-therapeutic dose was 10 (14) ms and the TQT was predicted to be positive; the largest dQTc in the TQT was 12 (14) ms
- - PK-QTc modeling informed early the necessity to plan for appropriate ECG monitoring in Phase 2/3 and helped negotiate less stringent monitoring

Drug B: aid in design of TQT, negotiate ECG strategy for Ph3

- - Ph1 C-QTc predicted <2 msec QTc prolongation at Ph III doses, with a predicted QTc change of <10 ms occurring at a 4.5 to 5.5-fold margin over clinical exposures
- - The predicted QTc prolongation at supra-therapeutic dose was 4.5 (6.8) ms and the TQT is predicted to be negative (ongoing).
- - Modeling permitted earlier Ph3 start prior to conduct of TQT study without the need for extensive ECG measurements in Ph3.

Drug C: de-risking TQT

- - A Ph1 C-QTc analysis predicted no drug effect on QTc changes (drug effect slope was not significantly different from zero), which enabled more rapid development with deferral of TQT to be in parallel to Phase IIB.

The TQT was negative.

Conclusions: Population C-QTc models were successfully fitted to the data of Phase 1 trials for three compounds. The Ph1 C-QTc analyses were predictive of the TQT for Drugs A and C; study is ongoing for B. These early results were useful not only for internal decision making but also in the dialog with regulators.

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Hyeong-Seok Lim III-18 Pharmacokinetics of S-1, an Oral 5-Fluorouracil Agent in Patients with Gastric Surgery

Hyeong-Seok Lim* (1), Young-Woo Kim (2), Keun Won Ryu (2), Jun Ho Lee (2), Young-Iee Park (2), Sook Ryun Park (2)

1) Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, Ulsan University College of Medicine, Pungnap-2-dong, Seoul, Republic of Korea (2) Research Institute and Hospital, National Cancer Center, 809 Madu 1, Ilsan, Goyang, Gyeonggi, 410-769, Republic of Korea

Objectives: S-1 is an oral 5-Fluorouracil (5-FU) agent containing tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate. Tegafur is converted into 5-FU in body, which is an effector. CDHP induces long-term retention of an increased concentration of 5-FU in blood by reversibly inhibiting dihydropyrimidine dehydrogenase [1]. This study explored the pharmacokinetics (PK) of S-1, and PK changes after gastric surgery in patients with gastric cancer.

Methods: Serial blood samples were collected on day 1 of cycle 1 for the PK from 37 patients. Patients were 18-70 years old, biopsy-proven locally advanced gastric cancer of clinical stage of IIIA, IIIB, or IV (M0) [2]. Blood was drawn before (0 h) and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h after treatment initiation on day 1 and pre-dose on day 8 of each 1st cycle of preoperative and postoperative treatment. Plasma concentrations of tegafur, 5-FU, CDHP were measured using liquid chromatography-tandem mass spectrometry. PK was analyzed by non-compartmental (NCA) methods using WinNonlin® 5.2 (Pharsight Corporation, Mountain View, CA), and by compartmental modeling using NONMEM® 7.2 (ICON Development Solutions, USA). In modeling analysis, PK models for tegafur and 5-FU were fitted sequential, with individual parameter estimates of tegafur as input for 5-FU model. CHDP concentration data were modeled separately, and the predicted CHDP

concentrations were incorporated in the tegafur and 5-FU model as a time varying covariate which inhibits the clearance of 5-FU by inhibitory Emax model.

Results: In the NCA analysis, the PK's of tegafur and 5-FU before and after gastric surgery were similar except for higher maximum average concentrations of 5-FU. Medan Tmax of tegafur was shorter after surgery with no statistical significance. In the modeling analysis, tegafur were best fitted by mixed zero and first order absorption model and two compartment disposition model. 5-FU was best described by one compartment disposition model. The tegafur model was significantly improved when the different first order (Ka), zero order absorption (D1), and absorption lag (ALAG1) parameters were included before and after gastric surgery. However, in Monte-Carlo simulation, plasma concentration profiles of tegafur and 5-FU were very similar between before and after the surgery. There was a significant improvement in the tegafur and 5-FU model when the model-predicted CDHP concentrations were incorporated.

Conclusions: Although there were statistically significant findings on the changes of absorption processes after gastric surgery, the changes were so small that the clinical significances should be evaluated by further studies. This study also evaluated the PK with the quantification of the effect of CDHP on the 5-FU PK.

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Andreas Lindauer III-19 Comparison of NONMEM Estimation Methods in the Application of a Markov-Model for Analyzing Sleep Data

Lindauer, A (1); Guo, Z (2); Zajic, S (3); Huang, S (2); Mehta, K (4); Kumar, B (3); Elassaiss - Schaap, J (1); Bauer, R (5); Clements, JD (3)
(1) Clinical PKPD, Merck & Co., Inc. (Oss, NL); (2) Biostatistics, Merck & Co., Inc. (US); (3) Clinical PKPD, Merck & Co., Inc. (US); (4) Informatics, Merck & Co., Inc. (US); (5) Icon Dev. Solutions (US)

Objectives: Nonlinear mixed-effects modeling of polysomnographic (PSG) data has been shown to provide quantitative insight into the time course of transitioning between sleep stages. However, these models are relatively complex and the amount of data is enormous. As part of an effort to assess the utility/feasibility of this modeling approach for in-house development programs, it was of interest to evaluate the performance of the various estimation methods available in NONMEM 7.2 and select the 'best' method for future analyses.

Methods: The model described by Kjellson et al. has been adapted for this purpose [1]. Parameter estimates were taken from this publication and considered as 'true' values. 100 PSG datasets with 100 subjects each were simulated using R. A PSG recording consists of a categorical observation (i.e. awake, stage 1, stage 2, slow-wave-sleep, rapid-eye-movement) per 30-sec epoch during an 8-hour-night. All datasets were analyzed with the following estimation methods: BAYES, SAEM, IMP, IMPMAP, ITS, LAPLACE (LAPL). The initial estimates were set to the true value; only for LAPL the analysis was also performed with randomly changed initial values. The relative errors of the parameter estimates were calculated for each run and summarized for each method.

Results: The LAPL-method clearly outperformed the other methods with fixed-effects parameter estimates usually within 1.5-fold of the true value. For some parameters ITS, IMP, and IMPMAP resulted in extremely biased estimates - less so with SAEM. Randomly changing initial values had no significant impact on the accuracy and precision of the estimates obtained with LAPL. With the BAYES-method all runs terminated during the burn-in phase. Over 80% of the LAPL-runs converged successfully, while for the other methods optimization was completed ~60% of the time. The median run time was shortest using SAEM (1.4 h), followed by LAPL (2.2 h), ITS (7.2 h), IMP (9.7 h), and IMPMAP (290 h).

Conclusions: The present evaluation shows that for analyzing PSG data with a Markov-model the LAPL method provides the most accurate parameter estimates and is most efficient regarding run times. However, due to the complex model structure appropriate MU-referencing was not possible which may explain the suboptimal performance of the other methods. Not providing priors to the model parameters was likely the reason for the premature termination of runs using the BAYES-method. The LAPL method will be used for future internal analysis of PSG data.

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Jesmin Lohy Das III-20 Simulations to investigate new Intermittent Preventive Therapy Dosing Regimens for Dihydroartemisinin-Piperaquine

Jesmin Permala(1), Joel Tarning(2, 3), François Nosten(2, 3, 4), Mats O. Karlsson(1),Nicholas J. White(2, 3), Martin Bergstrand(1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (2) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (3) Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (4) Shoklo Malaria Research Unit (SMRU), Mae Sod, Thailand

Objectives: A fix combination of dihydroartemisinin (DHA)-piperaquine (PQ) has been suggested as a new alternative for Intermittent Preventive Therapy (IPT) in response to the emergence of resistance to other treatment alternatives [1]. This project aim to explore alternative dosing regimens for DHA-PQ to those studied in clinical trials by the application of simulations with a PKPD model.

Methods: A time-to-event model characterizing the concentration-effect relationship for the malaria preventive effect of DHA-PQ has been developed [2-3] in application to a study of 1000 healthy male subjects in Northern Thailand [1]. The clinical trial featured treatment regimens with DHA-PQ dosing on three consecutive days repeated every month or every second month. Simulations based on the PKPD model have been used to compare the clinical utility of these regimens to novel regimens primarily based on once weekly dosing. The benefit of an initial loading dose strategy was investigated both for monthly and weekly dosing regimens. All scenarios were simulated under the assumption of different levels and patterns of

treatment compliance (100%, 80% and 60%). All simulations were carried out using the software Berkeley Madonna.

Results: Assuming perfect compliance a weekly dosing regimen with an initial 3 day loading dose session was predicted to result in a yearly malaria incidence of less than 1 %, compared to approximately 3% for the once monthly dosing regimen and 52% for placebo. Assuming on average 80% compliance the weekly dosing regimen maintained the incidence below 1% whereas the incidence for a monthly regimen would increase to 8%. In case of very poor compliance (60%) the weekly dosing regimen was predicted to result in a 3% incidence compared to >15% for any monthly regimen.

Conclusions: Simulations with a PKPD model for the malaria preventive effect of DHA-PQ was useful in investigations of alternative dosing regimens. A novel weekly dosing regimen was indicated to outperform the previously suggested monthly regimen especially with regards to being less sensitive to poor compliance.

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Dan Lu III-21 Semi-mechanistic Multiple-analyte Population Model of Antibody-drug-conjugate Pharmacokinetics

Dan Lu (1), Jin Yan Jin (1), Priya Agarwal (1), Sandhya Girish (1), Dongwei Li (1), Saileta Prabhu (1), Denise Nazzal (1), Ola Saad (1), Randy Dere (1), Neelima Koppada (1), Chee Ng (2, 3)
(1) Genentech, South San Francisco, CA, USA; (2) Children Hospital of Philadelphia, Philadelphia, PA, USA (3) School of Medicine, University of Pennsylvania, Philadelphia, PA

Objectives: Monomethyl auristatin E (MMAE) containing antibody-drug-conjugates (ADCs) are complex mixtures, therefore their pharmacokinetics are assessed by evaluating multiple analytes including total antibody (TAB), antibody-conjugated MMAE (acMMAE) and unconjugated MMAE after ADC dosing. Both TAB and acMMAE concentrations represent mixtures of various drug-to-antibody ratio (DAR) species. The objective of this analysis is to develop a semi-mechanistic multiple-analyte population model to better understand the major pathways of ADC elimination and unconjugated MMAE formation by ADC catabolism.

Methods: The pharmacokinetic (PK) data of multiple analytes for anti-CD79b ADC after a single intravenous dose (0.3, 1, 3 mg/kg) and multiple intravenous doses (1, 3, 5 mg/kg every-three-week for 4 doses), and the PK data of MMAE after a single intravenous dose administration of unconjugated MMAE (0.03 and 0.063 mg/kg) in cynomolgous monkeys were used together for modeling. Multiple semi-mechanistic models were explored to describe the PK of TAB, acMMAE and unconjugated MMAE simultaneously. Parallel hybrid ITS-MCPEM estimation algorithm was used for parameter estimation in S-ADAPT 1.57. The observed below quantification limit data were modeled using M3 method.

Results: ADC elimination clearance pathways are comprised of both deconjugation and proteolytic degradation pathways. A multiple-compartment PK model assuming a sequential deconjugation from high DAR species to low DAR species with a Weibull model for description of the deconjugation rate constant change with the DAR and michaelis-menton kinetics of proteolytic degradation adequately described the PK data of TAB and acMMAE simultaneously. The fraction of formation from the proteolytic degradation pathway to unconjugated MMAE was ~ 66%, while the fraction of formation from the deconjugation pathway was only ~ 2%.

Conclusions: The final model well described the observed TAB, acMMAE and unconjugated MMAE PK data in cynomolgous monkeys simultaneously. The model suggested ADC is eliminated via both the deconjugation pathway and the proteolytic degradation pathway, while the unconjugated MMAE is formed mainly via the proteolytic degradation pathway. This finding suggested that the unconjugated MMAE level after ADC dosing might be modulated by modifying the binding affinity of the ADC to FcRn and/or target and consequently the rate of FcRn and/or target-mediated proteolytic degradation.

Viera Lukacova III-22 Physiologically Based Pharmacokinetic (PBPK) Modeling of Amoxicillin in Neonates and Infants

Viera Lukacova, Michael B. Bolger, Walter S. Woltosz
Simulations Plus, Inc., Lancaster, CA, USA

Objectives: An amoxicillin PBPK model was previously developed and validated in several adult populations. The purpose of this study was to explore the utility of the model in describing amoxicillin pharmacokinetics (PK) in neonates and infants.

Methods: An absorption/PBPK model for amoxicillin PK in adult populations was previously developed and validated [1-2] using GastroPlus™ 8.0 (Simulations Plus, Inc.). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the absorption of the drug, while PK was simulated with its PBPKPlus™ module. Intestinal absorption and tissue distribution accounted for both passive diffusion and carrier-mediated transport. Total clearance consisted of renal (major) and hepatic (minor) components. Physiologies for infants and neonates were based on information collected from literature. These account for body weight, height, tissue sizes and blood flows, as well as rapid changes in extracellular water and renal function during first few weeks of life. Plasma protein and red blood cell binding was adjusted to account for infant plasma protein levels and hematocrit. The PBPK model, along with observed Cp-time profiles after i.v. administration was used to estimate the ontogeny of renal transporters.

Results: The PBPK model for amoxicillin correctly predicted volume of distribution in infants. The age-dependent glomerular filtration rate (GFR) was incorporated as reported in the literature for full-term and pre-term infants [3-4]. Renal transporter expression levels were fitted against observed Cp-time profiles from some studies and validated by using the final model to

simulate amoxicillin PK in subjects of similar age from different studies. The differences in scaling for GFR and renal transporters are in line with the reported rates of maturation of GFR and active tubular secretion [5].

Conclusions: Amoxicillin is eliminated primarily by renal secretion. A physiological model that included relevant distribution and clearance mechanisms was previously fitted and validated in different adult populations. In the current work the model was applied to simulations of amoxicillin PK in neonates and infants: (1) to fill-in missing pieces of physiological information (ontogeny of renal transporters) using available in vivo data; and (2) to explore sources of variability in amoxicillin PK and provide insights into the drug's behavior in populations where large scale clinical studies are not feasible.

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Panos Macheras III-23 On the Properties of a Two-Stage Design for Bioequivalence Studies

Vangelis Karalis, Panos Macheras
Laboratory of Biopharmaceutics-Pharmacokinetics, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece.

Objectives: To introduce and unveil the properties of a two-stage design (TSD) for bioequivalence (BE) studies.

Methods: A TSD with an upper sample size limit (UL) is described and analyzed under different conditions using Monte Carlo simulations. This TSD was split into three branches: A, B1, and B2. The first stage included branches A and B1, while stage two referred to branch B2. Sample size re-estimation at B2 relies on the observed geometric mean ratio (GMR) and variability of the pharmacokinetic parameters at stage 1. The properties studied were % BE acceptance, % uses and % efficiency of each branch, as well as the reason of BE failure.

Results: No inflation of type I error was observed. Each TSD branch exhibits different performance. Branch A exerts the highest ability to declare BE either when variability is low to moderate, or an adequately high number of subjects is recruited.Second stage becomes mainly useful when highly variable drugs are assessed with a low number of subjects (N1) enrolled at stage 1 and/or the two drug products differ significantly. Branch A is more frequently used when variability is low, drug products are similar, and a large N1 is included. BE assessment at branch A exhibits high efficiency to declare BE. On the contrary, branches B1 and B2 are usually less efficient in declaring BE.

Conclusions: BE assessment at branch A exhibits high efficiency to declare BE, while branches B1 and B2 are usually less efficient. Inclusion of a UL is necessary to avoid inflation of type I error.

Merran Macpherson III-24 Using modelling and simulation to evaluate potential drug repositioning to a new therapy area

M Macpherson (1), A Viberg (1, 2), R Riley (1)
(1) AstraZeneca, UK, (2) qPharmetra, Stockholm, Sweden

Introduction: Two doses of drug x were explored in initial phase IIa trials in over 300 patients. The lower dose was judge to be the minimally efficacious dose based on preclinical data and the other dose was chosen to represent maximum anticipated well tolerated dose. A consequence of target inhibition with drug x, was an increase in serum levels of a biomarker and this biomarker was used as a surrogate for receptor occupancy. A review of internal and external data suggested that this compound/target could be repositioned into another therapy area and, in order to robustly test the hypothesis, the dose required for a clinically relevant response was targeted to achieve ≥ 90% receptor occupancy in 80% of patients.

Objectives: Develop a PKPD model from the patients in these trials and investigate the dose required for 90% receptor occupancy in 80% of patients in a new patient population.

Methods: A two-step sequential population pharmacokinetic-pharmacodynamic (PK-PD) analysis was performed using NONMEM 7.2.0. A two-compartment population PK model was fitted to the PK data and subsequently an inhibitory Emax pharmacodynamic model was fitted to the biomarker data accounting for the relationship between drug concentration and effect. Various simulations of the final sequential PK-PD model were performed.

Results: Based on simulations of the final model, it is unlikely that 90% receptor occupancy will be achieved in 80% of patients at the highest

investigated dose. A doubling of exposure would be required to approach this target value. In the populations under consideration, this could be achieved through a reduction in CL/F or an increase in dose. It is also likely that variability in exposure may increase in the new target population as a consequence of reduced hepatic and renal function and an indication of this effect was demonstrated.

Conclusions: This analysis demonstrates a range of possible receptor occupancies and the impact patient specific variables may have on this assessment. Given the higher doses required and the additional potential DMPK and safety risks in the target patient population at these doses, an informed decision was made to suspend the project.

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Paolo Magni III-25 A PK-PD model of tumor growth after administration of an anti-angiogenic agent given alone or in combination therapies in xenograft mice

Massimiliano Germani (1), Maurizio Rocchetti, Francesca Del Bene (1), Nadia Terranova (2), Italo Poggesi (3), Giuseppe De Nicolao (2), Paolo Magni (2)
(1) PK & Modeling, Accelera srl, Nerviano (MI), Italy, (2) Dipartimento di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Italy, (3) Johnson & Johnson, c/o Janssen Cilag S.p.A., Via M. Buonarroti 23, 20093, Cologno M.se, MI, Italy.

Objectives: PK–PD models able to predict the action of anticancer compounds in tumor xenografts have an important impact on drug development. In case of antiangiogenic compounds, many of the most common models are inadequate , as they are based on a cell kill hypothesis, while these drugs mainly act on the tumor vascularization, without a direct tumor cell kill effect. For this reason, a PK–PD model able to describe the tumor growth modulation following treatment with a cytostatic therapy, as opposed to a cytotoxic treatment, is proposed here.

Methods: *Experimental Methods*
The experimental setting is that of a typical in vivo study routinely performed within several drug development projects using human carcinoma cell lines on xenograft mice [1]. Bevacizumab (Avasin) was given either alone or in combination with a polo-like kinase 1 (PLK1) inhibitor synthesized by Nerviano Medical Sciences (NMS). Average data of tumor weight of control and treated groups were considered.
The mathematical model
Untreated tumor growth was described using an exponential growth phase followed by a linear one. The effect of anti-angiogenic compounds was implemented using an inhibitory effect on the growth function. A

combination model was also developed under a 'no-interaction' assumption [2] to assess the effect of the combination of bevacizumab with a target-oriented agent. Nonlinear regression techniques were used for estimating the model parameters.

Results: The model successfully captured the tumor growth data following different bevacizumab dosing regimens, allowing to estimate experiment-independent parameters. In combination therapies, the observation of a significant difference between model-predicted (under the no-interaction hypothesis) and observed tumor growth curves [3] was suggestive of the presence of a pharmacological interaction that was further accommodated into the model.

Conclusions: This approach can be used for optimizing the design of preclinical experiments and for investigate the best combination treatments.

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Mathilde Marchand III-26 Population Pharmacokinetics and Exposure-Response Analyses to Support Dose Selection of Daratumumab in Multiple Myeloma Patients

M. Marchand (1), L. Claret (1), N. Losic (2), TA Puchalski (3), R. Bruno (1)
(1) Pharsight Consulting Services, Pharsight, a CertaraTM Company, Marseille, France (2) Genmab, Copenhagen, Denmark, (3) Janssen Research & Development, LLC, Spring House, PA, USA

Objectives: Daratumumab is a human CD38 monoclonal antibody with broad-spectrum antitumor activity. The aim of this project was to explore the pharmacokinetics (PK), pharmacodynamic (PD) response and the exposure-response relationship of daratumumab from a Phase I/II study in patients with advanced multiple myeloma (MM). This information was an integral aspect of dose selection.

Methods: Data were available from 25 MM patients with measurable PK who received daratumumab 0.1 to 16 mg/kg weekly by intravenous infusion (data cut 31 July 2012). A population PK model was developed to derive systemic exposure to daratumumab in patients. A simplified tumor growth inhibition (TGI) model [1] was used to estimate response metrics based on time profiles of M-protein and involved free light chain (FLC) after daratumumab administration. Relationship between these TGI metrics and progression free survival (PFS) were assessed.

Results: A 2-compartment population PK model with parallel linear and Michaelis-Menten eliminations best described daratumumab pharmacokinetics, as often described for monoclonal antibodies targeting receptors [2]. Estimated response metrics, i.e. M-protein and involved FLC time to nadir were correlated with daratumumab exposure ($p<0.05$). Involved FLC and M-protein time to nadir were predictors of PFS ($p<0.01$).

Conclusions: Daratumumab was shown to inhibit tumor growth and to prolong PFS in an exposure-dependent manner. M-protein and involved FLC TGI responses metrics are biomarkers of response to daratumumab. The PK/PD model together with drug independent clinical endpoint models [3] may be used to optimize dose and schedule for daratumumab and support the Phase II study design.

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Eleonora Marostica III-27 Population Pharmacokinetic Model of Ibrutinib, a BTK Inhibitor for the Treatment of B-cell malignancies

Eleonora Marostica(1), Juthamas Sukbuntherng(2), David Loury(2), Jan de Jong(3), Xavier Woot de Trixhe(4), An Vermeulen(4), Giuseppe De Nicolao(1), Danelle James (2), Italo Poggesi(4)
(1) Department of Industrial and Information Engineering, University of Pavia, Via Ferrata 1, 27100 Pavia, Italy; (2) Pharmacyclics, 999 East Arques Avenue, Sunnyvale, CA 94085; (3) Clinical Pharmacology, Janssen R&D, LLC, 3210 Merryfield Row, San Diego, CA; (4) Model-Based Drug Development, Janssen R&D, Turnhoutseweg 30, 2340 Beerse, Belgium.

Objectives: Ibrutinib (PCI-32765) is an oral Bruton's tyrosine kinase (BTK) inhibitor currently under development for the treatment of B-cell malignancies. Here we evaluated a population pharmacokinetic model for describing the pharmacokinetic data collected to date in clinical trials with ibrutinib.

Methods: Preliminary ibrutinib plasma data were available from 3 clinical studies: i) a phase 1 dose-escalation study, in recurrent B-cell malignancies (doses of 1.25-12.5 mg/kg and fixed doses of 560 mg); ii) a phase 1b/2 dose-finding study in chronic lymphocytic leukemia (doses of 420 and 840 mg); iii) an open-label phase 2 fixed-dose study, in mantle cell lymphoma (dose level of 560 mg). Overall, approximately 2700 observations were collected in 197 subjects following single and repeated daily dosing, at different days of the treatment cycles. A 2-compartment model with sequential zero-first order absorption and elimination was implemented. Analyses were performed by adopting a log transform-both-sides approach and an additive error model. Inter-individual variability was implemented using an exponential model. The

first-order conditional estimation method was implemented using NONMEM v 7.1.

Results: A linear model, constructed with data collected following single and repeated doses of ibrutinib at different dose levels, demonstrated that the compound pharmacokinetics were dose- and time-independent. Ibrutinib was rapidly absorbed and was characterized by a high oral plasma clearance (approximately 1000 L/h) and a high apparent volume of distribution at steady-state (approximately 10,000 L). Although both values are confounded by absolute bioavailability, these values suggest that ibrutinib clearance and volume are high. The half-lives of the distribution and terminal phases were estimated to be less than one hour and approximately 16 hours, respectively. Pharmacokinetic parameters were not found to be significantly different between dose levels, studies, and clinical indications. Population parameters and their inter-individual variability were estimated with good precision. The model proved to be satisfactory in terms of goodness-of-fit, individual fittings, and visual predictive checks.

Conclusions: The proposed population pharmacokinetic model was able to describe the plasma concentration-time profiles of ibrutinib from trials in different indications well.

Hafedh Marouani III-28 Dosage regimen individualization of the once-daily amikacin treatment by using kinetics nomograms.

Hafedh Marouani PhD(1), Claire Contargyris MD(2), Stamatios Anastopoulos(1), Ioannis Kartsonakis(1), Christian Woloch PhD(1), Athanassios Iliadis Pr(1)
(1) Dpt. of Pharmacokinetics, UMR INSERM 911 CRO2, Aix-Marseille University, France. (2) Intensive care Dpt., Laveran Military Hospital, 13 Bd Laveran, 13013 Marseille, France.

Objectives: Amikacin is concentration-dependent antibiotic used against severe gram-negative infections. The use of amikacin is difficult because of its narrow therapeutic index (renal and auditory toxicities) and its wide pharmacokinetic variability. The aim of this work is to propose, in a population of critically ill patients, a rapid and simple bedside tool which allows precisely reaching the amikacin efficiency target concentrations of 80 mg/L without exceeding the toxic threshold of 2.5 mg/L for residual concentrations.

Methods: 1) Population PK study: sparse, retrospective therapeutic drug monitoring data for amikacin were obtained from 91 critically ill septic patients during the first 24 to 96 hours after treatment. All patients received 30 min intravenous infusion of doses ranging from 750 mg to 4 g of amikacin in a once daily regimen. Population modeling was performed using Monolix software [1]. Covariate analysis included weight, gender, age, total proteins and renal clearance (RC). 2) Kinetic nomograms (KN) [2]: based on the population analysis, three groups of patients were identified according to the renal impairment status. For each group, kinetic nomograms were obtained for the individualization of amounts and schedules in the regimens. All calculations were performed with the MATLAB software [3].

Results: A two-compartment model with first-order elimination best fitted the amikacin concentrations. RC was revealed significant covariate in the final model; it allows identification of 3 groups of patients: RC<20, 20<RC<90 and 120<RC mL/min. Population analysis confirmed the wide interindividual PK variability (51.5% for amikacin clearance) and subsequent need for individual dosage adjustment. For each group, the first KN uses the assayed amikacin concentration from samples drawn between 0 and 6h to adjust the amount of the next administration, and the second KN uses assayed drug concentration between 18 and 30h to adjust the timing for the next administration.

Conclusions: KN were successfully developed for amikacin therapy in critically ill septic patients. They allow reliable dosage and schedule adjustment immediately for the second administration of amikacin. Based on only two samples, dose and schedule of further amikacin administration were individualized, thus maximizing bactericidal killing while minimizing the risk for adaptive resistance and avoiding severe drug toxicity.

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Amelie Marsot III-29 Population pharmacokinetics of baclofen in alcohol dependent patients

A. Marsot (1), B. Imbert (2), JC. Alvarez (3), S. Grassin-Delyle (3), I. Jaquet (2), C. Lançon (2), N. Simon (1,2)
(1) Service de Pharmacologie Clinique, Hôpital Timone, APHM, Aix Marseille Université, France, (2) Service d'Addictologie, Hôpital Sainte Marguerite, APHM, Aix Marseille Université, France, (3) Laboratoire de Pharmacologie-Toxicologie, CHU Raymond Poincaré, Garches, France

Objectives: Baclofen is a GABA-B receptor agonist used in the treatment of spasticity. Recently, baclofen is used out of its label to decrease craving of alcoholic patients. Its optimal use in these patients requires further pharmacokinetic informations. The objective of this study was to characterize the pharmacokinetics of baclofen in alcohol dependent patients. Randomized clinical trials are ongoing to evaluate the efficacy for this new indication.

Methods: 37 outpatients (weight: 74.0 kg [42.0 - 104.0]; Age: 49 years [31 – 68]) followed in the addictology unit, were studied. Total mean dose of 77.9 mg (30 - 240) per day was administered by oral route. Therapeutic drug monitoring allowed the measurement of 139 plasma concentrations. The following covariates were evaluated: demographic data (age, body weight, height, sex), biological data (creatinine, urea, AST, ALT, albumin, PR, VGM, PAL, CDT, GGT) and tobacco consumption (number of cigarettes and Fagerstrom test). Pharmacokinetic analysis was performed by using a non-linear mixed-effect population model (NONMEM 7.2 software).

Results: Data were modelled with a one-compartment pharmacokinetic model. The population typical mean (percent relative standard error (%RSE)) values for clearance (CL), apparent volume of distribution (V) and constant of absorption (Ka) were 10.3 L/h (6.3%), 81.1 L (12.1%) and 3.61 h-1 (50.4%),

respectively. The interindividual variability of CL (%RSE) and V (%RSE), and residual variability (%RSE) were 53.9% (24.7%), 73.5% (45.5%) and 0.096 mg/l (20.0%), respectively.

Conclusions: Baclofen exhibited a linear pharmacokinetic with a proportional relationship from 30 to 240 mg per day, the dose range currently used in alcoholic patients. A wide inter-patient variability was observed which could not be explained by the covariates. This high variability of baclofen exposure may explain the lack of response observed for some patients.

María Isabel Mas Fuster III-30 Stochastic Simulations Assist to Select the Intravenous Digoxin Dosing Protocol in Elderly Patients in Acute Atrial Fibrillation

Ramon-Lopez Amelia (1), Más-Serrano Patricio (1,2), Mas-Fuster Maria Isabel (1), Carlos Pastor-Cerdán (2), Nalda-Molina Ricardo (1).
(1) Department of Engineering, Pharmacy and Pharmaceutics Division, University of Miguel Hernandez, San Juan de Alicante, Spain. (2) Clinical Pharmacokinetics Unit, Pharmacy Department, Hospital General Universitario de Alicante, Alicante, Spain)

Objective: To select the optimal intravenous (IV) loading dose schedule for digoxin in patients under acute atrial fibrillation (AAF), by using stochastic simulations of a previously published population pharmacokinetic model [1].

Methods: Five different IV dosing protocols of digoxin in AAF described in the literature [1,2,3,4] have been evaluated in terms of efficacy and toxicity. In three of them, either creatinine clearance or weight was included in the protocol to select the IV dosing schedule. The other two protocols did not include any covariate to select the IV dosing, relying it on the physician criteria. To evaluate these protocols, 1000 patients were simulated using NONMEM 7.2, based on a previously published population pharmacokinetic model [1]. To generate the input dataset, the covariates of 100 elderly patients with AAF, obtained from a dataset of the University Hospital of Alicante were resampled 1000 times. The criteria for toxicity and inefficacy of treatment were digoxin plasma concentrations at 8 hours after the last dose > 2 ng/mL and < 0.8 ng/mL, respectively.

Results: The simulations showed significant differences in the outcomes of the different protocols. The best protocol had 81% of the simulated patients within the proposed therapeutic range (0.8-2 ng/mL). The other protocols

had lower percentages of 52%, 65%, 70% and 80%. Once the best protocol was selected, a simplification of this protocol was proposed with the objective of starting the maintenance dose at the usual time in hospital wards (08 00 am) and achieve the maximum percentage of patients within the therapeutic range. To do so, the last dose included in the protocol was either given or not, depending on the time of the initiation of the therapy.

Conclusion: Although IV digoxin is a drug widely used in AAF, there is not a gold standard for the IV loading dose schedule. Stochastic simulations are useful to evaluate the different protocols described in the literature and assess the impact of patients' covariates as well as the time of the initiation of the therapy.

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Pauline Mazzocco III-31 Modeling tumor dynamics and overall survival in patients with low-grade gliomas treated with temozolomide.

P. Mazzocco (1), G. Kaloshi, D. Ricard, J.Y. Delattre, F. Ducray, B.Ribba (1)
(1) INRIA Grenoble Rhône-Alpes, Numed Project Team, 655 avenue de l'Europe, 38330 Montbonnot-Saint-Martin, France

Objectives: To develop a model able to predict tumor size dynamics and overall survival (OS) in patients with low-grade gliomas (LGG) treated with temozolomide between 1999 and 2012.

Methods: We used tumor size measurements from 120 patients treated at Salpêtrière hospital (Paris) between 1999 and 2012 representing 1434 observations in total [1]. During this study, 60 patients (50%) died and the median survival time was 7 years. Biomolecular data including 1p19q codeletion, p53 and IDH mutation status were also available for 42 patients (35%). We first extended the tumor-growth-inhibition (TGI) model from [2] distinguishing proliferative and quiescent cells by 1) incorporating a resistance term as consequence of the observation that tumor regrows during treatment for 45 patients (38%) and 2) including biomolecular data as potential model covariates. Parameters were estimated with MONOLIX (Lixoft). Survival data were then described in a parametric model through the screening of relevant TGI model outputs.

Results: The model with the resistance term and covariates correctly fitted individual profiles. As expected, it was found that p53 mutation leads to faster tumor proliferation. IDH mutation was found to induce higher sensitivity of quiescent cells to apoptosis resulting in better tumor shrinkage. Tumor growth velocity before treatment, tumor size at treatment and

relative change in tumor size after 8 weeks were found as best predictors for survival data.

Conclusions: The developed model can potentially be used to optimize temozolomide delivery in LGG patients as regards of tumor shrinkage and survival. Interestingly, as previously found for lung and thyroid cancer, the relative change after 8 weeks is a relevant predictor for low-grade gliomas.

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Litaty Céphanoée Mbatchi III-32 A PK-PGx study of irinotecan: influence of genetic polymorphisms of xenoreceptors CAR (NR1I3) and PXR (NR1I2) on PK parameters

L.C. Mbatchi(1)(2), S. Khier(3), J. Robert(4), A. Iliadis(5), A. Evrard(1)(2)
(1) Biochemistry and Toxicology division, University Hospital CAREMEAU, Nîmes, France; (2) Institut de Genomique Fonctionnelle CNRS UMR5203 INSERM U661, Université Montpellier 1 et 2, Montpellier; (3) Pharmacokinetic Department, Université Montpellier 1, France (4) Institut Bergonié, Bordeaux, France ; (5) Pharmacokinetic Department, Université Aix-Marseille, France

Objectives: Irinotecan is an anticancer agent broadly used in the treatment of colorectal cancer. The main genetic factor associated with the PK variability of CPT11 is a UGT1A1 polymorphism (UGT1A1*28)1, the enzyme which detoxify the active metabolite (SN38) into an inactive glucuronide form (SN38G). The xenoreceptors PXR (gene NR1I2) and CAR (gene NR1I3) are the transcriptional regulators of all the genes which control the CPT11 metabolism, including UGT1A1. We hypothesize that polymorphisms of PXR and CAR can explain a part of the variability of the PK of irinotecan.

Methods: A population pharmacokinetic analysis was performed using Monolix™ based on plasma samples from 109 patients traited by FOLFIRI (leuvocorin, 5FU and irinotecan). Four sequential models of Irinotecan and each of its metabolites have been designed. We made a selection of 13 SNPs (Single Nucleotide Polymorphism) of NR1I2 and 6 SNPs of NR1I3, selected on the basis of their association with the PK of other drugs in the literature2 or as tagSNP to ensure good coverage of the genetic variability of these genes (Haploview™ Software). Then, an exploratory study of genetic covariables was conducted by testing the association between the empirical Bayesian estimation of the parameter of irinotecan and metabolites with the genotype of the patients for UGT1A1*28, NR1I2, and NR1I3. For the single locus

analysis, we used the SNPassoc package of R, and for the haplotype analysis we used the package Haplo.stat. Finally, the significant genotypes were introduced in the PK model using 2 selection methods: a selection method from a full model using Wald tests, and forward inclusion method using the log-likelihood ratio test.

Results: The data were best fit with a model with 3 compartments for irinotecan, 2 compartments for SN38 the active metabolite, and a one compartment for the inactive metabolites (SN38G, APC and NPC), with a linear elimination in each case. We found significant association between several SNPs located abroad the promoter of NR1I2 and distribution volume of the central compartment for irinotecan both with single locus analysis and haplotypic approach. Furthermore we confirmed the pivotal role of UGT1A1*28 in the clearance of SN38.

Conclusions: Genetics polymorphisms of the promoter of NR1I2 are associated with the PK of irinotecan. Our data demonstrate that genetic variations of the transcriptional regulators of genes involved in the metabolism of drugs can impact the pharmacokinetic variability and suggest that this should take into account in adaptative dosing strategies.

Sarah McLeay III-33 Population pharmacokinetics of rabeprazole and dosing recommendations for the treatment of gastro-esophageal reflux disease in children aged 1-11 years

Sarah McLeay (1), Bruce Green (1), William Treem (2), An Thyssen (3), Eric Mannaert (3), Holly Kimko (2)
(1) Model Answers Pty Ltd, Brisbane, Queensland, Australia, (2) Janssen Research & Development, LLC, Raritan, New Jersey, USA, (3) Janssen Research & Development, LLC, Turnhout, Belgium

Objectives: To develop a population PK model for rabeprazole that describes concentration-time data arising from Phase 1 and Phase 3 studies in adult and pediatric subjects, including neonates and preterm infants, and propose dosing recommendations for pediatric subjects aged 1-11 years for the treatment of gastroesophageal reflux disease (GERD).

Methods: A total of 4417 PK observations from 597 subjects aged 6 days to 55.7 years with body weights of 1.15-100 kg were used to develop the population PK model using nonlinear mixed effects modeling techniques. Weight and age were included in the structural model to describe clearance (CL) and central volume of distribution (Vc). Other covariates considered during model development included sex, race, creatinine clearance, hepatic function, formulation, feeding status, and route of administration. The final model was used to determine doses for pediatric subjects aged 1-11 years to achieve AUCs within the target adult AUC range obtained following a 10 mg rabeprazole dose.

Results: The best model to fit the data was a 2-compartment disposition model with a sequential zero-order (D1), first-order (KA) absorption following

a lag time (ALAG), with weight and age effects on CL and Vc. Formulation type and feeding status described some of the variability in bioavailability and the absorption parameters ALAG, D1, and KA. A dosage regimen of 5 mg once daily for children < 15 kg, and 10 mg for children ≥ 15 kg is recommended for 1-11 year old pediatric patients with GERD.

Conclusions: The model described the PK of rabeprazole with good precision following administration of rabeprazole across a range of doses and in a range of formulations.

Christophe Meille III-34 Modeling of Erlotinib Effect on Cell Growth Measured by in vitro Impedance-based Real-Time Cell Analysis

C. Meille (1), S. Benay (2), S. Kustermann (3), I. Walter (4), E. Pietilae (3), P-A. Gonsard (4), N. Kratochwil (4), A. Walz (1), A. Roth (3) and T. Lavé (1)
F. Hoffmann-La Roche Ltd, Non-Clinical Safety, (1) Modeling and Simulation, (3) Mechanistic Safety, (4) ADME, Basel, Switzerland; (2) Dpt. of Pharmacokinetics, INSERM U911 CRO2, Aix-Marseille University, Marseille, France

Objectives: Signal distribution models have been developed to describe the time dependent effects of cancer drugs *in vitro* [1] and *in vivo* [2]. Real-Time Cell Analysis (RTCA) systems allow continuous in vitro monitoring of drug effect on cancer cell count [3]. Our objective was to explore benefit of such data for refinement of signal distribution models by describing the effect of Erlotinib on A431 epidermoid human carcinoma cell line in an impedance-based RTCA assay.

Methods: At 0, 4, 8 and 16 µM Erlotinib concentrations, the cellular effect was evaluated through cell index time course of xCELLigence system [4]. In addition, in vitro Erlotinib concentration was determined at 3 time points during the incubation using LC-MS/MS. The obtained in vitro PK data were described by a single-compartment model with linear elimination and unspecific binding. An exponential model was selected to describe control cell growth. A nonlinear model associated concentration to cell kill rate signal resulting in cytostatic or cytotoxic effect. As described in the signal distribution models, the delay between Erlotinib in vitro PK and effective cell kill was reproduced by 4 transit compartments with a respective mean transit time tau. The main PK-PD model parameters were estimated using

population approach with Monolix 4.1.3 software [5] by considering the well as the statistical unit.

Results: At 16 µM, a decrease of cell index was observed followed by a regrowth after 130h. A significant decrease in drug concentration was observed and the cell regrowth could be associated to this phenomenon by the PK/PD model. The PK model determined an in vitro half-life of 264 h with an inter-well variability of 7% and an unspecific binding of 34%. Drug concentrations ranging from 3 to 8 µM achieved killing rate close to the growth rate of A431 cells (0.033 h^{-1}). Beyond 9 µM, killing rate exceeded the growth rate and reached 0.05 h^{-1}. The mean transit time tau decreased with increasing concentrations, ranging between 2 and 17 h.

Conclusion: New insights were gained by combining modeling with rich dynamic in vitro data. It could be shown that the drug concentration determines the cytostatic or cytotoxic effect and influences the delay in the cell kill rate signal. This model based approach can help to build and test hypotheses of drug action as well as quantifying drug effect kinetics at a cellular level.

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Olesya Melnichenko III-35 Characterizing the dose-efficacy relationship for anti-cancer drugs using longitudinal solid tumor modeling

O. Melnichenko (1), M. Savelieva Praz (2), A. M. Stein (3)
(1) Novartis Pharma, Moscow, Russian Federation; (2) Novartis AG, Basel, Switzerland; (3) Novartis Institute for Biomedical Research, Cambridge, USA

Objectives: Dose escalation trials in oncology are aimed to identify the Maximum Tolerated Dose and by design, adverse events often lead to dose interruptions and modifications. These dose modifications may impact significantly the dynamics of tumor shrinkage/growth. The standard approach for assessing the relationship between dose and efficacy characterizes the relationship between the dose at randomization and the best overall tumor response. This approach does not take into consideration the dynamics of dose changes and tumor shrinkage and may be sub-optimal for assessing the dose-efficacy relationship. The aim of this work is to apply a tumor growth modeling approach, which takes into account the full dosing history and longitudinal dose-response analysis, in order to establish a dose-efficacy relationship for a new drug.

Methods: The population dose-response analysis was performed with Monolix using tumor size measurements and dosing history from 84 Phase I clinical trial patients. Only patients with baseline and at least one post-baseline assessment of tumor size were included in the analysis. Several structural and dose-effect models were tested, the influence of demographic and clinical characteristics on tumor growth rate and efficacy parameters were examined.

Results: The model with a dose-proportional effect describes the data well. Of the covariates evaluated, the ECOG performance status had a statistically

significant effect on the rate of tumor shrinkage. Model-based prediction showed that at the maximum dose level, 91% of patients will have tumor shrinkage, with 40% of them having shrinkage of more than 50%. If dose is halved, 77% of patients will have tumor shrinkage, with only 15 % of them having shrinkage of more than 50%.

Conclusions: The modelling results confirmed that the maximum dose tested was also the most efficacious one for shrinking tumors and was recommended to be taken forward in future trials.

Enrica Mezzalana III-36 A Target-Mediated Drug Disposition model integrated with a T lymphocyte pharmacodynamic model for Otelixizumab.

E. Mezzalana (1), A. MacDonald (2), G. De Nicolao (1), S. Zamuner (2)
(1) Department of Computer Engineering and Systems Science, University of Pavia, Pavia, Italy; (2) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stockley Park, UK;

Objectives: Otelixizumab is a monoclonal antibody currently being investigated in autoimmunity. It is directed against human CD3ε on T lymphocytes. Its pharmacological effects include 1) down modulation of the CD3/T cell receptor complex on T lymphocytes and 2) a decrease of T cells in blood. The aim of the present work was to integrate a mechanistic target-mediated drug disposition (TMDD) model [1] to a T lymphocyte pharmacodynamic (PD) model.

Methods: Free drug in serum and CD4+ and CD8+ T lymphocytes counts were measured using immunoassay and flow cytometry, respectively. Free, bound and total receptors were then obtained for both CD4+ and CD8+ T lymphocytes [2]. A QSS-TMDD model accounting for Otelixizumab binding to receptors on both CD4+ and CD8+ cells was implemented [3]. Direct and indirect inhibition models were investigated to describe the observed T cell reduction in blood. Analyses were conducted using NONMEM version 7.2. FOCEI and IMP estimation methods were used and compared. Final models were selected based upon change in OFV, precision estimates, diagnostic plots and visual predictive checks (VPCs).

Results: First, a simple one-compartment PK model with MM elimination was identified using available PK data. This PK model was used to drive a direct or an indirect lymphocyte PD model. Both sequential (IPP) and simultaneous PK-

PD (T lymphocytes) analyses were implemented. Based on VPCs, the indirect model provided a slightly better description of lymphocyte time-course and variability. Then, our previous QSS-TMDD model [3] was improved including a 'Study' covariate on linear elimination rate constant (K) with a consequent reduction of the estimated high BSV on K. This QSS-TMDD model was used as input for both lymphocyte PD models. Sequential and simultaneous TMDD-lymphocyte analyses were conducted. To overcome problems with OF minimization and covariance step failure with FOCEI the IMP method was used to achieve minimization with covariance step completion. Both TMDD+direct and TMDD+indirect models adequately described the lymphocyte data.

Conclusions: A QSS-TMDD model integrated either to a direct or an indirect inhibitory model was proposed to describe Otelixizumab binding to CD3/TCR on T lymphocytes and subsequent decrease of T lymphocytes in blood. The IMP estimation method proved a useful alternative to FOCEI in case of such complex PK/PD models. Further strategies to improve lymphocytes model integration into TMDD are discussed.

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Iris Minichmayr III-37 A Microdialysate-based Integrated Model with Nonlinear Elimination for Determining Plasma and Tissue Pharmacokinetics of Linezolid in Four Distinct Populations

I.K. Minichmayr (1,2), A. Schaeftlein (1,2), M. Zeitlinger (3), C. Kloft (1)
(1) Dept. of Clinical Pharmacy and Biochemistry, Freie Universitaet Berlin, Germany, (2) and Graduate Research Training program PharMetrX, Germany, (3) Dept. of Clinical Pharmacology, Medical University Vienna, Austria

Objectives: Linezolid (LZD) provides a valuable treatment option in a wide range of infections across variant patient groups. Sufficient drug concentrations at the target site of infection form a key prerequisite for treatment success and can be assessed e.g. by means of microdialysis. The objective of the present study was to build a population pharmacokinetic (PK) model accommodating both an integrated model for microdialysis data [1] and a concentration- and time-dependent nonlinear elimination model [2] for the simultaneous description of LZD concentrations in plasma and peripheral tissues of four heterogeneous populations.

Methods: In total, 52 individuals (healthy volunteers (n=10, [2]) and patients with sepsis (n=24, [2]), diabetes-related soft-tissue infections (n=10, [3]) or cystic fibrosis (n=8, [4])) from three different studies were pooled for analysis. Modelling of plasma (n=1635), ultrafiltrate (n=1182) and microdialysis (s.c.: n=1468, i.m.: n=1127) concentrations obtained after single and multiple dosing of 600 mg LZD was conducted in NONMEM 7.2.

Results: Both total LZD concentrations and unbound concentrations in plasma, interstitial s.c. and i.m. tissue fluid were adequately described by a two-compartment (CMT) model. Due to rapid tissue penetration of LZD the

measurements of all matrices were assigned to the central CMT. In order to distinguish between the matrices, scaling factors (SF) related to plasma were introduced, suggesting highest concentrations in plasma followed by ultrafiltrate (SF 0.88), i.m. (SF 0.86) and s.c. interstitial concentrations (SF 0.81). Interindividual variability was included for ten model parameters and tendentially high (%CV 3.8-90). Overall, the model yielded plausible estimates (V=44.7 L, initial CL 8.17 L/h, maximal decrease to 5.23 L/h) with overall good precision (0.9-33% RSE).

Conclusions: A complex PK model incorporating both a microdialysate-based integrated model and a nonlinear concentration- and time-dependent elimination model was successfully developed and able to simultaneously describe plasma, ultrafiltrate, interstitial s.c. and i.m. concentrations after both single and multiple applications of LZD. In order to account for differences between healthy volunteers and the distinct patient groups and thereby decrease the remarkable unexplained variability in the estimated model parameters, a covariate model needs to be established.

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Jonathan Mochel III-38 Chronobiology of the Renin-Angiotensin-Aldosterone System (RAAS) in Dogs: Relation to Blood Pressure and Renal Physiology

Jonathan P. Mochel (1,2), Martin Fink (2), Mathieu Peyrou (3), Cyril Desevaux (4), Mark Deurinck (5), Jérôme M. Giraudel (6), and Meindert Danhof (1)
(1) Department of Pharmacology, Leiden-Academic Centre for Drug Research, 2300 Leiden, The Netherlands. (2) Department of Modeling and Simulation, Novartis Campus St. Johann, 4002 Basel, Switzerland. (3) Department of Therapeutics Research, Novartis Centre de Recherche Sante Animale SA, 1566 St-Aubin, Switzerland. (4) Department of Pre-Clinical Safety, Novartis Centre de Recherche Sante Animale SA, 1566 St-Aubin, Switzerland. (5) Department of Pre-clinical Safety, Novartis Institutes of Biomedical Research, 4002 Basel, Switzerland. (6) Yarrandoo Research and Development Centre, Novartis Animal Health Australasia Pty Limited, 2178 Kemps Creek, Australia.

Objectives: Although observations of time-variant changes in the renin cascade are available in dogs, no detailed chronobiological investigation has been conducted so far. The present studies were designed to explore the circadian variations of plasma renin activity (RA) and urinary aldosterone to creatinine ratio (UA:C) in relation to blood pressure (BP), sodium (UNa, UNa,fe), and potassium (UK, UK,fe) renal handling.

Methods: Data derived from intensive blood and urine sampling, as well as continuous BP monitoring were collected throughout a 24-hour time period, and analyzed by means of NLME models, using NONMEM version 7.2[1]. Covariate search was performed using the stepwise covariate model building tool of Perl-speaks-NONMEM[2]. Model selection was based on statistical significance between competing models using OFV, graphical evaluation and validity of parameter estimates. Differences between the geometric means of day and night observations were further compared by parametric statistics.

Results: Our results show that the RAAS, BP and urinary electrolytes oscillate with significant day-night differences around the clock in dogs. An approximately 2-fold change between the average day and night measurements was found for RA ($p<.001$), UA:C ($p:.02$), UK ($p<.001$), and UNa ($p:.007$). For all endpoints but UNa and UNa,fe the levels were higher at night than during the day. The data also indicate that blood pressure oscillates in parallel to the RAAS, such that, as opposed to healthy humans BP does not drop at night in dogs. A cosine model with a fixed 24-hour period was found to fit the variations of RA, UA:C, UK, UK,fe, and BP well, while changes in UNa and UNa,fe were best characterized by a surge model. Sodium intake was found to interact with the tonic and the phasic secretion of renin, suggesting that varying feeding time could also impact the chronobiology of the renin cascade.

Conclusions: This research offers the first chronobiological characterization of the RAAS and BP in dogs. Cosine and surge models were able to describe and predict the time-variant changes of the experimental data with high accuracy, as shown by the quality of the standard goodness-of-fit diagnostics. Additional investigations on the chronobiology of the RAAS and BP are required in diseased dogs under ACEI to determine whether it is possible to improve drug therapy of RAAS-related diseases with bedtime administration as compared with morning dosing.

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Dirk Jan Moes III-39 Evaluating the effect of CYP3A4 and CYP3A5 polymorphisms on cyclosporine, everolimus and tacrolimus pharmacokinetics in renal transplantation patients.

Moes D.J.A.R, Swen J.J., den Hartigh J, van der Straaten T., Homan van der Heide J.J. Bemelman F., de Fijter J.W., Guchelaar H.J.
Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands.

Objectives: Cyclosporine, everolimus and tacrolimus form the cornerstone of maintenance immunosuppressive therapy in renal transplantation. These drugs have a small therapeutic windows and highly variable pharmacokinetics which make it difficult to maintain adequate exposure and prevent serious adverse effects. Cyclosporine, everolimus and tacrolimus are metabolized by enzymes of the CYP3A subfamily. A small part of the variability in pharmacokinetics can be explained by genetic variation in CYP3A5. Recently *CYP3A4*22* was identified as a possible predictive marker for tacrolimus pharmacokinetics [1]. The aim of this study was to investigate the effect of the CYP3A4*22 and CYP3A5 polymorphisms on tacrolimus, everolimus and cyclosporine pharmacokinetics after kidney transplantation using population pharmacokinetic methodology.

Methods: Renal transplant patients on maintenance cyclosporine (298), everolimus (97) and tacrolimus therapy (101) were included. Blood concentrations were determined with fluorescence polarization immunoassay or liquid chromatography-tandem mass spectrometry as part of routine patient care and recorded in the electronic patient record. Available data on cyclosporine (6800), everolimus (1807) and tacrolimus (921) blood concentrations were extracted. Population pharmacokinetics

analysis was performed for each immunosuppressive drug using NONMEM (non-linear mixed effects modeling) and demographic factors, *CYP3A4*22* (rs35599367) and *CYP3A5* (rs776746) genetic polymorphisms were included as covariates. The final models were validated by using a bootstrap and visual predictive check.

Results: The pharmacokinetics of cyclosporine were best described by two compartment model disposition model with delayed absorption. The pharmacokinetics of tacrolimus and everolimus were best described by a two-compartment model with lag-time. Bodyweight, prednisolone dosage (cyclosporine), Ideal weight (everolimus), hematocrit (tacrolimus) were identified as demographic covariates. The effect of *CYP3A4*22* on the pharmacokinetics of cyclosporine, everolimus and tacrolimus was less than 17%. Carriers of the CYP3A5*1/*3 had 1.5 fold higher tacrolimus clearance than CYP3A5*1/*3 carriers. CYP3A5 had no significant influence on everolimus and ciclosporin pharmacokinetics.

Conclusions: Our data suggests that *CYP3A4*22* is not likely to be suitable as a clinically relevant predictive marker for cyclosporine, tacrolimus or everolimus pharmacokinetics during maintenance therapy in renal transplantation patients. Therefore dose adjustments based on *CYP3A4*22* genotype does not appear to be indicated. CYP3A5 is only suitable as a clinically relevant predictive marker for tacrolimus pharmacokinetics.

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John Mondick III-40 Mixed Effects Modeling to Quantify the Effect of Empagliflozin Exposure on the Renal Glucose Threshold in Patients with Type 2 Diabetes Mellitus

J. Mondick (1), M. M. Riggs (1), S. Macha (2), A. Staab (3), G. Kim (4), H. J. Woerle (4), U. C. Broedl (4), S. Retlich (3)
(1) Metrum Research Group LLC, Tariffville, CT, USA; (2) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; (3) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; (4) Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Objectives: Empagliflozin, a selective and potent SGLT2 inhibitor, reduces renal glucose reabsorption by lowering the renal threshold for glucose (RT_G) leading to increased urinary glucose excretion (UGE) and decreased plasma glucose (PG) in patients with type 2 diabetes mellitus (T2DM). This analysis aimed to quantify the impact of empagliflozin on RT_G by characterizing the relationship between empagliflozin exposure and UGE in patients with T2DM using nonlinear mixed-effects modeling.

Methods: A pharmacokinetic (PK)-pharmacodynamic (PD) model was developed using UGE, PG, PK and estimated glomerular filtration rate (eGFR) data from three Phase I/II trials (N=223; placebo, empagliflozin 1 to 100 mg once daily [QD]). The model assumed that when $PG>RT_G$, UGE increased with increasing PG and eGFR; and when $PG\leq RT_G$ slight glucose leakage into urine occurred (estimated as fraction reabsorbed [FRAC]). Reabsorption was estimated by a nonlinear function parameterized in terms of maximum reabsorbed glucose concentration (G_{max}) and PG concentration to reach half maximum transport (K_m). Maximum inhibitory effect (I_{max}) and half maximal inhibitory concentration (IC_{50}) described inhibition of renal glucose absorption. RT_G was calculated as the difference between maximum reabsorption (including drug effect) and K_M. The model was evaluated via

bootstrap and external predictive check of an empagliflozin renal impairment study.

Results: The parameter estimates (95% CI) were G_{max}: 374 (347, 391) mg/dL; K_m: 144 (113, 163) mg/dL; I_{max}: 0.559 (0.545, 0.607); IC_{50}: 5.28 (3.53, 8.91) nmol/L; FRAC: 0.999 (0.998, 0.999). The calculated RT_G for placebo was 230 mg/dL. RT_G decreased with increasing empagliflozin concentration; doses of 1, 5, 10, and 25 mg yielded RT_G values of 100.5, 43.8, 33.1, and 26.0 mg/dL, respectively. External predictive check demonstrated unbiased prediction of UGE across a range of eGFR values (end-stage renal disease to normal renal function). Simulation indicated that for 10 and 25 mg QD, >50% and 90% of subjects, respectively, maintained steady-state empagliflozin concentrations >*IC*80 for RT_G lowering over the dosing interval.

Conclusions: The model provided a reasonable description of the empagliflozin exposure-UGE response relationship across a broad range of renal function. Empagliflozin significantly lowered the RT_G from 230 mg/dL to 33.1 and 26.0 mg/dL for 10 and 25 mg QD respectively, with both doses providing near maximal efficacy.

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Morris Muliaditan III-41 Model-based evaluation of iron overload in patients affected by transfusion dependent diseases

Morris Muliaditan (1), Francesco Bellanti (1), Meindert Danhof (1), Oscar Della Pasqua (1, 2)
(1) Division of Pharmacology, Leiden University, Leiden, The Netherlands; (2) GlaxoSmithKline, London, United Kingdom

Objectives: Patients affected by transfusion-dependent diseases who suffer from iron overload resulting from life-long blood transfusion require chelation therapy for the removal of iron excess. Deferiprone (DFP) is one of the most extensively studied oral iron chelators to date. In association with the **DE**feriprone **E**valuation in **P**aediatric (DEEP) project [1], the aim of this analysis was to develop a PKPD model with the purpose of characterising the course of iron overload (i.e., the natural course of the disease) and the effect of the chelation therapy on ferritin levels in the target population.

Methods: Literature search based on PubMed's database was initially performed to retrieve all pertinent publications. A population PKPD model was subsequently developed using published data. Serum ferritin was chosen as primary clinical endpoint and normal turnover of serum ferritin was modelled with an indirect response model, followed by the integration of the effect of blood transfusion to account for disease progression. Subsequently, the effect of chelation therapy was implemented to describe the effect of deferiprone, which is administered at a dose of 75 mg/kg/day. Simulations were performed and results were subsequently validated using published data from retrospective clinical trials [2]. The analysis was performed using a non-linear mixed effect approach, as implemented in NONMEM 7.2.

Results: Ferritin turnover in normal health conditions was described by an indirect response model. The relationship between the amount of blood units and serum ferritin in untreated patients was translated in terms of conversion rate and then incorporated into the initial model using a hyperbolic function. Simulation scenarios were performed under different conditions to explore model performance with regard to disease progression. Finally, DFP effect was included using an Emax model. Disease and treatment effects for treated and untreated patients with initial mean serum ferritin of 4622.5 mg/L (2607-11550 mg/L) were simulated as and compared to references.

Conclusion: This is the first time a population PKPD model has been used to describe iron overload in patients affected by transfusion-dependent diseases. The model accounts for the effect of blood transfusion and treatment response, mimicking the time course of the clinical endpoint of interest. External validation of the model is currently being performed using data from a 10-year follow-up cohort in patients undergoing deferoxamine treatment.

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Flora Musuamba-Tshinanu III-42 Modelling of disease progression and drug effects in preclinical models of neuropathic pain

FT Musuamba (1), VL di Iorio (1), M Danhof (1), O Della Pasqua (1,2)
(1) Leiden Academic Center for Drug Research, Division of Pharmacology, Leiden, The Netherlands; (2) Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, United Kingdom

Background: Neuropathic pain arises as direct consequence of a lesion or disease affecting the somatosensory system. Despite the wide range of experimental models available for drug screening, neuropathic pain remains an unmet medical need, with available treatments showing limited or no efficacy in patients. Whilst many questions regarding the construct validity of animal models are still unanswered, the use of pharmacokinetic-pharmacodynamic modelling may facilitate the translation and extrapolation of preclinical findings.

Objectives: The aim of this study was to develop a semi-mechanistic model to characterise the time course of allodynia and hyperalgesia in two models neuropathic pain in rats. A secondary objective was to identify model parameters that best describe drug effects, providing a more robust basis for the ranking of candidate molecules during the screening of novel compounds.

Methods: Allodynia and hyperalgesia data from experiments based on chronic construction injury and spinal nerve ligation were used for the purpose of our investigation. Model building was performed taking into account the use of drug- and system-specific parameters. The effect of different compounds (duloxetine, gabapentin, pregabalin, and venlafaxine) was then evaluated in terms of potency and maximal pain inhibition.

Parameter estimates were subsequently ranked and compared to the exposure levels observed at currently approved clinical doses. Analysis was performed in NONMEM v7.2. R was used for data manipulation, statistical and graphical summaries.

Results: A semi-mechanistic model enabled characterisation of the different phases of allodynia. This model was sensitive to drug effects on different disease parameters. Goodness of fit and validation procedures show appropriate model performance, despite high variability in the data. In addition, clear differences in potency were observed for the different compounds, which seem to reflect pharmacological activity. The drug ranking based on the relative potencies was comparable for both models, but discrepancies exist between clinical exposure and drug levels observed in these models.

Conclusion: Current protocol sampling and dosing schemes represent a major limitation for accurate characterisation of drug effects in preclinical experiments. A meta-analytical approach is essential to ensure that system-specific parameters are estimated independently from treatment effect. Differences in construct validity of these models are compounded by poor precision and inaccuracy in parameter estimation.

Kiyohiko Nakai III-43 Urinary C-terminal Telopeptide of Type-I Collagen Concentration (uCTx) as a Possible Biomarker for Osteoporosis Treatment; A Direct Comparison of the Modeling and Simulation (M&S) Data and those Actually Obtained in Japanese Patients with Osteoporosis Following a Three-year-treatment with Ibandronic Acid (IBN)

Kiyohiko Nakai, Satofumi Iida, Hidenobu Aso, Masato Tobinai, Junko Hashimoto, and Takehiko Kawanishi
Chugai Pharmaceutical CO., LTD.

Objectives: M&S is a well recognized useful tool to simulate values related to certain endpoints for any clinical trials. Unfortunately, however, only limited numbers of reports are available up to now, where direct comparative analyses were conducted between the values simulated according to M&S and those actually obtained in patients. In the present study, therefore, in order to examine the validity of prospective M&S, we undertook direct comparisons between these two data sets on bone mineral density (BMD).

Methods: Modeling was performed based on both uCTx and BMD obtained in a Phase II clinical trial, where IBN was administered intravenously once a month for successive 6 months to Japanese patients with osteoporosis. The model[1] includes parameters of the dosage of IBN, uCTx and BMD was employed, and the linkage among each three parameters was analyzed. By employing this model, simulation was performed on BMD to be achievable in a Phase III clinical trial, in which IBN is to be successively administered for as long as 3 years. Finally, for the validation of the M&S, direct comparative analyses were conducted between the values simulated and those obtained in a Phase III clinical trial.

Results: At a dose level of 1 mg of IBN intravenously administered once a month, 50 percentile of the BMD changes from baseline simulated were 3.70, 6.60, 7.66 and 7.91%, following 6, 12, 24 and 36 months, respectively. The median BMD changes actually observed, on the other hand, at each respective month of these treatments were found to be 4.46, 5.69, 6.87 and 8.01%. Thus, the simulated values and those actually observed well coincided with each other (the percent differences between them are below 20%).

Conclusions: The major findings that have been disclosed from the present study are the following three.

1. The excellence of M&S for predicting the clinical effects of IBN against osteoporosis was verified.
2. Beneficial clinical efficacies based on BMD following the treatments with IBN were found to be simulated in a quantitative manner by means of M&S.
3. It can be envisaged that M&S is one of the powerful tools for significantly shortening development periods at least as far as the osteoporosis treatment is concerned.

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Thu Thuy Nguyen III-44 Mechanistic Model to Characterize and Predict Fecal Excretion of Ciprofloxacin Resistant Enterobacteria with Various Dosage Regimens

Thu Thuy Nguyen (1,2), Jeremie Guedj (1,2), Elisabeth Chachaty (3), Jean de Gunzburg (4), Antoine Andremont (1,5,6), France Mentré (1,2,6)
(1) University Paris Diderot; (2) INSERM, UMR 738, Paris, France; (3) Institut Gustave-Roussy, Paris, France; (4) Da Volterra, Paris, France; (5) EA3964, "Emergence de la résistance bactérienne in vivo", Paris, France; (6) AP-HP, Hospital Bichat, Paris, France

Objectives: Environmental dissemination of antibiotic resistant enterobacteria (EB) via fecal excretion upon fluoroquinolone (FQ) treatment is a major public health burden [1]. Modeling approach can provide new insights into this problem and is increasingly performed in in vitro studies [2-5]. However little has been done to gain a precise understanding of the in vivo kinetics of antibiotic sensitive and resistant EB during and after FQ treatment. Here we aimed to characterize by mathematical modeling the relationship between intestinal exposure to ciprofloxacin (CIP) and excretion of resistance for various dosage regimens.

Methods: 29 piglets were randomly assigned (9:10:10) to oral treatment with placebo, CIP 1.5 or 15 mg/kg/day for 5 days. CIP concentrations and counts of resistant and total EB were obtained from fecal samples during and after treatment. A mechanistic model was developed to fit CIP pharmacokinetics (PK) as well as total and resistant EB kinetics, using elements of earlier models from in vitro studies [2-5], with new elements for the intestinal flora. The joint modeling of data from all piglets was performed by nonlinear mixed effect model, using SAEM algorithm [6] in MONOLIX 4.2.0. We also evaluated by simulation the effect of various dosage regimens on fecal excretion of resistance.

Results: The PK model was a one compartment model with first-order elimination and constant rate of CIP during 5 days. In the bacterial model, we assumed that resistant EB were present in absence of treatment due to random mutation and continuously incoming in the digestive tract by ingestion. Initiation of treatment resulted in a concentration-dependent killing rate of sensitive EB through an Emax model. This model described adequately data from all dose groups. CIP concentrations rapidly reached a plateau (8.7 and 87 µg/g in the 1.5 and 15mg/kg groups, respectively) and the C50 was equal to 5 µg/g, well below this plateau. Thus, susceptible EB rapidly decreased with a half-life of 37 minutes. Although resistant EB had a low replicative fitness of 14%, this rapid elimination of susceptible EB allowed with both dosage regimens the inverse expansion of resistance which remained in high counts up to 3 weeks after treatment end.

Conclusions: To our knowledge, this is the first model to characterize the dynamics of resistance to FQ in the intestinal flora. This approach can be used to design strategies to reduce dissemination of resistance during treatments [7].

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Thi Huyen Tram Nguyen III-45 Influence of a priori information, designs and undetectable data on individual parameters estimation and prediction of hepatitis C treatment outcome

Thi Huyen Tram Nguyen (1), Jeremie Guedj (1), Jing Yu (2), Micha Levi (3) and France Mentré (1,4)

(1)University of Paris Diderot, Sorbonne Paris Cité, UMR 738, F-75018, Paris, France; INSERM, UMR 738, F-75018 Paris, France (2) Novartis Institutes for BioMedical Research, Inc, Cambridge MA 02139, USA (3) Novartis Pharmaceutical Corp., East Hanover NJ 07936, USA (4) AP-HP, Bichat Hospital, Biostatistics Service, F-75018 Paris, France

Objectives: Viral kinetics analysis based on nonlinear mixed effect models is a useful tool for individualized hepatitis C virus (HCV) treatment [1-3]. For that purpose, it is necessary to obtain precise individual parameters estimation. We evaluated the influence of a priori population parameters, sampling designs and methods handling data below detection limit (BDL) on Bayesian individual parameter estimation and prediction of response to therapy.

Methods: A viral kinetics model was used to simulate viral load profile under PegIFN/Ribavirin in 1000 HCV Genotype (G) 2/3 patients [4-6]. The estimation of four parameters was evaluated (infection rate β, death rate of infected cells δ, virion clearance c and treatment efficacy ε). Additionally, the effect of four sampling schedules was investigated (D24w with 12 measurements in 24-week (W) treatment; D4w with 6 data points within 4 weeks; D4w_sparse having 4 data points within 4 weeks but no data during W1; D4w_challenge having only 2 measurements at day 0 and W4. We used a detection limit of 45 IU/mL. Virus eradication was assumed if the infected cells reached a cure boundary during treatment [2]. Three sets of a priori information were

evaluated: true model with parameters used for simulation; false model Mδε with δ and ε modified to values obtained in G1 patients; false model Mβ with a modified β. BDL data were either omitted or handled in the likelihood function. Population parameters were fixed at different a priori information to estimate individual parameters using MONOLIX 4.1.2. We used mean relative error, root mean square of relative error and shrinkage to evaluate estimation quality. We also evaluated the ability of treatment outcome prediction by comparing the response predicted using individual estimates and the simulated treatment response.

Results: Precise estimation of individual parameters and treatment outcome was obtained using only 6 data points in the first month of PegIFN/Ribavirin therapy. This result remained valid even though wrong a priori population parameters were set as long as the parameters were identifiable (δ, ε) and BDL data were properly handled. False a priori information on estimable parameters (δ, ε) could lead to severe estimation/prediction errors if BDL data were omitted and not properly accounted in the likelihood function.

Conclusions: Bayesian estimation of individual viral kinetic parameters could provide precise early prediction of treatment outcome.

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Xavier Nicolas III-46 Steady-state achievement and accumulation for a compound with bi-phasic disposition and long terminal half-life, estimation by different techniques

Xavier Nicolas(1), Clemence Rauch(1), Eric Sultan(3), Celine Ollier(2) and David Fabre(1)
(1)Modeling and Simulation Entity, (2)Pharmacokinetic Entity, (3)Dedicated Project Expert, Drug Disposition Domain, Disposition, Safety and Animal Research, Sanofi-Aventis R&D Montpellier, France

Objectives: - Understand the differences observed in the pharmacokinetic analysis (steady state and accumulation assessments) of a repeated dose administration of a compound with bi-phasic disposition and long terminal t1/2 in a pool of healthy young and elderly subjects using NCA (Non Compartmental Analysis) and PopPK analysis approaches. - Show NCA limitation for estimation of steady state and accumulation.

Methods: Data were collected in two clinical studies (Phase I). The data Set was composed of 52 subjects (1591 samples) for who age ranged from 18 to 79 years. The Non Compartmental Analysis was performed with WinNonLin software. The PopPK model was developed and validated with the NONMEM computer program (version VII) running on LINUX. Steady state achievement was determined graphically, based on individual and mean Ctrough, for NCA and by simulation using individual parameters for PopPK.

Results: The structural PK model was a bi-compartment model with a lag time (LAG, h-1), an absorption constant (Ka, h-1), characterizing the first-order absorption process from the depot to the central compartment which was described by an apparent central distribution volume (V2/F, L). The peripheral compartment was related to the central one by an inter-compartmental clearance (Q/F, L/h) and described by an apparent

distribution volume (V3/F, L). The elimination was characterized by a first-order process and described as an apparent clearance (CL/F, L/h). Terminal t1/2 estimated by NCA and PopPK were consistent (300-600 hrs). Results regarding steady-state achievement show inconsistency between the two approaches, 12 days for NCA vs. 33 (young) to 77 (elderly) days for PopPK. With Boxenbaum's formula (based on RAC AUC), t1/2eff was 41 hours compatible with steady-state achievement predicted graphically. When the t1/2eff was computed with the t1/2 value and the contribution of each phase (Rowland), the t1/2eff of 450 hours obtained was compatible with results obtained by PopPK simulation.

Conclusions: NCA has a limited use to characterize steady-state achievement for compound combining both poly-exponential disposition and long terminal t1/2. The PopPK model and t1/2eff formula based on t1/2 and contribution of each phase works well. Anyway the appropriate solution is the simulation based on individual PopPK parameters, which takes into account all the PK data available, including those of the disposition phases after the last dose.

Ronald Niebecker III-47 Are datasets for NLME models large enough for a bootstrap to provide reliable parameter uncertainty distributions?

Ronald Niebecker (1), Mats O. Karlsson (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Sweden.

Objectives: Nonparametric bootstrap is a frequently employed method to determine parameter precision. This work aims to explore whether typical combinations of model complexity and dataset size are compatible with appropriate behaviour of such a bootstrap procedure. It further introduces a method to diagnose whether a bootstrap will not provide appropriate parameter uncertainty distributions.

Methods: Real data (number of model parameters: 7–12, datasets including 59–74 individuals, 2.6–14 observations per individual [1–3]) and simulation examples were investigated. For each investigated scenario, three dOFV distributions were generated. (i) The theoretical dOFV distribution was derived from a Chi square distribution (degrees of freedom=number of model parameters). (ii) A bootstrap was performed. Each bootstrap parameter vector was evaluated on the original dataset and dOFVs relative to the original model fit formed the bootstrap dOFV distribution. (iii) Stochastic simulation and reestimation (SSE) were performed. The OFVs for both the simulation and estimation parameter vectors were evaluated on each simulated dataset and the difference formed the reference dOFV distribution. Confidence intervals (CIs) determined by bootstrap, SSE and log-likelihood profiling (LLP) were compared. The analysis was carried out in NONMEM 7.2 [4] aided by PsN [5].

Results: For investigated real data examples, 27% to 51% of the bootstrap dOFV values exceeded the 95th percentile of the theoretical dOFV

distributions. Bootstrap CIs were inflated relative to those derived from SSE. Simulation and reestimation of equal-sized datasets confirmed these findings. For increased dataset sizes, the bootstrap dOFV distribution converged to the theoretical and reference distributions (which were superimposed for all studied datasets). In parallel, bootstrap CIs were more in accordance with those obtained from SSE and LLP. Additional simulations further confirmed the dependency between information in the dataset, difference of the dOFV distributions and quality of CIs.

Conclusions: This analysis showed that bootstrap may be unsuitable already for NLME analyses where datasets would commonly be considered "large enough". As a diagnostic of inflated CIs, determination of the bootstrap dOFV distribution is recommended.

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

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Lisa O'Brien III-48 Implementation of a Global NONMEM Modeling Environment

Lisa M. O'Brien (1), Ron J. Keizer (2), Jonathan Klinginsmith (1), Charles Ratekin (1), Michael A. Heathman (1)
(1) Eli Lilly and Company, Indianapolis, IN, USA; (2) Pirana Software & Consulting BV, the Netherlands

Objectives: Lilly is a global corporation with research facilities in many parts of the world, including North America, Europe, and Asia. A distributed NONMEM [1] environment had previously been developed to support these users, and had been in use for more than twenty years. While this UNIX-based, command line system had many benefits for experienced users, a more user-friendly solution was desired.

Methods: System development was undertaken with the following goals:

- enable scientists with varying backgrounds to perfrom modeling and simulation within a unified framework
- take advantage of existing infrastructure, including the distributetd Linux compute environment and automated parallel NONMEM execution
- leverage available open-source tools for automation of common tasks
- reduce required training for new users by providing a graphical interface
- provide command line access for experienced users
- automate generation of figures and tables
- improve performance for users outside of the United States (OUS).

Results: A group was convened to evaluate available software, both open-source and commercial solutions. Based on group consensus, PsN [2,3] and Pirana [4] were selected as the foundation of the new system. PsN provided an industry standard automation tool for NONMEM analysis, while Pirana provided a user-friendly interface.
Several solutions for hardware infrastructure were evaluated, including: Windows desktop deployment, a Windows-based virtual desktop, and a Linux server using NoMachine's Server software for remote desktop access. The Linux implementation was chosen for its ease of support, superior performance, and the availability of UNIX command line access for experienced users.
Linux servers were installed in Lilly's US, UK, and Asia research facilities to provide better performance for OUS users. The servers were integrated with existing computational infrastructure using Sun Grid Engine [5] for batch execution. A common file system was placed in the US facility, with local scratch for the UK and Asian servers to facilitate local access.

Conclusions: Implementation of a user-friendly interface to the existing NONMEM system will significantly increase overall throughput and efficiency. The interface will make population analysis more readily available to scientists cross-functionally, thereby allowing modeling and simulation to be applied to a broader range of drug development programs.

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Kayode Ogungbenro III-49 A physiological based pharmacokinetic model for low dose methotrexate in humans

Kayode Ogungbenro and Leon Aarons
Centre for Applied Pharmacokinetic Research, The University of Manchester, Manchester, M13 9PT, United Kingdom

Objectives: Methotrexate is an antimetabolite and antifolate drug used in the treatment of cancer and autoimmune disorders [1]. Its volume of distribution is equal to the volume of body water and it is about 30-40% bound in plasma. Elimination of methotrexate is renal (70-80%), biliary (25-15%) and metabolic (5%). Renal elimination is mainly by filtration, and active secretion and reabsorption also play significant roles. Oral methotrexate is rapidly absorbed and bioavailability is highly variable (50-90%) [2]. The aim of this work was to develop a physiologically based pharmacokinetic model for low dose methotrexate following intravenous and oral dosing in human.

Methods: A physiologically based pharmacokinetic model with separate compartments for plasma, red blood cells, liver, gut tissue, enterocyte, stomach, gut lumen, kidney, skin, bone marrow, spleen, thymus muscle and rest of the body was developed using plasma and intracellular red blood cell concentrations. Nonlinear tissue binding and enterohepatic recirculation were incorporated. A kidney model with compartments for kidney vascular, kidney tissue, glomerulus and proximal tubule was incorporated to account for filtration, secretion and active reabsorption. System parameters such as blood flows and organ volumes were obtained from the literature. Some drug parameters were obtained from the literature and the rest were optimised.

Results: The model adequately predicts plasma concentration following intravenous and oral dosing in humans. Simulations suggest that the nonlinearity in the observed profile is as a result of saturable active

reabsorption and nonlinear distribution into the red blood cells. At low doses active reabsorption is very important.

Conclusions: A physiologically based pharmacokinetic model that can predict concentrations in different tissues has been developed and this can be used for dose optimisation.

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Jaeseong Oh III-50 A Population Pharmacokinetic-Pharmacodynamic Analysis of Fimasartan in Patients with Mild to Moderate Essential Hypertension

Jaeseong Oh, MD, Jongtae Lee, MD, In-Jin Jang MD, PhD, and Howard Lee, MD, PhD
Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea

Objectives: Fimasartan is a novel nonpeptide angiotensin II receptor antagonist with a selective AT1 receptor blockade effect. The objective of this study was to develop a population pharmacokinetic (PK) - pharmacodynamic (PD) model, which can adequately describe and predict the PK-PD profiles of fimasartan in patients with mild to moderate hypertension.

Methods: A total of 1,438 fimasartan plasma concentrations and 759 clinic blood pressure measurements from 42 healthy subjects and 59 patients with mild to moderate essential hypertension (assigned to one of the following dose groups: placebo, 20 mg, 60 mg and 180 mg) were pooled to develop a population PK-PD model using the nonlinear mixed-effects method in NONMEM (ver. Ⅵ).

Results: A two-compartment open linear model with mixed zero- and first-order absorptions and firs-order elimination as the final PK model. The typical values of apparent clearance (CL/F), apparent central volume of distribution (V2/F) and fraction absorbed via first-order process (F1) were 176 L/h, 371 L and 56.4%, respectively.
The final PK-PD model was a random baseline effect compartment Emax model with placebo response. The equilibrium constants for the effect compartment were 0.052 and 0.0263 hr-1 for DBP and SBP, respectively. The

maximum blood pressure reduction effects were estimated to be 20.9 and 38.8 mmHg for DBP and SBP, respectively. The plasma concentrations at 50% of maximum effect were 23.3 and 30.2 ng/mL for DBP and SBP, respectively.

Conclusions: The final PK-PD model of fimasartan adequately described the observed blood pressure profiles in patients with mild to moderate hypertension. The model developed in this study could be applied in guiding further clinical development of fimasartan.

Fredrik Öhrn III-51 Longitudinal Modelling of FEV1 Effect of Bronchodilators

Fredrik Öhrn, PhD, Magnus Åstrand, PhD and Adriaan Cleton, PhD
Clinical Pharmacology and Pharmacometrics, Global Medicines Development, AstraZeneca R&D Mölndal, Sweden.

Objectives: Understanding the bronchodilatory potential and dose response profile early in the development programme is important for informing future investment decisions and dosing regimens. To this end, data from single-dose cross-over studies were used to model the FEV_1 (Forced Expiratory Volume during one second) effect over time.

Methods: FEV_1 was measured during 26 hours after a single dose cross-over study. The placebo data was modelled as a circadian rhythm as well as a linear trend to account for any increase in time over the 26 hours. Since no PK data from the lung were available, an underlying PK profile was assumed to drive the placebo-corrected FEV_1 effect. Parameters for the rate of onset and offset were estimated.

Results: An emax model with one parameter for onset of effect and one for offset was found to describe the data well. IIV and IOV variability was estimated for several parameters. A confidence interval for the mean placebo-corrected effect at trough, as well as other timepoints, was obtained by simulating from the variance-covariance matrix of the parameter estimates from the final model.

Conclusion: Longitudinal modeling of FEV_1 data from the entire 26 hour profile, as well as incorporating competitor information, can be helpful for understanding the dose response profile and inform decisions about future development.

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Andrés Olivares-Morales III-52 Qualitative prediction of human oral bioavailability from animal oral bioavailability data employing ROC analysis

Andrés Olivares-Morales (1), Leon Aarons (1) and Amin Rostami-Hodjegan (1, 2)

(1) Centre for Applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK. (2) Simcyp Limited, Blades Enterprise Centre, Sheffield, UK.

Objectives: The aim of this study was to develop a Receiver Operating Characteristic (ROC) analysis to evaluate the performance of animal oral bioavailability (F_{oral}) data as a predictor of human F_{oral} and to identify the optimum cut off values of F_{oral} for the implementation of a classification model.

Methods: F_{oral} data for both human and preclinical species - mouse, rat, dog and non-human primates (NHP) - for around 180 compounds was collated from literature as described elsewhere [1]. For implementation of the ROC analysis, human F_{oral} was defined as high (≥ 50%, positive) or low (< 50%, negative). The construction of the ROC curve was implemented in Matlab 2012a by varying the animal threshold (t_A) for high and low F_{oral}, the resulting specificity and sensitivity for any t_A was recorded and plotted. The evaluation of animal models for the prediction of high and low human F_{oral} was determined by the area under the ROC curve (AUC)[2-4]. In addition, the optimal operating points for the animal models were calculated by cost analysis assuming identical cost for false positive (FP) and false negatives (FN)[2, 4].

Results: Employing F_{oral} data for all the species combined, AUC for the animal model was 0.79 whereas the specific values by species were 0.82, 0.73, 0.80

and 0.96 for mouse, rat, dog and NHP, respectively. The optimal operating point for animal F_{oral} was calculated as 46.5%, for all the species combined, whereas for the particular species, values were around 67%, 22%, 58% and 35%, respectively. The results suggest that animal models can be employed for categorical prediction of human F_{oral}. NHP showed the highest AUC value which is consistent with previous results [1, 5, 6]. The results suggest that a value around 50% for animal F_{oral} could predict high and low human F_{oral} with a high sensitivity and moderate specificity. Species specific results suggest a similar approach, consistent with the values reported previously [1, 5-8].

Conclusions: ROC analysis is a powerful tool for the evaluation of the performance of animal F_{oral} as predictor of human F_{oral}. High and low human F_{oral} could de predicted with an acceptable level of confidence from animal F_{oral}. The resulting cut off values could be employed, together with other analysis, as a tool in the decision making process during development within the pharmaceutical industry.

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Erik Olofsen III-53 Simultaneous stochastic modeling of pharmacokinetic and pharmacodynamic data with noncoinciding sampling times

E. Olofsen
Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands

Objectives: Tornoe et al. introduced the application of stochastic differential equations to pharmacokinetic-pharmacodynamic (PK-PD) modeling in NONMEM.[1] One of their examples was to identify a time-varying absorption rate. When during drug absorption both pharmacokinetic and pharmacodynamic data are available, but not necessarily sampled at coinciding time instants, the questions arise (1) if these can be analyzed simultaneously and (2) how this would affect PK and PD parameter estimation.

Methods: A three-compartmental model, consisting of an absorption, disposition, and effect compartment was implemented in NONMEM incorporating a Kalman filter with (A) bivariate PK and PD feedback, (B1) alternating univariate PK and PD feedback, or (B2) idem, but with PK and PD information only fed back to the respective PK and PD parts of the model. The state (co)variance matrix was integrated using eqs(3) from Jorgensen et al.[2] Model versions B were fitted to simulated single-subject data, generated with various values of the blood-effect-site equilibration rate (ke0), to assess bias and standard error of model parameters. The absorption rate (ka) and ke0 were governed by stochastic differential equations. At the first sampling time a PD measurement was generated, a PK measurement at the next, et cetera.

Results: Kalman filter A and B1 configurations yielded identical parameter estimates when the PK and PD sampling times coincided (only NONMEM's S matrices differed fittingly). In the setting of a randomly varying ka but constant ke0, simultaneous PK and PD analysis increased the precision of the estimates of ke0 (configuration B1 versus B2). Except when ke0 was relatively small, the improvement approached the expected one based on the increased number of measurements (and measurement noise levels).

Conclusions: PK and PD data can be analyzed simultaneously using an "alternating Kalman filter" configuration, which has the advantage that the PK and PD sampling times do not need to coincide. This approach is similar to "sequential processing" [3], with missing data. When ke0 is identified as being essentially constant, simultaneous analysis may decrease its estimation error.

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Sean Oosterholt III-54 PKPD modelling of PGE2 inhibition and dose selection of a novel COX-2 inhibitor in humans.

Sean Oosterholt (1), Amit Taneja (1), Oscar Della Pasqua (1, 2)
(1) Division of Pharmacology, Leiden University, Leiden, The Netherlands; (2) GlaxoSmithKline, London, United Kingdom

Objectives: The assessment of the analgesic effect of NCEs is primarily based on qualitative behavioral measures of pain [1]. This however, does not reflect the mechanisms underlying the anti-inflammatory response in chronic inflammatory pain conditions. In contrast, prostaglandins are known to be important mediators of inflammation, resulting from the activation of cyclo-oxygenase (COX) after tissue damage. Our investigation shows how inflammatory mediators, such as PGE_2, can be used as biomarker of the analgesic effect and contribute to the rationale for the dose selection in humans. We illustrate the concept using a model-based approach to GW406381, an investigational COX-2 inhibitor with anti-hyperalgesic activity preclinical models of inflammatory pain.

Methods: Data from a multiple dose phase I study in 24 healthy subjects were used for the PK and PD analysis. Concentration *vs.* time data were simulated as basis for the assessment of the exposure-response relationship using a threshold for sustained PGE_2 inhibition levels as the primary criterion for dose selection, with concentrations around IC_{80} considered as the optimal exposure level [2] and concentrations > IC_{95} assumed to exceed the therapeutic window. The impact of different clinical scenarios was then evaluated using simulations. Among other factors, metabolic induction, hepatic impairment and severity of inflammatory response were evaluated.

Results: The PK was best described by a two-compartment model with first order absorption and a lag time. The PD, as determined by prostaglandin

inhibition was described by an I_{max} model. Model predictions show that the therapeutic dose range of GW406381 in patients with normal organ function should be between 150-250mg. Dose adjustments were anticipated for patients showing hepatic impairment and induced metabolism. In addition, we also demonstrate that drug concentrations remain within the therapeutic range longer when the drug is administered according to a twice daily dosing regimen.

Conclusions: The use of pharmacodynamic markers to guide dose selection offers a more robust basis for the dose rationale for analgesic drugs. Moreover, the use of simulation scenarios enables one to identify opportunities for personalisation of the dose and titration requirements for different patient sub-populations.

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Ignacio Ortega III-55 Application of allometric techniques to predict F10503LO1 PK parameters in human

Ortega, I.(1), Ganza, A.(1), Arteche, J.(1), Ledo, F.(1), Gonzalo, A.(1)
(1) Research, Development and Innovation Department, FAES FARMA, S.A. 48940 Leioa-Bizkaia (Spain).

Objectives: F10503LO1, a small molecule of FAES FARMA R&D portfolio, is an antitumoral drug under preclinical development. At this stage, information from PK in different species was gathered and analyzed in an allometric exercise to estimate the PK parameters of F10503LO1 in humans.

Methods: Three animal species (mouse, rat and dog) and a total of 294 plasmatic samples from different studies were included in this exercise. All data were fitted to a pharmacokinetic model using non-linear mixed effect modelling implemented in NONMEM 7.2. This approach estimates coefficients and exponents that characterize the relationship between pharmacokinetic parameters and species features in a single step. Non-parametric bootstrap and VPC were conducted to evaluate the adequacy of the model to describe the plasmatic observations.

Results: A two-compartment PK model with first-order elimination from central compartment was selected as the best model, describing F10503LO1 pharmacokinetics after intravenous administration in the 3 evaluated species. The coefficient and exponents estimated by the model have been applied to simulate PK parameters of F10503LO1 in man in different scenarios.

Conclusions: The model selected describes plasmatic observations in the 3 evaluated species correctly, and allows the extrapolation of PK parameters to humans. These parameters in combination with information of in vitro

efficacy and pharmacology security will be applied for simulation of different scenarios and to select first-in-man dose.

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Jeongki Paek III-56 Population pharmacokinetic model of sildenafil describing first-pass effect to its metabolite

Jeongki Paek(1,2), Seunghoon Han (1,2), Jongtae Lee (1,2), Sangil Jeon (1,2), Taegon Hong (1,2), Dong-Seok Yim (1,2)
(1) Department of Pharmacology, College of Medicine, The Catholic University of Korea, (2) Department of Clinical Pharmacology and Therapeutics, Seoul St.Mary's Hospital

Objectives: Recently, many comparative pharmacokinetic (PK) studies are conducted in Korea using Viagra® (Pfizer Inc., NY, USA) as the reference drug. This study was to investigate the PK characteristics of sildenafil(Viagra®) with data from several different studies on healthy male Korean subjects. The major metabolite (N-desmethyl sildenafil, NDS) was also taken into consideration because it also had similar pharmacologic activity to that of the parent drug.

Methods: Non-linear mixed effect analysis(NONMEM ver 7.2) was performed using a total of 6,130 observations (3,065 for each chemical entity) from 223 subjects (27.5 observations / subject) obtained after single 50-100 mg sildenafil citrate dose in 7 PK studies. The samples were collected just before and 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12 and 24 hours after dosing. First-order conditional estimation method with interaction option was used for all applicable minimization process.

Results: Two-compartment models were used to describe the disposition of both sildenafil and NDS. The central and peripheral volumes of distribution, instead of the metabolic fraction, were fixed to those of the parent drug. An additional elimination pathway of sildenafil was allowed other than NDS metabolism. Use of a pathway for the first-pass metabolism resulted in improved model fit. The absorption of sildenafil and the first-pass

metabolism to NDS were best described with zero-order process. All other PK processes were assumed to follow first-order kinetics. The total number of parameters was 17 including 6 between-subject random effects. The precision and shrinkage levels were within acceptable limits for all parameters.

Conclusions: Currently, the structure and predictive performance of the model is considered acceptable. We are to perform a covariate analysis and to incorporate handling methods for missing data to further improve the model.

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Sung Min Park III-57 Population pharmacokinetic/pharmacodynamic modeling for transformed binary effect data of triflusal in healthy Korean male volunteers

Sung Min Park1,2, Joomi Lee1,2, Sook-Jin Seong1,2, Jong Gwang Park1, Jeong Ju Seo1,2, Mi-Ri Gwon1,2, Hae Won Lee1, Young-Ran Yoon1
1 Clinical Trial Center, Kyungpook National University Hospital, Daegu, Korea
2 Department of Biomedical Science, Kyungpook National University Graduate School, Daegu, Korea

Objectives: Triflusal (2-acetoxy-4-trifluoromethyl benzoic acid; CAS 322-79-2) is a platelet antiaggregant with structural similarities to salicyclates, but which is not derived from aspirin. The main goal of this study is to develop a population pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation of triflusal in healthy Korean male volunteers.

Methods: A randomized, open-label, two-period, multiple-dose, crossover study was conducted in 38 subjects. All eligible subjects received the test (enteric-coated formulation of triflusal) or reference (triflusal) formulation as a single 900 mg loading dose (day1) followed by eight 600 mg/day maintenance doses on days 2 - 9, with a 13-day washout period. Blood samples were drawn at 0 (pre-dose; baseline), 24, 48, 96, 144, 168, 192, 192.5, 193, 194, 196, 199, 202 and 216 h (from day 1 to day 10) after administration of the loading dose. The samples were analyzed by HPLC/MS/MS, to determine the plasma concentrations of 2-hydroxy-4-trifluoromethyl benzoic acid (HTB), the main active metabolite of triflusal. To determine arachidonic acid-induced platelet aggregation, blood samples were collected at 0 (pre-dose), 24, 48, 96, 144, 168, 192, 196, 202 and 216 h after administration of the loading dose. The maximum platelet aggregation

at time t was transformed into binary data because it looked like having two opposed values at each time point. A population PK/PD modeling was performed using NONMEM (Ver. 7.1) and a simulated prediction study was performed by the visual predictive check (VPC) or the plots of observed and predicted values (POP).

Results: A 1-compartment model with first-order absorption best described the plasma concentrations of HTB. Estimates of the population PK parameter were as follows; *CL/F*, 0.19 L/h; *V/F*, 8.31 L; K_a, 0.34 h^{-1}. CLCR and body weight were selected as covariates through Generalized Additive Modeling (GAM). A PD model with a logistic function described the binary data. Estimated of the PD parameter were as follows; K_{in} , 0.04 h^{-1}; α (the intercept in the model), -4.69; β (the slope in the model), 0.05. The simulation method was conducted by the VPC or the POP and the result exhibited the acceptable predictive performance of the final PK/PD model.

Conclusions: A population PK/PD model for triflusal in healthy volunteers was successfully developed and reasonable parameters were obtained. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of triflusal.

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Zinnia Parra-Guillen III-58 Population semi-mechanistic modelling of tumour response elicited by Immune-stimulatory based therapeutics in mice

Zinnia P Parra-Guillen (1), Pedro Berraondo (2), Emmanuel Grenier (3), Benjamin Ribba (4) and Iñaki F Troconiz (1)
(1) Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra. Pamplona (Spain), (2) Division of Hepatology and Gene Therapy, Centre for Applied Medical Research, University of Navarra. Pamplona (Spain), (3) INRIA Rhône-Alpes, Project-team NUMED, Ecole Normale Supérieure de Lyon. Lyon (France), (4) INRIA Grenoble-Rhône-Alpes, Project-team NUMED. Saint Ismier (France)

Objectives: Quantitative analysis applying population pharmacokinetic/ pharmacodynamic principles is still scarce in the area of immunotherapy especially in pre-clinical tumour models. The aim of this work was (i) to develop a semi-mechanistic population pharmacodynamic model to describe the effects of a vaccine (CyaA-E7) able to trigger a potent and specific immune response in xenografts mice, and (ii) to assess the applicability of the model under different immune-base treatments.

Methods: Data published previously were used [1]. Briefly, $5x10^5$ tumour cells expressing HPV-E7 protein were injected in C57BL/6 mice (day 0) and a single 50 µg dose of CyaA-E7 vaccine was administered intravenously either on day 4, 7, 11, 18, 25 or 30. For the combination studies, 50 µg of CyaA-E7 in combination with 30 µg of CpG (a TLR ligand) and/or 2.5 mg of cyclophosphamide (CTX) on the previous day were given on days 25, 30 or 40. Additional groups of mice receiving PBS on day 4 or CPG or/and CTX on day 25 and 24 respectively were also included. Applicability of the model was tested using published data with IL12 as immunotherapeutic agent [2]. All

analyses were performed in NONMEM 7.2. Bootstrap analysis, visual and numerical predictive checks were generated to evaluate the model.

Results: The final model had the following features: (i) Tumour growth independent of tumour size (Ts), (ii) a K-PD model [3] describing vaccine effects over Ts through a delayed and permanent vaccine signal (SVAC), (iii) a Treg cells compartment controlled by Ts and able to inhibit vaccine efficacy to account for the decrease in vaccine response, and (v) finally, the existence of a subpopulation (mixture model [4]) of mice where only a temporal tumour response was triggered. CpG effects were modelled as an amplification of the immune signal triggered by the vaccine, shortening in addition its delay with respect time, and CTX effects were included through a direct decrease in the Treg synthesis process, along with a delayed induction of tumour cell death. CyaA-E7, CpG and CTX models were coupled to simulate tumour size profiles corresponding to the tritherapy administration on days 25, 30 and 40 resulting in a very good description of the data. Moreover, the model was capable to successfully describe data outcome after IL-12-based immune-stimulatory study without any further structural modification.

Conclusions: This work presents a novel mathematical model were different modelling strategies such as censored data or mixture model have been integrated to successfully describe different immunotherapeutic strategies. This model can be used to maximize the information obtained from preclinical settings, optimizing the design of clinical trials of immune modulating drugs.

Aknowlegments: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also financially supported by contributions from Academic and SME partners

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Ines Paule III-59 Population pharmacokinetics of an experimental drug's oral modified release formulation in healthy volunteers, quantification of sensitivity to types and timings of meals.

I.Paule (1), S.Dumitras (2), R.Woessner (2), S.Ganesan (2), E.Pigeolet (1)
(1) Modeling & Simulation, Novartis Pharma AG, Basel, Switzerland. (2) DMPK, Novartis Institutes of BioMedical Research, Basel, Switzerland.

Objectives: The objective of this analysis was to understand the modified (extended) release formulation PK characteristics of an experimental drug, the extent and sources of its variability in healthy volunteers.

Methods: The population pharmacokinetic analysis was performed using MONOLIX 4.1.3 based on plasma samples from three studies with oral administration (n=65, n=29, n=39) and one study with i.v. administration (n=15) in healthy volunteers. The studies had rich sampling, single and multiple dosing in an almost 10-fold range of doses, were done in several ethnicities, in fasted and fed conditions (different types and timings of meals). The candidate covariates were body weight, BMI, race, sex, food (with different types and timings relative to dosing). Dose-dependencies were also investigated. To best characterize complex patterns in absorption, a transit compartment model was used.

Results: The final model had two disposition compartments, transit compartments for absorption and linear elimination. There were no dose-dependencies in disposition, but some differences between races. Concomitant high-fat high-calorie food had a strong effect on absorption (increase in F, delay of Tmax), with differences between races. Moreover, absorption showed some dose-dependency in fasted conditions.

Conclusions: The present population analysis identified the structural model and most influential factors of the experimental drug's PK profiles in healthy volunteers. The model will be subsequently updated with patients' data, where the effects of smoking, age, elimination organ functions can be assessed.

Sophie Peigne III-60 Paediatric Pharmacokinetic methodologies: Evaluation and comparison

Sophie Peigné1, Charlotte Gesson1, Vincent Jullien2,3 and Marylore Chenel1
1Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier,

Objectives: The "first dose in children" could be determined mainly by two approaches:

- A physiological approach (PBPK "Physiollogically based PharmacoKineticsmodel)
- A compartmental approach using allometric scalling and maturation function

Comparison of these two methods had already been performed [1]. The aim of this work was to provide another example with a drug X metabolized only via CYP3A4 (80%) and with CL_R (20 %). A study performed in paediatric population with this drug is currently underway.

Methods: Four children age classes were defined

- 20 infants in age-subset [6-12[months received 0.02 mg/kg twice daily
- 20 infants in age subset [1-3[years received 0.05 mg/kg twice daily
- 20 infants in age subset [3-18[years with weight <40 kg received 0.05 mg/kg twice daily
- 20 infants in age subset [3-18[years with weight ≥ 40 kg received 2.5 mg twice daily

A full PBPK model with Kp predicted by Poulin and Theil's method was previously developed in adult and was used to simulate 10 times the four children age classes concentration-time profiles with SimCyp.

Simultaneously, an adult semi- physiologic joint PK model for the drug X and its active metabolite was scaled to children. The parent drug X part of the model was a three-compartment model while the metabolite was a two compartment model. These two parts were linked by two additional compartments representing liver. Weight effects were fixed to the allometric values of 0.75 and 1 on clearances and volumes of distribution, respectively [2]. In addition, a maturation function was added on clearance for the youngest age classes [3]. The concentration-time profiles of the 800 children obtained with SimCyp were compared to 1000 simulations performed with NONMEM using the same demographic data.

Results: The two approaches predicted the same magnitude of concentrations for the parent drug. On the contrary, some differences were observed between the two approaches on the metabolite PK profiles. For the absorption phase, refinement of the PBPK model was necessary (ADAM absorption model or ka).

Conclusions: Two approaches were compared and showed differences especially for the metabolite. Clinical PK data in children will be available by the end of the year and compared to the two sets of prediction.

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Nathalie Perdaems III-61 A semi-mechanistic PBPK model to predict blood, cerebrospinal fluid and brain concentrations of a compound in mouse, rat, monkey and human.

Nathalie Perdaems, Kathryn Ball, François Bouzom
Technologie Servier, Orléans, France

Objectives: To develop a semi-mechanistic PBPK model to predict blood, cerebrospinal (CSF) and brain concentrations acrossdifferent species.

Methods: PK studies in the different species were performed: blood and brain were sampled in mice - blood, CSF and brain were sampled in rat and extracellular fluid in brain (ECF) and plasma samples from a microdialysis study in rat - blood and CSF were sampled in monkey & blood and CSF were sampled in human. A semi-mechanistic model was developed usingacslX 2.5.0.6 and Phoenix WinNonlin 6.3.

Results: A PK model to describe blood concentrations in each specieswas developed. Then, a semi-mechanistic PBPK model usingblood concentrations and CSF, brain and/or ECF concentrations was built in rat. The semi-mechanistic model parameters weretransposed toenable simulations in theother species, and the observed concentrations were compared with the model predictions.

Conclusions: The semi-mechanistic model allows the description of concentrations in the various CNS compartments in the rat. The transposition between species is ongoing.

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Chiara Piana III-62 Optimal sampling and model-based dosing algorithm for busulfan in bone marrow transplantation patients.

C. Piana (1), F. A. Castro (2), V.L. Lanchote (2), B.P. Simões (3); O.E. Della Pasqua (1,4)

(1) Division of Pharmacology, Leiden Academic Center for Drug Research, The Netherlands; (2) Department of Toxicology, University of São Paulo, Brazil; (3) Division of Haematology, Hospital das Clínicas, University of São Paulo, Brazil; (4) Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Stockley Park, UK

Objectives: Busulfan is an alkylating agent used as part of a conditioning regimen in patients undergoing bone marrow transplantation. Busulfan presents high inter- and intra-individual variability in pharmacokinetics and has a very narrow therapeutic window, which has been linked to several adverse events [1]. Currently used therapeutic monitoring protocols are therefore aimed at busulfan dose individualisation, but evidence of achieving target exposure is not warranted. The aim of the current investigation was to determine the optimal scheme for PK sampling and develop a model-based dosing algorithm for busulfan in bone marrow transplantation patients.

Methods: Clinical data (n=29) from an ongoing study were used in our analysis. An existing one-compartment model with first order absorption and elimination [2] was selected as basis for sampling optimization and subsequent evaluation of a suitable dosing algorithm. Internal and external model validation procedures were performed prior to optimisation steps using ED- optimality criterion in PopED. Clearance and volume of distribution were considered as parameters of interest. The final sampling scheme was selected based on the predicted $AUC_{(0-6)}$ deviation from target exposure range obtained in a variety of simulation scenarios.

Results: A one-compartment model with ideal body weight [IBW] and alanine transferase [ALT] as covariates on clearance was found to accurately describe busulfan exposure after oral administration. The use of a model-based dosing algorithm appears to ensure that patients achieve the expected target exposure. In addition, a sparse sampling scheme with five samples per patient (t = 0.5, 2.25, 3, 4 and 5 hours after dose) was found to be sufficient for the characterization of busulfan pharmacokinetics. In contrast to the current clinical protocol, which relies on a linear correlation between dose and body weight, our findings reveal the clinical implications of a nonlinear correlation between body size, liver function and drug elimination.

Conclusions: The reduction from 15 to 5 blood samples constitutes an important improvement in routine therapeutic drug monitoring. Moreover, the availability of a model-based dosing algorithm for dose individualisation that accounts for the effects of IBW and ALT levels on busulfan clearance, may contribute to considerable improvement in the safety and efficacy profile of patients undergoing treatment for bone marrow transplantation.

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Sebastian Polak III-63 Pharmacokinetic (PK) and pharmacodynamic (PD) implications of diurnal variation of gastric emptying and small intestinal transit time for quinidine: A mechanistic simulation.

S.Polak(1,2), D.Tomaszewska(1), N.Patel(2), M.Jamei(2), A.Rostami-Hodjegan(2,3)

(1) Unit of Pharmacoepidemiology and Pharmacoeconomics, Faculty of Pharmacy, Jagiellonian University Medical College, Poland; (2) Simcyp, a Certara Company, Sheffield, UK; (3) Centre for Applied Pharmacokinetics Research, School of Pharmacy and Pharmaceutical Sciences, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK

Objectives: Chronopharmacology may play an important role for drugs with narrow therapeutic window particularly for patients predisposed to safety issues due to the genetic factors. Clinical studies are not common to test the diurnal variation in PK and/or PD effects. The objective of this study was to establish and validate methodology allowing for simulation of QT change for an orally taken drug with use of mechanistic methods accounting for population variability.

Methods: The PK simulations for quinidine and its 3-hydroxy metabolite were carried out using Simcyp platform (V12) and its compound library files in virtual healthy Caucasians. It was assumed that the morning/night differences in PK are predominantly caused by the differences in absorption and bioavailability as the known chronological variations in gastric emptying time (h) and small intestinal transit time (h) can influence these parameters. Gastric emptying half-life in fasted state was set to 0.4 and 2 h and corresponding intestinal transit times were 3.5 and 7 h (1,2) for 10am and 10pm respectively. Virtual patients mimicked the clinical study reported by

Rao (3) (8 males, 18-26 yo). PD endpoint was ΔQTcF derived from the pseudoECG simulated by the ToxComp system based on the in vitro currents inhibition and the predicted free plasma concentrations separately for all individuals (4). Circadian changes to baseline and drug effects on QT were accounted for by applying the diurnal changes to heart rate and K+, Na+, Ca2+ ions in plasma.

Results: Observed study reported prolongation of Tmax (1.29 fold), no change in Cmax (0.97 fold) and 1.13 fold increase in AUC with the pm administration. Simulated diurnal changes in Cmax (0.98 fold) and AUC (1.13 fold) were consistent with observations. Simulated prolongation of Tmax (1.61 fold) appeared to be more than observed magnitude. Predicted ΔQTcF values were concentration dependent and followed circadian rhythm. Maximum population ΔQTcF for 10pm and 10am scenarios were 38 (3am) and 43 (1pm) ms respectively.

Conclusions: Results demonstrate the potentials of the mechanistic in vitro in vivo extrapolation (IVIVE) for incorporating the knowledge of chronological variations in physiological system parameters leading to PK or PD variations. The simulations may assist with determining the PD variability occurring diurnally using the in vitro data on drugs and are suitable for designing studies which might be affected by the chronobiology of PK and/or PD.

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Angelica Quartino III-64 Evaluation of Tumor Size Metrics to Predict Survival in Advanced Gastric Cancer

AL. Quartino (1), L. Claret (2), J. Li (1), B. Lum (1), J. Visich (1), R. Bruno (2), J. Jin (1)

(1) Genentech Research and Early Development (gRED), Roche, South San Francisco, CA (2) Pharsight Consulting Services, Pharsight, a CertaraTM Company, Marseille, France

Objectives: A disease model framework has been successfully applied to predict overall survival (OS) in cancer patients based on observed longitudinal tumor size data (1-4) to aid early clinical development decision-making (4-6). The aim of this project is to evaluate metrics of tumor size response and prognostic factors to predict OS in patients with HER2 positive advanced gastric cancer (AGC).

Methods: The change in tumor size in AGC patients following treatment with trastuzumab plus chemotherapy (n=228) or chemotherapy (n=228) in the Phase III study ToGA was described by longitudinal tumor size models; the simplified tumor growth inhibition model (sTGI) (1) or the empirical tumor size model (7). Model-predicted metrics of tumor response (e.g. time to tumor growth (TTG) derived from the sTGI model and the tumor growth rate parameter (G) in the empirical tumor size model), patients characteristics and drug effect were evaluated as predictors for OS in a parametric survival model assuming a log-logistic density function for the survival time distribution. The predictors were explored in multivariate analysis: backward elimination ($p<0.01$) of the covariates significant ($p<0.05$) in univariate non-parametric Cox regression. The models were assessed by posterior predictive checks where the OS and hazard ratios (HR) of trastuzumab plus chemotherapy vs. chemotherapy were simulated in multiple replicates (n=1000) of the original study.

Results: The best predictor for OS was G, followed by TTG (ΔOFV 7.5). The trastuzumab effect on G fully captured the trastuzumab effect on survival. In addition to G, survival was associated with baseline ECOG performance status, number of metastatic sites, HER2 expression, Asian origin and serum albumin. Simulations showed that the model accurately predicted the OS distribution in each study arm and subpopulation as well as trastuzumab HRs (e.g. model prediction [95% prediction interval]: 0.71 [0.58 - 0.86] vs. 0.65 for OS in trastuzumab plus chemotherapy).

Conclusions: This analysis propose that the metrics (G and TTG) of longitudinal tumor size response models are good predictors of OS and fully captured the effect of trastuzumab on survival in AGC patients including the shorter survival observed in patients with low trastuzumab exposure (Cmin) (8). The identified prognostic baseline factors for survival are in line with literature (8, 9). The developed disease model for AGC patients is drug-independent and thus is a useful tool in design and evaluation of clinical trials of also new investigational agents under development for treatment of HER2 positive AGC and allows early prediction of OS.

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Khaled Abduljalil IV-01 Prediction of Tolerance to Caffeine Pressor Effect during Pregnancy using Physiologically Based PK-PD Modelling

K. Abduljalil(1), R. Rose(1), T.N. Johnson(1), T. Cain(1), L. Gaohua(1), D. Edwards(1), M. Jamei(1), A. Rostami-Hodjegan(1,2)
(1) SIMCYP Limited (a Certara Company), Sheffield, UK, (2) School of Pharmacy and Pharmaceutical Sciences, the University of Manchester, UK

Objectives: To simulate the concentration-response of caffeine after 150mg daily dose, in a virtual healthy pregnant population using the Simcyp Simulator.

Methods: Gestational age-dependent PBPK parameters [1], including CYP1A2 activity, were incorporated into the Simcyp V12 Release 2 Simulator and added to prior *in vitro* information on the metabolism and kinetics of caffeine available in Simcyp. The PD custom scripting module was used to define a tolerance model, which was not available in the pre-defined library of models within the Simulator. This was then linked to the systemic concentration of a full PBPK model. The change in mean arterial pressure was used as the PD marker of the pressor effect of caffeine. The PK-PD relationship represented by an empirical tolerance model, as adopted by Shi et al., 1993 and the simulated PBPK-PD profiles were compared to the reported observed values [2, 3].

Results: Predicted caffeine plasma levels and response for different doses and routes of administrations were in agreement with the clinical observations. The predicted area under the concentration curve, AUC0-72hr, was 2.2-fold higher in pregnant compared to non-pregnant women (78 *vs* 35 mg/L.h). Similarly, the predicted area under the effect curve, AURC0-72hr,

was 1.84-fold higher in pregnant women compared to the baseline (311 *vs* 169 mmHg). In comparison with non-pregnant women, who did not show the persistence of the tolerance response based on a daily dose of 150mg caffeine, tolerance to the pressor effect is still apparent in pregnant women based on this dosing regimen.

Conclusions: The link between PD and PBPK, combined with *in vitro in vivo* extrapolation, offers an extension of the success of PBPK in drug development [4]. In this case study, the implemented approach allowed successful simulation of the effect of caffeine observed in clinical studies and offers prediction of the response in a pregnant population. The decreased activity of CYP1A2 during pregnancy results in the reduction of drug elimination and prolongation of the effect. The custom PD tool facilitates the linkage of more flexible PD models to the Simcyp PBPK models. This can extend the capability of clinical trial simulations similar to the one shown in this study and can be used to investigate the design and power of POPPK-PD studies performed across a variety of clinical settings such as sub-populations and drug-interactions.

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Rick Admiraal IV-02 Exposure to the biological anti-thymocyte globulin (ATG) in children receiving allogeneic-hematopoietic cell transplantation (HCT): towards individualized dosing to improve survival

Rick Admiraal, MD (1,2,3), Charlotte van Kesteren, PharmD PhD (1,2), Maarten JD van Tol, PhD (4), Cornelia M Jol van der Zijde, BSc (4), Robbert GM Bredius, MD PhD (3), Jaap Jan Boelens, MD PhD (1), Catherijne AJ Knibbe, PharmD PhD (2)

(1) Department of Pediatric Immunology, University Medical Centre Utrecht, the Netherlands, (2) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands, (3) Department of Pediatrics, Leiden University Medical Centre, Leiden, the Netherlands, (4) Pediatric Immunology Laboratory, Leiden University Medical Centre, Leiden, the Netherlands

Objectives: To prevent graft versus host disease (GvHD) and rejection in hematopoietic cell transplantation (HCT), children receive anti-thymocyte globulin (ATG), a polyclonal rabbit-derived antibody, as part of the conditioning regimen to deplete T-cells. Besides T-cells, ATG is known to bind to antigens expressed by other lymphocytes, monocytes and endothelium. The therapeutic window is critical: overdosing leads to slow or absent reconstitution of donor T-cells, increasing the risk of viral infections, whereas underdosing may cause GvHD, both causing significant morbidity and mortality. Previous studies have shown drug concentrations to be highly variable over the entire pediatric population when dosing a fixed amount per kg, with older children reaching higher concentrations. The aim of this study is to develop a new dosing regimen in order to improve outcome in pediatric SCT. To reach this goal, a population PK/PD model will be developed to

describe T-cell reconstitution, incidence of GvHD and survival in relation to ATG-concentrations.

Methods: Pharmacokinetic and -dynamic data were available from all pediatric HCT's performed between 2004-2012 in the Netherlands. 260 patients were included with ages varying 0.1 to 22 years. Patients received a cumulative dose of 10 mg/kg ATG divided in four infusions over 4 consecutive days, starting 4 to 15 days before infusing the graft. A median of 12 samples per patient were available, as well as an extensive amount of data on covariates and pharmacodynamic endpoints, including T-cell concentrations and clinical outcomes such as survival, infections and GvHD. NONMEM VII was used for population PK modeling and to perform a covariate analysis characterizing the influence of e.g. bodyweight and age.

Results: Various models have been tested, including models with non-linear clearance. Preliminary results show pharmacokinetics of ATG can be described adequately using a 2-compartment model in terms of volume of distribution, intercompartimental clearance and first-order clearance. Weight is a significant covariate for clearance, volume of distribution and intercompartimental clearance using a power function. Currently, this model is further extended to describe immune reconstitution.

Conclusions: This far, ATG pharmacokinetics can be well described using a two-compartment model with weight as an important covariate. In future, various pharmacodynamics, such as immune reconstitution, will be incorporated in this model to derived evidence based dosing guidelines.

Wafa Alfwzan IV-03 Mathematical Modelling of the Spread of Hepatitis C among Drug Users, effects of heterogeneity.

W Alfwzan, D Greenhalgh
Department of Mathematics and Statistics, University of Strathclyde.

Objective: We develop the model of Corson et al. [1] to study the effects of heterogeneity in spread HCV among drug users. We derive the system equations, describing the spread of HCV in addicts and needles. We determine a formula for the basic reproduction number R0, key parameter. Mathematical results are shown and followed by a numerical simulation results.

Methods: Exploring the effects of heterogeneity and disease behaviour by dividing population into groups. We allow for variability in the sharing rate, their choice of shooting gallery. Six models are studied each model has different number of groups and sharing rates. This was displayed where R0 <1 or >1. Data of survey Glasgow drug users in 1990-93 [2] to calculate sharing rate.

Results: If R0 <1 model has unique equilibrium solution where the disease has died out. Disease will die out whatever the initial conditions if R0 <1. If R0 >1 the DFE is unstable, and there is a non-zero endemic equilibrium solution. Simulation results are compatible with these mathematical results. When R0 >1(1990) the disease takes off over time and has endemic equilibrium prevalence. Homogeneous model has highest proportions of infected addicts whilst heterogeneity model has lowest. This indicates that increasing of heterogeneity in may reduce spread of HCV. When R0<1(1993) in homogenous model, disease may die out. It is observed that highest proportion of prevalence of HCV is in two group model whilst lowest

proportion is in homogenous. Thus as number of groups increases, initial speed of increase of the epidemic (related to R0) increases.

Conclusion: We have studied the effects of heterogeneity on the spread of HCV. We divide the population into groups, along with different shooting galleries. The results fit into a familiar pattern followed by most simple epidemic models. R0, determines the behaviour of the disease. The simulation results emphasize the importance of R0 and the importance of heterogeneity on the spread of HCV.

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Sarah Alghanem IV-04 Comparison of NONMEM and Pmetrics Analysis for Aminoglycosides in Adult Patients with Cystic Fibrosis

Alghanem S(1), Neely M(2), Thomson A(1,3)
(1)Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, UK. (2)Laboratory of Applied Pharmacokinetics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. (3)Pharmacy Department, Western Infirmary, NHS Greater Glasgow and Clyde, Dumbarton Road, Glasgow G11 6NT, UK.

Objectives: The aim of this study was to compare the performance of parametric and nonparametric approaches in population pharmacokinetic analysis for cystic fibrosis patients.

Methods: The study involved a retrospective analysis of a database of aminoglycoside concentration measurements in patients with cystic fibrosis from Glasgow and The Hague. The data had previously been analysed using a traditional parametric population modelling approach using NONMEM (version 7) (1). The present analysis focuses on population analysis using a non-parametric approach with the software Pmetrics (2). One and two compartment models and the influence of covariates, using both simple and mechanistic approaches, were compared for parametric and non-parametric approaches.

Results: The combined dataset included 331 patients (166 from Glasgow) with 1490 courses of therapy and 3690 aminoglycoside concentration measurements. The NONMEM analysis found that a two compartment model was superior to a one compartment model. This was confirmed using the non-parametric approach where the two compartment model was again

superior (-2 likelihood value 9004 vs 9618). The population estimates of clearance (CL) and V_1 generated from NONMEM and Pmetrics were very similar. In addition, both NONMEM and Pmetrics identified creatinine clearance and height as factors influencing CL and height influencing V_1.

Conclusions: Similar results were obtained when parametric and nonparametric approaches were used to analyse aminoglycoside data from patients with cystic fibrosis

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Nidal Al-huniti IV-05 A Nonlinear Mixed Effect Model to Describe Placebo Response in Children and Adolescents with Major Depressive Disorder

Nidal Al-Huniti and Diansong Zhou
Clinical Pharmacology & Pharmacometrics, AstraZeneca, Wilmington, DE 19803, USA

Objectives: Many antidepressants failed to demonstrate superiority in double blinded clinical trials due to significant placebo response (PR) in children. The purpose of current study was to explore an appropriate placebo effect model.

Methods: PR from randomized controlled trials studying antidepressants in children (6-18 yrs) with MDD was obtained from literature. The PR described as Children's Depression Rating Scale-Revised (CDRS-R) score was used to develop a nonlinear mixed effect model with NONMEM 7.2 and nlme package in R. PR was modeled as $E0*(1-E_{max}*time/(ET_{50}+time))$. 1000 trial simulations were conducted to evaluate the variability of placebo effect.

Results: There were 81 CDRS-R observations from 13 clinical trials for 9 drugs. The number of patients from placebo arm was in the range of 15 to 187 in these studies and the average CDRS-R score at study entry was in the range of 52 to 64.6. Parameter estimates were similar using NONMEM and nlme. The baseline CDRS-R score was estimated to be 58.6 ± 1.1 while the maximum effect (E_{max}) for PR was 42% ± 2%, indicating the significant PR in the clinical trials. The ET_{50}, time inducing a response equals to one-half of E_{max}, was 1.9 ± 0.3 weeks. The simulations for PR also indicated significant variability of placebo effect in MDD clinical trials.

Conclusions: The nonlinear mixed effect PR model in MDD children demonstrated significant and variable placebo response. The model can provide a useful tool for evaluating time course of placebo effect.

Hesham Al-Sallami IV-06 Evaluation of a Bayesian dose-individualisation method for enoxaparin

Hesham S Al-Sallami (1), Michael Barras (2,3), Stephen B Duffull (1)
(1) School of Pharmacy, University of Otago, Dunedin – New Zealand (2) Royal Brisbane & Women's Hospital, Brisbane, Australia (3) School of Pharmacy, University of Queensland, Brisbane, Australia

Objectives: The current approved treatment dose of the anticoagulant enoxaparin is based on total body weight and its dosing frequency is based dichotomously on creatinine clearance. Recent evidence has shown these dosing strategies to be suboptimal and adaptive dose-individualisation (based on Bayesian statistics) has been proposed as a safer and a more effective alternative. A Bayesian dose-individualisation software (TCIWorks) is available but its predictive performance of enoxaparin dosing has not yet been evaluated. The aim of this study was to evaluate TCIWorks use for enoxaparin dosing.

Methods: Demographic data, dosing history, and anti-Xa concentrations of 109 patients who received enoxaparin treatment (Barras, 2008) were entered into TCIWorks. The mean error (ME) and root of mean squared error (RMSE) for the prior predictions (calculated from patient covariates) and posterior predictions (estimated from the posterior parameter estimates) to the future observed anti-Xa concentration were calculated to determine the bias and precision of model predictions.

Results: There were a total of 238 anti-Xa measurements in the dataset: 109 first observations (mean = 4.1 mg/L), 98 second observations (mean = 8.6 mg/L), 26 third observations (mean = 6.9 mg/L), and 5 fourth observations (mean = 8 mg/L). The RMSEs for the posterior predictions decreased from 3.3 to 1.8 mg/L after the third observation. The RMSEs for the prior predictions

did not improve and were 2.5, 4.2, 2.8, and 2.8 mg/L for the first, second, third, and fourth observations, respectively.

The prior was negatively biased. The posterior predictions were initially also negatively biased but this became non-significant after the third observation (-0.6, 95% CI -2.3 to 1.1).

Conclusions: TCIWorks provided acceptably accurate predictions of anti-Xa concentrations. There appears to be limited benefit in obtaining more than three observations during dose-individualisation.

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Oskar Alskär IV-07 Modelling of glucose absorption

Oskar Alskär (1), Jonatan I. Bagger (2), Marie Berglund (1) Mats O. Karlsson (1), Filip K. Knop (2), Tina Vilsbøll (2), Maria C. Kjellsson (1)
(1) Pharmacometrics research group, Department of Pharmaceutical biosciences, Uppsala University, Sweden and (2) Diabetes Research Division, Department of Internal Medicine F, Gentofte Hospital, University of Copenhagen, Denmark

Objectives: The ingestion of glucose is an extensively studied process. However, few publications describe this process using a population approach and none have investigated this process over a wide range of glucose doses including knowledge of physiology. Therefore, the objective of this work was to develop a semi-mechanistic population model describing intestinal absorption of different glucose doses to be used in conjugation with the integrated glucose insulin (IGI) model and compare that to the performance of more empirical models.

Methods: Data of plasma glucose and plasma insulin from three 4-h oral glucose tolerance test (OGTT) with different glucose loads (25, 75 and 125 g) was used in this population analysis. The previously published study [1] was conducted in eight patients with type 2 diabetes mellitus and eight gender, age and body mass index-matched healthy control subjects. In addition to glucose the subjects ingested 1.5 g of paracetamol dissolved in the glucose solution to monitor the rate of gastric emptying. The glucose homeostasis was accounted for by using the IGI model using observed insulin to drive glucose elimination; all parameters unrelated to absorption were kept fixed to the reported values [2]. Linear and saturable absorption through the intestinal membrane was investigated as well as different models for absorption delay such as lag time, transit compartment and semi-mechanistic models which accounts for gastric emptying. The rate of gastric emptying in

the subjects was described by a flexible input model using the paracetamol data. Paracetamol data and glucose was modelled sequentially. Model development was guided by goodness of fit and objective function value. All modelling was performed using NONMEM 7.2.

Results: Saturable absorption was superior to linear absorption regardless of the absorption model applied. The semi-mechanistic models were sensitive to the assumed small intestinal transit time and the benefit of the semi-mechanistic models was cancelled out by the increased run-times. The finding that glucose absorption is saturable at high concentrations is consistent with Pappenheimer et al and Kellet et al whom measured the rate of glucose absorption over a range of glucose concentrations in perfused intestine [3, 4].

Conclusions: These results will further improve the performance of the IGI model and allow for investigations of drug effects on glucose absorption.

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

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Helena Andersson IV-08 Clinical relevance of albumin concentration in patients with Crohn's disease treated with infliximab for recommendations on dosing regimen adjustments

H. Andersson (1,2), A. Keunecke (1), A. Eser (3), W. Reinisch (3), W. Huisinga (4), C. Kloft (1)

(1) Dept. of Clinical Pharmacy and Biochemistry, Freie Universitaet Berlin, Germany and (2) Graduate Research Training program PharMetrX, Germany. (3) Department for Gastroenterology and Hepatology, Medical University of Vienna, Austria. (4) Institute of Mathematics, Universitaet Potsdam, Germany.

Objectives: A high proportion of patients affected by Crohn's disease (CD) lose response to infliximab (IFX) in the long-term. Patients with trough concentrations of IFX (Cmin) > 0.5 mg/L are more likely to exhibit maintained clinical remission [1]. Hypoalbuminaemia is seen in patients with severe disease status due to ulcerated mucosa, leading to loss of proteins as well as of IFX [2]. Based on the population pharmacokinetic model for IFX by Fasanmade et al. [3] and the clinical insight from [1, 2], we designed a simulation study to assess the clinical relevance of the serum albumin concentration (sALB) in patients with CD and establish recommendations for dose adjustments.

Methods: Concentration-time profiles of IFX were simulated in NONMEM using the model published in [3]. The covariates were sampled from realistic distributions in agreement with the observed population. The percentage of patients above the cut-off of 0.5 mg/L at steady state was calculated, both for the total population and for the two subpopulations with physiological (≥ 35 g/L) or low (< 35 g/L) sALB. New dosing regimens were simulated for the

group with low sALB to achieve the same proportion of patients > 0.5 mg/L as in the group with physiological sALB. The sensitivity of using 0.5 mg/L is 86% [1], i.e., 86% of the patients with Cmin > 0.5 mg/L will truly exhibit maintained response.

Results: Application of the cut-off resulted in proportions of patients with maintained response similar to previous reports for IFX in CD [4]. The group with low sALB had a considerably smaller proportion of patients above the cut-off compared to the group with physiological sALB. Increasing the dose in these patients did not increase this proportion to a large extent but increased the maximal concentration (Cmax). Reducing the dosing interval, however, resulted in a larger increase of the proportion, without a high impact on Cmax.

Conclusions: A Cmin > 0.5 mg/L seems to be a good predictor for maintained response in patients with CD. Patients with low sALB exhibited lower Cmin than patients with physiological sALB. Shortening the dosing interval was preferred compared to increasing the dose. However, the variability in IFX clearance in this population is substantial. A model with covariates explaining more of the inter-individual variability is needed to be able to give more precise recommendations for dose adjustments.

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Franc Andreu Solduga IV-09 Development of a Bayesian Estimator for Tacrolimus in Kidney Transplant Patients: A Population Pharmacokinetic approach.

Franc Andreu (1), Helena Colom (1), Núria Lloberas (2), Ana Caldés (2), Joan Torras (2), Josep Maria Grinyó (2)
(1) Department of Pharmacokinetics, Faculty of Pharmacy, University of Barcelona. (2) Nephrology service, Hospital de Bellvitge, Barcelona.

Objectives: The aims of this study were (1) to develop a population pharmacokinetic (PPK) model for tacrolimus (TAC) in renal transplant recipients, (2) to identify demographic, biochemical and pharmacogenetic determinants of TAC exposure; and (3) to establish a Limited Sampling Strategy (LSS) to predict the area under the concentration-time curve (AUC) from 0 to 12 hours.

Methods: 16 patients received oral doses of TAC (1-4mg/day) together with mycophenolate mofetil (2g/day). The demographic, biochemical and genotyping for ABCB1 protein (C3435T and G2677T) were recorded. Full pharmacokinetic profiles from 5 occasions (1 week and 1, 3, 6 and 12 months post-transplant) were simultaneously analyzed with NONMEM ver. 7.2 using Perl-Speaks-NONMEM (PsN) and R code version 2.15.2. The final model predictive performance was evaluated with a validation group according to the method proposed by Sheiner and Beal. A LSS was established by the Bayesian estimation method.

Results: TAC PK was best described by a two-compartment model combined with a 3 transit-compartment absorption model, parameterized in terms of clearance (CL), central and peripheral volume (Vc, Vp), intercompartmental clearance (CL_D), absorption constant (Ka) and mean transit time (MT). The FOCE interaction estimation method was used. Between-patient variability

(BPV) was associated with CL (39%), Ka (35%) and MT (32%). Between-occasion variability was associated with CL (29%). Residual error consisted of a proportional error of (20%). None of the covariates tested were statistically significant ($p<0.05$) excepting total bilirubin on CL. However, BPV reduction was <10% and it was removed from the final model. The final PK parameters estimates were 16.5L/h (CL), 9.89L (Vc), 526L (Vp), 35.56L/h (CL_D), 0.47h^{-1} (Ka) and 0.89h (MT). External validation provided a media prediction error (bias) =0.37 µg/L and median root squared error (precision)=0.38 µg/L. A LSS of two sampling times, at 0h [pre-dose] and 1.5 hour post-dose, allowed accurate and precise prediction of the AUC_{0-12h} with a non significant median AUC percentage bias of 4% and good precision (median absolute percentage prediction error=7.8%).

Conclusions: A PPK model for TAC in renal transplant recipients was successfully modeled with a 3 transit compartment absorption model. External validation confirmed its predictive ability. It allowed a Bayesian estimator development suitable for clinical practice being able to accurately predict TAC AUC_{0-12h}

Yasunori Aoki IV-10 PopED lite an easy to use experimental design software for preclinical studies

Yasunori Aoki (1), Monika Sundqvist (2), Carl Whatling (3), Anna Rönnborg (3), Peter Gennemark (2), and Andrew C. Hooker (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (2) CVGI iMED DMPK AstraZeneca R&D, Sweden, (3) CVGI iMED Bioscience AstraZeneca R&D, Sweden

Objectives: In drug discovery, accurate and precise estimation of drug potency from in vivo data is crucial to select the right compound. Proper design of experiments is a fundamental requirement to obtain such estimates. Through this work, we wish to investigate how optimization of the experimental design can be utilized in compound selection studies, and then generalize our findings with a software tool dedicated for drug discovery applications to automate and accelerate the experimental design optimization processes.

Methods: In order to understand the challenges in designing the in vivo studies for drug discovery applications, we have chosen an ongoing compound selection study at AstraZeneca as a case study and used optimization techniques when designing new experiments.
For each new experiment, the experimental design was optimized using the experimental design optimization software PopED [1] and the theoretical optimal experimental design was suggested to the project team. The design was modified considering all the practical aspects of the experiment, and the changes were re-evaluated using PopED. Then, the experiment was conducted and once the experimental results were available, the experimental design was again evaluated. In addition, possible improvements of the design optimization processes for new experiments were explored.

Results: The study shows that the optimization of both sampling time and dosing scheme, especially the latter, can increase the accuracy of the estimation of the potency of the drug as well as other drug related parameters. Also, it is important to identify the practical experimental design constraints, such as the possible timeframe of observations, the possible time interval between observations, or the total amount of the compound available, that can influence the optimal experimental design, and incorporate these constraints into the design optimization algorithm.

Conclusions: In order to automate and accelerate the experimental design processes, we have implemented a simplified version of PopED that can be used in preclinical studies. This software features rich graphical representation of both the model simulations and the accuracy of the model parameter estimates together with an easy to use graphical user interface.

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Eduardo Asín IV-11 Population Pharmacokinetics of Cefuroxime in patients Undergoing Colorectal Surgery

Asín E (1), Trocóniz IF (2), Campos E (3), Errasti J (3), Sáenz de Ugarte J (3), Gascón AR (1), Isla A (1)

(1) Pharmacokinetics, Nanotechnology and Gene Therapy Group, Faculty of Pharmacy, University of the Basque Country; Vitoria-Gasteiz, Spain. (2) Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Navarra; (3) Service of General Surgery, University Hospital of Alava (seat of Txagorritxu); Vitoria-Gasteiz, Spain.

Objectives: The aim of this study is to develop a population pharmacokinetic model for cefuroxime used as prophylaxis in patients undergoing colorectal surgery in order to quantify the degree of inter-individual variability (IIV) and identify the patient and surgery characteristics responsible for such variability.

Methods: A prospective, open-label study was conducted with patients electively undergoing colorectal surgery. The study was conducted at University Hospital of Alava (seat of Txagorritxu) in Vitoria, Spain. Sixty-four patients older than 18 years were included in the study. According to the surgical protocol of the Hospital, all patients received 1.5 g of cefuroxime concomitantly with 1.5 g of metronidazole as intravenous infusion previously to the surgery. A predose blood sample and three to five samples during the next 24 h were collected from each patient. Determination of cefuroxime plasma concentrations was carried out by HPLC. A population pharmacokinetic model was developed using NONMEM 7.2 and the FOCE estimation method with interaction. Compartmental models were used to fit the data. Selection between models was based on the decrease of the objective function value, the precision of parameter estimates and the goodness of fit plots.

Results: Seventeen surgery and patients characteristics were studied as covariates in order to explain the IIV for the parameters. Cefuroxime concentrations were best described by a two-compartment model. IIV was included in the total body clearance (CL) and the apparent volume of distribution of the central compartment (Vc). Cefuroxime is eliminated renally by a one-order process (glomerular filtration) dependent directly on the creatinine clearance and a saturable process (active secretion) which is dependent on the concentration achieved. The body weight and the ASA score were significant covariates for the Vc. The inclusion of covariates allowed to reduce the unexplained IIV from 37% to 17% for the CL, and from 56% to 40% for the Vc.

Conclusions: A two-compartment pharmacokinetic model for cefuroxime in patients submitted to colorectal surgery was developed. The inclusion of covariates reduced significantly the unexplained IIV of the pharmacokinetic parameters. This model could be useful to study whether antibiotic concentration is able to inhibit the bacteria growth until the wound closing time, and to establish recommendations to reduce the incidence of infection in this type of surgery.

Ioanna Athanasiadou IV-12 Simulation of the effect of hyperhydration on urine levels of recombinant human erythropoietin from a doping control point of view

I. Athanasiadou(1,2), A. Dokoumetzidis(1), C. Georgakopoulos(3), G. Valsami(1)

(1)Laboratory of Biopharmaceutics & Pharmacokinetics, Faculty of Pharmacy, National & Kapodistrian University of Athens, Panepistimiopolis-Zographou 15771, Athens, Greece, (2)Doping Control Laboratory of Athens, Olympic Athletic Center of Athens 'Spiros Louis', 37 Kifissias Ave., 15123 Maroussi, Greece, (3)Anti Doping Lab Qatar, P.O. Box 27775, Doha, Qatar

Objectives: To study the effect of hyperhydration on the urine pharmacokinetic profile of recombinant human erythropoietin (rHuEPO) and its possible role as a doping masking procedure used by athletes.

Methods: 1000 subjects administered subcutaneously a single dose of 3000 IU rHuEPO were simulated, by a two-compartment popPK model taken from literature [1], using MatLab SimBiology toolbox. Urine production was modelled based on the renal regulation of urine volume [2] and the conditions of water retention [3]. The normal rHuEPO PK urine profile and additional PK profiles simulating hyperhydration effect were simulated for 3 hydration levels, expressed as 10, 20 and 30 ml of water consumption/kg of body weight. Simulation of urine sampling collection schedule was used to evaluate the effect of hyperhydration on measured rHuEPO urine concentration during doping control analysis.

Results: Simulation analysis revealed that rHuEPO urine concentration follows the circadian rhythm of urine production regardless of hydration state. Moreover, at the time points of hyperhydration, a significant decrease on rHuEPO concentrations was observed compared to the normal profile; the

difference was more pronounced as the hydration level increased. Cases of undetectable rHuEPO have been reported in literature, attributed to inhibition of EPO production following EPO doping, highly diluted urine, and/or manipulation of urine samples with proteases [4]. However, our simulations results showed that even in the normal PK profile, low concentrations compared to the sensitivity of the applied analytical methods [5] may exist, due to the circadian rhythm of urine production. The effect of rHuEPO dose and different hyperhydration intake scenarios on rHuEPO PK urine profile is also studied.

Conclusions: Clear effect of hyperhydration on rHuEPO urine profile was shown, supporting the reported cases of undetectable EPO urine levels. These findings may have practical implications regarding the timing of urine collection during anti-doping control sampling procedure and the subsequent detection of doping agents if hyperhydration could be used by athletes as a masking procedure. To verify this hypothesis, a single dose rHuEPO PK study in healthy male athletes with or without hyperhydration is designed, based on the present simulation analysis.

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Guillaume Baneyx IV-13 Modeling Erlotinib and Gefitinib in Vitro Penetration through Multiple Layers of Epidermoid and Colorectal Human Carcinoma Cells

G. Baneyx (1), C. Meille (1), S. Belli (2), A. Iliadis (3) and T. Lavé (1)
F. Hoffmann-La Roche Ltd, Non-Clinical Safety, (1) Modeling and Simulation, (2) Drug Metabolism and Pharmacokinetics (DMPK), Basel, Switzerland; (3) Dpt. of Pharmacokinetics, INSERM U911 CRO2, Aix-Marseille University, Marseille, France

Objective: Penetration of anticancer drug in tumor tissue is an important factor to achieve exposure of cancer cells to efficacious concentrations and thus a therapeutic effect [1]. The objective of this study was to develop a model based approach to characterize and differentiate the in vitro penetration of Erlotinib and Gefitinib for 2 cancer cell lines.

Methods: Erlotinib and Gefitinib are selective and potent inhibitors of the epidermal growth factor (EGFR) in human [3]. EGFR is expressed in the selected epidermoid (A431) and colorectal (DiFi) human carcinoma cells [4]. A multicellular layers (MCL) system [2] was used to generate the drug penetration kinetics through a Teflon membrane (control) and through 3 or 6 layers of A431 or DiFi cells. Drug concentrations were measured by LC-MS/MS in donor and receiver chambers and cell lysates. The model structure consisted in a set of compartments corresponding to donor, each cell layer and the receiver chamber. Drug exchanges were driven by passive diffusion between compartments, unspecific binding to MCL system and specific binding to cells. Main model parameters (permeability, binding and volumes) were estimated using population approach with the software Monolix 4.1.3 [5] considering the well as the statistical unit.

Results: MCL data exploration clearly showed much more limited penetration for Gefitinib than Erlotinib especially with the DiFi cell line. Model parameters were accurately estimated with RSE from 4 to 39%. Permeability values through A431 and DiFi cells for Gefitinib were 12.6 and 2.7 nm/min respectively and 2.5 and 10 fold higher for Erlotinib. In the model, the low mass balance of Gefitinib with DIFI cells was explained by unspecific and specific binding whereas no binding was required for Erlotinib. After 6 and 24h, fraction of dose reaching receiver chamber was respectively 8.3 and 3.7 fold lower for Gefitinib than Erlotinib.

Conclusion: The developed PK model was able to capture the dynamics of drug penetration for both cell lines. In this multicellular layers system, Gefitinib showed much more limited penetration than Erlotinib, especially with DiFi cells. Model based analysis allowed characterization and differentiation of drugs with similar chemical structures. The model can be used to provide mechanistic insights for tumor drug distribution and to explore, by changing experimental conditions, impact of pH on drug penetration.

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Aliénor Bergès IV-14 Dose selection in Amyotrophic Lateral Sclerosis: PK/PD model using laser scanning cytometry data from muscle biopsies in a patient study

Alienor Berges (1), Jonathan Bullman (2), Stewart Bates (3), David Krull (4)
(1)Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stockley Park, UK: (2) Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stevenage, UK: (3) Biopharm Biomarker Discovery, GlaxoSmithKline, Stevenage, UK: (4) Safety Assessment, GlaxoSmithKline, Research Triangle Park, North Carolina US.

Objectives: Amyotrophic Lateral Sclerosis (ALS) is a rare and ultimately fatal progressive neurodegenerative disease, associated with loss of upper and lower motor neurons and a high unmet medical need for efficacious treatments. Ozanezumab, under development for ALS, is a humanised IgG monoclonal antibody (mAb) that targets Nogo-A protein, an oligodendrocyte expressed negative regulator of neuronal growth and a potent neurite outgrowth inhibitor in the adult central nervous system[1,2]. While not significantly expressed in healthy skeletal muscle, Nogo-A, has been shown to be over-expressed in the skeletal muscle of ALS subjects, and consequently proposed both as a biomarker of ALS and a potential therapeutic target[3-5].

We propose the development of a PK/PD model using laser scanning cytometry (LSC) data from muscles biopsies in a small patient study. The model is aimed to inform dose selection, based on target engagement.

Methods: Data was utilised from a placebo controlled, double blind, ascending dose study in ALS patients[6] Blood samples and skeletal muscle biopsies (pre-and post-dose) were taken from patients to evaluate the Ozanezumab PK and a variety of biomarkers. LSC evaluated the percentage of skeletal muscle cell membrane where Nogo-A co-localised with Ozanezumab

(percentage of co-location). For each patient biopsy, LSC results were replicated three times on different sections of the muscle biopsy. Plasma Ozanezumab concentrations were estimated with a two-compartment linear PK model. PK and LSC data were used to develop a PK/PD model using a non-linear mixed effect approach in NONMEM V7[7].

Results: PK and LSC data were best described by an effect compartment model and a sigmoid equation. The model included the level 2 (L2) data item for NONMEM to group the replicate measurements such that the residual error was divided into a replicate-specific error and a common residual error. The PK/PD model performed fairly well in diagnostics, despite limited LSC data and sensitivity, and provided predictions of co-location between Ozanezumab and Nogo-A at various dosing regimens (in terms of dosing frequency and dose levels).In addition, based on a graphical evaluation, the PK profile in the effect compartment predicted from the PK/PD model appeared to be consistent with the few drug concentrations measured in the muscle biopsy.

Conclusions: The model will assist in estimating Ozanezumab co-localised with Nogo-A in different Ozanezumab dosing regimens.

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Shanshan Bi IV-15 Population Pharmacokinetic/Pharmacodynamic Modeling of Two Novel Neutral Endopeptidase Inhibitors in Healthy Subjects

Shanshan Bi1, Wei Lu2, Feng Guo3, Eliane Fuseau4, Mathilde Marchand4, Pierre Roy4, Steven Martin5
1Pfizer Ltd, Shanghai, China. 2Peking University, Beijing, China. 3Pfizer Ltd, Wuhan, China. 4EMF Consulting, France. 5 Pfizer Ltd, Cambridge, US.

Objectives: UK-447,841 and UK-505,749 are two selective NEP inhibitors that are being investigated for the 'as required' treatment of the symptoms of Female sexual arousal disorder (FSAD). The objective of this study was to understand the pharmacokinetic characteristics of the two drugs, and develop a PK/PD (biomarker) model to quantitatively assess the relationship between drug concentration and the effects of the two drugs on plasma concentration of big endothelin-1 (big ET-1) and atrial natriuretic peptide (ANP) in healthy subjects.

Methods: Data from 3 phase I studies including a total of 89 (44 male: 55 female) subjects were used to build the population PK/PD model. The sequential PK and PK/PD analyses were performed using NONMEM. The parameter-covariate combinations that were considered for inclusion in the model were estimated. A complete battery of diagnostic plots and visual predictive checking were produced to evaluate the models.

Results: The PK for both molecules were described using two-compartment model with zero order and first order absorption processes simultaneously, parameterized in terms of apparent clearance (CL/F) , apparent volume (V/F) zero order absorption duration (D1), and first order absorption rate constant (Ka). A combined big ET-1/ANP indirect response model was developed to describe the relationship between the 2 drugs' concentration and their effect

on NEP inhibition. The concentration to achieve half the maximum inhibition effect on big ET-1 and ANP degradation were, respectively, 1.808 and 54.3 mg/L for UK-447,841 and 0.2667 and 5.408 mg/L for UK-505,749. Age was found to be the significant covariate affecting the ANP production rate. In addition, analysis indicated that ANP and big ET-1 enhanced each other's plasma concentrations via big ET-1 stimulating production rate of ANP and ANP slowing down the degradation rate of big ET-1. The goodness-of-fit diagnostic plots showed that the proposed PK/PD model described the PK and two biomarkers data well. Visual predictive checks showed that the model adequately describes the median of the effects but had a slight over predicts the variability especially for ANP.

Conclusions: Two drugs' pharmacokinetic character was well described by proposed model with the physiological values for PK parameters. The drugs' effect was consisted with prior knowledge about UK-505,749 showed 10-fold greater potency than UK-447,841 for both biomarkers.

Bruno Bieth IV-16 Population Pharmacokinetics of QVA149, the fixed dose combination of Indacaterol maleate and Glycopyrronium bromide in Chronic Obstructive Pulmonary Disease (COPD) patients

Bruno Bieth (1), Aurelie Gautier (1), Michael Looby (1), Gordon Graham (1), Romain Sechaud (2)
(1) Modeling and Simulation, Novartis, Basel, Switzerland. (2) DMPK, Novartis, Basel, Switzerland

Objectives: QVA149 is an inhaled, once-daily, first fixed-dose combination of indacaterol maleate (long-acting β2-agonist) and glycopyrronium bromide (long acting muscarinic antagonist) for the treatment of COPD [1,2]. The objective of the population pharmacokinetics analysis was the assessment of the pharmacokinetic of the fixed dose combination and the comparison of the its dose exposure to the monotherapies (providing an additional level of complexity) .

Methods: A phase III 26-weeks treatment multi-center, randomized, double-blind, parallel-group study was performed on 190 patients. All subjects received either the fixed dose combination (110ug/50ug) or the monotherapy (indacaterol 150ug / glycopyrronium 50ug). Blood samples were collected at pre-dose and over 4 hours after dosing with a total of 10 samples at two different days at steady state. Population PK modeling was performed using NONMEM (version 6 and 7).

Results: The final population models for indacaterol and glycopyrronium bromide given as a fixed dose combination were both a two-compartment disposition model with first-order absorption and first-order elimination. A visual predictive check (VPC) and normalized prediction distribution errors

(NPDE) displayed no serious model misspecification. A covariate search found lean body weight as a significant covariate on the relative bioavailability. In addition, the correlation in exposure of the combined drugs observed on the data was fully assessed by a combination model successfully implemented in NONMEM 7.

Conclusions: A population pharmacokinetic model incorporating day and between occasion effects was developed for the monotherapy and combination therapy arms that adequately described the study data. Lean body weight was found as a covariate on the relative bioavailability. The observed correlation in exposure between the therapies was further confirmed by an innovative nonlinear mixed-effects combination model.

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Roberto Bizzotto IV-17 Characterization of binding between OSM and mAb in RA patient study: an extension to TMDD models

Roberto Bizzotto (1) and Stefano Zamuner (2)
(1) Institute of Biomedical Engineering, National Resource Council, Padua, Italy; (2) (2) Clinical Pharmacology - Modelling and Simulation, GlaxoSmithKline, Stockley Park, UK

Objectives: A humanised IgG1 monoclonal antibody (mAb) against human Oncostatin M (OSM) is being developed for the treatment of rheumatoid arthritis (RA) [1]. Oncostatin M is a member of the interleukin (IL)-6 family of secreted cytokines and is present in the inflamed synovium and blood of patients with RA. This works aims to describe and explain the relationship between mAb and OSM plasma levels and to characterize the *in vivo* equilibrium dissociation constant.

Methods: Plasma levels of free drug (mAb), and free and total OSM (free + mAb-OSM complex) were measured after intravenous and subcutaneous administration of various drug amounts. Using Monolix 4.1.4 software, a mixed-effect model for mAb pharmacokinetics (PK) was developed and estimated on the available measures to discard possible non linearity in the kinetics due to the binding of the drug with the target. The individual estimates of the PK parameters were included in a binding model implemented to fit the observed kinetics of free and total OSM. The target-meditated drug disposition (TMDD) model [2] was not able to contemporary fit the two sets of measures, and the equilibrium dissociation constant (K_D) value estimated from the total OSM measures (less noisy than the free OSM measures) was far from the *in vitro* value (~ 1 nM). Berkeley Madonna 8.3.18 software was then used to explore more elaborated models able to describe all the data together.

Results: Drug kinetics was found to be linear. The best model able to reproduce the relationship between drug level, free and total plasma OSM includes the activation of a gradient-related OSM release in plasma from a separated OSM pool. Such hypothesis is supported by consequent K_D estimates similar to the *in vitro* measure, and by the existence of intracellular preformed stocks of OSM in human neutrophils from which the cytokine is released besides being synthesised *de novo* [3].

Conclusions: Understanding antibody interaction with its target at physiological level is essential in better predicting clinical outcomes and TMDD models are generally adopted for this purpose. This analysis provides a real case in which TMDD models have been extended with the inclusion of a pool compartment to successfully describe the kinetics of drug and target and to provide *in vivo* estimates of their binding rates.

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Marcus Björnsson IV-18 Effect on bias in EC50 when using interval censoring or exact dropout times in the presence of informative dropout

Marcus A. Björnsson (1,2), Lena E. Friberg (2), Ulrika S.H. Simonsson (2)
(1) Clinical Pharmacology & Pharmacometrics, AstraZeneca R&D, Södertälje, Sweden; (2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: The objective of this simulation study was to compare bias in EC_{50} estimates when using interval censored dropout and data where the exact time of dropout is known, in the case of informative dropout.

Methods: An efficacy variable was simulated using an inhibitory E_{max} drug effect model combined with an exponential placebo effect model. Simultaneously, dropout was simulated using a hazard function in which the hazard was exponentially related to the individual predicted efficacy variable, adapted from Björnsson and Simonsson [1]. In the simulations, the dropout was either recorded at the actual time of dropout, or interval censored, i.e. dropout occurred somewhere between two pre-defined assessment times. The impact of number of pre-defined assessment times, and hence the interval between assessments, as well as the impact of extent of dropout was evaluated. The dataset consisted of a placebo group and three active treatment groups, each with 45 subjects, and with a dropout rate between 25 and 55% in the base scenario. The simulated efficacy and dropout data were simultaneously analysed using non-linear mixed effects modelling. The Laplacian estimation method in NONMEM 7 and PsN [2] were used for the stochastic simulations and estimations.

Results: In all simulations bias in EC_{50} was low, less than 10%. When simulations were performed without recording the exact time of dropout

(interval censoring), bias in EC_{50} was higher than when the exact time of dropout was recorded. This was especially evident when there were few measurements of the effect variable. When there were only three measurements of the effect variable, bias in EC50 was almost five times higher for interval censoring, compared to when the exact time of dropout was known. Bias in EC_{50} also increased with increasing dropout rate, regardless of whether exact times or interval censoring is used.

Conclusions: When a dropout model is used, bias in EC_{50} is low, regardless of whether the exact dropout times or interval censoring is used. Bias is, however, lower if the exact dropout times are used, especially if the interval between observations is long or the extent of dropout is large.

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Karina Blei IV-19 Mechanism of Action of Jellyfish (Carukia barnesi) Envenomation and its Cardiovascular Effects Resulting in Irukandji Syndrome

Karina Claassen (1), Stefan Willmann (2), Tobias Preusser (1, 3), Michael Block (2)

(1) Jacobs University Bremen, School of Engineering and Science, Campus Ring 1, 28759 Bremen, Germany; (2) Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, Building 9115, 51368 Leverkusen, Germany; (3) Fraunhofer MEVIS, Universitätsallee 29, 28359 Bremen, Germany

Objectives: Jellyfish stings in northern Australia cause significant morbidity and mortality [1]. One of the most popular jellyfishes, Carukia barnesi (CB) is a small and extremely venomous jellyfish whose sting causes Irukandji syndrome [2]. During envenomation a two phasic reaction takes place. The initial phase is dependent on severity of envenomation and culminates in hypertension and tachycardia. In mild envenomation a prolonged hypertension can be found. In severe syndromic cases hypotension and pulmonary oedema occur, caused by life threatening cardiac failure. Large knowledge gaps exist in the toxin's mechanisms of actions [2]. This work is aimed to show the effects of CB venom on the cardiovascular system (CVS) in a newly developed physiologically based pharmacodynamical (PD) model for the CVS. Several hypotheses of toxin mode of actions are discussed.

Methods: The physiologically based PD model was established by usage of PK-Sim® and MoBi® based on data for physiological factors determining the blood pressure (BP) and the circulation in human. CV relevant data of human CB envenoming have been collected for both phases [1, 3-7]. These data were used to establish a proof of concept study. Different possible mechanisms of action causing hypertension (sympathetic and vagal influence,

even as changes in resistances) and hypotension (heart failure causing changes in elastance, resistance or pump function) were investigated and simulated with the presented model. Finally both effects were combined to simulate the full CV changes of jellyfish envenomation. Effects on the mean arterial blood pressure, the sympathetic and parasympathetic activity even as the dynamic changes in heart rate will be shown in detail.

Results: The results show different possible modes of action of CB toxin, causing hypertension and hypotension. The CV model is able to describe and explain the cardiovascular effects of the toxin with sufficient agreement to experimental data.

Conclusions: The physiologically based PD model of the CVS is able to represent the pharmacodynamics of CB toxin sufficiently well, indicating a reasonable description of the underlying physiological processes. Furthermore, the accurate prediction of the BP, HR and activity of the autonomic nervous system are shown. This provides a proof of concept of how CB envenomation causes CV effects.

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Michael Block IV-20 Predicting the antihypertensive effect of Candesartan-Nifedipine combinations based on public benchmarking data.

Michael Block (1), Thomas Mrziglod (1), Soundos Saleh (2), Corina Becker, Erich Brendel (2), Rolf Burghaus (2), Jörg Lippert (2).
(1) Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, Leverkusen, Germany; (2) Bayer Pharma AG, Clinical Pharmacometrics, Wuppertal, Germany.

Objectives: Calcium channel blocker (CCB) and Angiotensin II receptor blocker (ARB) have demonstrated their efficacy in reducing blood pressure in patients with mild to moderate essential hypertension [1-7]. The aim of this study was to analyze the pharmacological potency of combinations of Nifedipine and Candesartan by integrating all available relevant study information into a unified and consistent model and to predict the expected clinical endpoint variables for combinations of these drugs. The results of the afterwards performed clinical trial were compared to the prediction of the model and discussed in detail.

Methods: Based on data from literature an analysis of monotherapies of dihydropyridines and ARBs was performed by a “maximum effect approach”. Outcome of this first modeling step was a model-based representation of the pharmacological efficacy following a monotherapeutic treatment of selected CCBs and ARBs separately. In the second step a model was trained to best reflecting the study data including both, monotherapies and combination therapies. This model then was the base for a systematic prediction of the blood pressure reductions and the defined specific clinical endpoints for 20 combinations of Nifedipine and Candesartan (reduction in comparison to Nifedipine monotherapy). The resulting effect matrix for the diastolic and

systolic blood pressure reduction was then recalculated to give access to the clinical endpoints.

Results: The model approach resulted in a consistent very accurate representation of both monotherapies and combination therapies for all included CCBs and ARBs. The prediction of combinations for Candesartan and Nifedipine could be performed based on this model and were used for the decision on doses in the clinical trial. As an outcome of the clinical trial the predicted ranges for the clinical endpoints showed a very good agreement with the clinical study, so that the prediction of the endpoints was overall very successful.

Conclusions: A data-based model was developed to predict the blood pressure reduction for Nifedipine and Candesartan combinations. Predictions of blood pressure reductions and clinical endpoints could successfully be made for the different possible combinations of standard doses of Candesartan and Nifedipine. The comparison to the outcome of the later performed clinical trial showed that such model predictions can support the decision making and planning of clinical trials.

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Michael Block IV-21 Physiologically-based PK/PD modeling for a dynamic cardiovascular system: structure and applications

Michael Block (1), Rolf Burghaus (2), Karina Claassen (1), Thomas Eissing (1), Jörg Lippert (2), Stefan Willmann (1), Katrin Coboeken (1)
(1) Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, Leverkusen, Germany; (2) Bayer Pharma AG, Clinical Pharmacometrics, Wuppertal, Germany

Objectives: A physiologically-based (PB) cardiovascular (CV) model including a representation of heart (left, right atrium and ventricle), pulmonary, organ and venous/arterial hemodynamics was developed. The model is aimed to represent all relevant pressures and blood flows of the CV system at a physiological level under different healthy and pathophysiological conditions. Further the model aims for application in a full coupled PBPK/PD context including submodels for different drug-specific MoA's like the Renin-Angiotensin-Aldosterone system.

Methods: The PB CV model was developed by use of the systems biology platform for PBPK and PD modeling including PK-Sim and MoBi. All relevant parameters (such as resistances, compliances, inertances, volumina..) were included based on available literature information [1-4]. The model was applied to different physiological states to investigate in detail the processes and mechanisms leading to changes in blood pressure, blood flows and related physiological conditions of the cardiovascular system. The model is designed in a manner ready to address short term hemodynamics at a scale of single heart beats and detailed changes of heart dynamics and the long-term changes on a timescale of weeks and months by a switch between a detailed model and a mean one acting on a larger timescale. Processes included in the model are the feedback mechanisms of the sympathetic and parasympathetic response on reduced oxygen consumption and changes by

workload. For the analysis of pathophysiological disease states the corresponding conditions to address different types of hypertension (pulmonary/arterial) are included.

Results: The developed cardiovascular model is able to represent all relevant properties including the dynamic changes of related blood pressures including systemic arterial diastolic and systolic blood pressure and pulmonary pressures, as well as blood flows in the different parts (heart, lung, other organs). The influence of feedback mechanisms and the changes under workload and under different pathophysiological could be shown to be very well represented by the model. As exemplified for Enalapril, this model can be extended to a full PBPK/PD model and close the gap from PBPK approaches to predictive PBPK/PD simulations [5].

Conclusions: In conclusion, the developed physiologically-based model for the dynamics of the cardiovascular system is capable of simulating a broad range of relevant physiological conditions for healthy and diseased individuals. The model is able to cover the changes under workload, oxidative stress showing the detailed interplay of the different feedback mechanisms influencing the hemodynamics. The simulations were able to explain/represent different pathophysiological states in arterial and pulmonary hypertension.

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Irina Bondareva IV-22 Population Modeling of the Time-dependent Carbamazepine (CBZ) Autoinduction Estimated from Repeated Therapeutic Drug Monitoring (TDM) Data of Drug-naïve Adult Epileptic Patients Begun on CBZ-monotherapy

I. Bondareva, K. Bondareva
The Research Institute of Physical - Chemical Medicine, Moscow, Russia

Objectives: CBZ has been established as an effective anticonvulsant for partial and generalized seizures. The literature results for CBZ are consistent with self-induction of microsomal enzymes, but only few studies with small sample size have reported the pharmacokinetic (PK) characteristics of CBZ autoinduction. Although the PK changes are well documented in general, their magnitude varies among studies. The objective of the study is to identify parameters of a nonlinear PK model for time course of CBZ autoinduction from TDM data.

Methods: TDM data were collected in the Laboratory of Pharmacokinetics of Moscow Medical University. CBZ levels were measured by high performance liquid chromatography. The assay error pattern was used as: SD=0.1+0.1C (where SD is standard deviation of the assay at measured CBZ concentration C). The PK analysis was performed using the USC*PACK based on a one-compartment model with linear absorption. In this nonlinear model, the metabolic rate of elimination asymptotically increases from a preinduction value (D) during time-lag (Lamda) to a maximum value (D+A) after autoinduction. The model was fitted by the NPEM to TDM data of 19 outpatients closely monitored (6 – 13 peak-trough observations per patient) from 1-2 day up to 1.5 - 2 months of started CBZ-monotherapy.

Results: The postinduction CBZ half-lives were estimated as 3.2 – 50.6h (median = 10h) using a one-compartment linear model and TDM data of 99 adult epileptic patients on chronic CBZ-monotherapy [1]. The preinduction CBZ T1/2 values ranged from 26-63h after 200mg CBZ as a single dose in 16 adult healthy volunteers [1]. The mean elimination parameters of the non-linear autoinduction model (D = 0.02 and D+A=0.06 1/h) are in good agreement with the metabolic rate constants in the pre- (0.018 1/h, CV=22.5%) and postinduction (0.07, CV=97.2%) studies. In 19 patients, the mean ratio of post- to preinduction metabolic rate was 2.2 (CV=40%).

Conclusions: The modeling results indicate that CBZ markedly induces its own metabolism. CBZ autoinduction was completed within the first 1 - 3 weeks of monotherapy. The study demonstrated wide interindividual PK variability in CBZ autoinduction and the need for TDM.

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Jens Borghardt IV-23 Characterisation of different absorption rate constants after inhalation of olodaterol

J. Borghardt (1, 2), A. Staab (2), C. Kunz (2), J. Schiewe (2), C. Kloft (1)
(1) Dept. Clinical Pharmacy & Biochemistry, Freie Universitaet Berlin, Germany; (2) Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Objectives: As there is a lack of quantitative mechanistic understanding about plasma concentration-time profiles after inhalation of drug formulations, the objective of this work was to initiate a workflow to increase the understanding about how deposition, dissolution and absorption of drugs after inhalation impact their plasma concentration-time profiles [1, 2]. Therefore the different absorption rates of a long acting beta-agonist, olodaterol, administered as a solution, were investigated.

Methods: Plasma concentration-time profiles after intravenous infusion, oral and inhalative administration were available from different trials in healthy volunteers. The analyses were performed using NONMEM 6.2 and R. First, a model for the intravenous data has been developed which allowed to simulate a typical concentration-time profile after a bolus injection of olodaterol. This profile was then used as a weight function for a numerical deconvolution (area-point method coded in R) to characterise the absorption behaviour in the lung after inhalation.

Results: By deconvolving the geometric mean concentration-time profile after inhalation with the weight function the unabsorbed fraction per time was calculated. By plotting these values versus time in a semilogarithmic graph the slope between two points could be computed. This slope resembled the negative absorption rate constant at a given time. Hence, it was shown that the absorption kinetics of olodaterol administered by inhalation was best described by several first-order absorption rate

constants. The highest contributed to the early t_{max} after 10 to 20 minutes, whereas the lowest caused drug uptake even after several hours.

Conclusions: The results obtained are in agreement with physiological characteristics of the lung. Particles deposited in the alveolar space may be absorbed fast, whereas absorption of particles deposited in the conducting airways may be slow. As the bioavailability of olodaterol after oral administration was shown to be negligible a slower absorption process due to swallowed droplets can be ruled out. As a next step, the fractions absorbed associated with a certain absorption rate constant will be determined and then will be correlated with the total lung dose and the droplet distribution patterns across the lung described by an *in vitro* Finlay-throat assay [3]. Furthermore, these fractions will be included into a semi-mechanistic model to predict concentration-time profiles.

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Karl Brendel IV-25 How to deal properly with change-point model in NONMEM?

Brendel
SERVIER

Objectives: A change-point model is a model in which a parameter's value discontinuously changes at a given time (named change-point). It can be used to modify model behaviour (e.g. shift in absorption parameter value) or update the system (e.g. Enterohepatic recycling). In addition to parameter values, such models require the definition of change-point, and its implementation in NONMEM is not as intuitive as it looks, especially in repeated doses and at steady state.

Methods: Three methods of change-point definition were evaluated: firstly the reference method, using model event time parameter (MTIME) directly implemented in NONMEM (*MTIME_meth*); secondly the use of a fictive change point compartment (CMT) with an associated lag time (*CMT_meth*) [1]; finally a change point function (FCT) with an analytical expression of a rectangular wave function (*FCT_meth*).

Each method was evaluated with a simulated population PK example: a 2 compartment model with a changing first-order absorption rate. Simulations were performed after single administration, repeated doses and at steady state and 90% prediction interval (PI) and the median were plotted. Graphical comparison and run time duration were used to evaluate each method. Practical constraints in terms of coding and/or data preparation were also discussed.

Results: After single administration, the three methods give the same expected results. After multiple administrations, no difference in term of

simulation output is observed between the three methods. As the reference method *MTIME_meth* allows the use of an adapted NONMEM subroutine, run duration is smaller than *CMT_meth* and *FCT_meth*, which require using differential equations. At steady state (using the implemented NONMEM SS option) only the *FCT_meth* is able to give the correct simulation results. From a practical point of view, *MTIME_meth* involves heavy code adjustment and *CMT_meth* requires specific dataset modification, while *FCT_meth* can be used without significant modifications of both code and dataset.

Conclusions: In order to implement a change-point model after a single dose administration, the *MTIME_meth* was the easiest way to do it, allowing to the modeller to use NONMEM subroutines.For multiple dosing, the *CMT_met* and *FCT_met* are good alternatives when the number of doses increases. However, only the *FCT_meth* is able to perform correct simulation at steady state using NONMEM SS option.

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Frances Brightman IV-26 Predicting Torsades de Pointes risk from data generated via high-throughput screening

Frances Brightman, Hitesh Mistry, Jonathan Swinton, Eric Fernandez, David Orrell, Christophe Chassagnole
Physiomics plc, Oxford, United Kingdom

Objectives: In the 90s and 00s, a dozen compounds were withdrawn from the market because of association with a rare but fatal heart arrhythmia known as Torsade de Pointes (TdP). The occurrence of TdP is assumed to associate with prolongation of the QT interval in the ECG, and this in turn is linked with inhibition of the hERG potassium channel. However, rejecting compounds based on hERG IC50 alone risks rejecting valuable compounds for treating disease, and the absence of hERG inhibition is not a guarantee that a compound will have no effect on the QT interval [1]. Furthermore, an association between QT prolongation and TdP risk is not necessarily valid for non-cardiac drugs [2]. These reports highlight a need to quantitatively assess the relationship between QT prolongation and other markers for TdP propensity for non-cardiac drugs. Here we present a new method for effective prediction of TdP risk categories [3], based on the IC50 values of hERG and two other cardiac ion channels

Methods: We have developed a mathematical model to predict TdP propensity that takes as input: 1) IC_{50}s against a small number of specified ion channels that are routinely screened in early development and 2) the likely highest exposure in man. A leave-one-out cross validation was performed to assess the predictivity of the model against: 1) measuring just hERG alone versus hERG + hNav1.5 + hCav1.2 and 2) other models in the literature.

Results: We have shown that measuring hERG + hNav1.5 + hCav1.2, rather than hERG alone, improves the ability to predict TdP risk categories by a

significant factor for two sets of compounds available in the literature. In addition, we have shown that our approach is more predictive than the standard approach, as well as being marginally better than the current state of the art [4].

Conclusions: Our initial modelling approach has demonstrated that it is possible to predict TdP risk categories, which correspond to the number of reported incidents of TdP, quite well. The model is also computationally far simpler and more efficient than a recently published mechanistic approach [4] and has marginally improved predictivity. A future project will assess how well activity against ion channels compares with changes in QT interval in terms of predicting TdP risk categories. Our ultimate goal is to assess whether some combination of ion-channel activity and ECG measurements is able to predict the propensity for TdP better than QT prolongation alone.

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Margreke Brill IV-27 Population pharmacokinetic model for protein binding and subcutaneous adipose tissue distribution of cefazolin in morbidly obese and non-obese patients

Margreke JE Brill(1,5), Aletta PI Houwink(2), Stephan Schmidt(3), Eric J Hazebroek(4), Bert van Ramshorst(4), Eric PA van Dongen(3), Catherijne AJ Knibbe(1,5)

(1) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands; (2) Department of Anaesthesiology and Intensive Care, St. Antonius Hospital, Nieuwegein, The Netherlands; (3) Center for Pharmacometrics & System Pharmacology, Department of Pharmaceutics, University of Florida, U.S.A. (4) Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands; (5) Division of Pharmacology, Leiden/ Amsterdam Center for Drug Research, Leiden University, Leiden, The Netherlands

Objectives: Morbidly obese patients are prone to surgical site infections. To reduce the risk of infection a prophylactic antibiotic agent is administered before initial surgical incision to attain adequate levels of antibiotic in the bloodstream and subcutaneous tissues. For gastric surgery, cefazolin is the prophylactic antibiotic agent of choice. Currently it is unknown how morbid obesity affects cefazolin pharmacokinetics. In this study, we aimed to investigate the pharmacokinetics of cefazolin, in particular regarding protein binding and subcutaneous adipose tissue distribution in morbidly obese patients and non-obese patients.

Methods: Eight morbidly obese patients, of which seven were eligible for inclusion, with a mean body mass index (BMI) of 48 ± 6 kg/m^2 (range 41 - 57 kg/m^2) and seven non-obese patients with a mean BMI of 28 ± 3 kg/m^2 (range 24 - 31 kg/m^2) received cefazolin 2 gram i.v. at the induction of anesthesia. Total cefazolin serum concentrations were measured at T= 10, 30 and 240

minutes. Unbound serum concentrations were measured at T=0, 5, 10, 30, 60, 120 and 240 min. Using microdialysis, samples to measure unbound cefazolin concentrations in subcutaneous adipose tissue of the abdomen were collected every 20 minutes until 240 minutes after dosing. Population pharmacokinetic modeling and covariate analysis characterizing the influence of body weight and other covariates was performed using NONMEM VI.

Results: A two compartment model consisting of a one compartment model with saturable protein binding (maximal bound concentration Bmax of 215 (6%) mg/L and KD of 73 (10%) microM) for total and unbound cefazolin in serum and a one compartment model for unbound cefazolin in subcutaneous adipose tissue best described the data. Distribution from the central to subcutaneous compartment was dependent on total body weight. Total body weight was a covariate for central volume of distribution ($P<0.01$) while there was no influence of total body weight on cefazolin protein binding parameters.

Conclusions: A population pharmacokinetic model for cefazolin in morbidly obese and non obese patients was derived with a saturable protein binding model for cefazolin in serum and a body weight dependent distribution to the subcutaneous adipose tissue.

Brigitte Brockhaus IV-28 Semi-mechanistic model-based drug development of EMD 525797 (DI17E6), a novel anti-αv integrin monoclonal antibody

B. Meibohm (1), B. Brockhaus (2), M. Zühlsdorf (2), A. Kovar (2)
(1) The University of Tennessee Health Science Center, Memphis, TN, USA, (2) Merck Serono, Darmstadt, Germany

Objectives: The objective of this analysis was to develop a semi-mechanistic population PK model for EMD 525797 incorporating receptor occupancy that forms the basis of a model-guided dose rationale.

Methods: A stepwise approach was used to develop and iteratively refine a population PK/PD model throughout clinical development of EMD 525797 using nonlinear mixed effect modeling with NONMEM. The model was initially derived for describing the PK data in a dose-escalation study in Cynomolgus monkeys, and was subsequently refined with human concentration-time data. At the current iteration of model refinement, 815 serum concentrations of 51 subjects have been included in the analysis: 37 healthy volunteers receiving EMD 525797 single doses of 35, 100, 250, 500, 1000, and 1500 mg, and 14 patients with metastatic castrate-resistant prostate cancer (mCRPC) receiving EMD 525797 250 or 500 mg every 2 weeks. EMD 525797 was administered as intravenous infusion over 1 hour.

Results: The disposition of EMD 525797 was best described by a 2-compartment model with 2 parallel elimination pathways, an unspecific proteolytic pathway, and a saturable, target-mediated process with Michaelis-Menten-type kinetics, which is an approximation of the target-mediated drug disposition model (TMDD) [1]. A disease modifier function was included for V_{max} based on disease status. The obtained parameter point estimates and their between-subject variability (% CV) were: V_{max}=493 µg/hr

(21.4%), with a 35.3% increase in mCRPC patients, K_m=0.571 µg/mL, V_1=4.41 L (22.0%), V_2=3.44 L (40.4%), Q=0.0444 L/hr (56.9%), and $CL_{proteolytic}$=0.00857 L/hr (25.8%). Saturation of the saturable elimination process was assumed to be indicative of receptor occupancy for the targeted αv integrins, and IC_{90}, IC_{95}, and IC_{99} of αv integrin inhibition could be derived from K_m. Model-based stochastic simulations were performed to explore dosing regimens with regard to their likelihood to achieve steady-state trough concentration exceeding these landmarks.

Conclusions: Modeling and simulation provides a rational basis for EMD 525797 dose selection. Next steps are to use the model to compare between different populations and to test whether other TMDD model approximations could fit better the data [2].

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Vincent Buchheit IV-29 A drug development tool for trial simulation in prodromal Alzheimer's patient using the Clinical Dementia Rating scale Sum of Boxes score (CDR-SOB

Sylvie Retout (1), Isabelle Delor (2), Ronald Gieschke (1), Philippe Jacqmin (2), Jean-Eric Charoin (1) for Alzheimer's disease Neuroimaging Initiative
(1) F. Hoffmann-La-Roche Ltd, Basel, Switzerland, (2) SGS-Exprimo, Mechelen, Belgium

Objectives: Population Alzheimer's disease (AD) progression models have been developed using the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) scores to describe the dementia stage of the disease [1-2]. However, those models cannot be used in the context of drug development projects focusing on earlier stages of the disease such as with prodromal patients, and for which endpoint is assessed by CDR-SOB scores. Our objectives were then to support the development of an AD progression model based on CDR-SOB scores and to demonstrate, by simulation, the usefulness of such a model for clinical trial optimisation.

Methods: An AD progression population model was developed [3] using the CDR-SOB scores from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [4]. That model enables the estimation of a disease onset time and a disease trajectory for each patient. The model also allows distinguishing fast and slow progressing sub-populations according to, the functional assessment questionnaire (FAQ), the normalized hippocampus volume and the CDR-SOB score at study entry. We used that model in a simulation mode to explore its potential impact in terms of quantitative understanding design elements (inclusion, trial duration, etc) of a respective clinical trial.

Results: The AD model enables clinical trial design optimization, by 1- understanding the impact of inclusion criteria/disease severity on treatment

effect and required trial length; 2- simulating the time course of the placebo and treatment trial arms under different scenarios (e.g. alternative sample size, trial durations and measurement times) in order to determine how and when enough effect size should be achieved for differentiation. Furthermore, a robust analysis of the data can be performed at the end of a study, by implementing and quantifying a possible drug effect (e.g. time to maximal effect, effects that increase or decrease over time) on one or more of the parameters of the natural history disease progression model [3].

Conclusions: The use of this novel AD disease progression model is a powerful tool in the context of drug development to optimize clinical trial designs and therefore to maximize the likelihood to bring new medicine to Alzheimer's patients.

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Vincent Buchheit IV-30 Data quality impacts on modeling results

Vincent Buchheit, Nicolas Frey
Hoffmann-La Roche, Basel, Switzerland

Objectives: Highlight the importance of cleaned PK data, on the results of a population PK analysis, using a real case example

Methods: The PK data from one phase III study and three phases II studies, from an oncology drug, have been pool together in order to study the sources and correlates of variability in drug concentrations among individuals. The most important data issues, such as covariate outliers, infusion rate physiologically impossible have been fixed. From this pooled dataset, we generated a second dataset where additional PK data issues, mainly identified using a previous developed PK model with a Bayesian feedback analysis, haven been corrected. The base and final models, developed from the cleaned dataset, have then been run with the non-fully cleaned dataset and modeling results were compared.

Results: Results will be shared during the poster session.

Conclusions: Data collected during a clinical trial will never be 100% accurate. The author believes that the effort (time and resources) spent on exploring data and fixing data issues bring quality and efficiency to the modelling flow. [1]The use of Model Based Drug Development is more and more advocated in the pharmaceutical industry, sometimes to answer questions such as "What is the best dose?", or "What is the best dose regimen?" The matter of data quality is essential to help responding to those questions.

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Núria Buil Bruna IV-31 Modelling LDH dynamics to assess clinical response as an alternative to tumour size in SCLC patients

Núria Buil-Bruna (1,2), Benjamin Ribba (2), José María López-Picazo (3), Iñaki F. Trocóniz (1)

(1) Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona 30180, Spain ; (2) INRIA Grenoble Rhône-Alpes, Numed Project Team, 38330 Montbonnot-Saint-Martin, France ;(3) Department of Oncology, University Hospital, University of Navarra, Pamplona 31008, Spain

Objectives: Lactacte dehydrogenase (LDH) is a glycolytic enzyme easily measured in blood. Previous studies have shown that pre-treatment levels of LDH have prognostic value for several solid tumours, including small cell lung cancer (SCLC)[1]. The aim of this work was to investigate whether a dynamic model for LDH longitudinal data could be used to assess clinical response in SCLC patients as an alternative to tumour size evaluation through imaging techniques.

Methods: Data included 25 patients diagnosed with extensive-stage SCLC in the University Hospital of Navarra receiving Etoposide plus either Cisplatin or Carboplatin. Typical treatment regimen included 6 chemotherapy cycles given every 3 weeks. A median of 8 concentrations per patient were included in the analysis (n total=173). Median follow-up time was 22 weeks. Clinical response was defined by ordered categorical response following RECIST criteria based on CT/SCANs. A median of 2 CT/SCANs per patient were obtained at different time points where LDH was also measured. The LDH model was developed using a non-linear mixed effect approach. Model parameters were estimated in Monolix 4.2.

Results: The model was comprised of a classic turnover model, where LDH synthesis was driven by a virtual disease compartment representing the tumour. The drug effect was characterised as an increase in the elimination rate of the disease. Resistance was modelled by linking cumulative dose to decreased drug effect (allowing for LDH increase during treatment, as observed in 52% of the patients).Despite high variability within patients, the model correctly described the individual LDH profiles. The half-life of LDH turn-over was estimated to be 20.2 hours. After two chemotherapy cycles, formation of resistance reduced drug effect by 75%. Model simulations showed that changes in LDH values were strongly correlated to observed RECIST data ($p<0.001$).

Conclusions: We showed that in our patient dataset, modelling LDH dynamics to predict clinical efficacy in SCLC patients can be a powerful alternative to the tumour size measurement approach. Future work will include limited-disease SCLC patients and the effect of concurrent radiotherapy.

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Martin Burschka IV-32 Referenced VPC near the Lower Limit of Quantitation.

Martin A. Burschka (1), Heiner Speth (2)
1.Medical Informatics, University Cologne, 2. sanofi, Frankfurt

Background: The model-based adjustment of measured and simulated concentrations for dose and individual covariates (fixed effects) by multiplication with a factor only allows for multiplicative not additive error models. This results in misleading over- or under adjustments of values close to the lower limit of quantitation(LLOQ).

Objectives: Extend the referenced Visual Predictive Check (rVPC) to times when a considerable part of the concentrations are close to or under the LLOQ.

Method: The rVPC is extended to address mixed-error models with additive as well as multiplicative errors, based on maximum-likelihood estimates of the errors.

Result: For the mixed error model, the rVPC for measured concentrations above the LLOQ does not depend on the LLOQ cut-off value in the example data set.

Conclusion: The mixed-error model allows to extend the credible range of the rVPC to low values.

Theresa Cain IV-33 Prediction of Rosiglitazone compliance from last sampling information using Population based PBPK modelling and Bayes theorem: Comparison of prior distributions for compliance.

T. Cain(1), K.Feng(1), M. Jamei(1), A. Rostami-Hodjegan(1,2)
(1) SIMCYP Limited (a Certara Company), Sheffield, UK, (2) School of Pharmacy and Pharmaceutical Sciences, the University of Manchester, UK

Objectives: To predict the compliance scenario of Rosiglitazone from a patient's last PK sampling point and to compare the predictive ability when compliance scenarios are assumed equally likely and when they occur randomly.

Methods: We applied the Barriere *et al.* [1] method to predict patient's compliance when taking a 4 mg daily dose of Rosiglitazone (ROS) for 5 days. This involved the use of a Bayesian approach, where the probability of a compliance scenario given the final observed concentration was calculated. Prior in vitro and physicochemical parameters for ROS and the Healthy Volunteer population of Simcyp (V12 R2) were used to generate plasma concentration profiles of 500 patients where the first three doses were taken and the final two doses varied over five scenarios: full compliance, missing the first dose, missing the second dose, taking both doses together and missing both doses. Two prior distributions were investigated for compliance and their predictive ability determined by comparing the % of true positive/negative cases. First, uniform distributed scenarios and second a distribution of scenarios generated using an algorithm written in an R script.

Results: For the uniform prior, 100 patients were assumed to have each compliance scenario, and for the second prior the numbers of patients

randomly assigned each compliance scenario varied between 267 for full compliance and 32 for taking neither dose. The probabilities of a true positive and a true negative using a uniform prior were between 0.41 to 0.95, and between 0.78 and 0.98 respectively. For the randomly generated compliance these probabilities were between 0.65 and 0.99, and between 0.91 and 1 respectively. In both cases the scenarios for full compliance, two missed doses and taking both doses together had the greatest probabilities of a true positive.

Conclusions: The probability of a true positive/negative for each compliance scenario is greater when assuming the randomly generated compliance scenario, which is arguably more representative of the true population. Compliance scenarios where only one dose was taken tended to be the hardest to predict from the final concentration. The concentrations in these two cases were probably more likely to be closer to those from the three other compliance scenarios. These results, which can be expanded to response, demonstrate the value of population PBPK modelling in identifying potential predictive compliance indicators

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Vicente G. Casabo IV-34 Modification Of Non Sink Equation For Calculation The Permeability In Cell Monolayers

Mangas-Sanjuan,V.(1), Gonzalez-García, I.(2), Gonzalez-Alvarez, I.(1), Bermejo, M.(1), Casabo, VG.(2)
(1) Pharmacy and Pharmaceutical Technology Area, Miguel Hernández University; (2)Pharmacy and Pharmaceutical Technology Department, University of Valencia.

Introduction: The permeability calculation is derived from the Fick's Law, which its first approximation is a lineal regression model where sink conditions and constant donor concentrations are assumed[1] (Sink model). Artursson et al.[2] published a linear regression model to estimate the permeability under sink conditions, where the donor concentration changes in time, using the accumulated transported fractions (Corrected Sink model). Tavelin et al.[2] proposed a non linear regression model (No Sink model), but could not correctly predict the permeability when there is a lag time and when it is an increased permeation at initial phases of the experiment.

Objectives: The aim was to develop a new non linear model which could estimate the permeability in all types of profiles, simulating different scenarios of variability.

Methods: The non linear model proposed in this work is a modification of Tavelin's non linear model. The comparison between four models was done simulating 1000 experiments with 3 well for each experiment with exponential interindividual and residual errors. Three types of profiles were simulated under sink and non sink conditions and four types of interindividual and residual variabilities combinations (H-H, H-L, L-H, L-L). Permeability was calculated using the four models described. Mean estimation error, intraassay estimation error and individual estimation error

were calculated using simulated and estimated values. ANOVA was performed with the mean estimation error using SPSS 20.0.

Results: Modified non sink model presented the lowest estimation error in most of the cases. Linear regression models estimation error were similar to modified non sink model under sink conditions, but higher under non sink conditions with statistical significance. Non sink model obtained higher estimation errors in profiles 1 and 3, compared to modified non sink model with statistical significance.

Conclusions: The modified non sink equation predicts under the standards of accuracy and precision in all types of profiles and variability scenarios.

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Anne Chain IV-35 Not-In-Trial Simulations: A tool for mitigating cardiovascular safety risks

Anne Chain (1), Meindert Danhof (2), Miriam CJM Sturkenboom (3), Oscar E Della Pasqua (2, 4)

(1) Modeling and Simulations, Merck Research Labs, Rahway, New Jersey, USA (2) Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden University, The Netherlands (3) Department of Medical Informatics and Epidemiology & Biostatistics, Erasmus University Medical Center, The Netherlands (4) Clinical Pharmacology/Modelling and Simulation, GlaxoSmithKline, United Kingdom

Objectives: QT/QTc-interval prolongation continues to be a concern in drug development today. More effort is needed to explain the discrepancies between trial outcomes and real life data from epidemiological studies. The objective of this study is to better translate clinical findings to real life situations and resolve the discrepancies in pre- vs. post-market estimates of QTc-interval prolongation.

Methods: Using *d,l*-sotalol as a paradigm compound, the gap between clinical trial outcomes and epidemiological observations was identified by simulating the drug-induced effects of a population with the same demographic properties as real life users. Any additional effects were evaluated by calculating the absolute differences in QTc prolongation between taking the drug alone and in conjunction with co-medications and comorbidities using the Rotterdam Study cohort as the reference population. A new mechanism-based tool was developed: QTc (real life population) = baseline + circadian rhythm + drug exposure + effects of co-medications and co-morbidity conditions. Distribution of simulated and observed values were then compared non-parametrically. Finally, the approach was validated using the compound, cisapride.

Results: The weight distribution of the Rotterdam cohort showed that 10.8% of the male and 3.4% of the female population would be excluded from clinical trials. Similarly, 21.9% male and 14.9% female would not be included due to baseline measurements. Relative risks were statistically different ($p<0.01$) between sotalol users and those without heart failure, hypertension, diabetes and myocardial infarction. The presence of diabetes increased QTc-interval prolongation from 4.0 to 6.5; whilst with myocardial infarction it increased from 3.4 to 15.5. By combining all the causal factors in a single simulation, the distribution of the observed QTc values was confirmed to fall within the simulated distribution. The same results were seen with cisapride users.

Conclusions: The underlying assumption in conducting clinical trials is that findings about drug effect are generalisable to the real life population. However, in the case of sotalol, our results showed that only part of the observed QTc distribution in the real life population could be attributed to the drug effect. The new approach demonstrated and validated here enabled better estimation of the true risk that could mitigate future drug-withdrawal due to cardiovascular safety.

Kalayanee Chairat IV-36 A population pharmacokinetics and pharmacodynamics of oseltamivir and oseltamivir carboxylate in adults and children infected with influenza virus A(H1N1)pdm09

Kalayanee Chairat (1), Nguyen Van Kinh (2), Nguyen van Vinh Chau (3), Nguyen Thanh Liem (4), Truong Huu Khanh (5), Ha Manh Tuan (6), Peter Horby (7, 14), Charoen Chuchottaworn (8), Laura Merson (9), Ninh Thi Thanh Van (9), Vu Thi Lan Huong (9), Chariya Sangsajja (10), Tawee Chotpitayasunondh (11), Kulkanya Chokephaibulkit (12), Pilaipan Puthavathana (12), Wirongrong Chierakul (13), Bob Taylor (1, 14), Heiman Wertheim (7, 14), Tran Tinh Hien (9, 14), H. Rogier van Doorn (9, 14), Pham Van Toi (9), Nicholas P. Day (1, 14), Jeremy Farrar (9, 14), Nicholas J. White (1, 14), Joel Tarning (1, 14).

(1) Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. (2) National Institute of Infectious and Tropical Diseases, Hanoi, Vietnam. (3) Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. (4) National Hospital of Pediatrics, Hanoi, Vietnam. (5) Pediatric Hospital No.1, Ho Chi Minh City, Vietnam. (6) Pediatric Hospital No.2, Ho Chi Minh City, Vietnam. (7) Oxford University Clinical Research Unit, National Hospital of Tropical Diseases, Hanoi, Viet Nam. (8) Chest Disease Institute, Nonthaburi, Thailand. (9) Oxford University Clinical Research Unit, Hospital of Tropical Diseases, Ho Chi Minh City, Vietnam. (10) Bamrasnaradura Infectious Disease Institute, Ministry of Public Health, Nonthaburi, Thailand. (11) Queen Sirikit National Institute of Child Health, Ministry of Public Health, Bangkok, Thailand. (12) Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. (13) Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. (14) Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom.

Objectives: Our objective was to characterize the population pharmacokinetics and pharmacodynamics of oseltamivir and its active metabolite oseltamivir carboxylate in adults and children infected with influenza virus A(H1N1)pdm09.

Methods: Patients over 1 year of age with confirmed influenza virus A(H1N1)pdm09 infection who presented at 12 hospitals in Vietnam and Thailand were treated with oseltamivir at a standard oral dose regimen of 75 mg twice daily for 5 days or an adjusted dosage regimen for patients with renal impairment or children under 15 years of age. All patients with clinical and/or virological failures at day 5 were treated with oseltamivir for an additional 5 days. One hundred adults and 8 children had at least 4 plasma samples collected according to a randomized time schedule during the course of treatment. Forty-three adults and 17 children had only one plasma sample collected at 4 hours after the first dose on Day 3. Blood chemistry, hematology and virological analyses were performed on admission, during the treatment and/or after the treatment. Nonlinear mixed-effects modelling was performed using NONMEM v.7.

Results: The population pharmacokinetic properties of oseltamivir and oseltamivir carboxylate in adults and children with influenza virus A(H1N1)pdm09 infection were described successfully by a simultaneous 2-compartment oseltamivir and 1-compartment oseltamivir carboxylate model. Body weight was incorporated allometrically on all clearance and volume parameters. Patient age affected oseltamivir and oseltamivir carboxylate volume of distribution. Oral clearance of oseltamivir carboxylate decreased linearly with decreasing creatinine clearance. Time to virologically negative nasal and throat swab results were evaluated with a PK/PD time-to-event approach and revealed no statistically significant correlation between drug concentrations and time to viral clearance. Age was found to have an effect on baseline hazard where younger patients needed longer time to clear the virus.

Conclusions: This is the first population pharmacokinetic/pharmacodynamic analysis of oseltamivir and oseltamivir carboxylate in patients infected with the influenza virus A(H1N1)pdm09. The study provides insight into the impact

of patient disease, age, and body weight on the pharmacokinetic properties of oseltamivir.

Acknowledgement: This study was collaboration between hospitals in Vietnam and Thailand and undertaken as part of the South East Asia Infectious Disease Clinical Research Network (SEAICRN) supported by Oxford University, the Wellcome Trust (UK) and the National Institutes of Health (USA).

Quentin Chalret du Rieu IV-37 Hematological toxicity modelling of abexinostat (S-78454, PCI-24781), a new histone deacetylase inhibitor, in patients suffering from solid tumors or lymphoma: influence of the disease-progression on the drug-induced thrombocytopenia.

Q. Chalret du Rieu (1, 2), S. Fouliard (2), E. Chatelut (1), M. Chenel (2)
(1) Institut Claudius Regaud, Toulouse, France; (2) Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Suresnes, France

Objectives: To develop a semi-mechanistic PKPD model of thrombocytopenia, taking into account differences within patients, treated with abexinostat for either solid tumors or various types of lymphoma, notably the effect of disease progression on circulating platelet levels in patients with liquid tumors.

Methods: 925 platelet samples from the first 3 cycles of abexinostat treatment coming from 95 patients (i.e. 49 [465 platelet samples] and 46 [460 platelet samples] suffering from solid tumor and lymphoma, respectively) included in 4 different phase I clinical studies, were analyzed. A sequential PKPD modelling approach [1] was performed in NONMEM 7.2, with FOCEI. Individual Empirical Bayesian Estimates of PK parameters (from a previous validated PK model) obtained using the POSTHOC method were input into a PKPD model of platelet dynamics, based on original Friberg et al's one [2;3]. Improvements concerning disease progression were tested on BASE parameter (platelet count at inclusion). The Likelihood-Ratio-Test allowed the discrimination between hierarchical models. Model evaluation was based on standard goodness-of-fit plots, parameter precisions of estimation and Normalized Prediction Distribution Error (NPDE) [4;5].

Results: The original semi-mechanistic myelosuppression structural model was refined [2;3]. A feedback mechanism was added in the mean maturation time in order to quicken the production of circulating platelets by bone marrow in cases of thrombocytopenia and vice versa. Each types of patients were distinguished by estimating two different BASE parameters. A slight decrease in the platelet count over the time in lymphoma patients was modelled by adding an Imax disease progression effect on their BASE parameter, mimicking a pathological effect. Model evaluation by individual fit analysis, goodness of fit plots and NPDE vs TIME graphs showed that this model could fully describe and predict available platelets count in both populations.

Conclusion: A semi-mechanistic PKPD model able to predict toxicity in patients treated by abexinostat, particularly over the time by taking into account physiological or pathological characteristics of the bone marrow according to the patients' disease, was described. Consequently with such a model including disease progression, an optimal administration schedule could be determined particularly in lymphoma patients, for who previous predictions were not as good as for patients with solid tumors.

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Phylinda Chan IV-38 Industry Experience in Establishing a Population Pharmacokinetic Analysis Guidance

Wonkyung Byon (1), Phylinda Chan (2), Carol Cronenberger (1), Haiqing Dai (1), Jennifer Dong (1), Steve Riley (1), Ana Ruiz-garcia (1), Mike K Smith (2), Kevin Sweeney (1), Michael A Tortorici (1)
(1) Global Clinical Pharmacology, Pfizer, U.S.A.; (2) Global Clinical Pharmacology, Pfizer, U.K.

Objectives: Population pharmacokinetic (POPPK) modelling has become an integral part of model-based drug development and a standard component of regulatory submissions. Some of the assumptions and choices made by analysts before and during model building can be subjective, and are often influenced by the analyst's experience, expertise, and tools used. Within a large pharmaceutical organization, the development and implementation of a more standardized, objective and transparent procedure for conducting and reporting POPPK analyses would greatly facilitate the consistently and quality of output.

Methods: In our attempt to improve consistency, efficiency, and provide a more systematic approach to model building we developed a guidance for POPPK analyses. We considered aspects pertaining to base, full and final models, model selection and diagnostics within the Pharmacometrics group in order to elucidate some initial recommendations. An internal wiki repository was then created to function as a hub for collating viewpoints across the Pfizer Global Clinical Pharmacology (PGCP) organization. An editorial board was formed to consolidate these recommendations, capture pertinent examples, draft and revise the guidance. The draft guidance was circulated to PGCP and senior management for review and endorsement.

Results: The resultant guidance consists of four areas: 1) Considerations prior to conducting a POPPK analysis; 2) Considerations for base model development; 3) Development of a final model, including covariate model building; and 4) Standardizing graphical/numerical diagnostics. The "standardized practices" included, but were not limited to, the following: 1) Development of an analysis plan; 2) Thorough data checks in advance of analyses to understand data and eliminate potential errors; 3) Inclusion of structural covariate parameters in the base model to ensure model stability when highly influential covariates are known; 4) Incorporation of systematic procedures for covariate model building to improve consistency and harmonization across analyses; 5) Sensitivity analyses to check and challenge assumptions; 6) Development of a population modelling analysis report.

Conclusions: The importance and necessity of implementing a systematic, streamlined, and standardized approach to optimize and harmonize the processes which contribute to the POPPK analysis cannot be overstated. As population modelling is an area of continually evolving science and technology, the guidance will be regularly updated and revised.

Pascal Chanu IV-39 Simulation study for a potential sildenafil survival trial in adults with pulmonary arterial hypertension (PAH) using a time-varying exposure-hazard model developed from data in children

Pascal Chanu (1), Xiang Gao (2), Rene Bruno (1), Laurent Claret (1), Lutz Harnisch (3)

(1) Pharsight Consulting Services, A division of Certara, St. Louis, MO, USA, (2) Pfizer, Clinical Pharmacology, Groton, CT, USA, (3) Pfizer, Clinical Pharmacology/Pharmacometrics, Sandwich, UK

Objectives: Sildenafil (REVATIO®), 20mg TID, received approval for the treatment of adult PAH in US and EU. A pediatric study had been performed in patients[1] and sildenafil was approved in Europe for the treatment of pediatric PAH, at 10mg for children ≤20kg body weight, and 20mg above 20kg. The long-term extension of the pediatric study revealed very good overall survival results with 84% of patients still alive after 4 years of treatment. However, an increase in mortality with higher doses was also observed[2]. The objectives of this analysis were to adequately characterize the exposure-mortality relationship by accounting for longitudinal changes of covariates and to utilize the resulting model to assess the interpretability of a potential mortality trial in adults[3].

Methods: During the extension of the pediatric trial (n=234, 1-17y), patients were randomized to Low/Medium/High dose groups with nominal doses ranging from 10mg to 80mg TID depending on patients' body weight. Doses were adjusted according to body weight changes. A survival analysis using a time varying hazard model was performed in NONMEM7 to characterize the relationship between survival, and baseline or time varying covariates such as etiology, body weight, WHO functional class, hemodynamics and drug

exposure. Clinical trial simulations were performed to assess a potential survival trial in adults at a wide range of doses, to quantify the impact of confounding factors such as add-on therapy on its readout.

Results: Survival in pediatrics was found to be mainly impacted by etiology; with primary PAH patients having a worse outcome. The higher mortality with higher doses was adequately described by steady state concentration as a time varying variable which integrated sildenafil clearance and changes in body weight and dose. Simulations revealed that if the exposure-mortality response observed in children would apply to adults, the risk of wrongly concluding non-inferiority between a high and low dose is predicted to be low. But this risk could significantly increase if the trial conduct is impacted by longitudinal confounding factors especially in combination.

Conclusions: The adequate characterization of survival drivers made it possible to assess the outcome of a non-inferiority survival trial design in adults and the impact of external confounding factors. This work contributes to the design of a potential adult mortality trial and the assessment of its interpretability.

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Christophe Chassagnole IV-40 Virtual Tumour Clinical: Literature example

Hitesh Mistry, Christophe Chassagnole, Frances Brightman, Eric Fernandez, David Orrell.
Physiomics plc

Objectives: Combination therapies of targeted agents with generics and/or radiotherapy in oncology are becoming more widespread within the pharmaceutical industry as healthcare providers ask for "game-changing" improvements in response and survival rates at an affordable price. In order to obtain substantial breakthroughs in survival rates, clinical investigators are looking at increasingly complex schedules that are challenging to optimise[1]. A prominent example of the difficulty of finding the correct schedule in combination therapy is given by the search for clinically effective combinations of EGFR inhibitors with chemotherapy in NSCLC. After a series of expensive Phase 3 failures, pursuing a schedule that was successful in pre-clinical studies[2], clinical investigators eventually found a schedule with promising results[3]. Here we present an initial example highlighting the potential applicability of Virtual Tumor™ (VT) Clinical in the above setting.

Methods: We used simulated data from a published tumour size model[4] to calibrate our VT model for each of the treatments. The calibration also used data available in the literature to understand the mechanism of action of each compound. The survival model suggested that change in tumour size at week 8 is an important predictor[4], thus we simulated Phase 2 and 3 schedules and analysed changes at this time point.

Results: We have shown that our model can qualitatively predict that an intercalated schedule[3] is better than simultaneous treatment with an EGFR inhibitor and chemotherapy.

Conclusions: Our initial attempt at bridging our VT technology from the pre-clinical to clinical arena appears to be promising. We are able to qualitatively predict that certain schedules already explored in the clinic for EGFR inhibitors in combination with chemotherapy can lead to very different outcomes depending on the sequence used.

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Chao Chen IV-41 A mechanistic model for the involvement of the neonatal Fc receptor in IgG disposition

Monica Simeoni, Chao Chen
Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, London, UK

Objectives: One of the recognised functions of the neonatal Fc receptor (FcRn) is to protect IgG from catabolism by endosomal proteases, via FcRn-IgG binding in endosomes. The bound IgG is recycled back into circulation, escaping the catabolism. Successful quantification of this binding/recycling process can inform the understanding of the kinetics and effect level of an endogenous or exogenous IgG. The objective of the work presented here was to build a mathematical model that could be used to describe the circulating level of an endogenous or exogenous IgG under normal physiological conditions and to predict its level when the system would be perturbed by a number of causes such as disease conditions and pharmacological treatments.

Methods: A mechanistic model was constructed using literature knowledge, including alternative or component models, on the pharmacokinetics of IgG and the involvement of FcRn. The model was coded in ordinary differential equations; and the parameters were identified in literature reports or were derived by steady-state principles. Volume-related parameters were scaled cross species by direct proportion to body weight. To enhance computation speed, quasi equilibrium of the FcRn-IgG binding was assumed. We first conducted simulations to compare this model with alternative or component models that were found in the literature and to reconcile apparent differences. The model was then used to predict reported blood IgG levels in human and other species during various therapeutic interventions.

Results: The mechanistic model involving IgG and FcRn had three compartments. The IgG was produced in a blood compartment which was connected to a peripheral compartment through 2-way processes. Blood IgG was also distributed into an endosome compartment where IgG was eliminated; FcRn was produced and eliminated; and a reversible 1:1 binding between FcRn and IgG occurred. The IgG and the FcRn of the binding complex were recycled (instantly) to blood and to the endosome free FcRn pool, respectively. All processes were first-order, except for the syntheses of IgG and FcRn which were zero-order. The model was capable of reproducing simulations which were reported in the literature by alternative models. Preliminary simulations of changes in blood IgG level during various interventions were in broad agreement with those reported in the literature.

Conclusions: We have used literature findings to construct a versatile model to describe the FcRn involvement in the disposition of IgG in human. Emerging results showed that the model could successfully reproduce the reported changes in blood IgG during several types of system perturbation. Upon further development, the model can potentially be used to evaluate the pharmacological potential of certain therapeutic approaches.

Chunli Chen IV-42 Design optimization for characterization of rifampicin pharmacokinetics in mouse

Chunli Chen(1), Fatima Ortega(2), Raquel Moreno(2, 3), Mats O. Karlsson(1), Santiago Ferrer(2), Ulrika SH Simonsson(1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden ; (2) GlaxoSmithKline Diseases of Developing World (DDW) Medicines Development Campus, Tres Cantos (Madrid), Spain ; (3) Tecnalia Research&Innovation-UPV, Vitoria (Alava), Spain

Objectives: To develop a population pharmacokinetic (POPPK) model for rifampicin in mice and to optimize pharmacokinetic sampling schedule for rifampicin oral administration.

Methods: Rifampicin blood concentrations after different single oral doses, single intravenous and multiple oral administrations were used in the POPPK analysis. One sample from each mouse after single dosing administration and several samples from each mouse were available from multiple dosing administrations. All modeling were done using NONMEM 7.2. Model development was based on goodness of fit plots, objective function value, scientific plausibility, parameters precision and predict performance, assessed using Visual Predictive Check (VPC). In order to search for an informative design using potentially less animals, a simulation and re-estimation approach (SSE) was done using the final POPPK model with 1000 replicates for each scenario. The precision and bias of the simulation results were thereafter judged.

Results: A one compartment model with first-order absorption and elimination provided the best fit to the data. The volume of distribution was significantly lower for the lowest oral dose. Inter-individual variability (IIV) in

absorption rate constant (ka) and clearance (CL) were estimated to 43.8% and 18.9%, respectively.

Conclusions: The final POPPK model described the data well. A framework was established for exploring different designs in order to collect adequate information for pharmacokinetic characterization and at the same time reduce the number of animals.

Acknowledgement: The research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (http://www.imi.europa.eu/) under *grant agreement* n°115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution All animal studies were ethically reviewed and carried out in accordance with European Directive 86/609/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

Nianhang Chen IV-43 Comparison of Two Parallel Computing Methods (FPI versus MPI) in NONMEM 7.2 on complex popPK and popPK/PD Models

Yan Li, Nianhang Chen and Simon Zhou*
Celgene Corporation

Objectives: To evaluate efficiency gain of the two parallel computing methods in resolving complicated popPK and popPK/PD models.

Methods: Subjects from 8 clinical studies were included the popPK and popPK/PD models. The PK model has 3 compartments, with saturable elimination from the central compartment, saturable distribution between the central and first peripheral compartments, and linear distribution between the central and second peripheral compartments. The PK/PD model has 8 compartments, mimicking physiologic processes of neutrophil precursor cell maturation. There were 18 parameters (10 for fixed effect and 8 for random effect) in the PK model and 11 parameters (6 for fixed effect and 5 for random effect) in the PK/PD model.

Results: Use of parallel computations with 8 cores running on the same computer improved the speed significantly. In PK modeling, maximum efficiency was achieved when the numbers of nodes were set to 4 for FPI method, reducing running time by ~55% (from 21 min to 9.1 min), while further increase the nodes to 8 increased run time to 13 min. The maximum efficiency was achieved when the number of nodes was set to 8 for MPI method, reducing running time by ~70% (from 21 min to 6.1 min).

In PK/PD modeling, maximum efficiency was achieved when the numbers of nodes were set to 8 for FPI method, reducing running time by ~74% (from

266 min to 69 min), and the maximum efficiency was achieved when the number of nodes were set to 8 for MPI method, reducing running time by ~75.8% (from 266 min to 64 min).

FPI methods were also tested on multiple computers. Similar results were observed when the slower computer was configured as the master, and the faster computer was configured as the slave. Interestingly, when the faster computer was configured as the master, and the slower computer was configured as the slave, instead of increasing the computation efficiency, the overall performance of FPI parallel computation was worse than the performance on each individual computer.

Conclusions: Both FPI and MPI can significantly improve the computation efficiency. Due to the inherent difference between these two methods, the improvement of the speed is more proportional to the number of processors (cores) from MPI than that from FPI. For complicate PK/PD models, FPI and MPF provided similar efficiency. For FPI method across multiple computers, the computer with faster CPU should be always set as the master with the slower CPU as slaves.

Marylore Chenel IV-44 Population Pharmacokinetic Modelling to Detect Potential Drug Interaction Using Sparse Sampling Data

Anne Dubois, Maud Bénéton and Marylore Chenel
Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Suresnes, France

Objectives: Simultaneous administration of several treatments can lead to pharmacokinetic interactions (PKI) of one administered drug on another. For examples, the cytochrome P450 isozymes or transporters (PgP, BcRP...) are implicated in the ADME of many drugs and may be influenced by the administration of others. In this context, our objective was to evaluate the potential PKI of a drug S (in development at Servier) on the pharmacokinetics (PK) of the prednisolone using population PK modelling.

Methods: We used prednisolone PK data of 15 patients from a clinical trial where drug S was evaluated. To be included in this study, patients must be receiving stable oral dose of prednisolone for at least 4 weeks. The concentration of total prednisolone was measured in plasma at one sampling time before any drug S treatment and at several visits under drug S treatment. A maximum of 4 observations per patient was available. For some patients, prednisolone concentrations were available only after drug S administration. Moreover, the PK samples were performed at different times after last prednisolone administration. Due to the very sparse sampling and the heterogeneous sampling times, classic statistical methods such as ANOVA could not be used to compare the prednisolone concentration level before and after drug S administration. So, we used published population PK modelling on prednisolone PK. First we simulated unbound plasma prednisolone concentrations using the model of Mager et al [1]. Then, we derived the corresponding total plasma concentrations using the model of

Petersen et al [2] describing the nonlinear binding of prednisolone to the plasma proteins. We computed the 5^{th}, 50^{th} and 95^{th} percentiles of the distribution of the simulated plasma concentrations. At last, we graphically superimposed the predicted and observed plasma concentrations. If there was no major PKI, we expected that most of the observed concentrations should lie in the 90^{th} predicted interval.

Results: Most of the observed concentrations of total prednisolone in plasma were comprised in the 90^{th} predicted interval. No major difference could be observed in the prednisolone concentration levels before and after drug S administration.

Conclusions: Using population PK modelling, we demonstrated that there is no major PK interaction of drug S on prednisolone. This methodology will be applied for the other drugs co-administered with drug S. However, using such approach to conclude on PKI should be discussed with the regulatory agencies.

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Jason Chittenden IV-45 Practical Application of GPU Computing to Population PK

Jason T. Chittenden, Robert H. Leary, and Brett Matzuka
Pharsight Corporation

Objectives: Recent advances in the general computing capabilities of readily available graphics processing units (GPUs) make them appropriate tools for the solution of nonlinear mixed effects problems. The architecture of the GPU presents challenges for their general use for population pharmacokinetic/pharmacodynamic (popPK/PD) applications. The solution of ordinary differential equation (ODE) models can cause the execution paths of the concurrently executing threads to diverge, destroying the computational efficiency and obliterating the benefits of the GPU. Thread divergence is aggravated by adjustable step-size ODE solvers and different event times (observations, doses, time-lags, reflux, etc...) between subjects. In this work we demonstrate an implementation that circumvents these issues and lays the groundwork for professional application of GPUs to popPK/PD problems.

Methods: A novel version of a stiff ODE solver was implemented as a GPU kernel. The entire process of generating individual predictions is run on the GPU, with the CPU handling the parameter estimation process with a Quasi-Random Parametric Expectation Maximization (QRPEM) algorithm. An OpenMP implementation of the same ODE solver on the CPU was used for comparison.

The test problem was a single dose, intravenous bolus, saturating clearance, simulated dataset. The problem was run with various numbers of subjects and samples to test the scaling of the GPU and CPU implementations.

Results: The GPU implementation was between 10 and 100 times faster than the CPU implementation on a single core. The CPU and GPU both exhibited linear scaling with number of subjects for large problems, but the GPU showed linear scaling with small problems.

Conclusions: Computing the objective function for popPK/PD problems on the GPU is a feasible and possibly worthwhile opportunity. For particularly large and/or computationally intensive problems the cost of custom coding could result in tremendous time savings. Commercially viable GPU solutions for popPK/PD are needed to make these benefits generally accessible to the pharmacometrics community.

References: Available on request.

Yu-Yuan Chiu IV-46 Exposure-Efficacy Response Model of Lurasidone in Patients with Bipolar Depression

Chapel S (1), Chiu Y(2), Hsu J(2), Cucchiaro J(2), Loebel A(2)
(1) Ann Arbor Pharmacometrics Group, Inc (A2PG), Ann Arbor, MI (2) Sunovion Pharmaceuticals, Inc, Ft. Lee, NJ

Objectives: Characterization of dose- response relationships for psychotropic agents may be difficult to determine based on results of individual clinical trials, due to various confounds such as variability in attrition, background medications, flexible dosing designs, and placebo-response rates. The goal of this exposure-efficacy response analysis was to characterize dose-response effects for lurasidone and to predict efficacy at Week 6, based on the results of two recently completed placebo-controlled studies in patients with bipolar depression.

Methods: The exposure-efficacy response analyses were derived from two randomized, 6-week, double-blind, placebo-controlled, flexible-dose (20-120 mg in adjunctive Study D1050235; 20-60 or 80-120 mg in monotherapy Study D1050236) studies in subjects with bipolar depression. A total of 5245 Montgomery-Asberg Depression Rating Scale (MADRS) observations from 825 patients (who had received lurasidone or placebo treatments, with or without lithium or valproic acid background medication) were included in the analysis.

Results: The time profile of MADRS on placebo was adequately described using an exponential asymptotic model. MADRS vs. time profiles for either placebo or lurasidone were adequately described using a linear dose-response relationship built on an exponential asymptotic placebo model. A net improvement in MADRS due to lurasidone treatment (the drug effect) was significant ($p<0.001$) and a positive dose-response was detected.

Covariate effects were significant only on placebo effect parameters, thus no dose adjustment is necessary based on demographic covariates. Age and use of concomitant medication had statistically significant covariate effects on placebo effect. Overall, the dose-dependent effect of lurasidone indicates that higher doses are likely to produce higher drug effect. The dose-response was consistent for both monotherapy and adjunctive therapy studies.

Conclusions: The effect of lurasidone was described using a linear dose-response model for drug effect, with increased treatment response in patients with bipolar depression observed at higher doses of lurasidone.

Steve Choy IV-47 Modelling the Effect of Very Low Calorie Diet on Weight and Fasting Plasma Glucose in Type 2 Diabetic Patients

Ellen Evbjer, Steve Choy, Mats O. Karlsson, Maria C. Kjellsson
Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Background: Change in weight (WT) as a result of diet changes is closely associated with change in fasting plasma glucose (FPG) in type 2 diabetes mellitus (T2DM) patients. Exactly what this relationship depends on is unknown but two hypotheses are 1) weight loss induces a change in an intermediary effector that reduces FPG, or 2) an underlying change of the system that affects weight as well as FPG; the latter being driven by the intermediary effector. The intermediary effector in both hypotheses is presumed to be insulin sensitivity (IS) [1], and the underlying change of the system is thought to be the concentration of free fatty acids (FFA), which is known to affect IS [2]. The aim of this study was to implement and test these hypotheses using non-linear mixed effects modelling on summary level data from publications of weight loss and FPG with very low calorie diets (VLCD).

Methods: Summary level data was gathered from 8 clinical studies of diabetic patients treated with VLCD where weight as well as FPG was measured [3-10]. The studies consisted of 13 number of arms with varying number of subjects per arm (median = 8; range = 6-62), varying baseline weight (median = 106 kg; range = 93-118 kg), baseline FPG (median = 253 mg/dL; range = 91-321 mg/dL) with varying disease duration (median = 8.9 yrs; range = 0.8-13.3 yrs), treated with diets ranging from 330 to 909 kcal/day for a period of up to 224 days. Measurements of WT and FPG were taken regularly throughout the course of the studies. Non-linear mixed-effects modelling was performed using NONMEM 7.2 with the FOCEI method.

Results: Both weight and FPG was modelled using indirect response models. For hypothesis 1, the diet was implemented as an instantaneous inhibitory effect on the input of the weight model. The change in weight was then used to influence a mediator which was allowed to affect FPG by a stimulatory effect on the output. For hypothesis 2, the diet was implemented as a step model inhibiting both the weight and the FPG input. The same model was applied on both weight and FPG but the non-linearity of the effect was estimated using a power relationship to allow for slightly different time-course effects on the two entities. The objective function value for hypothesis 2 was significantly lower than for hypothesis 1 and the goodness-of-fit diagnostics also supported the model for hypothesis 2. The diet was estimated to reduce 12.1% of the Kin of both weight and FPG, and the estimated Kout for WT and FPG was 0.00974 and 0.0195 day-1, respectively.

Conclusions: The model with an underlying mechanism that affects both weight and FPG was found to better describe the data than using weight loss as an effector on a mediator through which FPG is reduced.

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Oskar Clewe IV-48 A Model Predicting Penetration of Rifampicin from Plasma to Epithelial Lining Fluid and Alveolar Cells

Oskar Clewe (1), Mats O Karlsson (1), Sylvain Goutelle (2, 3), John E. Conte, Jr. (4, 5), Ulrika SH Simonsson (1)

(1) Uppsala Pharmacometric Research Group, Department of Pharmaceutical Biosciences, Uppsala University, Sweden; (2) Hospices Civils de Lyon, Hôpital A. Charial, Service Pharmaceutique, ADCAPT, Francheville, France; (3) Université Lyon 1, UMR CNRS 5558, Biométrie et Biologie Evolutive, Villeurbanne, France; (4) Department of Epidemiology and Biostatistics, Infectious Disease Research Group, University of California, San Francisco, California; and (5) American Health Sciences, San Francisco, California

Objectives: In a non-tuberculosis infected population describe rifampicin´s (RIF) autoinduced plasma concentrations and predict the concentration ratios between epithelial lining fluid, alveolar cells and plasma.

Methods: Data from a previously published study (1) were used in this population analysis. The data analysis was performed with a nonlinear mixed-effects approach as implemented in the software NONMEM, version 7.2 (ICON Development Solutions). The model building process was performed in a stepwise fashion, starting from a previously published rifampicin pharmacokinetic enzyme turn-over model (2). Rifampicin's autoinduction was described with an enzyme turn-over-model, where rifampicin's plasma concentration increase the enzyme production rate which in turn increases the enzyme pool in a non-linear fashion by means of an E_{MAX}-model. The epithelial lining fluid and alveolar cell drug penetration were described using effect compartments (3), where the penetration coefficients between plasma and epithelial lining fluid (P_{elf}) and plasma and alveolar cells (P_{ac}) were estimated. The time rate constants k_{elf} and k_{ac} were fixed to a value

mimicking an almost instantaneous transfer of drug from plasma to epithelial lining fluid or alveolar cell due to the sparse sampling design.

Results: The final RIF plasma model was a one compartment model with transit absorption compartments and an enzyme turn-over model describing rifampicin's autoinduction. Parameters related to the absorption and enzyme turnover was fixed to previously published values (2). Oral clearance and volume of distribution were estimated to 4.8 L/h and 50 L respectively. The data supported inclusion of inter individual variability on oral clearance (69%). At four hours post dose the RIF's penetration coefficients for epithelial lining fluid and alveolar cells were estimated to 0.27 and 1.17 respectively. This resulted in a mean epithelial lining fluid to plasma ratio of 1.36 and a mean alveolar cell to plasma ratio of 5.81 when compensating for the free fraction (0.2) of RIF concentration in plasma (4).

Conclusions: The final model propose a way to describe the often sparse data originating from the use of bronchoalveolar lavage, where only one or a few samples are possible to withdraw from each subject. The model characterizes RIF's plasma pharmacokinetic properties including auto-induction as well as the penetration of drug from plasma to epithelial lining fluid and alveolar cells.

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Teresa Collins IV-49 Performance of Sequential methods under Pre-clinical Study Conditions

Teresa Collins (1, 2), James WT Yates (1), Amin Rostami-Hodjegan (2)
(1) Innovative Medicines, AstraZeneca, Alderley Park, UK. (2) School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK

Objectives: To assess the performance of sequential methods simulated under typical pre-clinical-type study designs and to make a recommendation of a quick and robust sequential method for performing population PKPD analysis.

Methods: Using NONMEM stochastic simulation and estimation, 200 datasets were simulated and fitted using a simultaneous pharmacokinetic/pharmacodynamic fit. For the sequential methods: IPP, IPPSE and PPP&D, which are described elsewhere [1, 2, 3], a pharmacokinetic model was fitted to the concentration data from the simulated datasets then PK information included in the subsequent pharmacodynamic model fit. Structural models explored included a one compartment oral pharmacokinetic model, direct EMAX and indirect response IMAX model. A maximum of 5 concentration samples per individual per dose was explored under single and multiple dosing scenarios. Each method was compared in terms of success rate, bias and time saved to the simultaneous fit in a 3 dimensional plot.

Results: The criteria set for bias was exceeded particularly with precision on the EC50 or IC50 at lower numbers of PK observations per individual. With the direct PD model PPP&D was slower but had less bias, but success rates were similar across sequential methods. Success rates for simultaneous fit were lower with the indirect model fit making this a more important factor. IPP and IPPSE showed much higher success rates, with bias and time saved

being less distinguishing between sequential methods. In contrast to discussion of the propagation of PK parameter estimates between methods in earlier studies [2], IPPSE and PPP&D are quite different as IPPSE is largely constrained to the PK parameter estimated from the PK step; whilst for PPP&D, because the PD estimation step has concentration data available it is most similar to a simultaneous fit.

Conclusions: Despite differences in the simulation settings, results with previously investigated structural models agreed well with previous studies in terms of bias, time saved and success rates. However when other structural models were explored the ranking of sequential methods and importance of performance criteria was different. Therefore it seems not possible to recommend a sequential method based on a single set of simulation conditions.

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Francois Combes IV-50 Influence of study design and associated shrinkage on power of the tests used for covariate detection in population pharmacokinetics

F. Combes (1,2,3), S. Retout (2, 3), N. Frey (2) and F. Mentré (1)
(1) INSERM, UMR 738, Univ Paris Diderot, Sorbonne Paris cité, Paris, France; (2) Pharma Research and Early Development, Clinical Pharmacology, F. Hoffmann-La Roche ltd, Basel, Switzerland; (3) Institut Roche de Recherche et Médecine Translationnelle, Boulogne-Billancourt, France

Objectives: In 2009, Savic et al [1] showed that high shrinkage caused by poorly informative study designs can hide or induce correlation between estimated individual parameters (EBE) and covariates. That work did not explore the impact on the power of tests used for covariate detection. The present work investigates the impact of various designs, along with the associated shrinkages, on the power to detect the effect of a continuous covariate of i) the correlation test (CT) based on EBEs, ii) the likelihood ratio test (LRT).

Methods: A one compartment pharmacokinetic (PK) model with oral first-order absorption and a weight (WT) effect on volume (coded with a power function) was used for simulation. To obtain various level of shrinkage, different values of random effect variability (20 and 50%), of proportional residual error (30 and 40%), of β (0, 0.2, 0.5 and 1), as well as different number of PK samples per subject (2, 3 or 5), were combined. Each combination was simulated 1000 times with 500 subjects. Predicted shrinkage was computed using the approximation of the Bayesian information Matrix [2-3]. NONMEM 7.2 [4] with algorithms FOCEI and SAEM (followed by IMP for likelihood computation) was used to perform parameter estimation [5]. The type 1 error and the power of LRT and CT (from EBEs after each estimation) were computed as well as the observed shrinkage.

Results: The observed shrinkages were similar with both algorithms and were in agreement with the predicted shrinkages. As expected, the power of LRT and CT for detecting the WT effect decreased with the informativeness of the study design and its associated shrinkage. However, two unexpected outcomes were found: 1) analysis of the EBEs by CT had the same power as the LRT even in case of a sparse PK sampling and high shrinkage; 2) population parameters estimated by SAEM were less biased and less spread than with FOCEI even in case of a rich PK sampling.

Conclusion: As expected, informativeness of study design influenced the power of tests used for covariate detection. CT based on EBEs, even with a sparse PK sampling, was as powerful as LRT to detect covariate influence. These results need to be confirmed by varying model complexity, covariate effects and design. SAEM was a more accurate and precise algorithm than FOCEI to estimate population parameter even with rich PK sampling and a simple model.

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Emmanuelle Comets IV-51 Additional features and graphs in the new npde library for R

Emmanuelle Comets (1), Thi Huyen Tram Nguyen (1), France Mentré (1)
(1) INSERM, UMR 738, Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, Paris, France

Objectives: (1) to present new features of the npde library 2.1 for the computation and diagnostic of normalised prediction discrepancies [1-3]; (2) to propose a new method to re-scale the npd/npde maintaining the shape of the profile of the observations.

Methods: The normalised prediction discrepancy (npd) for observation yij is obtained by computing the prediction discrepancy (pd) as the quantile of yij within its predictive distribution, and transforming the pd using the inverse normal function. Normalised prediction distribution errors (npde) are obtained using a similar approach but after decorrelation of both the observed and simulated values, and are needed for statistical tests. npde were recently extended to handle BQL data using imputation methods [4]. Under the null hypothesis of model adequacy, both npd and npde should follow a normal distribution. Visual assessment of the fit is usually performed via scatterplots of npd/npde versus time or model predictions, which are akin to residual plots and should exhibit no trend. Prediction intervals using model simulations can be added to highlight model misspecification [5]. Version 2.1 of the npde library includes these new features.
Here, we propose additional graphs obtained by transforming the npd/npde using the mean and standard deviation of the simulated observations at each time point (or within each bin). This preserves the shape and variability of the profile.

Results: We illustrate the new features and graphs on two simulated examples, a PD study of viral load data (COPHAR3-ANRS 134 trial) [4] and a PK example based on the theophylline data [3]. We show examples of handling various levels of BQL data. In unbalanced designs, transformed npd/npde (tnpd/tnpde) using a reference profile provide a similar pattern to VPC, without the need to stratify the data according to design or covariate, and can therefore be used in conjunction with npd/npde plots.

Conclusion: npd/npde are widely used to assess nonlinear mixed effect models, and show good statistical properties [6]. They handle design and covariate heterogeneity naturally. This is particularly valuable in unbalanced designs, and distinguish these metrics from VPC and their many flavors (pcVPC [7],...). Transformed npd/npde, which help visualise the shape and variability of the process being modelled, provide an alternative to npd/npde in the scatterplots versus time or predictions, and will be included in the next version of the library.

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Camille Couffignal IV-52 Population pharmacokinetics of imipenem in intensive care unit patients with ventilated-associated pneumonia

C. Couffignal (1,5), O. Pajot (2), L. Massias (3), A. Foucrier (4) , C. Laouénan (1,5), M. Wolff (4) and F. Mentré (1,5)
(1) AP-HP, Hop Bichat, Biostatistic Dept, Paris, France, (2) Hop V Dupouy, Intensive Care Unit, Argenteuil, France, (3) AP-HP, Hop Bichat, Pharmacy Dept, Paris, France, (4) AP-HP, Hop Bichat, Intensive Care Unit, Paris, France, (5) Univ Paris Diderot, Sorbonne Paris Cité and INSERM, UMR 738, Paris, France

Objectives: Imipenem is often used for empirical treatment of ventilated-associated pneumonia (VAP). Large interindividual variations in the pharmacokinetic parameters (PK) in intensive care unit (ICU) patients have been reported [1]. The aim of our study was to determine more accurately population pharmacokinetics (PopPK) parameters of imipenem in ICU patients and the impact of covariates.

Methods: Prospective study conducted in ICU patients with presumptive diagnosis of gram-negative bacilli VAP. Imipenem was administrated every 8 h as an infusion over 0.5 h (500 to 1000 mg). Blood samples were collected at 0, 0.5, 1, 2, 5 and 8 h after the 4^{th} dose. Imipenem plasma concentrations [C] were measured by HPLC (LOQ 0.5 mg/L). PopPK parameters were estimated by nonlinear mixed effects models using SAEM algorithm in MONOLIX 4 [2]. Influence of covariates (age, gender, weight, creatinin clairance (CrCL), serum albumin, edema score, SOFA, SAPS II, shock, PEEP, PaO_2/FiO_2) on PK parameters was determined using Spearman or Wilcoxon tests.

Results: 51 patients (41 males), median (range) age 60 yr (28-84) were included. Imipenem [C] at peak (0.5h) and trough were 34.1 mg/L (12.3-67.5)

and 1.9 mg/L (0.5-10.1), respectively. Imipenem PK was best described by a two-compartment model. The mean and between-patient variability (%) for clearance CL and central volume of distribution V_D were 12.7 L/h (43%) and 16.3 L (45%), respectively. CL was found to increase significantly with CrCL and decrease with age, SOFA and SAPS II. V_D was found significantly to increase significantly with weight and edema score.

Conclusions: There is a wide variability of imipenem PK parameters in ICU patients with VAP that could lead to suboptimal antibiotic exposure in some pts. Our findings are in accordance with previous studies and we identified covariates that may explain variability of PopPK parameters [3;4].

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Damien Cronier IV-53 PK/PD relationship of the monoclonal anti-BAFF antibody tabalumab in combination with bortezomib in patients with previously treated multiple myeloma: comparison of serum M-protein and serum Free Light Chains as predictor of Progression Free Survival

Pascal Chanu (1), Laurent Claret (1), Rene Bruno (1), David B. Radtke (3), Susan P. Carpenter (2), James E. Wooldridge (3), Damien M. Cronier (4)
(1) Pharsight Consulting Services, Lyon and Marseille, France, (2) Applied Molecular Evolution, San Diego, USA, (3) Eli Lilly and Company, Indianapolis, USA, (4) Eli Lilly and Company, Windlesham, UK

Objectives: The serum levels of M-protein were recently used in a PK/PD modeling study as a surrogate for tumor burden in multiple myeloma (MM) patients. The decrease in serum M-protein after 8 weeks of treatment proved successful as a predictor of progression-free survival (PFS) and overall survival (OS) [1-3]. However, patients with oligo- or non-secretory disease cannot be included in such analyses. Alternatively, serum Free Light chains (FLCs) can be measured in a greater number of MM patients [4,5], and could represent a useful tool to predict survival in a broader patient population. Here we present a PK/PD study aimed at comparing the use of M-protein and FLCs as surrogates for MM tumor burden and as a predictor of PFS.

Methods: Tabalumab is a human mAb that neutralizes membrane-bound and soluble B cell activating factor (BAFF). A combination of tabalumab and bortezomib (BTZ) was evaluated in a Phase 1 study in multiple myeloma patients [6,7]. The serum levels of tabalumab, M-protein and FLCs were connected in PK/PD models by Non Linear Mixed Effect Modeling [8]. The predicted decrease in serum levels of M-protein and FLCs were used to predict PFS using a previously published model [2].

Results: The PK of tabalumab was described by a 2-compartment model with mixed clearance. The PD model previously developed for M-protein [1] proved adequate to describe both M-protein and FLCs serum levels, with parameter estimates for FLCs reflective of their faster turn over. The models predicted a different dose-response relationship of tabalumab for the decrease in serum M-protein or FLCs at week 8 of treatment. However, the decrease in the serum levels of both M-prot and FLCs were predictive of preliminary PFS results in the patient population.

Conclusions: The time course of serum levels of M-protein and FLCs were successfully described by the PK/PD models developed in this study. The models characterized a different dose-response relationship for the activity of tabalumab on the 2 biomarkers. Both M-protein and FLCs responses were, however, predictive of PFS in the patient population.

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Zeinab Daher Abdi IV-54 Analysis of the relationship between Mycophenolic acid (MPA) exposure and anemia using three approaches: logistic regression based on Generalized Linear Mixed Models (GLMM) or on Generalized Estimating Equations (GEE) and Markov mixed-effects model.

Z. Daher Abdi (1, 2), JB. Woillard (1,2), A. Prémaud (1,2), Y. Le Meur (3), P. Marquet (1, 2,4), A. Rousseau (1,2).
(1) Inserm, UMR-S850, Limoges, F-87025, France ; (2) Université Limoges, F-87025, France; (3) CHU Brest, Département de Néphrologie, Brest, France; (4) CHU Limoges, Pharmacologie, Toxicologie et Pharmacovigilance, Limoges, F-87042, France.

Objectives:
The goal of this study was to evaluate the influence of MPA exposure on the occurrence of anemia in a one year longitudinal study using 3 modeling approaches.

Methods:
One hundred thirty renal transplant patients (APOMYGRE trial) treated with MPA were analyzed (1). Both MPA area under the curve (AUC) previously estimated (2) (2.5^{th}-97.5^{th} percentiles: 13-73 mg.h/L) and the presence of anemia (i.e. hemoglobin -Hb- < 10 g/dL) were collected at different visits post graft.
The association between anemia and the previous measurement of MPA AUC carried forward was investigated using: i) a regression logistic with fixed and random effects (GLMM),ii) a regression logistic using the generalized estimating equations (GEE) and iii) a Markov mixed effects model. GLMM and GEE models were fitted in R using lme4 (3) and geepack (4) packages respectively. Markov models were fitted in NONMEM® using the Laplacian

method; the probabilities of occurrence anemia and return to normal Hb level were estimated.
Effect of covariates (donor and recipient ages, sex, dosing strategy, baseline Hb level) was investigated. Odds ratios (OR) and 95% confidence interval (CI) of OR were calculated for the 3 models. For the Markov model, the 95% CI of OR were based on the 2.5^{th} and 97.5^{th} percentiles of parameter estimates obtained from 500 bootstrap samples. The Markov model was evaluated by performing posterior predictive checks (PPC) using 200 simulated datasets.

Results:
The Hb baseline and the MPA AUCs were significant predictors of anemia with the 3 approaches. In the GLMM approach, visit, baseline Hb levels and MPA AUC were used as fixed effects; random effects were added on visit and subjects (as correlated random effects). With the GEE approach, an unstructured matrix was used for correlation within subjects. The ORs associated with a *one*-unit increase of AUC [95%CI] were: 1.027 [1.001-1.053], p=0.044 for the GLMM model; 1.016 [1.002-1.031], p=0.029 for the GEE model and 1.020 [1.003-1.444] for the Markov model. The PPC showed that, for the transition to anemia, the observed number was within the 95% prediction interval.

Conclusions:
The 3 models evidenced a significant MPA exposure-anemia relationship; OR were estimated with good precision. 95% CI OR was smaller using GEE, this advocates for this method when subject-specifics parameter estimates are not of special interest. Markov model could allow to identify predictors to obtain an Hb >10 g/dL (reverse transition).

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Elyes Dahmane IV-55 Population Pharmacokinetics of Tamoxifen and three of its metabolites in Breast Cancer patients

E. Dahmane (1) (2), K. Zaman (3), L. Perey (4), A. Bodmer (5), S. Leyvraz (3), C.B. Eap (6) (1), M. Galmiche (3), L. Decosterd (2) (7), T. Buclin (2), M. Guidi (1) (2), C. Csajka (1) (2)

(1) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland; (2) Division of Clinical Pharmacology, Department of Laboratories, University Hospital Lausanne; Lausanne, Switzerland; (3) Breast Center, Multidisciplinary Center for Oncology (CePO), University Hospital Lausanne; Lausanne, Switzerland; (4) Medical Oncology, Hospital of Morges; (5) Breast Center, University Hospital Geneva, Geneva, Switzerland; (6) Center for Psychiatric Neurosciences, University Hospital Lausanne; Lausanne, Switzerland; (7) Innovation and Development Unit, Department of Laboratories, University Hospital Lausanne; Lausanne, Switzerland.

Objectives: Tamoxifen (Tam) is a pro-drug metabolized to endoxifen and other active metabolites through cytochromes (CYP) 2D6 and 3A4 pathways. Patients with null or reduced CYP2D6 activity display lower endoxifen concentrations and might thus experience lower benefit from their treatment [1]. High variability in Tam and its metabolites levels has been reported and partially attributed to genetic polymorphism in CYP2D6. The aim of this analysis was to characterize the population pharmacokinetics of Tam and its major metabolites, to quantify the inter- and intra-individual variability and to explore the influence of genetic and non-genetic factors on their disposition. Model-based simulations will be performed to derive dose optimization strategies.

Methods: Patients under Tam 20mg/day were genotyped and phenotyped for CYP2D6 and CYP3A4/5. Plasma levels of Tam, N-desmethylTam (NDTam), 4OHTam and endoxifen were measured at baseline (20mg/day), then at 30, 90 and 120 days after a dose escalation to 20 mg twice daily [2]. A stepwise procedure with sequential addition of metabolites was used to find the full structural model that best fitted the observed data (NONMEM®). Owing to identifiability problem, the volume of distribution of Tam and its metabolites were assumed to be equal.

Results: A total of 457 samples were collected from 97 patients. The full model consisted in a 4-compartment model with first-order absorption and elimination and linear conversion to the three metabolites. Average Tam oral apparent clearance (CL/F_{Tam}) was 5.8 L/h (CV 32%), apparent volume of distribution 1113 L with an absorption constant rate (k_{12}) fixed to 0.7 h^{-1}. Estimated apparent Tam to NDTam (k_{23}), Tam to 4OHTam (k_{24}) and NDTam to Endoxifen (k_{35}) metabolic constant rates were 0.008 (13%), $8.5x10^{-5}$ (29%) and $6.3x10^{-4}$ h^{-1} (59%), respectively. NDTam, 4OHTam and endoxifen apparent clearances were 5.6 L/h, 7.8 L/h and 19 L/h (conditional on Tam bioavailability and equal volumes of distribution).

Conclusions: Metabolic formation rates were subject to an important variability, in particular regarding endoxifen. The influences of genetic polymorphisms, as well as other factors such as CYP-interfering comedications, compliance, demographics and clinical characteristics were tested on the kinetic parameters in order to identify relevant sources of variability.

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Adam Darwich IV-56 A physiologically based pharmacokinetic model of oral drug bioavailability immediately post bariatric surgery

Adam S. Darwich (1), Devendra Pade (2), Karen Rowland-Yeo (2), Masoud Jamei (2), Anders Åsberg (3), Hege Christensen (3), Darren M. Ashcroft (1), Amin Rostami-Hodjegan (1,2)
(1) Centre of Applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK, (2) Simcyp Ltd, Blades Enterprise Centre, Sheffield, UK, (3) Department of Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Oslo, Norway.

Objectives: The prevalence of bariatric surgery has increased dramatically over the last decade. Bariatric surgery leads to changes in the gastrointestinal physiology which affect oral drug bioavailability (Foral). Due to sparse clinical data, a "bottom-up" approach using in vitro-in vivo extrapolation (IVIVE) in conjunction with systems pharmacology may be valuable in predicting trends in oral drug exposure post surgery [1].

Methods: Post bariatric surgery population models were created using the 'Advanced Dissolution Absorption and Metabolism (ADAM) model' within the Simcyp Simulator (v10). General application was demonstrated on a set of drugs and validity demonstrated for cyclosporine and atorvastatin acid where clinical data post bariatric surgery were available [2].

Results: Overall, simulated trends in Foral were drug and surgery specific. The oral exposure of cyclosporine post surgery was reduced due to a lower fraction absorbed (fa) and the reduced peak plasma concentrations were consistent with the reported clinical observations. Simulated oral drug exposure of atorvastatin acid post Roux-en-Y gastric bypass surgery was also

reflective of the observed data with indications of counteracting interplay between a reduced fa and increased fraction that escapes gut wall metabolism (FG). Observed exposure profiles with regards to tmax of atorvastatin acid post biliopancreatic diversion with duodenal switch were not fully recovered by simulations.

Conclusions: Trends in oral drug bioavailability pre to post bariatric surgery seem to be highly dependent on drug specific parameters such as affinity to CYP3A, solubility, permeability and surgery specific systems alterations. The potential of a systems pharmacology physiologically-based pharmacokinetic modelling approach was demonstrated, allowing a framework for optimisation of oral drug therapy post bariatric surgery. Inability to fully recover observed changes in tmax in certain scenarios suggests that additional systems parameters, which are currently unknown, may play a vital role.

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Camila De Almeida IV-57 Modelling Irinotecan PK, efficacy and toxicities pre-clinically

Camila de Almeida (1), Frank Gibbons (2) and James Yates (1)
(1) Oncology iMed DMPK, AstraZeneca, Alderley Park, UK; (2) Oncology iMed DMPK, AstraZeneca, Boston, USA

Objectives: Irinotecan (CPT-11, Camptosar) is a topoisomerase I inhibitor, approved for use in colorectal cancer. Although CPT-11 shows anti-tumor activity alone, its active metabolite SN-38 is up to 100-fold more potent. The conversion from parent to active metabolite by carboxylesterases in preclinical species and humans is different in that different ratios of parent/metabolite are observed. The major toxicities in patients treated with this drug are gastrointestinal and myelosuppresion. It is important to account for both parent and metabolite when considering the overall anti-tumour activity, toxicity and to understand the additive/synergistic effects of combinations with novel anti-cancer agents. Literature and internal evidence shows profound species differences in pharmacokinetics (PK) [1], SN-38 levels and half-life [2], as well as bone marrow sensitivities to the active metabolite [3]. This highlights the need for mathematical models to describe the preclinical results and allow a more robust translation to the observed clinical results.

Methods: Efficacy studies were conducted in a xenograft mouse model at 50 mg/kg of CPT-11 given once weekly. PK studies to support efficacy modelling were carried out at two dose levels (30 and 50 mg/kg) in mice bearing patient-derived xenograft (PDX) tumours.
To assess toxicity, a time course study on neutrophil count was carried out, following a single dose of 100 mg/kg CPT-11 in non-tumour bearing rats. PK studies supported the neutrophil modelling by measuring CPT-11 and SN-38 levels at a range of different doses (from 50 to 150 mg/kg).

Results: A PK model for CPT-11 and SN-38 was developed to describe the PK in tumour bearing mice and non-tumour bearing rats across a dose range.
A tumour growth inhibition model [4], driven by SN-38 PK was developed to describe the efficacy of CPT-11 in mouse xenografts.
To model CPT-11 toxicity, the Friberg model [5] was fit to time course data on neutrophils after a single dose of 100 mg/kg CPT-11 in non-tumour bearing rats.

Conclusions: Modelling and simulation provide a useful tool to quantify the levels of CPT-11's active metabolite in different species and assess its pre-clinical efficacy and toxicity. It offers a robust method to translate pre-clinical results to the clinic and provides a useful starting point to better understand enhanced/synergistic effects of combination approaches using this cytotoxic agent with novel anti-cancer agents.

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Willem de Winter IV-58 Population PK/PD analysis linking the direct acute effects of canagliflozin on renal glucose reabsorption to the overall effects of canagliflozin on long-term glucose control using HbA1c as the response marker from clinical studies

Willem De Winter (1), Dave Polidori (2), Eef Hoeben (1), Damayanthi Devineni (3), Martine Neyens (1), An Vermeulen (1)
(1) Janssen Research and Development, Turnhoutseweg 30, Beerse, Belgium, (2) Janssen Research and Development, LLC, 3210 Merryfield Row, San Diego, CA, USA, (3) 920 Route 202, Raritan, NJ, USA

Objectives: Canagliflozin is an orally active inhibitor of SGLT2, currently in development for the treatment of patients with T2DM. A population PK/PD analysis is presented which identifies the canagliflozin plasma exposure-response relationship on HbA_{1c} in subjects with T2DM, and integrates this with a previously identified relationship between plasma canagliflozin exposure and reduction in renal threshold for glucose excretion (RT_G) [1].

Methods: A mathematical model relating exposure of canagliflozin to reductions in HbA_{1c} was developed using observed relationships between canagliflozin exposure and the effect of canagliflozin on RT_G, observed relationships between changes in RT_G and mean plasma glucose (MPG), and known relationships between MPG and HbA_{1c}. The model was implemented as a population PK/PD model in NONMEM 7.1 using observed HbA_{1c} responses and estimated individual canagliflozin plasma exposures from 1445 subjects with T2DM from four pooled studies: a 12-week Phase 2b study (N=352) and three 26-week Phase 3 studies (N=1093, including 249 subjects from a dedicated study in patients with moderate renal impairment).

Covariate effects were evaluated for age, body weight, BMI, sex, race and estimated glomerular filtration rate (eGFR).

Results: The population PK/PD model provided a satisfactory fit to the observed data. The effects of placebo (including diet and exercise) and canagliflozin were found to be dependent on baseline HbA_{1c}. The model included an E_{max} that increased with increasing baseline HbA_{1c} and increasing eGFR, with a value of -0.73% obtained for a typical subject with baseline HbA_{1c} of 7.77% and baseline eGFR of 90 ml/min/1.73m^2. A significant covariate effect was identified only for eGFR on E_{max}. In addition to the exposure-dependent reductions in HbA_{1c} attributable to decreases in RT_G, an additional HbA_{1c}-lowering effect of canagliflozin 300 mg compared to canagliflozin 100 mg of -0.15% was identified, which was additive to the effect described by the E_{max} model.

Conclusions: A significant covariate effect of eGFR was identified on the maximum HbA_{1c}-lowering effect of canagliflozin (E_{max}), which is consistent with the renal mechanism of action of canagliflozin. An additional HbA_{1c}-lowering effect for the 300 mg dose strength on top of the HbA_{1c}-lowering effect of canagliflozin attributable to RT_G-lowering, is consistent with a potential secondary effect of the 300 mg dose to delay intestinal glucose absorption [2].

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Joost DeJongh IV-59 A population PK-PD model for effects of Sipoglitazar on FPG and HbA1c in patients with type II diabetes.

Fran Stringer (1), Joost DeJongh (2), Graham Scott (3) and Meindert Danhof (4)

(1) Clinical Pharmacology Dept, Takeda Pharmaceutical Company, Osaka, Japan; (2) LAP&P Consultants BV, Leiden, The Netherlands; (3) Clinical Pharmacology, Takeda Global Research & Development Centre Ltd. Europe, London, United Kingdom; (4) Leiden-Amsterdam Centre for Drug Research, Division of Pharmacology, Leiden, The Netherlands

Objectives: Sipoglitazar is a PPAR γ, α & δ agonist for treating type 2 diabetes mellitus (T2DM) by improving insulin sensitivity. Sipoglitazar undergoes phase II biotransformation by conjugation catalyzed by UGT. UGT2B15 genotype is a covariate for clearance in individual patients as was reported previously from a population PK analysis[1]. The present population PK-PD analysis was performed to study the role of PK in differences of drug effects in sipoglitazar on both fasting plasma glucose (FPG) and HbA1c observed between the different UGT2B15 genotypes (UGT2B15*1/*1, UGT2B15*1/*2, and UGT2B15*2/*2).

Methods: Efficacy and safety of sipoglitazar compared to placebo were assessed in T2DM patients in two Phase II randomized, double-blind studies (sipoglitazar QD: 8, 16, 32 or 64 mg; sipoglitazar BID: 16 or 32 mg; placebo). All patients were treatment naïve and received lifestyle and dietary counseling prior to and during the study. Drug intake started after a 7-10 day run-in for a total period of 13 weeks. PK and PD data for FPG and HbA1c were collected throughout the trial. The individual PK parameters derived from a previous analysis were used to calculate individual exposure. Changes in FPG

and HbA1c levels over time were described as a function of individual drug exposure using a simultaneous, cascading indirect response model structure.

Results: The effects on FPG and HbA1c could successfully be described for placebo and sipoglitazar treated groups in all three UGT2B15 genotypes. Differences in drug effects between genotypes were fully explained by differences in drug exposure. Maximum reduction of FPG (Emax) due to sipoglitazar exposure was approximately 50% for the typical patient. In addition, a small but significant reduction of HbA1c was observed independent of FPG reduction, in placebo and sipoglitazar treated subjects.

Conclusions: The current PK-PD analysis confirms that UGT2B15 genotype is a major determinant for differences in FPG and HbA1c response to sipoglitazar treatment between diabetes patients, due to related differences in drug exposure. Part of the reduction in HbA1c levels was independent of the drug effects on FPG and a dedicated model parameter could be identified for this process.

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Paolo Denti IV-60 A semi-physiological model for rifampicin and rifapentine CYP3A induction on midazolam pharmacokinetics.

Paolo Denti (1), Yanhui Lu (2), Erin Bliven-Sizemore (3), Kelly E. Dooley (2)
(1) University of Cape Town, Cape Town, South Africa, (2) The Johns Hopkins University School of Medicine Baltimore, MD, United States, (3) Centers for Disease Control and Prevention, Atlanta, GA, United States

Objectives: Rifamycins are antibiotics largely used in the treatment of tuberculosis and are potent inducers of a wide range of drug-metabolising enzymes, including most notably the cytochrome P450 (CYP) family. Consequently, this gives rise to a number of drug-drug interactions. The objective of this analysis is to quantify the level of CYP3A induction caused by escalating doses of rifapentine (RPT). To do this, midazolam (MDZ) has been used as a probe drug for CYP3A and rifampicin (RIF) as a comparison inducer. MDZ is first hydroxylated to α-OH-MDZ by CYP3A which is then glucuronidated by UDP-glucuronosyltransferases.

Methods: On day 1 of the study [1], 29 healthy volunteers received a single oral dose of MDZ (15 mg). Thereafter, either RIF or RPT was administered daily, and on day 15 participants received a second single dose of MDZ. Intense PK sampling was performed on both occasions, and the plasma was assayed for MDZ and its main metabolite, α-OH-MDZ. The participants were randomised into 5 cohorts; subjects received 10 mg/kg of RIF or 5, 10, 15 or 20 mg/kg of RPT. The data were interpreted with a nonlinear mixed-effects model implemented in NONMEM VII. A well-stirred liver model [2] was assumed to capture with a single hepatic parameter (CLint) both CL and first-pass metabolism. Allometric scaling [3] adjusted for body size, the M3 method [4] was used to handle BLQ values, and BSVs and BOVs were

included using a lognormal distribution. The effect of the rifamycins on MDZ PK was investigated.

Results: Including in the model only the effect of rifamycins on hepatic CLint, prolonged exposure to RIF increased CLint of MDZ approximately 8 fold, while the effect of RPT was even stronger, about 20 fold. Also the levels of α-OH-MDZ were found decreased after rifamycin exposure, but to a lower extent than MDZ: this was captured in the model with an increase in CLint of α-OH-MDZ by more than 3 and 5 fold for RIF and RPT, respectively. No significant increase in the induction effect was detected with escalating doses of RPT.

Conclusions: The well-stirred liver model can be used to describe the PK of MDZ and captures well the induction effect of rifamycins. With the current data it is not possible to separate pre-hepatic CYP3A metabolism, although some may be expected (i.e. in the enterocytes). Inclusion of IV midazolam data in the model may help address this. Another improvement could result from the use of RIF exposure, rather than dose, since large variability was detected in RIF induction.

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Cheikh Diack IV-61 An indirect response model with modulated input rate to characterize the dynamics of Aβ-40 in cerebrospinal fluid

Cheikh Diack (1), Christophe Boetsch (1), Valerie Cosson (1), Nicolas Frey (1), Eric Worth (2)
(1) F. Hoffmann-La Roche Ltd, Switzerland, (2) Roche Products, UK

Objectives: The improving understanding of the brain pathology dementia has led to several clinical trials with focus upon the dominating theory known as the amyloid hypothesis [1]. The amyloid hypothesis suggests that increased production or reduced clearance of amyloid beta (Aβ) species (mainly Aβ-40 and Aβ-42) and their subsequent deposition as plaques in the brain play a critical role in the cascade of biological events involved in the pathogenesis of Alzheimer's disease. Biomarkers of brain Aβ amyloidosis include reductions of the Aβ level in the cerebrospinal fluid.
A number of clinical trials have shown a high intra-individual variability of CSF Aβ level which also tended to rise when sampled repeatedly by means of an indwelling lumbar catheter over a number of hours [2]. Some recent findings have associated the rise of CSF Aβ to the sampling frequency or sampling volume or both [2] while others postulated a diurnal change [3] in CSF Aβ to explain the intra-individual variability observed.
It is therefore important to characterize the dynamic of Aβ in CSF when sampled in this manner.

Methods: Placebo (10 subjects) and baseline data (40 subjects including the placebo group) were collected from a clinical trial of healthy volunteers. CSF was sampled (2mL sample every 2 hours) for each subject at 19 time points over 36 hours. Based on these data three different turnover models were developed all with modulated production rate:

- Model 1: the input rate is function of the sampling frequency
- Model 2: the input rate is function of the sampling volume
- Model 3: the input rate is periodic (circadian variation)

All models were tested against published data on 21 healthy subjects from three different studies [2] with different sampling frequencies and volumes.

Results: This an on-going work. However first modeling results suggest that the observed rise of CSF Aβ 40 may not be due to sampling frequency or sampling volume but, at least in part, to its hypothesized diurnal variation.

Conclusions: The dynamic of CSF Aβ 40 was characterized using an indirect response model with modulated input rate. First results seem to indicate that the high intra-individual variability of Aβ 40 in CSF is due to its circadian variation, however further investigations are needed to validate this approach.

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Laura Dickinson IV-62 Population Pharmacokinetics of Twice Daily Zidovudine (ZDV) in HIV-Infected Children and an Assessment of ZDV Exposure Following WHO Dosing Guidelines

Laura Dickinson (1), Quirine Fillekes (2), Tim R. Cressey (3,4), Kulkanya Chokephaibulkit (5), Gerry Davies (1), Victor Musiime (6), Philip Kasirye (7), Saye Khoo (1), David Burger (2), Sarah Walker (8)
(1) University of Liverpool, Liverpool, UK; (2) Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; (3) Program for HIV Prevention and Treatment (IRD URI 174), Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand; (4) Harvard School of Public Health, Boston, MA, USA; (5) Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; (6) Joint Clinical Research Centre, Kampala, Uganda; (7) PIDC, Mulago Hospital, Kampala, Uganda; (8) MRC Clinical Trials Unit, London, UK

Objectives: Zidovudine (ZDV) is a component of HIV therapy for children but limited PK data are available on the widely applied twice daily dose. WHO guidelines aim to provide a simplified dosing approach based on weight bands. In 2010, the WHO increased ZDV doses in several weight bands compared to 2006 guidelines. Our aim was to develop a model to describe ZDV plasma concentrations in HIV-infected children and estimate exposures following WHO dosing.

Methods: Rich and sparse data were combined from 6 paediatric studies. A total of 773 plasma concentrations were available from 100 children (n=63 girls) stable on ZDV tablets (n=54 PK profiles) or syrup (n=73 PK profiles) dosed according to WHO or National guidelines. Median (range) ZDV dose was 150mg (60-300) [9mg/kg (5.1-24.0)]. Median age and weight were 5yr (1-

18) and 18kg (6-59). Nonlinear mixed effects modelling (NONMEM v.7.2) was applied to estimate ZDV population PK. Covariates that could potentially influence ZDV PK were evaluated. Validity of the model was assessed using visual predictive check. Comparison of ZDV exposures based on WHO 2006 and 2010 guidelines was performed using simulations.

Results: ZDV PK was described by a 2-compartment model with first-order (tablet; k_a 3.0h^{-1}) or zero-order (syrup; D2 0.7h) absorption. Weight on clearance and volume of distribution parameters using allometric scaling improved the fit. A positive linear relationship was observed between ZDV CL/F and age. ZDV CL/F, Q/F, Vc/F and Vp/F were 62, 7L/h/18.3 kg and 66, 53L/18.3 kg, respectively (IIV CL/F 32%). Of the observed ZDV concentrations 91% were within the 90% prediction interval. Mean ZDV AUC_{0-12} was 25% higher compared to published adult data [1] (2.81 *vs*. 2.24mg.h/L). Simulated mean AUC_{0-12} for WHO 2010 guidelines (2.52-3.55mg.h/L) were higher than those for 2006 guidelines (2.10-3.13mg.h/L) in the majority of weight bands due to increased doses. Stratifying simulated ZDV AUC_{0-12} according to arbitrary low and high thresholds of half and double the average adult exposure resulted in 0-7% and 0-3% of AUC_{0-12} below 1.12mg.h/L and 3-16% and 6-25% above 4.48mg.h/L for 2006 and 2010 guidelines, respectively.

Conclusions: Mean ZDV exposure was higher in children than adults. Additional safety and tolerability data at higher WHO 2010 doses are needed to establish a toxicity threshold for ZDV. Impact on active intracellular ZDV triphosphate requires investigation; however, predicted plasma exposures are reassuring.

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Christian Diedrich IV-63 Using Bayesian-PBPK Modeling for Assessment of Inter-Individual Variability and Subgroup Stratification

Markus Krauss (1,2), Rolf Burghaus (3), Jörg Lippert (3), Mikko Niemi (4,5), Andreas Schuppert (1,2), Stefan Willmann (1), Lars Kuepfer (1), C. Diedrich (1), Linus Görlitz (1)

(1) Bayer Technology Services GmbH, Computational Systems Biology, 51368 Leverkusen, Germany; (2) Aachen Institute for Advanced Study in Computational Engineering Sciences, RWTH Aachen, Schinkelstr. 2, 52062 Aachen, Germany; (3) Bayer Pharma AG, Clinical Pharmacometrics, 42117 Wuppertal, Germany; (4) Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland; (5) HUSLAB, Helsinki University Central Hospital, Helsinki,

Objectives: To combine Bayesian statistics with detailed mechanistic physiologically-based pharmacokinetic (PBPK) models in order to provide a powerful tool to investigate inter-individual variability in groups of patients and to identify clinically relevant homogenous subgroups in an unsupervised approach. And to support knowledge based extrapolation to other drugs or populations.

Methods: PBPK models are based on a large amount of prior physiological and anthropometric information which is integrated into the model structure. Because the large-scale PBPK models that we use here explicitly distinguish between compound and patient specific properties, they allow for separation of physiological and drug-induced effects as it is needed for knowledge based extrapolation. In order to introduce a rigorous treatment of parameter variability into the methodology a Bayesian-PBPK approach, based on a Markov Chain Monte Carlo (MCMC) algorithm is pursued. In this way the PBPK model parameters are sampled along a Markov chain, which has the

posterior distribution as its stationary distribution from which parameter variability is extracted. Bayesian approaches have already been used before in conjunction with PBPK modeling, especially in toxicological questions [1], but also for population PK [2]. However, often the PBPK models used were comparatively small and contained lumped parameters carrying mixed information, in contrast to the large-scale models that we use here.

Results: Considering pravastatin pharmacokinetics as an application example, Bayesian-PBPK is used to investigate inter-individual variability in a cohort of 10 patients [3]. Correlation analyses infer structural information about the PBPK model. Moreover, homogeneous subpopulations are identified a posteriori by examining the parameter distributions and this subgroup stratification can even be assigned to a polymorphism in the hepatic organ anion transporter OATP1B1.

Conclusions: The presented Bayesian-PBPK approach systematically characterizes inter-individual variability within a population by updating prior knowledge about physiological parameters with new experimental data. Moreover, clinically relevant homogeneous subpopulations can be mechanistically identified. The large scale PBPK model separates physiological and drug-specific knowledge which allows, in combination with Bayesian approaches, the iterative assessment of specific populations by integrating information from several drugs.

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Christian Diestelhorst IV-64 Population Pharmacokinetics of Intravenous Busulfan in Children: Revised Body Weight-Dependent NONMEM® Model to Optimize Dosing

Christian Diestelhorst (1), Joachim Boos (2), Jeannine S. McCune (3), Georg Hempel (1,2)

(1) Department of Pharmaceutical and Medical Chemistry - Clinical Pharmacy, University of Münster, Germany; (2) Department of Paediatric Haematology and Oncology, University Children's Hospital Münster, Germany; (3) Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA

Objectives: Busulfan (Bu), a DNA-alkylating agent, is widely used for conditioning prior to bone marrow transplantation in both children and adults. Low Bu plasma exposure, expressed as area under the curve (AUC), is associated with a higher risk of graft rejection while an elevated Bu AUC is associated with a higher risk of toxicity. Therefore, optimal dosing of intravenous (i.v.) Bu is critical. Despite years of investigation there are still open questions regarding the best schedule of administration as well as the optimal dosing in children. According to the European Medicines Agency (EMA) labelling of i.v. Bu in children, dosing is based on five different body weight strata. In addition, current pharmacokinetic (PK) studies showed conflicting results regarding an optimal dosing of Bu in children, especially for underweight or obese patients. In this context, the external evaluation of two models from our working group [1] indicated a bias caused by inclusion of data after oral administration. Therefore, a new merged dataset with data only after i.v. administration was used to develop a revised population pharmacokinetic (PopPK) model for Bu in children. Subsequently, dosing based on the final PopPK model was compared with dosing strategies suggested by other groups.

Methods: Model building was done with NONMEM® 7.2. The model building dataset is based on 82 children receiving Bu four-times daily for four days. Model evaluations were performed by a bootstrap analysis and a Standardized Visual Predictive Check (SVPC) procedure (internal evaluation, each with 1,000 runs) and by comparison to an external dataset (external evaluation).

Results: Data were best described by a one-compartment model, inter-individual variability (IIV) and inter-occasion variability (IOV) on both clearance (CL) and volume of distribution (V) and a proportional residual error model. Covariates included were body surface area (BSA) as an exponential function on V and actual body weight (ABW) as an allometric function on CL. The final model-derived dosing strategy was:

$$\text{Dose [mg]} = \text{Target AUC [mg*h/L]} \times 3.04\ \text{L/h} \times (\text{ABW}/16.1)^{0.797}$$

Nomograms were used to compare the different suggested dosing recommendations demonstrating differences for the very small and heavyweight patients.

Conclusion: Dosing strategies for i.v. busulfan differ for the very young and heavyweight patients and need to be evaluated in a prospective study.

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Aris Dokoumetzidis IV-65 Bayesian parameter scan for determining bias in parameter estimates

Dimitra Nikopoulou, Aris Dokoumetzidis
School of Pharmacy, University of Athens, Greece

Objectives: In a badly designed study, a NONMEM run often gives not only large standard errors, but also biased estimates and an overall unstable performance. A methodology is developed based on a parameter scan using a series of informative Bayesian priors that allows the location of bias in NONMEM parameter estimates.

Methods: Various scenarios of datasets were simulated using a one-compartment pharmacokinetic model with first order absorption, with 40 subjects and 2 points per subject, where the last sampling time was deliberately early, such that it did not allow an accurate estimation of clearance (CL). NONMEM with FOCE was used for parameter estimation while their standard errors were estimated by bootstrapping. Nine different percentiles (10% to 90% increasing by 10%) of the bootstrap distribution of CL were determined. Informative Bayesian priors were setup using the $PRIOR option of NONMEM where the value of prior for CL was set to each of the percentiles of its distribution while the variance of the prior was chosen at 30% CV for CL and noninformative for all other parameters (other options were also investigated). The criterion for determining bias and for selecting the percentile most likely to be closest to the correct parameter value was considered to be the one with the lowest value of the Objective Function (OF).

Results: For most scenarios a plot of the OF vs the corresponding percentile of the prior exhibited a smooth minimum at the correct percentile (corresponding to the simulated values) which was in some cases different

from the median. For an extreme where the correct simulated value fell at the 90th percentile of the bootstrap distribution the method reached its limits and was difficult to determine a trend in the OF vs the percentiles. Sensitivity of the method from the strength of the prior was also investigated.

Conclusions: A method of scanning along a posterior distribution of a badly estimated parameter by using a series of informative Bayesian priors can locate parameter values with lower OF than the median which are closer to the unbiased value of this parameter.

Gregory Ferl S-01 Literate Programming Methods for Clinical M&S

Gregory Z. Ferl
Genentech, Inc.

Objectives: Develop an effective Literate Programming/Reproducible Research environment for Modeling and Simulation of clinical data that serves as a "back-end" to NONMEM analysis.

Methods: Literate Programming[1] (LP) is a computer programming methodology developed by Don Knuth, a computer scientist who invented the TeX typesetting system. His first iteration of the LP methodology combined the programming language PASCAL with the typesetting system TeX and was called WEB, "…partly because it was one of the few three-letter words that hadn't already been applied to computers"[1]. LP can be described as a system that makes the process of writing, running and evaluating computer programs more easily understood by people. This requires explanation. A data analysis workflow can have many steps, looking something like 1) write a computer program, 2) run the program on data, 3) generate summary figures and tables, 4) paste the figures and tables into a final report written using a word processor. Essentially, what we are doing is writing a program that instructs a computer what to do with our data; then, in a series of separate steps, we translate relevant output into a form that is readable by a person (a final document that contains text, figures, tables). The LP approach automates these translation steps by formally combining, in a single file, the code that performs the analysis with a document preparation system. Using LP, the final report is re-created on the fly each time a data set is analyzed and automatically reflects any changes that may have been made to methods of analysis or the data set. Key pieces of code can (and should) be automatically included within prose sections of the final report, where they

are printed in the final document exactly as they are written in the code. Thus, a reader can be 100% certain of how results presented in a report were generated and can easily update the report if any changes are made to the analysis method or data set.

Results: Here, we describe an implementation of LP for population modeling analysis of clinical imaging data, using Sweave 2, a tool that allows one to use NONMEM [3], R [4] and LaTeX [5] within the literate programming environment. Using simulated data, we illustrate how a detailed population PK/PD report and companion slides decks may be generated and updated on the fly as data and analysis methods are updated. The LP workflow is driven by a single Sweave master file containing code for population modeling (NONMEM), data post processing/generation of graphs (R), and markup used to generate a comprehensive PDF report (LaTeX). If at any time we decide to alter the analysis methodology, such as adding or removing a patient(s) from the data set or changing an equation, all that needs to be done is modify the data set and/or the master LP file accordingly and run it to generate a completely updated report.

Literate Programming workflow. The Sweave master file contains the NONMEM control file, R code and LaTeX markup for document text/layout:

Sweave Master File & NONMEM data file → Run Sweave → PDF report

Conclusions: Our Literate Programming approach facilitates construction of generic templates that can be used to analyze any clinical data set with the appropriate format/structure, creating a report that can be easily reproduced, effectively archived and/or passed on to collaborators for further analysis.

References:

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Bruce Green S-02 DoseMe - A Cross Platform Dose Individualised Program

Robert McLeay and Bruce Green
DoseMe Pty Ltd

Introduction
DoseMe is an easy-to-use Bayesian dose-individualisation platform designed for clinicians and healthcare practitioners to optimise patient care. DoseMe currently supports several classes of drugs, including antibiotics, anti-coagulants, and chemotherapeutic agents.

Designed for the Clinic
DoseMe has been designed from the ground-up to seamlessly fit into a clinical workflow. DoseMe supports use by the bedside (iPads), the desktop (web interface), as well as integrating into existing patient management software.

Clinically Tested
DoseMe is currently being used in clinical trials to dose gentamicin at the Royal Brisbane and Women's Hospital, and warfarin at Sullivan Nicolaides Pathology.
These trials report extremely positive findings, both for clinical outcomes, and DoseMe's ease-of-use. We expect to have the results published by Q3, 2013.

Fully Supported
DoseMe is a fully-supported product 24x7, with continual monitoring to maintain availability. You can rely on DoseMe being there when you need it. Every time a new DoseMe installation occurs, or an update is prepared for release, a large set of tests are automatically performed to determine that

DoseMe remains numerically precise. Before releasing updates, DoseMe Pty Ltd performs user acceptance testing - making sure that DoseMe is not only numerically accurate, but also suitable for clinical practice.

Drug Support
DoseMe currently supports the following drugs:

- Gentamicin (adult, paediatric coming soon)
- Tobramycin (adult and paediatric)
- Vancomycin (adult)
- Warfarin (adult)
- Busulfan (adult and paediatric)

New drugs are being added continually, and DoseMe can support specific drugs on request. DoseMe does not limit the number of compartments or the types and kinds of covariates supported in drug models.

Cloud-Based and Scalable
DoseMe is a cloud-based solution that can be deployed and made available for use immediately, without requiring lengthy and difficult IT compatibility projects. However, we do support integration with in-house systems if required. Being cloud-based, DoseMe scales seamlessly, supporting 1 to more than 100,000 patients.

Safe & Secure
DoseMe Pty Ltd is 100% committed to safe and secure data storage and transmission. DoseMe encrypts all communication between clinicians and the cloud using industry-standard levels of encryption; the same as your bank.

- All communications are encrypted and secured with SSL.
- All data cached on iPads are encrypted.
- All data stored on our servers (including the entire hard disks) are encrypted.
- All servers are housed in datacentres approved for medical record keeping (video-cameras, man-traps, and very high physical security).
- All servers used by a given clinical practice are hosted in the same country, simplifying legal requirements.

Roger Jelliffe S-03 The MM-USCPACK Pmetrics research software for nonparametric population PK/PD modeling, and the RightDose clinical software for individualizing maximally precise dosage regimens.

R Jelliffe, A Schumitzky, D Bayard, R Leary, M Van Guilder, S Goutelle, A Bustad, A Botnen, J Bartroff, W Yamada, and M Neely.
Laboratory of Applied Pharmacokinetics, USC Keck School of Medicine, Los Angeles, CA, USA

The **Pmetrics** population modeling software is embedded in R, called by R, and output into R. It runs on PC's and Macs. Minimal experience with R is required, but the user has all the power of R for further analyses and displays, for example. Libraries of many models are available, and differential equations may also be used. Large models of multiple drugs, with interactions, and multiple outputs and effects may be made if desired. Analytic solutions may also be used if feasible. The model is compiled with GFortran. Runs are made with simple R commands. Routines for checking data and displaying results are provided. Likelihoods are exact. Behavior is statistically consistent - studying more subjects yields parameter estimates closer to the true ones. Stochastic convergence is as good as theory predicts. Parameter estimates are precise [1].The software is available freely for research uses. In addition, prototype new nonparametric Bayesian (NPB) software has been developed. Standard errors of parameter estimates and rigorous Bayesian credibility intervals are now available. This work, presented at this meeting, is progressing.

The **RightDose** clinical software [2] used Pmetrics population models, currently for a 3 compartment linear system, and develops multiple model (MM) dosage regimens to hit desired targets with minimum expected

weighted squared error, thus providing maximally precise dosage regimens for patient care. If needed, hybrid MAP and NP Bayesian posteriors provide maximum safety with more support points and more precise dosage regimens. In addition, the interacting multiple model (IMM) sequential Bayesian analysis when model parameter distributions are changing during the period of data analysis [[3] has been upgraded by using the hybrid analysis in advance to provide more support points than were present in the original population model, again for more capable Bayesian parameter distributions and more informed dosage regimens than were available before. This work was also presented at this meeting. IMM has tracked drug behavior better than other methods in unstable post surgical cardiac patients [4]. In all the software, creatinine clearance is estimated in either stable or changing clinical situations, based on analyzing pairwise serum creatinine values, age, gender, height, weight, muscle mass, and dialysis status [5]. It also now runs on IPads and IPhones as virtual machines to access a PC. A new method for optimal experimental design for nonparametric population models has been developed and will soon be incorporated into the software. It avoids the circular reasoning flaw in D-optimal design [6].

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Niclas Jonsson S-04 Reproducible pharmacometrics

Justin J. Wilkins (1), E. Niclas Jonsson (2)
(1) SGS Exprimo NV, Mechelen, Belgium; (2) Pharmetheus AB, Uppsala, Sweden

Reproducibility is the cornerstone of scientific research, but is nonetheless a challenging area in pharmacometric data analysis. The large number of intermediate steps required, often involving multiple versions of datasets, combined with a mixture of software tools and the substantial quantity of results that must be tracked and summarized renders traceability an onerous and time-consuming business.

The concept of "reproducible research" is that the final product of scientific research is not just the text of a report or research article, but should also include the full computational environment used to produce the results, including all the associated code and data - and that this bundle of data and scripts should be shared with others who wish to reproduce these results. Although this is not often possible in pharmacometrics, given that data are usually confidential and that it may not be practical to reproduce hundreds of model fits, we can apply the *process* of reproducible research to our activities as far as possible to ensure that traceability is maintained.

Although there are many approaches that may be taken to adopting this principle, we shall focus on the combination of R, knitr and LaTeX. These tools together enable the end-to-end scripting of data file creation, capture of results from external software tools and subsequent analyses, and can automate the creation of publication-quality reports, articles and slide decks.

We shall provide a live demonstration of our implementation of this process in a production context, using a real dataset [1].

References:

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Oral: Animal Health

Jim Riviere **A-09** Food safety: the intersection of pharmacometrics and veterinary medicine

George Gettinby **A-11** Two models for the control of sea lice infections using chemical treatments and biological control on farmed salmon populations

Dan Haydon **A-12** From Epidemic to Elimination: Density-Vague Transmission and the Design of Mass Dog Vaccination Programs

Oral: Clinical Applications

Jonas Bech Møller **A-07** Optimizing clinical diabetes drug development – what is the recipe?

S. Y. Amy Cheung **A-35** Using a model based approach to inform dose escalation in a Ph I Study by combining emerging clinical and prior preclinical information: an example in oncology

Oral: Drug/Disease modelling

Jonathan French **A-06** Can methods based on existing models really aid decision making in non-small-cell lung cancer (NSCLC) trials?

Martin Bergstrand **A-15** Modeling of the concentration-effect relationship for piperaquine in preventive treatment of malaria

James Lu **A-23** Application of a mechanistic, systems model of lipoprotein metabolism and kinetics to target selection and biomarker identification in the reverse cholesterol transport (RCT) pathway

Rollo Hoare **A-24** A Novel Mechanistic Model for CD4 Lymphocyte Reconstitution Following Paediatric Haematopoietic Stem Cell Transplantation

Huub Jan Kleijn **A-25** Utilization of Tracer Kinetic Data in Endogenous Pathway Modeling: Example from Alzheimer's Disease

Shelby Wilson **A-34** Modeling the synergism between the anti-angiogenic drug sunitinib and irinotecan in xenografted mice

Sonya Tate **A-36** Tumour growth inhibition modelling and prediction of overall survival in patients with metastatic breast cancer treated with paclitaxel alone or in combination with gemcitabine

Oral: Lewis Sheiner Student Session
Abhishek Gulati **A-18** Simplification of a multi-scale systems coagulation model with an application to modelling PKPD data
Nelleke Snelder **A-19** Mechanism-based PKPD modeling of cardiovascular effects in conscious rats - an application to fingolimod
Nadia Terranova **A-20** Mathematical models of tumor growth inhibition in xenograft mice after administration of anticancer agents given in combination

Oral: Methodology - New Modelling Approaches
Wojciech Krzyzanski **A-14** Physiologically Structured Population Model of Intracellular Hepatitis C Virus Dynamics
Matt Hutmacher **A-16** A Visual Predictive Check for the Evaluation of the Hazard Function in Time-to-Event Analyses
Vittal Shivva **A-30** Identifiability of Population Pharmacokinetic-Pharmacodynamic Models
Leonid Gibiansky **A-31** Methods to Detect Non-Compliance and Minimize its Impact on Population PK Parameter Estimates
Julie Bertrand **A-32** Penalized regression implementation within the SAEM algorithm to advance high-throughput personalized drug therapy
Chuanpu Hu **A-39** Latent variable indirect response modeling of continuous and categorical clinical endpoints

Oral: Methodology - New Tools
Celine M. Laffont **A-17** Non-inferiority clinical trials: a multivariate test for multivariate PD
Nick Holford **A-28** MDL - The DDMoRe Modelling Description Language
Anne-Gaelle Dosne **A-40** Application of Sampling Importance Resampling to estimate parameter uncertainty distributions
Hoai Thu Thai **A-41** Bootstrap methods for estimating uncertainty of parameters in mixed-effects models
Celia Barthelemy **A-42** New methods for complex models defined by a large number of ODEs. Application to a Glucose/Insulin model

Oral: Other Topics
Dyfrig Hughes **A-05** Quantitative benefit-risk analysis based on linked PKPD and health outcome modelling

Oral: Tutorial
Justin Wilkins **A-27** Reproducible pharmacometrics

Poster: Absorption and Physiology-Based PK
Rachel Rose **I-05** Application of a Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Model to Investigate the Effect of OATP1B1 Genotypes on the Cholesterol Synthesis Inhibitory Effect of Rosuvastatin
Stephan Schmidt **I-14** Mechanistic Prediction of Acetaminophen Metabolism and Pharmacokinetics in Children using a Physiologically-Based Pharmacokinetic (PBPK) Modeling Approach
Nikolaos Tsamandouras **I-37** A mechanistic population pharmacokinetic model for simvastatin and its active metabolite simvastatin acid
Wanchana Ungphakorn **I-39** Development of a Physiologically Based Pharmacokinetic Model for Children with Severe Malnutrition
Nieves Velez de Mendizabal **I-46** A Population PK Model For Citalopram And Its Major Metabolite, N-desmethyl Citalopram, In Rats
Winnie Vogt **I-50** Paediatric PBPK drug-disease modelling and simulation towards optimisation of drug therapy: an example of milrinone for the treatment and prevention of low cardiac output syndrome in paediatric patients after open heart surgery
Mike Dunlavey **II-05** Support in PML for Absorption Time Lag via Transit Compartments
Taegon Hong **II-40** Usefulness of Weibull-Type Absorption Model for the Population Pharmacokinetic Analysis of Pregabalin
Rasmus Juul **II-55** Pharmacokinetic modelling as a tool to assess transporter involvement in vigabatrin absorption
Andreas Krause **III-02** Modeling the two peak phenomenon in pharmacokinetics using a gut passage model with two absorption sites
Kayode Ogungbenro **III-49** A physiological based pharmacokinetic model for low dose methotrexate in humans
Andrés Olivares-Morales **III-52** Qualitative prediction of human oral bioavailability from animal oral bioavailability data employing ROC analysis
Ines Paule **III-59** Population pharmacokinetics of an experimental drug's oral modified release formulation in healthy volunteers, quantification of sensitivity to types and timings of meals.

Khaled Abduljalil **IV-01** Prediction of Tolerance to Caffeine Pressor Effect during Pregnancy using Physiologically Based PK-PD Modelling
Jens Borghardt **IV-23** Characterisation of different absorption rate constants after inhalation of olodaterol
Vicente G. Casabo **IV-34** Modification Of Non Sink Equation For Calculation The Permeability In Cell Monolayers
Adam Darwich **IV-56** A physiologically based pharmacokinetic model of oral drug bioavailability immediately post bariatric surgery

Poster: CNS
Sylvie Retout **I-03** A drug development tool for trial simulation in prodromal Alzheimer's patient using the Clinical Dementia Rating scale Sum of Boxes score (CDR-SOB).
Eva Sverrisdóttir **I-30** Modelling analgesia-concentration relationships for morphine in an experimental pain setting
Sebastian Ueckert **I-38** AD i.d.e.a. – Alzheimer's Disease integrated dynamic electronic assessment of Cognition
Roberto Gomeni **II-27** Implementing adaptive study design in clinical trials for psychiatric disorders using band-pass filtering approach
Chihiro Hasegawa **II-36** Modeling & simulation of ONO-4641, a sphingosine 1-phosphate receptor modulator, to support dose selection with phase 1 data
Eef Hoeben **II-39** Prediction of Serotonin 2A Receptor (5-HT2AR) Occupancy in Man From Nonclinical Pharmacology Data. Exposure vs. 5-HT2AR Occupancy Modeling Used to Help Design a Positron Emission Tomography (PET) Study in Healthy Male Subjects.
Marija Jovanovic **II-54** Effect of Carbamazepine Daily Dose on Topiramate Clearance - Population Modelling Approach
Matts Kågedal **II-56** A modelling approach allowing different nonspecific uptake in the reference region and regions of interest – Opening up the possibility to use white matter as a reference region in PET occupancy studies.
Amelie Marsot **III-29** Population pharmacokinetics of baclofen in alcohol dependent patients
Nathalie Perdaems **III-61** A semi-mechanistic PBPK model to predict blood, cerebrospinal fluid and brain concentrations of a compound in mouse, rat, monkey and human.
Nidal Al-huniti **IV-05** A Nonlinear Mixed Effect Model to Describe Placebo Response in Children and Adolescents with Major Depressive Disorder

Aliénor Bergès **IV-14** Dose selection in Amyotrophic Lateral Sclerosis: PK/PD model using laser scanning cytometry data from muscle biopsies in a patient study
Irina Bondareva **IV-22** Population Modeling of the Time-dependent Carbamazepine (CBZ) Autoinduction Estimated from Repeated Therapeutic Drug Monitoring (TDM) Data of Drug-naïve Adult Epileptic Patients Begun on CBZ-monotherapy
Vincent Buchheit **IV-29** A drug development tool for trial simulation in prodromal Alzheimer's patient using the Clinical Dementia Rating scale Sum of Boxes score (CDR-SOB
Yu-Yuan Chiu **IV-46** Exposure-Efficacy Response Model of Lurasidone in Patients with Bipolar Depression

Poster: Covariate/Variability Model Building
Yoon Seonghae **I-16** Population pharmacokinetic analysis of two different formulations of tacrolimus in stable pediatric kidney transplant recipients
Herbert Struemper **I-28** Population pharmacokinetics of belimumab in systemic lupus erythematosus: insights for monoclonal antibody covariate modeling from a large data set
Adrien Tessier **I-35** High-throughput genetic screening and pharmacokinetic population modeling in drug development
Katarina Vučićević **I-53** Total plasma protein and haematocrit influence on tacrolimus clearance in kidney transplant patients - population pharmacokinetic approach
Yun Hwi-yeol **II-43** Evaluation of FREM and FFEM including use of model linearization
Dirk Jan Moes **III-39** Evaluating the effect of CYP3A4 and CYP3A5 polymorphisms on cyclosporine, everolimus and tacrolimus pharmacokinetics in renal transplantation patients.
Vincent Buchheit **IV-30** Data quality impacts on modeling results

Poster: Endocrine
Fran Stringer **I-26** A Semi-Mechanistic Modeling approach to support Phase III dose selection for TAK-875 Integrating Glucose and HbA1c Data in Japanese Type 2 Diabetes Patients
Christine Falcoz **II-07** PKPD Modeling of Imeglimin Phase IIa Monotherapy Studies in Type 2 Diabetes Mellitus (T2DM)

Daniel Hovdal **II-42** PKPD modelling of drug induced changes in thyroxine turnover in rat
Kanji Komatsu **II-63** Modelling of incretin effect on C-Peptide secretion in healthy and type 2 diabetes subjects.
Anna Largajolli **III-06** An integrated glucose-insulin minimal model for IVGTT
Jonathan Mochel **III-38** Chronobiology of the Renin-Angiotensin-Aldosterone System (RAAS) in Dogs: Relation to Blood Pressure and Renal Physiology
Oskar Alskär **IV-07** Modelling of glucose absorption
Steve Choy **IV-47** Modelling the Effect of Very Low Calorie Diet on Weight and Fasting Plasma Glucose in Type 2 Diabetic Patients

Poster: Estimation Methods
Tarjinder Sahota **I-09** Real data comparisons of NONMEM 7.2 estimation methods with parallel processing on target-mediated drug disposition models
Paul Vigneaux **I-49** Extending Monolix to use models with Partial Differential Equations
Jixian Wang **I-55** Design and analysis of randomized concentration controlled
Robert Leary **III-07** A Fast Bootstrap Method Using EM Posteriors
Andreas Lindauer **III-19** Comparison of NONMEM Estimation Methods in the Application of a Markov-Model for Analyzing Sleep Data
Erik Olofsen **III-53** Simultaneous stochastic modeling of pharmacokinetic and pharmacodynamic data with noncoinciding sampling times
Jason Chittenden **IV-45** Practical Application of GPU Computing to Population PK
Aris Dokoumetzidis **IV-65** Bayesian parameter scan for determining bias in parameter estimates

Poster: Infection
Gauri Rao **I-02** A Proposed Adaptive Feedback Control (AFC) Algorithm for Linezolid (L) based on Population Pharmacokinetics (PK)/Pharmacodynamics (PD)/Toxicodynamics(TD)
Alessandro Schipani **I-12** Population pharmacokinetic of rifampicine in Malawian children.
Joel Tarning **I-33** The population pharmacokinetic and pharmacodynamic properties of intramuscular artesunate and quinine in Tanzanian children with severe falciparum malaria; implications for a practical dosing regimen.
Elodie Valade **I-40** Population Pharmacokinetics of Emtricitabine in HIV-1-infected Patients

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