Pharmacokinetics (U.K.) PUK

Welcome to the Pharmacokinetics PKUK 2014 Meeting

Wednesday 5th November to Friday 7th November

The Macdonald Bath Spa Hotel
Sydney Road
Bath
BA2 6JF, UK

Programme and Abstract Book

Programme

Wednesday 5th November

REGISTRATION AT 12.00PM

LUNCH AT 12.30PM

Session 1: Modelling Methodology

14.00 Welcome - Gemma Dickinson

14.05 Welcome and Introduction to the First Session: Iva Gueorguieva and Leon Aarons

14.10 Structural Identifiability Analysis of Large Models of Dynamical Systems, Mats Jirstrand The Fraunhofer-Chalmers Research Centre for Industrial Mathematics

15.00 Handling parameter constraints in complex/mechanistic population pharmacokinetic models - An Application of the multivariate logistic normal distribution, Nikolaos Tsamandouras, The University of Manchester

15.40 *Coffee break*

16.10 Regulatory interface between "statistics" and Pharmacokinetics", Julia Saperia, MHRA

16:50 Quantifying synergy: a robust method for pre-clinical combination studies, Giovanni Y Di Veroli, CRUK Cambridge Institute

17.30 Session close

18.00 - 19.30 **POSTER SESSION WITH FREE BAR**

19.30 *Dinner*

Thursday 6th November

Session 2: Deconvolution of formulation performance: The IVIVC

Lloyd Stevens and Terry Shepard

9.00 Introduction, Lloyd Stevens, Quotient Clinical,

9.25 Solutions to non-ideal reference data: Stochastic Deconvolution – Jason Chittenden, qPharmetra

9.50 Challenges and benefits of using PBPK to evaluate an IVIVC for drugs with non-ideal solubility and/or permeability, Jennifer Dressman, Goethe University

10.15 Benefits and challenges in using Physiologically-Based IVIVC for drugs undergoing first pass metabolism, Shriram Pathak, Simcyp Ltd

10.40 Panel discussion (including speakers and Colm Farrell, ICON)

11.00 Concluding remarks, Lloyd Stevens, Terry Shepard

11.00 *Coffee break*

Session 3: Systems Toxicology & Biomarkers

James Yates and Peter Milligan

11.25 Introduction

11:30 QTc preclinical to clinical predictions,HERG vs non-HERG and operating characteristics of our traditional studies - Rob Wallis (Safety Pharmacology Consultant)

12:15 *Lunch*

13:30 Use of a Mathematical Model of Drug-InducedLiver Injury to Interpret Liver Safety Biomarker Data from Early ClinicalTrials for Entolimod, a Treatment for Life Threatening Radiation Poisoning, Diane Longo, DILI-sim Consultant

14:05 The Virtual Liver: a Multiscale Systems Biology Platform to Study Liver Function, Dysfunction & Injury, Lars Kupfer, Virtual Liver Network

15.00 *Coffee Break*

Session 4: Biologics PK/PD (anti-drug antibodies)

Ruth Oliver and Joe Standing

15.25 Introduction

15.30 Opening: Immunogenicity, the biology, the measurements, considerations: - Hishani Kirby, UCB

15.50 Simultaneous Modelling of PK and anti-drug Anti-bodies - Brigitte Lacroix, Uppsala University

16.10 The Use of Systems Modelling for Decision Making During Pharmaceutical R&D - Mark Penney, MedImmune

16.30 Target-Mediated Clearance and Immunogenicity – Two sides, one coin, Daren Austin, GlaxoSmithKline

Bar open from 18:30

The Peter Coates Lecture

19.00 Welcome - Gemma Dickinson

19.10 **Mats Karlsson, Uppsala University**

20:00 ***PKUK Banquet***

Friday 7th November

Session 5: Open Session

Gemma Dickinson and Alison Thomson

9.10 Introduction

9.15 Misconceptions on the issue of high vs low hepatic extraction ratio: the forgotten element of age variation - Khaled Abduljalil, Simcyp Ltd

9.40 Early estimation of clinically efficacious drug dose using systems pharmacology approaches; application to the nerve growth factor pathway - Neil Benson, Xenologiq Ltd

10.05 Development and Evaluation of Bayesian Software for Improving Therapeutic Drug Monitoring of Gentamicin in Neonates - Eva Germovsek, UCL

10.30 *Coffee Break*

11.00 Prostate specific antigen (PSA) kinetics and disease progression: is there a consistent connection? - Hitesh Mistry, University of Manchester

11.25 A semi-mechanistic PK/PD model of vemurafenib resistance and its rescue by LY2835219, a cyclin-dependent kinase 4/6 inhibitor, in mice bearing human melanomaxenograft tumours - Sonya Tate, Eli Lilly

11.50 Modelling a complex input process in a population pharmacokinetic analysis: example of mavoglurant oral absorption in healthy volunteers - Thierry Wendlng, University of Manchester

12.15 **Closing Remarks**

Conference ends with Lunch

Speaker Abstracts

Session 1: Modelling Methodology

1. Structural Identifiability Analysis of Large Models of Dynamical Systems

Johan Karlsson[1], Milena Anguelova[2,*], and Mats Jirstrand[1]
[1]Fraunhofer-Chalmers Research Centre for Industrial Mathematics
Chalmers Science Park, SE-412 88 Göteborg, Sweden
[2]SAAB AB, SE-412 89 Göteborg, Sweden

Background: Models of dynamical systems described by ordinary differential equations often contains a number of parameters to be determined by time-series measurements and non-linear regression. A necessary condition for successful non-linear regression is that parameters are identifiable. One usually distinguish between *practical* identifiability and *structural* identifiability. The former concerns to what extent the system is sufficiently perturbed and if uncertainty (noise) in measurements makes estimating parameters a feasible task while the latter is a property of the parametrized equations of the dynamical systems model. A model is structurally identifiable if its parameters can be uniquely determined under the assumption of perfect knowledge of the set of measured variables. Standard models in pharmacokinetics and pharmacodynamics are usually structurally identifiable since years of use and development have decontaminated the area of non-identifiable models. However, with the advent of quantitative systems pharmacology and efforts to increase the level of mechanistic detail in PK/PD models, novel and unexplored parametrized systems of ordinary differential equations appears. Hence, there is need for easy-to-use and efficient methods to decide structural identifiability of a proposed parametrized models prior to the application of numerical fitting and non-linear regression procedures.
Aim: To extend an existing highly efficient probabilistic method for structural identifiability analysis to include parametrized initial conditions and to provide an easy-to-use implementation in Mathematica to facilitate the use of identifiability analysis in systems pharmacology.
Methods: We describe the implementation of a recent probabilistic semi-numerical method for testing local structural identifiability based on computing the rank of a numerically instantiated Jacobian matrix (observability/identifiability matrix). To obtain this, parameters and initial conditions are specialized to random integer numbers, inputs are specialized to truncated random integer coefficient power series, and the corresponding output of a state space system is computed in terms of a truncated power series, which then is utilized to indirectly calculate the elements of the Jacobian matrix. To reduce the memory requirements and increase the speed of the computations all operations are done modulo a large prime number.
Results: A target mediated drug disposition model, a dose-response-time model, and four signaling pathway models (Ras, JAK-STAT, MAP Kinase Cascade, and NF-kB) have been analyzed with respect to structural identifiability.
Conclusion: Structural identifiability analysis can be carried out on a standard desktop computer on dynamical system models in the order of hundred parameters and equally many state variables.

[*]This work was carried out while the author was affiliated with Fraunhofer-Chalmers Centre.

2. Handling parameter constraints in complex/mechanistic population pharmacokinetic models – An application of the multivariate logistic normal distribution

Nikolaos Tsamandouras[1], Amin Rostami-Hodjegan[1,2], Aleksandra Galetin[1], Leon Aarons[1].

[1] Centre for Applied Pharmacokinetic Research, University of Manchester, UK, [2] Simcyp Ltd, Sheffield, UK

Background: Moving from empirical to more complex/mechanistic model structures, constraining model parameters is particularly crucial, as they represent actual physiological processes that may be defined only in a specific physiological range. In such situation, the traditional assumption that a model parameter is log-normally distributed in the population is not enough to avoid non-physiological estimates as the parameter might need a specific bounded support. Adding further complexity, in these complex high-dimensional parameter systems, certain physiological constraints may apply not on an individual model parameter, but on their joint population distribution. A characteristic example of such a challenging situation arises in hierarchical-population PBPK modelling, where the parameters representing organ blood flows should be variable in the population, however their sum in an individual should always be equal to his/her cardiac output. Similarly, organ volumes should be subject of population variability, but their sum should always be equal to the total body volume of each individual.

Aim: Investigate approaches to incorporate stochastic-random variability in complex/mechanistic model parameters which are subject to certain constraints.

Methods: Three different scenarios were investigated with regard to the nature of the constraint: firstly, the scenario of a single model parameter that exhibits population variability and needs to be bound inside a specific physiological range; secondly, the scenario of multiple correlated model parameters that exhibit population variability and each of them is bound inside a physiological range; and finally, the scenario of multiple (potentially correlated) model parameters that exhibit population variability and their sum needs to add up to a specific physiological value in each individual (compositional parameters). The approach to handle the last scenario is particularly illustrated with an example of a hierarchical whole-body PBPK diazepam model where stochastic variability was applied on organ blood flows and volumes. Finally, a simulation study was performed to investigate the degree of bias arising from the omission of population variability in these PBPK compositional model parameters.

Results: A generalisation of the logit-normal distribution and its multivariate case was applied to handle the constraints related to the first and the second scenario accordingly. Methods to relate the mean and variance of the logit-normally distributed variable of interest to the respective mean and variance (vector of means and variance-covariance matrix for the multivariate case) of the assumed normally distributed transformed variable were implemented through numerical integration. The multivariate logistic normal distribution [1] was proposed to handle the constraint related to compositional parameters (third scenario), taking advantage of its convenient property to be defined over the n-dimensional simplex. Using this approach we were able to successfully incorporate variability terms on compositional parameters firstly in a complex absorption PK model and secondly in the diazepam PBPK model. Simulations illustrated that omission of population variability in PBPK compositional system-related parameters will inflate either the estimate of the residual error or the estimates of variability in drug-related parameters depending on the parameterisation of the stochastic part of the model.

Conclusion: The proposed methods can facilitate the application of traditional mechanistic/PBPK approaches in a hierarchical-population modelling framework.

[1]. Aitchison J, Shen SM. Biometrika. 1980;67(2):261-272.

3. Regulatory interface between "statistics" and "pharmacokinetics"

Julia Saperia

The bulk of the work of a regulatory statistician is concerned with assessment of the design and results of efficacy trials in patients. At the Medicines and Healthcare products Regulatory Agency (MHRA), the statisticians and the pharmacokineticists are in the same team, enabling collaboration and exchange of ideas. In this talk, I aim to provide an insight into the regulatory statistician's view on modelling in the context of authorising drugs. The focus will be on efficacy and how to use PK data to improve the choice of dose carried forward from Phase II to Phase III. I will also explain the relevant regulatory interactions at the European level and discuss opportunities for innovation.

4. Quantifying synergy: a robust method for pre-clinical combination studies

Giovanni Y. Di Veroli, Frances M. Richards, Duncan I. Jodrell

CRUK Cambridge Institute, University of Cambridge, UK.

Background: Drug and other agent combinations are a strategic approach to cancer and other therapeutic areas.[1] So-called synergy studies are routinely conducted and claims of synergistic or antagonistic combinations regularly reported. The impact of inaccurate results can have dramatic consequences, from developing inefficient therapies to abandoning promising ones.

Aim: To highlight limitations of current approaches. To develop a robust method to analyse *in vitro* drug combination data that is in line with *in vivo* and clinical issues.

Methods: We derived a new mathematical model to identify synergy distributions in drug combination dose response surfaces. Our model and the traditional Bliss, Loewe and HSA[2] ones were incorporated in newly developed software for *in vitro* studies (http://www.cruk.cam.ac.uk/combenefit). We simulated several cases of hypothetical drug combinations and analysed them. We then proceeded to analyse hundreds of experimental combinations screened via a novel automated high-throughput assay.

Results: We found that false positive and false negative were systematically obtained if using wrong approaches or traditional mathematical models when analysing simulated combinations. We confirmed the impact of systematic inaccuracies via our large combinations screening analysis. We also found that the entire synergy distribution should be considered in order to effectively distinguish between promising combination candidates.

Conclusion: Standard models can severely mislead into pursuing unwarranted pre-clinical and clinical work. Our new mathematical model solves fundamental issues that are encountered with these models. Effective analysis of *in vitro* data can be achieved through the provided software implementation. The resulting procedure is better aligned with *in vivo* paradigms and is expected to have a major impact in drug combinations discovery.

References

1. Jia, J. *et al.* Mechanisms of drug combinations: interaction and network perspectives. *Nat. Rev. Drug Discov.* **8,** 111–28 (2009).
2. Borisy, A. a *et al.* Systematic discovery of multicomponent therapeutics. *Proc. Natl. Acad. Sci. U. S. A.* **100,** 7977–82 (2003).

Session 2: Deconvolution of formulation performance: The IVIVC

5. Solutions to non-ideal reference data: Stochastic Deconvolution

Jason Chittenden, qPharmetra

Background: Numerical convolution has long been a useful tool for estimating absorption profiles from in vivo data. Knowledge of the absorption profile can be used in developing IVIVC/R models, optimizing formulations, and improving the accuracy of PK models. Numerical deconvolution requires, however, that the pharmacokinetic system be linear and time-invariant, and known a priori (via a response function). In cases where, for instance, clearance is nonlinear or a unit impulse function is not available other techniques are needed to separate the underlying system response from the absorption process.
One technique with great promise treats the absorption profile as a random process arising from a time-varying absorption constant which is a realization of a random walk. The random walk can be combined with any pharmacokinetic model to obtain estimates for absorption over time, in an approach that has been dubbed "stochastic deconvolution" (Khaki & Chittenden, 2013). This approach relaxes many of the constraints and limitations of traditional convolution techniques, and is accessible to modelers with typical hardware and software platforms.
Aim: To investigate the implementation and results of stochastic deconvolution applied to several representative systems.
Methods: Simulated data for three different types of pharmacokinetic systems (linear, Michaelis-Menten clearance, and enterohepatic recirculation) have been used to characterize the performance of stochastic deconvolution in determining known absorption profiles. Three formulations were simulated in each case and mixed effects models with random absorption were used to estimate the absorption profiles. The estimated absorption profiles were compared to the simulated (known) profiles to evaluate the performance of the stochastic deconvolution process.
Results: Stochastic deconvolution attained nearly identical absorption profiles to numerical deconvolution for the linear, time-invariant system ($R^2>0.999$). For the Michaelis-Menten and enterohepatic recirculation data, it matched very well to the simulated absorption profiles ($R^2>0.999$).
Conclusion: Stochastic deconvolution, the estimation of a time-varying parameter by a random walk, reliably and accurately reproduces known absorption profiles of simulated data. This methodology could be used to gain insights into the time course of absorption or drug release for challenging cases where standard approaches are not applicable.

6. Challenges and benefits of using PBPK to evaluate an IVIVC for drugs with non-ideal solubility and/or permeability

Jennifer Dressman

In the development of new Active Pharmaceutical Ingredients (APIs) as well as new formulations of existing products (including generic products) it is of great interest to be able to predict to what extent the API can be absorbed from the gastrointestinal (GI) tract and how the formulation and dosing conditions may affect the absorption profile. The hypothesis behind Biorelevant testing is that "the closer the test conditions can simulate the gastrointestinal environment, the better the prediction will be". Typical aspects of GI physiology which can influence drug bioavailability are the composition of the GI fluids (which affects various processes including release from the dosage form and stability of the API), GI motility and hydrodynamics (transit characteristics of the dosage form, release from the dosage form etc.), permeability of the GI mucosa to the API as a function of location in the GI tract, and gut wall metabolism. While Biorelevant dissolution testing can be used to determine how the formulation will perform under GI conditions, it is often the interplay between release and permeability characteristics that drive the fraction of API absorbed. First pass metabolism is a further factor that cannot be overlooked in any consideration of API bioavailability. Thus, to gain a quantitative prediction of bioavailability for APIs which are problematic with respect to solubility and permeability, a model in which one can combine all three aspects: formulation performance, drug uptake through the gut wall and first pass metabolism, should be applied. This presentation will highlight the physiological conditions in the GI tract relevant to API and formulation performance in the fasted and fed states, and show examples of successful combination of Biorelevant dissolution testing with PBPK models to arrive at a better understanding of dosage form performance.

7. Benefits and challenges in using Physiologically-Based IVIVC for drugs undergoing first pass metabolism

Shriram M. Pathak
Simcyp Limited (a Certara Company), Sheffield, UK

Conventional deconvolution methods, such as Wagner Nelson (WN) and Numerical deconvolution (ND), for establishing *in vitro-in vivo* correlations (IVIVCs) estimate the rate of input of drug into the systemic circulation from observed plasma drug concentrations (C_p) of the oral formulation preferably using IV bolus parameters as the unit impulse response (UIR). These methods do not separate the multiple mechanisms that determine *in vivo* input rate – transit time, gut wall permeability, gut wall metabolism, and hepatic first-pass metabolism – from *in vivo* dissolution rate. Physiologically based pharmacokinetic (PBPK) models have been applied across all stages of the drug discovery and development and can also be used to develop IVIVC models. Physiologically Based-IVIVCs (PB-IVIVC) have advantages over conventional methods specifically for drugs with significant gut-wall metabolism/transport, regional permeability variations, and drugs exhibiting auto-induction/auto-inhibition of metabolising enzymes. Mechanistic absorption model such as the Advanced Dissolution Absorption and Metabolism (ADAM) model, by virtue of their nature, and if equipped by deconvolution capabilities can estimate *in vivo* dissolution profiles while separately accounting for permeation, GI transit and first pass elimination. These can facilitate establishing more robust and transparent IVIVCs and also can be used to predict population variability.
In this presentation, the following case studies using PB-IVIVC approach are presented: i) Metoprolol (high solubility, moderate permeability and high first-pass liver extraction); ii) Diltiazem (high solubility, moderate permeability and auto-inhibition of the metabolizing enzyme CYP3A4) and iii) Tramadol (high solubility, moderate permeability and high first-pass extraction by multiple pathways – CYP2D6, CYP3A4/CYP2B6). Further, potential application of PB-IVIVC in formulation safe space design will be illustrated. Present challenges and limitations of PB-IVIVC in the context of data requirements and model verification also will be highlighted and compared with other approaches.

Session 3: Systems Toxicology & Biomarkers

8. QTc preclinical to clinical predictions, HERG vs non-HERG and operating characteristics of our traditional studies.

Rob Wallis, Safety Pharmacology Consultant, Sandwich, Kent CT139LD.

Drug induced changes in the QT interval of the ECG continues to be used as a biomarker of proarrhythmic risk. Since the introduction of regulatory guidance (ICH S7B and ICHE 14) on the testing of drug liability to change the QT interval no compounds have been with drawn from the market because of QT prolongation and/or increased incidence of the arrhythmia, Torsade de Pointe.

In order to understand the concordance between non-clinical and clinical assays it is important to define the magnitude of effect that is a 'concern'. The clinical definition has been defined in ICH E14 – 'The threshold level of regulatory concern is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms'. The same guidance does not apply to non-clinical studies. Inhibition of the hERG channel is recognised as the major cause of QT prolongation in humans. Jonker *et al* developed a PKPD model to quantify the relationship between hERG inhibition by dofetilide and QT prolongation in humans and concluded that 10% inhibition of hERG corresponds to 20 msec QT prolongation (Jonker et al (2005) *Clinical Pharmacology & Therapeutics* (2005) **77**, 572–582). Using 10% inhibition of hERG as a predictor of the outcome of a clinical QT study (TQT) it has been shown that the predictivity of the hERG assay is good (sensitivity 0.82; specificity of 0.75) (Wallis *Br J Pharmacol*. (2010) **159**, 115-21).

A number of analyses have been conducted to understand the relationship between non-clinical *in vivo* studies and clinical outcome. A consortium of 7 pharmaceutical companies collected data on 113 small molecules and findings in the conscious telemetered dog and Phase I clinical trials for QTc and demonstrated that the concordance was good (sensitivity of 0.88; specificity of 0.76) (Ewart *et al* (2014) accepted for publication Toxicol Sci). PKPD modeling has been used to improve confidence in translation from non-clinical to clinical. Such analysis has suggested that a QTc change in the dog of 2.5 to 8 msec corresponds to a 10 msec change in human (Parkinson *et al* (2013) J Pharmacol Toxicol Methods **68,** 357 – 366). The effect of moxifloxacin on QTc has also been shown to fit a direct effect linear relationship in both the cynomologous monkey and human (Watson *et al* (2011) J Pharmacol Toxicol Methods **63,** 304 – 313).

As part of the continuing evolution of the cardiovascular safety testing strategy there is now a desire to focus more on measures of arrhythmia liabilities rather than the biomarker, QT/QTc. The goal of this new approach is to replace the need for a TQT study with non-clinical arrhythmia assessment. The strategy will involve testing compounds against a wider range of cardiac ion channels, simulating the effects on a cardiac action potential and measuring the effects on action potentials recorded from (Sager *et al* (2014) Am Heart J 0 1 – 9). The performance of these assays has yet to be defined.

9. **Use of a mathematical model of drug-induced liver injury to interpret liver safety biomarker data from early clinical trials for Entolimod, a treatment for life threatening radiation poisoning**

Diane M. Longo[1], Brett A. Howell[1], Lisl K.M. Shoda[1], Jeffrey L. Woodhead[1], Yuching Yang[1], Scott Q. Siler[1], Paul B. Watkins[1].
[1]The Hamner-UNC Institute for Drug Safety Sciences, Research Triangle Park, NC, USA.

Background: Entolimod (CBLB502) is a toll-like receptor 5 (TLR5) agonist in development as a single dose countermeasure against total body irradiation. The severe nature of the circumstances under which Entolimod would be administered is such that the FDA will assess efficacy based on animal studies alone. However, this "Animal Rule" does not apply to safety assessment, which must be determined in humans. Marked elevations of serum aminotransferases were observed in some healthy adult volunteers (NHV) receiving Entolimod in a safety study, threatening its continued development.
Aim: To utilize a mechanistic model of drug-induced liver injury (DILIsym®) to aid in the interpretation of the severity of the injury observed in the healthy subjects receiving Entolimod.
Methods: DILIsym® is a mechanistic, multi-scale, mathematical model being developed to assist in the safety characterization of compounds in clinical development. The initial focus is on *in vitro* to *in vivo* preclinical and *in vivo* preclinical to first in human clinical. Simulated humans, dogs, rats, and mice are included, with differences in biochemical variability amongst populations captured in simulated sample populations (SimPops™). The primary goals for the model include understanding how *in vitro* toxicity assay results translate to preclinical animal models, the relevance of preclinical results for humans, and how biomarker results translate to patient safety. In this case study, the percent of total hepatocytes undergoing necrosis in the healthy subjects was estimated using DILIsym®. This was accomplished through a two-phase process. Initially, DILIsym® was optimized to produce the liver enzyme profiles observed in healthy volunteers administered Entolimod. Second, the underlying level of hepatocyte loss predicted by the model to give such profiles was assessed for its relevance to the safety of the healthy volunteers.
Results: The simulated alanine transaminase (ALT) levels agreed with the NHV data by design. Aspartate transaminase (AST) levels were then used as confirmation that the baseline simulated human was reasonable. The AST simulation results were in line with the NHV outcomes observed. The predicted percentage of functional hepatocytes lost for the maximum observed ALT, 95th percentile observed ALT, and median observed ALT levels were around 3.5%, 1%, and 0.3% of viable hepatocytes. When variability was introduced to the key parameter values, the percentage of hepatocytes lost was predicted to range from 2.6% to 4.9% for the maximum ALT observed. The relevance of the magnitude of the predicted hepatocyte loss with Entolimod was put into context based on literature reports of liver excision, through simulation results compared to biomarker outcomes from NHV studies using heparins, and using historical liver biopsy data.
Conclusion: The simulations and associated analyses suggest that no subject in the clinical trial likely experienced more than a modest loss of hepatocytes, and that the levels lost were much lower than levels reportedly leading to serious health risks in other scenarios. This case study demonstrates the use of mechanistic models to interpret adverse event signals and how this information can help in communications with regulatory agencies.

10. The Virtual Liver: a Multiscale Systems Biology Platform to Study Liver Function, Dysfunction & Injury

Lars Kuepfer[1,2], Adriano M. Henney[1]
[1]Virtual Liver Network, Germany; [2] Computational Systems Biology, Bayer Technology Services GmbH, Germany

Background: The liver is the central detoxifying organ in the human body responsible for the removal of xenobiotics from the vascular system. A functional understanding of liver physiology is therefore mandatory in pharmaceutical research and development. The Virtual Liver Network (VLN) is a 5-year research program which focuses on the development of computational models of the liver.

Aims: The goal of VLN is to increase the mechanistic understanding of hepatic physiology. With regard to drug development, comprehensive physiologically-based pharmacokinetic (PBPK) models are used to support the various phases in pharmaceutical research by providing a platform for data integration, data analysis, and transfer of knowledge. Model-driven analyses can thus be used to optimize drug efficacy and patient safety.

Methods: Within the VLN different kinds of computational models have been developed, which specifically represent hepatic physiology at various levels of biological organization. This includes models for intracellular signaling or metabolic networks at the cellular scale, diffusion of proteins within the lobulus or liver perfusion at the organ level and ultimately distribution of compounds in pharmacokinetic models at the whole-body scale.

Results: Vertical integration of models from different levels of biological organization has been used to develop multiscale representations of liver physiology. To quantify liver detoxification capacity within the context of an organism the VLN uses a standardized cocktail of marketed drugs which is applied in both mice and humans. PBPK modeling together with targeted experimental data has been used to develop concepts for clinical trial design. Amongst others a standardized workflow for risk assessment has been developed to predict incidence rates of adverse events in specific subgroups. Likewise, Bayesian PBPK modeling has been used to identify pharmacokinetic phenotypes from cohorts of patients.

Conclusion: The specific experimental data generated within VLN allow a systematic physiological characterization of the liver from the cellular scale up to the patient level. The integration of such data within a comprehensive modeling framework significantly contributes to a mechanistic understanding of processes governing drug pharmacokinetics. Systems pharmacology approaches that consider physiological information from different levels of biological organisation will hence support the development of new drugs by evidence-based treatments in the future.

Session 4: Biologics PK/PD (anti-drug antibodies)

11. Immunogenicity of biotherapeutics

Hishani Kirby
Bioanalytical Sciences, UCB-Celltech, Slough,UK

It is well established that most biotherapeutics induce unwanted immune responses which may reduce drug efficacy and induce adverse effects. The term immunogenicity refers to the ability of a biotherapeutic to induce a specific cellular or humoral immune response which is triggered by the differences in structure between the 'foreign' (biotheraputic) protein and the bodies' natural proteins. The immune response to a biotherapeutic is measured as anti-drug antibodies (ADA). The presence of these anti drug antibodies can impact drug exposure (PK), response (PD) and safety. Reliable assessment of PK, PD and ADA can be influenced by assay design. In this presentation a broad overview of the factors that influence the induction, impact, measurement and interpretation of ADAs as a consequence of unwanted immune responses to biotherapeutics will be discussed.

12. Simultaneous modelling of the pharmacokinetics and immunogenicity of antibody drugs

Brigitte D. Lacroix[1,2], Ruth Oliver[3], Hishani Kirby[3], Lena E. Friberg[1], Mats O. Karlsson[1]
[1]Dept of Pharmaceutical Biosciences, Uppsala University, Sweden, [2]UCB Pharma, Braine, Belgium, [3]UCB Pharma, Slough, UK

Immunogenicity is an important aspect to take into account when characterizing the pharmacokinetics (PK) of a biologic drug. The relationship between immunogenicity and PK goes both ways. On one hand, the formation of antibodies against the drug increases the clearance of the drug ; on the other hand, the magnitude of exposure to the drug affects the probability of appearance of anti-drug antibodies (ADAs).
The overall objective of this study was to develop a model that simultaneously characterizes 1) the immunogenicity and 2) the drug concentration as function of levels of the appearance and eventually the titer of ADAs, in rheumatoid arthritis patients treated with certolizumab pegol (CZP) and to use this model to analyze whether the formation of ADAs could be prevented or the risk of developing antibodies reduced by adapting the frequency or dosage of CZP.
Data from 5 phase II and phase III clinical trials including both licensed and unlicensed doses of CZP (50 to 800 mg) in subjects suffering from rheumatoid arthritis were included in the analysis, and 1 clinical pharmacology study with rich sampling that was used to characterize the PK only (no ADA measurement). Treatment was administered subcutaneously every 2 weeks or every 4 weeks, as monotherapy or in combination with methotrexate (MTX). Two models were developed to characterize the pattern of immunogenicity as function of exposure to CZP and dose of methotrexate: 1) a time to event model describing the time to appearance of ADAs and 2) an indirect response model describing the formation and elimination of ADAs. A previously developed population PK model (unpublished) was used to characterize the pharmacokinetics of CZP, in which the ADA status (positive or negative) effect on CZP clearance was substituted by an effect based on the level of ADA estimated from the immunogenicity model. These models will be used to perform simulations of various treatment regimens (including the use of a loading dose, different frequency of dosing) in order to check the mid- and long-term impact on immunogenicity.

13. Mark Penny – no abstract

14. Target-Mediated Clearance and Immunogenicity – Two sides, one coin.

Daren Austin, GlaxoSmithKline

Therapeutic antibodies have several modes of action, with targets including soluble signalling molecules, decoy receptors and membrane bound proteins. Therapeutic peptides tend to target membrane bound receptors directly. Compared with small molecules, antibodies and peptides are under-dosed when compared with target expression levels. Nowhere is this more evident than when the target is a receptor, subject to regeneration and replacement on relatively rapid timescales. One of the consequences of this receptor cycling is that bound protein becomes internalized and subject to degradation by normal cellular proteolytic processes. For small proteins, this is the natural fate of the endogenous analogue, for large molecules, however, the consequences are faster clearance than endogenous immunoglobulin and the requirement for frequent and higher doses than otherwise necessary.

Immunogenicity is the process whereby the body's own immune system recognizes proteins as foreign and mounts an immune response, typically via the generation of antibodies against the foreign protein. Immunogenicity can be a desirable feature (vaccines), undesirable (exogenous therapeutic proteins) or of uncertain consequence (hypersensitivity, anaphylaxis), and there is therefore monitored carefully during all stages of drug development.

In this presentation I will provide examples of target mediated clearance, its role in the clearance of therapeutic proteins and how it can be used to provide information on the nature and expression levels of the target. By switching the notion of "target", I will give an overview of Immunogenicity and how by viewing the therapeutic antibody as the target, Immunogenicity can also be viewed in the same light.

Session 5: Open Session

15. MISCONCEPTIONS ON THE ISSUE OF HIGH VS LOW HEPATIC EXTRACTION RATIO: THE FORGOTTEN ELEMENT OF AGE VARIATION

Farzaneh Salem[1], Khaled Abduljalil[1], Yoshiteru Kamiyama[2], Amin Rostami-Hodjegan[1,3]

[1] Simcyp Limited, Sheffield, UK, [2] Drug Metabolism & Pharmacokinetics Management Analysis & Pharmacokinetics Labs. Astellas Pharma Inc, Japan [3] Manchester Pharmacy School, Manchester, UK

Background: Hepatic metabolic clearance of drugs is determined by their hepatic extraction ratio (E_H), commonly considered as an inherent attribute of drug with a fixed value. E_H consists of three age-dependent parameters: fraction of unbound drug in blood (fu_B), hepatic intrinsic clearance of unbound drug ($CLu_{int,H}$) and hepatic blood flow ($Q_{H,B}$).

Aim: To investigate age-related changes in E_H for midazolam and two other hypothetical drugs with ten-fold higher and lower $CLu_{int,H}$ by applying ontogeny functions to fu_B, $CLu_{int,H}$ and $Q_{H,B}$ of paediatric intravenous midazolam data.

Methods: In this study, E_H of midazolam and two other hypothetical drugs with ten-fold higher and lower $CLu_{int,H}$ compared to midazolam was calculated for subjects from birth to 17 years. Ontogeny of CYP3A4 in these simulations was based on models published using deconvolution of *in vivo* systemic clearance values of probe activity. Impact of age-related changes to fu_B, $CLu_{int,H}$ and $Q_{H,B}$ were investigated on relative paediatric to adult E_Hs. A comprehensive literature survey was carried out to identify commonly applied covariates in paediatric population pharmacokinetic studies.

Results: Midazolam categorised as a low extraction ratio drug until about 7 months after birth. E_H of midazolam increased from 0.02 in preterm neonates to about 0.6 in healthy adult volunteers. Mean hepatic blood flow increased from 3.5 L/h in preterm neonates reaching adult value of 83 L/h at about 13 years. Average midazolam fu_B decreased from 0.15 at the age of 2-4 days to 0.06 in adulthood, while $CLu_{int,H}$ increased from 0.05 L/h to 2057 L/h. A hypothetical drug with ten-fold higher $CLu_{int,H}$ than midazolam is categorised as high extraction from 4 days after birth although E_H reached adult level (0.9) at about 8 months. For a drug with ten-fold lower hepatic intrinsic clearance compared to midazolam only 30% of adult E_H value (0.1) is achieved by the first year and thus the drug can be categorised as low extraction across the paediatric age range. Analysis of population pharmacokinetic studies suggests that in around 50% of all studies (n=121) no interaction between covariate terms was considered.

Conclusion: Coining a drug as 'high extraction' cannot be universally applied at lower ages whilst if a drug was 'low extraction' in adults, it will be low extraction in paediatrics, too. This has implications for selecting covariates to study in populations involving wide age range and include neonates or young children. Moreover, attention should be paid to interaction terms of covariate during analysis of such data (e.g. age-albumin, genotype-age) as impact of some of the covariates might change with age.

16. EARLY ESTIMATION OF CLINICALLY EFFICACIOUS DRUG DOSE USING SYSTEMS PHARMACOLOGY APPROACHES; APPLICATION TO THE NERVE GROWTH FACTOR PATHWAY.

Neil Benson[1],

[1] Xenologiq Ltd, Canterbury Innovation Centre, University road, Canterbury, Kent. CT2 7FG. UK.

[Background]Arguably, the major challenge currently facing drug discovery is attrition [1]. In order to address this problem, improvements in the level of understanding of the complexity of human disease biology are required. This presentation will discuss why a mathematical systems pharmacology approach can add value in the pursuit of this improved knowledge, exemplified with the Nerve Growth Factor (NGF) pathway. The NGF pathway has been studied extensively and systems biology models of some of the signaling processes have been published [2, 3]. It is also a pathway of interest in drug discovery, for example for pain [4].

[Aim] To produce a tool using the published systems biology models of the NGF pathway and integrating cross membrane signaling, together with realistic physiological context. This tool could be used for exploring the likelihood of efficacy and identifying optimal targets and dose regimens.

[Methods] A mathematical ordinary differential equation (ODE) model of the NGF biology was constructed and via sensitivity analysis, the targets in the known pathway rank ordered with respect to a biomarker of pain response, the di-phosphorylated extracellular signal regulated kinase concentration in the nucleus. Once selected the concentrations of drug required to inhibit signaling through the pathway were explored. Using a simplified version of the model, lacking the interactions downstream of NGF binding to its receptor, the impact of the additional complexity on inhibition of signaling was investigated. Finally, in order to explore dose regimens that may result in maximal efficacy, a systems pharmacology model was constructed incorporating appropriate physiological context [5]. In order to enable this, cross membrane signaling was required and this was modeled assuming rapid transfer of receptor mass between neuronal and interstitial compartments [6].

[Results] It was concluded that NGF was the most sensitive druggable target in the known pathway, although TrA kinase and Ras signaling may also be of interest. It was found that the negative feedback loops in the pathway attenuate expected inhibitor potency at NGF and TrkA kinase and that non-intuitively high multiples of equilibrium binding constant were required to fully block signaling. These results were concordant with subsequent clinical data. Introducing appropriate physiological context into the model enabled quantitative study of drug dose and regimen.

[Conclusion] Systems pharmacology approaches can have had clear impact on drug discovery at the early research and clinical stages. Systematic application of systems pharmacology will become an important tool in tackling attrition.

REFERENCES

1. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J: Clinical development success rates for investigational drugs. *Nature biotechnology* 32(1), 40-51 (2014).
2. Sasagawa S, Ozaki Y, Fujita K, Kuroda S: Prediction and validation of the distinct dynamics of transient and sustained ERK activation. *Nature cell biology* 7(4), 365-373 (2005).
3. Fujioka A, Terai K, Itoh RE *et al.*: Dynamics of the Ras/ERK MAPK cascade as monitored by fluorescent probes. *The Journal of biological chemistry* 281(13), 8917-8926 (2006).
4. Lane NE, Schnitzer TJ, Birbara CA *et al.*: Tanezumab for the treatment of pain from osteoarthritis of the knee. *The New England journal of medicine* 363(16), 1521-1531 (2010).
5. Benson N, Matsuura T, Smirnov S *et al.*: Systems pharmacology of the nerve growth factor pathway: use of a systems biology model for the identification of key drug targets using sensitivity analysis and the integration of physiology and pharmacology. *Interface focus* 3(2), 20120071 (2013).
6. Benson N, Van Der Graaf PH, Peletier LA: Cross-membrane signal transduction of receptor tyrosine kinases (RTKs): from systems biology to systems pharmacology. *Journal of mathematical biology* 66(4-5), 719-742 (2013).

17. Development and Evaluation of Bayesian Software for Improving Therapeutic Drug Monitoring of Gentamicin in Neonates

Eva Germovsek[1], Alison Kent[2], Nigel Klein[1], Mark A Turner[3], Mike Sharland[2], Elisabet I Nielsen[4], Paul T Heath[2], Joseph F Standing[1]
[1]Inflammation, Infection and Rheumatology section, UCL Institute of Child Health, London WC1N 1EH, UK; [2]Paediatric Infectious Diseases Research Group, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK; [3]Liverpool Women's Hospital, Crown Street, Liverpool, Merseyside L8 7SS, UK; [4]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Background: Gentamicin is frequently used in neonatal intensive care. Due to a small difference between its toxic and effective concentration therapeutic drug monitoring (TDM) is required. Samples for TDM are currently taken just before the next dose is given. Using Bayesian methods allows TDM to be performed when samples for other purposes are taken, thus making it less invasive.
Aim: This study aimed to develop a Bayesian software (neoGent) for TDM use in neonates. The second objective was to evaluate neoGent on prospectively collected data.
Methods: Firstly, a population pharmacokinetic (PK) model for gentamicin in neonates was developed by pooling data from published studies and performing a PK meta-analysis. The predictive power of the model was then tested with prospectively collected data from five UK hospitals by comparing model predicted trough gentamicin levels with measured levels. To quantify the model's ability to predict, prediction errors (i.e. the difference between the predicted and the measured level) were calculated.
Results: A three-compartment model provided the best fit to the data. Allometric scaling and a function describing the maturation of glomerular filtration rate were included *a priori*. Other significant covariates were postnatal age and serum creatinine standardized for postmenstrual age (PMA). The evaluation dataset included 163 subjects with PMA ranging 23.9-42.3 weeks (median: 34.9 weeks). Median prediction error (95% non-parametric confidence interval) was -0.002 (-0.87, 0.85) mg/L suggesting that the model is able to make predictions of trough levels from opportunistic samples. Additionally, the model was shown to perform best when compared to 11 published models. NeoGent has now been implemented in statistical software R. It was designed to read in demographic features of a neonate, its dosing history and measured gentamicin levels. Real-time Bayesian predictions of the trough levels are then made. The output of the neoGent is a table showing the time when gentamicin concentration will go below a certain pre-specified threshold and a visual presentation of the predictions.
Conclusion: The neoGent software was developed and evaluated with prospective data. The results showed that it can be used for predicting trough levels from opportunistic samples taken at earlier time points, making TDM less invasive. Future work will involve developing a more user-friendly interface.
Acknowledgments: This project was funded by Action Medical Research. The authors would also like to thank all patients and collaborators (Dr Mark Anthony, Dr Tim Scorrer, Dr Prakash Satodia, Dr Nasreen Aziz) who participated in this study.

18. Prostate specific antigen (PSA) kinetics and disease progression: is there a consistent connection?

Hitesh B. Mistry

School of Pharmacy, University of Manchester, M13 9PL, UK.

Background: PSA is a glycoprotein enzyme that is secreted by epithelial cells of the prostate gland. In healthy men the serum values of PSA are quite low; but it is elevated in men with prostate cancer. However, PSA can also rise due to other medical conditions such as prostatitisis, benign prostatic hyperplasia and recent ejaculation. These factors clearly make interpretation of one-off values of PSA difficult and have led the US preventative services task force to cease PSA screening. However, PSA has re-surfaced within the recent literature as a predictive marker this time guised as PSA velocity/PSA re-growth and has been shown to have strong correlations to survival within the metastatic setting, although this has never been tested prospectively. Prospective validation or a consistent story across many studies is important for any marker to be used in decision making and until this has been achieved there will be continued scepticism, rightfully so.
Aim: To evaluate PSA kinetics through a model describing disease regression/progression as a marker for disease progression in the control arms of two phase 3 studies of casodex within the non-metastatic prostate cancer setting.
Methods: We develop a PSA growth law model based on preclinical observations and apply this law to the analysis of PSA time-series data in the clinic within a mixed-effects framework. The result of this analysis gives an estimate of each patients PSA growth/regression rate which we subsequently test within a cox proportional hazards model to assess its importance in disease progression. We also test initial PSA velocity from a discretized version of the model as this is something an everyday medic could calculate without a huge amount of modelling knowledge. Finally, we look at training a time-to-event model with one study and test against another.
Results: PSA kinetics was a significant covariate in one study but not another but a single measure (first PSA value) was a significant covariate within both studies. In addition a model built on one study and then used prospectively in another did not show a strong result.
Conclusion: The relationship between PSA kinetics, using a model based approach, and disease progression within the non-metastatic prostate cancer setting were inconsistent. A positive result was seen in one study but not another. However PSA baseline value was a significant prognostics indicator in both studies, suggesting the absolute value of the marker may well be more important within this setting than its rate of change.

19. A semi-mechanistic PK/PD model of vemurafenib resistance and its rescue by LY2835219, a cyclin-dependent kinase 4/6 inhibitor, in mice bearing human melanoma xenograft tumours

Sonya C. Tate[1], Teresa Burke[2], Shufen Cai[2], Daisy Hartman[2], Palaniappan Kulathaivel[2], Lawrence M. Gelbert[2], Richard P. Beckmann[2], Damien M. Cronier[1]
[1]Eli Lilly and Company, Windlesham, United Kingdom; [2]Eli Lilly and Company, Indianapolis, IN, USA

Background: Although vemurafenib demonstrates excellent clinical efficacy in the first-line treatment of BRAF V600E-mutated metastatic melanoma [1], resistance ultimately develops and patients relapse [2]. Experimental evidence in resistant melanoma cells indicates that MAPK pathway reactivation is a primary mechanism for resistance [3, 4]; however recent studies indicate that the acquisition of resistance may also be associated with an activation of the CDK4/6 pathway through upregulation of cyclin D1 [5, 6]. Consistent with these findings, CDK4/6 inhibition by LY2835219 overcomes resistance and produces tumour growth inhibition in vemurafenib-resistant A375 melanoma xenografts [6]. The objective of this study is to develop an integrated pharmacokinetic (PK)/pharmacodynamic (PD) model to characterize resistance to vemurafenib and its rescue by LY2835219 in A375 tumour xenografts.

Methods: The semi-mechanistic PK/PD model previously developed to describe cell cycle inhibition by LY2835219 [7] was extended to include vemurafenib-mediated BRAF inhibition on the MAPK pathway. Tumour shrinkage induced by vemurafenib was described by inhibition of pERK (major route) and pHH3 (minor route). A modulator compartment driving time-dependent upregulation of the MAPK pathway was incorporated to account for emerging vemurafenib resistance and increasing sensitivity to total Rb. Finally, rescue by LY2835219 was associated with LY2835219-mediated inhibition of total Rb.

Results: Vemurafenib-mediated tumour shrinkage was adequately described by the extended biomarker model. Inhibition of pERK was confirmed to be the primary contributor to tumour shrinkage, and a minor contribution of cyclin D1-mediated cell cycle arrest was identified. Resistance to vemurafenib was successfully accounted for by time-dependent over-expression of pMEK, pERK and cyclin D1. More importantly, inclusion of cyclin D1-mediated sensitivity to total Rb allowed LY2835219-mediated rescue of tumour shrinkage in resistant cells to be successfully characterised.

Conclusions: The PK/PD model successfully described the effect of LY2835219 in vemurafenib-resistant A375 melanoma xenografts. Vemurafenib anti-tumour effect and tumour resistance, followed by LY2835219-mediated rescue were described by an integrated semi-mechanistic PK/PD model. These results support the hypothesis that vemurafenib -resistant melanoma cells rely on total Rb levels for survival and support further exploration of the combination of LY2835219 and RAF inhibitors in melanoma.

References:

1. Chapman, P.B., et al., N Engl J Med, 2011. **364**(26): 2507-16.
2. Flaherty, K.T., et al., N Engl J Med, 2010. **363**(9): 809-19.
3. Su, F., et al., Cancer Res, 2012. **72**(4): 969-78.
4. Nazarian, R., et al., Nature, 2010. **468**(7326): 973-7.
5. Smalley, K.S., et al., Mol Cancer Ther, 2008. **7**(9): 2876-83.
6. Yadav, V., et al., Mol Cancer Ther, 2014.
7. Tate, S.C., et al., Clin Cancer Res, 2014. **20**(14): 3763-74.

20. Modelling a complex input process in a population pharmacokinetic analysis: example of mavoglurant oral absorption in healthy volunteers

Thierry Wendling[1,2], Kayode Ogungbenro[1], Etienne Pigeolet[3], Swati Dumitras[2], Ralph Woessner[2] and Leon Aarons[1].

[1]Manchester School of Pharmacy, The University of Manchester, United-Kingdom; [2]Advanced Quantitative Science, Novartis Pharma AG, Basel, Switzerland; [3]Clinical PKPD/DMPK, Novartis Institute for Biomedical Research, Basel, Switzerland.

Background: Mavoglurant is a structurally novel antagonist at the metabotropic glutamate receptor 5, currently under clinical development at Novartis Pharma AG for the treatment of fragile X syndrome. The pharmacokinetics of two oral formulations were evaluated during a Phase I clinical study in order to select a safe and convenient dosing regimen that would produce a desirable therapeutic effect in the target patient population. Since mavoglurant is considered as a BDDCS class II compound, the effect of a high fat meal on its input properties was also studied. Oral concentration-time profiles appeared complex and highly variable regardless of the formulation and food conditions (*e.g.* multiple-peak phenomenon). Development of a mechanistic model able to describe the erratic input profiles was too challenging given the lack of information on the drug and formulations at the time of the analysis. A flexible empirical input model was thus sought in this work.

Aim: To compare the pharmacokinetics of intravenous (IV), oral immediate-release (IR) and oral modified-release (MR) formulations of mavoglurant in healthy subjects, and to assess the food effect on the MR formulation's input characteristics.

Methods: IV and oral plasma concentration-time data from two clinical studies in healthy volunteers were pooled and analysed using NONMEM®. Drug entry into the systemic circulation was modelled using a sum of inverse Gaussian functions as an input rate function, which was estimated specifically for each formulation and food state. Using the derived input functions, the typical time course of the input rate and bioavailability were simulated for each formulation and food state. 1000 concentration-time profiles following a twice-daily repeated administration were also simulated under each formulation-food conditions. Dose superimposition was performed in NONMEM® using a user-supplied FORTRAN subroutine.

Results: Mavoglurant pharmacokinetics was best described by a two-compartment model with a sum of either two or three inverse Gaussian functions as input function. The mean absolute bioavailability from the MR formulation (0.387) was less than from the IR formulation (0.436). The MR formulation pharmacokinetics were significantly impacted by food intake: bioavailability was higher in the fed state (0.508) and the input process was shorter (complete in approximately 36 h *versus* 12 h for the fasted and fed states, respectively).

Conclusion: Modelling and simulation of mavoglurant pharmacokinetics indicate that the MR formulation might provide a lower steady-state concentration range with less fluctuation (thus potentially better drug tolerance) than the IR formulation, depending on the food conditions at drug administration.

The input function used in this analysis appeared very flexible and convenient to implement in a nonlinear mixed-effects model. Furthermore, although empirical, the derived function helped to gain insight into the input process. The model is however very specific to the data analysed as opposed to physiologically-based pharmacokinetic models.

Poster Abstracts

Develop of a PopPK model of doxorubicin and doxorubicinol in hematological patients

JS Pérez-Blanco[1,2], MJ García Sánchez[1,2], MM Fernández de Gatta[1,2], JM Hernández-Rivas[2,3], D Santos Buelga[1,2].

[1] *Department of Pharmacy and Pharmaceutical Technology, University of Salamanca, Salamanca, Spain,* [2] *Salamanca Institute for Biomedical Research (IBSAL), University Hospital of Salamanca, Spain,* [3] *Hematology Service, University Hospital of Salamanca and IBMCC, Cancer Research Center, Spain.*

Background: doxorubicin (DX) is an important component in the treatment of various solid tumours and haematological malignancies. Despite its frequent use in adults and children diagnosed with cancer, DX has a narrow therapeutic index with myelosuppression and cardiotoxicity being the main dose-limiting toxicities. Improving its pharmacokinetic knowledges in specific populations can be a helpful tool to manage its mainly toxicity limitations.

Aim: To develop a population pharmacokinetic (popPK) model for DX and doxorubicinol (DXol) in hematological patients.

Methods: The study has been conducted in 29 patients diagnosed of hematological malignancies and treated with 30 min intravenous infusion (25-71 mg/m^2 range doses) of DX included in different treatment schedules. From 80 pla sma samples, DX and DXol concentrations were measured and fitted to a PK model using non-linear mixed-effects modeling implemented in NONMEM V7.2 (FOCEI). The analyzed covariates were: age, gender, weight, height, BSA, LBM, BMI, AST, ALT, creatinine, serum albumin, bilirubin and hemoglobin. A preliminary screening of covariates with influence on PK parameters, using GAM implemented in Xpose4 (R v.3.0.3), was conducted. S-Plus applications were used to represent the goodness of fit plot of the tested models. The stepwise covariate model (SCM) was performed with the PsN program and this procedure was applied to select the final model. The evaluation of the model, using non-parametric bootstrap, was performed with PsN.

Results: A four compartment model, two for DX and the other two for DXol, both showing linear elimination, has been selected as the best structural model. The values of the distribution volumes to the different compartments were initially fixed to those proposed by Wilde et al. In the final model only LBM was included on the CLDX which explained a 12% of its variability. The relative standard error for all fixed effect parameters was lower than 20%. Residual variabilities for DX and DXol, estimated from a proportional error model, were 15% (shr = 41%) and 42% (shr = 15%), respectively. Gender, age, hemoglobin levels and ALT showed in the preliminary analysis some influence on the CLDX, but they did not fulfill statistical criteria to be included in the final model. A larger set of data should be considered to evaluate the possible contribution of these covariates on the variability of this parameter. The proposed model showed a reasonable suitability to describe the evolution of the plasma concentrations of DX and DXol in hematological patients.

Conclusion: A suitable population PK model of DX and DXol in hematological patients has been developed. Although the model only included LBM on CLDX, additional studies with a larger set of data should be performed to know if the other covariates selected in the preliminary analysis might be included in a future PK model.

Use of a physiologically-based pharmacokinetic modelling and simulation approach to rationalise actinomycin D dosing in paediatric oncology

Christopher Walsh[1], Jennifer Bonner[1], Gareth Veal[1], Alan Boddy[2]

[1] Northern Institute for Cancer Research, Newcastle University, UK; [2] Faculty of Pharmacy, University of Sydney, Australia.

Background: The majority of paediatric oncology cases are treated with drugs not licenced for use in children, with treatment protocols largely based on dose scaling relative to adults. This can be achieved using metrics involving age, weight and height. However, organ size and enzyme expression do not develop in a linear manner with age, which can impact on drug exposure in children. In order to accurately predict drug exposure in paediatric patients an approach based on physiological development is needed. Actinomycin D is an antibiotic used in the treatment of Wilms tumour and rhabdomyosarcoma in children. Despite being in use for over 40 years, very few studies have been conducted to characterise its pharmacokinetics. In particular the paucity of data available for very young children (<1 year) makes it hard to develop a sound rationale for dose selection in these patients.

Aim: To use physiologically-based pharmacokinetic (PBPK) modelling and simulation in the prediction of the pharmacokinetics of actinomycin D in children. The findings will support actinomycin D dose selection in clinical trials, particularly in age groups where limited pharmacokinetic data exist.

Methods: The project is being carried out using the PBPK modelling and simulation software Simcyp versions 13/14 (Simcyp Ltd., Sheffield, UK). Log P, pKa, blood to plasma ratio, cell monolayer permeability and p-glycoprotein transport data (Km, Jmax) were determined in house and combined with data sourced from the available literature, including information on renal and biliary clearance, to generate an actinomycin D compound file within Simcyp. For the simulation of clinical trial data, information was taken from previous work by Hill *et al*. (2014) which studied 117 patients <21 years old receiving 0.4-1.6 mg/m^2 actinomycin D. The population was split into three age categories: 1-6, 6-10 and 10-20 years. These age bins were further subdivided based on the dose received. Simulations were run for 26 hours following an IV bolus dose (relative to body surface area) over 3 mins. A subset of the 10-20 year age group receiving 1.24 mg/kg actinomycin D was used to develop the model which will then be tested against other age groups and adult data.

Results and conclusions: Simulations using p-glycoprotein transport information resulted in an over-prediction of drug clearance, potentially suggesting the involvement of additional transporters which were not accounted for in this model. The observed biliary and renal clearance values were not sufficient to account for total body clearance of actinomycin D and so an additional systemic clearance value was added. Preliminary visual checks suggest a reasonable fit of the model to observed data, although the model fails to fully capture the plasma concentration variability seen at some early time points. The mean AUC of simulated subjects is within 15% of the observed AUC (8.9 mg/L.min simulated vs. 10.5mg/L.min observed). The model using observed clearance translates well across patients within the same age bracket. The next steps will be to apply the model to observations of younger patients and evaluate how changes in age and body size impact on actinomycin D exposure.

Is PK from Satellite Animals sufficient to understand PKPD?

Emma C. Martin[1], Leon Aarons[1], James W. Yates[2]

1 Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, The University of Manchester, United Kingdom

2 AstraZeneca, Innovative Medicines, Oncology, Modelling and Simulation, Alderley Park UK

Background

Satellite groups are often used in preclinical studies for the collection of pharmacokinetic (PK) data, to avoid the taking of additional samples having physiological effects that may influence the pharmacodynamic (PD) endpoint. However the use of satellite animals means that individual PK parameters are not available to fit PD models. This can impact on parameter estimation, as differences in PK can explain some of the observed differences in PD. One proposed solution is to split the PK samples over a number of days, potentially taking PK and PD samples concurrently; however there is a possibility that because of the sparse sampling, inter-occasion variability (IOV) could affect model parameters.

Methods

In order to investigate these issues, the effect of an anti-cancer drug on neutrophil count in rats was modelled using the Friberg model. A simulation study compared two designs; first taking PK samples over a number of days (compact design), and secondly using satellite animals (satellite design). Results from a previous dose finding study in rats were used to fit the model, and the design of this study was the basis for the simulations. To address the potential issue of IOV impacting on parameter estimation a third simulation was carried out assuming the presence of IOV on selected PK and neutrophil model parameters. Further simulations were carried out to investigate the ability to separate out variation that is due to IOV and variation due to inter-individual variability (IIV). Using the same study design as the compact simulation, different combinations of high and low IIV and IOV were simulated to assess whether both could be accurately estimated simultaneously. A similar analysis was also carried out using a direct E_{MAX} model for comparison.

Results

When the satellite design was compared to the compact design, little difference was observed in the neutrophil model parameter estimates, with the exception of baseline circulation of neutrophils, where the satellite design performed slightly better. Where IOV was assumed on some parameters this also appeared to make little difference to the neutrophil model parameter estimates. However when the same analysis was carried out on a direct E_{MAX} PKPD model it was observed that the PD model estimates were improved when individual PK estimates were available.

Conclusion

This study suggests that using satellite animals and not having individual PK data does not adversely affect model estimation when observing neutrophil counts, even when IOV is present. Conversely when there is a direct effect, as in the E_{MAX} model, not having individual estimates can lead to a lack of precision in PD estimates. Potentially this difference could be due to the slow reaction of neutrophils in the Friberg model, as there is a lag of over 2 days in rats whilst the neutrophils mature, possibly reducing the importance of having individual PK.

A mechanistic PBPK model to predict subcutaneous absorption of therapeutic proteins and monoclonal antibodies

Kate Gill, Linzhong Li, Masoud Jamei, Iain Gardner
Simcyp Limited, Blades Enterprise Centre, Sheffield, UK

Background: Subcutaneous (SC) dosing is a common administration route for therapeutic proteins (TPs) including monoclonal antibodies. The ability to predict the absorption of TPs using a bottom up approach would be useful during clinical development. Therefore, an existing whole body PBPK model capable of predicting plasma and interstitial fluid concentrations of TPs in humans has been expanded to mechanistically predict SC absorption.
Aim: To assess the prediction accuracy of Cmax and tmax following SC dosing of TPs covering a large range of molecular sizes using the expanded PBPK model.
Methods: A whole body PBPK model previously developed in Simulink (Matlab) contains 12 tissues and each is described by three compartments, representing vascular, interstitial and intracellular spaces. This tissue structure was also used to represent the SC dosing site. Movement of TPs between vascular and interstitial spaces was described mechanistically by considering both convection and diffusion processes based on a 2-pore framework [1,2]. SC dose was described as a bolus input to the interstitial compartment of the SC dosing site. The model was optimised using percentage of dose absorbed in the lymph data reported for sheep [3], literature values of SC site lymph:plasma ratios in humans and experimental animals, and observed data showing loss of radiolabelled IgG from the SC dosing site in humans. The model was used to predict Cmax, tmax and plasma concentration profiles for 12 TPs (molecular weight: 8-150 kDa) following SC dosing. Simulation results were compared with observed data collated from the literature. The observed dataset contained 54 studies/dose levels, with up to 14 sets of observed data per TP. Prediction accuracy for Cmax and tmax were assessed using the fold error (predicted / observed). Correlations between prediction accuracy of Cmax or tmax and protein size or isoelectric point were also assessed.
Results: Simulated plasma concentration profiles for a variety of TPs following SC dosing were generally similar to observed data. Cmax was always predicted within 2.7-fold of observed values, with half the Cmax predictions falling within 1.25-fold of the observed values. There was no systematic bias for over or under prediction of Cmax, although a general trend for under-prediction of tmax was apparent. A third of tmax predictions were within 1.25-fold of observed values, with all predictions falling within 3.1-fold. No clear trend between prediction accuracy of Cmax or tmax was apparent based on isoelectric point or molecular size.
Conclusion: The mechanistic whole body PBPK modelling approach described here can be applied to predict absorption of TPs into blood and movement into target tissues following SC dosing. Further enhancement in the future to include mechanistic prediction of catabolism at the site of injection, and hence bioavailability, will allow a true bottom up approach for prediction of SC absorption.
References:
1. Rippe B. & Haraldsson B., 1987, Acta Physiol Scand, 131:411-28;
2. Baxter LT. et al., 1994, Cancer Res, 54:1517-28.
3. Supersaxo A. et al., 1990, Pharm Res, 7: 167-69.

Physiologically-based Pharmacokinetic (PBPK) model of Tapentadol and Tapentadol-O-Glucuronide in adult and pediatric population

Akash Khandelwal,[1] Michael Bolger,[2] Martin Brett,[1] Ronald Rosenburg,[1] Roberta Bursi[1]
[1] Grünenthal GmbH, Aachen, Germany; [2] Simulation Plus Inc, Lancaster, CA, USA

Background: Tapentadol is a centrally acting analgesic that acts through μ-opioid receptor agonism and noradrenaline reuptake inhibition. Tapentadol is primarily metabolized through conjugation to glucuronide and sulfate metabolites by UGT enzymes and sulfotransferases, respectively. Changes in the pharmacokinetics of tapentadol can occur in a pediatric population as a result of changes in organ maturation, changes in body composition and ontogeny of enzymes involved in the metabolism of tapentadol. These age related changes in pediatrics are often non-monotonic, hence traditional allometric-scaling based approaches often fail to accurately predict pharmacokinetic parameters (Mahmood I, 2006), especially in neonates and infants. Instead, Physiologically-based Pharmacokinetic (PBPK) modeling offers a more mechanistic approach in assessing the exposure in neonates, infants and children.

Aim: The objective of this study was to develop a PBPK model for tapentadol and tapentadol-O-glucuronide using available data in adults and pediatric subjects. This model will be used to predict a safe and efficacious dose in pre-terms and those less than 2 years of age with an oral solution or an IV formulation generating similar exposure as oral solution doses of 50 -100 mg in adults.

Methods: A PBPK model was developed using clinical data and biopharmaceutical data of tapentadol in a two-step process. In the first step, a PBPK model was developed that explained mean adult plasma concentration vs. time data for several doses and formulations of tapentadol. In the second step, the PBPK model was extended to include experimental distributions of UGT expression in gut, liver, and kidney. This step enabled the description of the observed pharmacokinetic data after administration of tapentadol oral solution in a pediatric population aged 2 to less than 18 years old. The model was then used for stochastic population simulations as well as to find the optimal dose required to achieve a therapeutic plasma concentration, in children from birth to less than 2 years old, equivalent to safe and efficacious adult doses of 50 to 100 mg. GastroPlus™ 8.5 was used for PBPK modeling and simulations.

Results: The PBPK model included detailed information on the maturation of enzymes known to substantially contribute to tapentadol metabolism. The PBPK model based on adult and pediatric data was able to characterize i.v. and oral dosed pharmacokinetic profiles of tapentadol and tapentadol-O-glucuronide. PBPK model-based simulations were subsequently used to identify doses in a pediatric population that would produce exposures similar to those after oral administration of tapentadol 50-100 mg in adults. The predicted doses will be initially used in the upcoming pharmacokinetic, safety and efficacy studies.

Conclusion: A PBPK model has been developed for tapentadol and tapentadol-O-glucuronide which describes all of the adult and pediatric clinical data (2 < 18 years old) for all doses and formulations using a consistent set of assumptions. The developed model will be used to predict exposure or optimal doses for future studies.

References:

Mahmood I. Br J Clin Pharmacol. 2006 May;61(5):545-57.
Lukacova, V., H. Zhou, et al. (2013). GastroPlus Manual.

The OrBiTo database: A step towards improving the prediction of oral drug bioavailability

Adam S. Darwich[1], Alison Margolskee[1], Shriram Pathak[2], Xavier Pepin[3], Alex Galetin[1], Leon Aarons[1], Amin Rostami-Hodjegan[1,2]

[1]Manchester Pharmacy School, University of Manchester, Manchester, UK; [2]Simcyp Ltd, Sheffield, UK; [3]Sanofi-Aventis Research and Development, Paris, France.

The OrBiTo (oral biopharmaceutics tools) project aims to increase our current understanding of the gastrointestinal processes that govern oral drug bioavailability. One of the main aims of the project is to evaluate and improve upon current physiologically-based pharmacokinetic (PBPK) absorption models in a systematic manner as part of the OrBiTo *in silico* work package by performing simulations and evaluating the predicted oral bioavailability for a number of compound submissions.

A novel database was set up with tailored features aiming to fulfil the project objectives, this included: Providing a secure database accessible by all parties, fully searchable, allowing interaction whilst maintaining anonymity, and allowing new fields to be captured. At submission deadline the OrBiTo database comprised 84 active pharmaceutical ingredients (APIs), 449 pharmacokinetic studies, 643 formulations, submitted by the involved EFPIA (European Federation of Pharmaceutical Industries and Associations) partners. Gap analysis of the database was carried out by three groups querying the database using different methods, these included: Using the built in 'OrBiTo Query Language' able to answer qualitative queries, downloading the generated XML-files, and using third party software to query the database in order to gather quantitative information regarding the APIs. The gap analysis concluded the composition of APIs to be comparable to previous large dataset PBPK evaluation efforts in terms of physiochemical properties (Poulin et al., 2011).

The evaluation process is being carried out using three well-established PBPK absorption models, namely GastroPlus (Simulations Plus), the Simcyp Simulator (Simcyp Ltd) and GI-Sim (AstraZeneca). API selection strategies were formalised independently by key contributors with final inclusion based on agreement between all groups. The final selection included 43 APIs based on the following criteria: Molecular weight, LogP/D, fraction unbound in plasma, solubility, permeability with reference, clearance or preclinical intravenous data. Each API was simulated at least once using the three models with 13 involved EFPIA and academic partners carrying out simulations. In order to test operator differences between sites, one API was selected to be modelled by all institutions, and 10 APIs were selected to be modelled by 4 different institutions.

Following completion of the simulation exercise clinical data will be made available and predictions will be subject to statistical evaluation including comparisons of the concentration-time profiles and secondary pharmacokinetic parameters, investigating where current modelling approaches fail to describe oral drug bioavailable, such as fasted-fed, formulation effects, and drug-specific properties. This is the perhaps most ambitious effort to systematically evaluate absorption PBPK models to date, the hope is to identify what direction absorption modelling refinement takes in the near future.

References:

Poulin P, Jones HM, Jones RD, Yates JW, Gibson CR, Chien JY, Ring BJ, Adkison KK, He H, Vuppugalla R, Marathe P, Fischer V, Dutta S, Sinha VK, Bjornsson T, Lave T, and Ku MS (2011) PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 1: Goals, properties of the PhRMA dataset, and comparison with literature datasets. *J Pharm Sci*.

Development and application of regional intestinal permeability surface area scaling factors for the prediction of oral drug absorption in the distal GI tract.

Andrés Olivares-Morales[1], Leon Aarons[1] and Amin Rostami-Hodjegan[1, 2]

[1]Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, University of Manchester, Manchester, UK.
[2]Simcyp Limited, Blades Enterprise Centre, Sheffield, UK.

Purpose: To develop and evaluate a method to scale human jejunal effective permeability (P_{eff}) values in order to account for the regional differences in the intestinal surface area (SA) along the human gastro intestinal (GI) tract and to indicate its application for the prediction of oral drug absorption from the distal regions ($Abs_{,distal}$) of the GI tract.

Methods: A literature search was conducted to identify the differences between cylindrical and mucosal SA across the small intestine (SI) and the colon, and the anatomical factors that might influence these: *i.e. plicae circulares*; villi; microvilli (MV); colonic haustra; crypts; and colonic microvilli (cMV). An equation that correlates the length of the SI with its mucosal SA for each region of the SI was developed. Regional surface area expansion factors ($SAEF_{region}$) were derived by comparing the SA estimated from the aforementioned equation and the SA for a cylinder in each region of the SI and the colon. To validate this approach the $SAEF_{region}$ were applied to correct P_{eff} values in the upper jejunum (cPeff) and subsequently employed to predict $Abs_{,distal}$ for 11 drugs reported in the literature1.

Results: Equation 1 was derived from the report by Wilson (1967) and describes the cumulative mucosal surface area (MSA, cm^2) of the SI at any position (*x*, cm)

$$MSA_{SI}(x) = 164.16 \times MV \times (0.08L_{si} + 0.276 \times L_{si}(1 - e^{\frac{-3.362}{L_{si}}x})) \text{ , for } x \leq L_{si}$$

where L_{si} is the anatomical length of the SI. From the literature search MV was taken as 20 fold. For the colon, the amplifications provided by CH and cMV were set to 2 and 4.5 fold, respectively. There was good agreement between the observed and predicted $Abs_{,distal}$ when cP_{eff} values were used (72% within the two fold error and a correlation concordance coefficient of 0.85).

Conclusions: $SAEF_{region}$ were successfully derived from the literature and applied for the prediction of $Abs_{,distal}$ of 11 drugs when using cP_{eff}. The predictions were in good agreement with the reported values.

References

1. Lennernas H. Mol Pharmaceutics (2014) 11(1): 12-23.
2. Wilson T. Gut (1967) 8: 618-21.

Impact of Differences in Regional Bioavailability on IVIVC Development for Modified Release Drug Products

Alison Wilby, Zoe Kane, Vanessa Zann, Lloyd Stevens, John McDermot, Peter Scholes

Quotient Clinical Ltd, Nottingham, NG11 6JS

Background: The assessment of an in vitro in vivo correlation (IVIVC) for a modified release (MR) dosage form is a key goal for a development team.
Cmp-1 is a BCS class II compound that at relevant doses behaves *in vivo* as a BCS class I due to elevated solubility in biological fluids. Solubility is pH independent across the physiologically relevant range.
A study to evaluate regional and absolute bioavailability in man confirmed the bioavailability (F) of the IR reference to be 74%, and that although relative bioavailability (Frel) reduced following delivery to the proximal small bowel (93%), distal small bowel (77%) and colon (50%), data supported MR development.
Aim: To optimize an IVIVC for a small molecule (Cmp-1) using a combined understanding of human regional bioavailability, intravenous pharmacokinetics (IVPK) and pharmaceutical and oral PK data for several MR prototypes.
Methods: *In vivo* pharmacokinetic data for five prototype MR and an immediate release (IR) reference formulation was obtained after administration in the fasted state in a six-way crossover study in healthy male subjects.
In vitro dissolution testing for the MR prototypes employed USP II apparatus, 75 rpm, 37°C and 900ml 0.3%SLS in acetate buffer.
Construction of the IVIVC was performed in Phoenix ver. 6.3 (IVIVC Toolkit ver. 2.1) and internal and external validation criteria were examined following investigation of (i) IV vs. IR reference formulations (ii) mean vs. individual concentration-time profiles (iii) time/absorption scaling and incorporation of a Tvivo cut off (iv) single vs. mixed dose correlations.
Results: Dose normalized in vitro dissolution results and plasma concentration time profiles were used to construct a level A IVIVC. The initial correlation was constructed using mean Cp-time data that was deconvoluted using the IR reference formulation. Associated Levy Plots showed that incorporation of a *Tvivo* cut-off would improve the predictability of the model as shown by the summarised percentage prediction errors where all prediction errors for AUC and Cmax were within 15%.
Conclusions: Establishing an IVIVC is a powerful biopharmaceutic tool for facilitating product development, setting specifications and underpinning quality by design (QbD). A validated Level A IVIVC has been developed for Cmp-1 and the predictability of the model improved when a Tvivo cut off of 8-10 h was employed.

Optimized Reduced Designs of Pharmacokinetic Clinical Trials Utilizing a Target Mediated Drug Disposition Model

Ari Brekkan Viggosson[1], Andrew C. Hooker[1], Mats O. Karlsson[1], Siv Jönsson[1]
[1] Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Background: Monoclonal antibodies (mAbs) may display target mediated drug disposition (TMDD) when target binding notably alters the disposition of the drug. In this work a TMDD model, combined with optimal design methods, was employed to evaluate the consequences of reducing the scope of trials featuring mAbs.
Aim: To reduced and optimize sampling schedules for a TMDD model and determine the consequences of reduced designs on parameter precision, precision of free target level predictions at certain time-points and on dose choice for future studies.
Methods: The quasi equilibrium (QE) approximation of the full TMDD model was used to describe the disposition and interaction of a mAb with a soluble target. A typical sampling schedule for mAbs was evaluated, reduced with respect to the number of samples, subjects in the trials and/or trial length and optimized using PopED in R. Expected parameter imprecision was evaluated and used to obtain population predictions of free target levels given each design. The reduced designs were compared to the original designs with respect to efficiency, parameter uncertainty and imprecision of free target levels at certain time-points. The Ds-criterion was used in the optimization and calculation of efficiency to focus on fixed-effect parameters. Based on population predictions of free target levels the likelihood of making an erroneous conclusion regarding dose selection was calculated.
Results: Reduction of the total number of samples from 1872 to 1440 in the QE model did not decrease the Ds-efficiency of the designs below 90%. Substantial reduction in information content (Ds-efficiency ≤ 60%) resulted in precision of free target predictions at 14 days of 4.49-22.21% (root-mean-squared error) over a dose range, compared with 3.31-17.77% for the original design. Designs with 69% fewer samples than the original were 33% more likely to result in an erroneous dose choice to reach target suppression. Reducing the amount of samples by 23% did not affect the dose choice at an 80% power level.
Conclusions: Rich sampling designs for mAbs may be superfluous depending on the purpose of the study. Parameter uncertainty and imprecision in prediction of target levels did not always increase for substantially reduced designs. The risk of making an erroneous dose choice for future studies was marginally increased for reduced designs.

Development and application of a novel pulmonary *in vivo* receptor occupancy methodology for the glucocorticoid receptor

Elin Boger[1,2], Pär Ewing[1], Britt-Marie Fihn[1], Ulf Eriksson[1], Mike Chappell[2], Neil Evans[2] Markus Fridén[1]
[1]Respiratory, Inflammation and Autoimmunity innovative Medicines, AstraZeneca R&D, Mölndal, Sweden; [2]School of Engineering, University of Warwick, Coventry, United Kingdom CV4 7AL

Background: The investigation of pharmacokinetic/pharmacodynamic (PK/PD) relationships for locally acting inhalation drugs is challenging due to the lack of relevant exposure measurements in the target organ. Drug concentration in blood/plasma, which is commonly used for establishing PK/PD relationship, should not be assumed to reflect the target site concentration in lung tissue, nor are there any methodologies for assessing this concentration. As receptor occupancy is driven by unbound drug concentration at the target site, it would clarify the PK evaluation following topical administration as well as provide a quantitative estimate of target engagement in the target organ.

Aim: To develop an *in vivo* receptor occupancy methodology for a receptor targeted by inhalation drugs, such as the glucocorticoid receptor (GR).

Methods: From AstraZeneca's chemical library of GR binders, a promising tracer candidate was identified. The compound proved to have beneficial tracer properties *in vitro* and it was shown to function as a tracer *in vivo* when it was given at an appropriate dose. Following establishment of an experimental protocol, occupancy of GR could be determined *in vivo* in rats after intravenous tracer administration and subsequent quantification of the unlabeled tracer by liquid chromatography tandem mass-spectrometry. The methodology was applied to study the dose and time-dependence of GR occupancy of fluticasone propionate in the lung and spleen. The spleen was intended for use as a reference organ for systemic exposure in future inhalation studies. Occupancy was measured 1.5 hours after three escalating intravenous doses (20, 150 and 750 nmol/kg) and the time-course of occupancy was studied over 48 hours after a 90 nmol/kg intravenous dose.

Results: A clear dose-occupancy relationship was observed and the occupancy was of the same magnitude in the lung and the spleen. ED_{50}, the dose which gives 50% occupancy at 1.5 hours, was estimated to be 47 ± 1.1 nmol/kg. A high initial occupancy was observed after intravenous administration of fluticasone propionate, which was then followed by a time-dependent decline between t=0.5 and t=7 hours. It was noted that the dissociation half-life of the drug-receptor complex, which has not been measured previously in an *in vivo* situation, appeared to be considerably shorter than in an *in vitro* setting.

Conclusion: The developed methodology was successfully used to show a dose-occupancy relationship as well as to characterise the time-course of GR occupancy after intravenous administration of a well-established GR agonist. As such, the methodology can henceforth be used as a powerful tool to clarify the pulmonary PK for inhaled GR binders. Furthermore, comparison of lung and spleen GR occupancy allows an early assessment of the therapeutic index of inhalation drugs since it provides an estimate of pulmonary targeting.

Acknowledgements
This work is funded through the Marie Curie FP7 People ITN European Industrial Doctorate (EID) project No.316736, **IMPACT** (Innovative Modelling for Pharmacological Advances through Collaborative Training).

Structural Identifiability in mixed-effects models

David Janzén[1,2,3], James Yates[1], Mats Jirstrand[2], Neil Evans[3], Michael Chappell[3]
[1]Astrazeneca, [2] Fraunhofer-Chalmers Research Centre Industrial Mathematics, [3]University of Warwick School of Engineering

Background: Structural identifiability concerns whether the parameters in a postulated model structure can be uniquely determined given the input and output functions to and from that model. What this means in practice is that if a model is structurally unidentifiable, the model structure itself allows a subset (or all) of the model parameters to vary while the model output remains unchanged. Conclusions drawn from such a model are potentially unreliable. For instance, if the estimated value of E_{max} is of interest, but if E_{max} is a member of the subset of unidentifiable parameters as a result of the model structure, the estimated value of E_{max} is effectively meaningless.

For deterministic models, there exist several different structural identifiability analysis techniques for both linear and nonlinear systems. However, little has been done on the identifiability analysis of models having a mixed-effects framework. Here the main challenge comes from the fact that, apart from having a deterministic part describing the typical individual, there is also an additional statistical sub-model describing the random effects for the parameters and the covariance between them. In population modelling, these parameters represent the variability in the population. Since estimation of the variability is often one of the main goals in population modelling, it is important to determine whether these parameters can be uniquely determined or otherwise. This motivates the need to extend the concept of structural identifiability for deterministic models to non-deterministic models such as mixed-effects models.

Aim: To develop ways of analysing structural identifiability in mixed-effects models.

Methods: In statistics, and in particular statistical inference, there exist problems which are similar to those encountered in parameter estimation for mixed-effect models. In this work, we make use of these similarities and use these relevant relations to study structural identifiability in mixed-effects models.

Results: Some initial results from a structural identifiability analysis on a particular mixed-effects model structure are presented.

Acknowledgement: This work is funded through the Marie Curie FP7 People ITN European Industrial Doctorate (EID) project, IMPACT (Innovative Modelling for Pharmacological Advances through Collaborative Training).

A physiologically based pharmacokinetic model for 6-mercaptopurine in adults and children: exploring the role of genetic polymorphism in TPMT enzyme activity

Kayode Ogungbenro and Leon Aarons
Manchester Pharmacy School, The University of Manchester, Manchester, M13 9PT, United Kingdom

Background: 6-mercaptopurine is a purine antimetabolite and prodrug that undergoes extensive intracellular metabolism to produce thionucleotides, active metabolites which have cytotoxic and immunosuppressive properties. Combination therapies involving 6-MP and methotrexate have shown remarkable results in the cure of childhood ALL in the last 30 years. 6-MP undergoes very extensive intestinal and hepatic metabolism following dosing due to the activity of xanthine oxidase leading to very low and highly variable bioavailability. TPMT enzyme, an enzyme responsible for intracellular metabolism of 6-MP has shown three genetic polymorphic groups; high (homozygous wild-type), intermediate (heterozygous mutant) and low (homozygous mutant) activity groups. Despite the success recorded in its use there is still lack of effect and presence of life threatening toxicity in some patients due to variability in the PK. This has also been linked to genetic polymorphism in TPMT enzyme activity.

Aims: To develop a PBPK model for 6-MP in childhood ALL and to explore the role of genetic polymorphism in TMPT enzyme activity on the PK of 6-MP.

Methods: A PBPK 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 body was developed. The model accounts for intracellular metabolism of 6-MP and genetic polymorphism in TPMT activity. 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 from studies reporting plasma and intracellular RBC concentrations of 6-MP and its metabolites. Age-dependent changes in parameters were implemented for scaling and variability was also introduced on the parameters for prediction. The effect of genetic polymorphism in TPMT enzyme activity was also investigated.

Results: The model adequately predicts plasma concentration after intravenous and oral doses. The model also provides encouraging results in terms of the prediction of the concentration of 6-MP and its metabolites in plasma and RBC in the different polymorphic groups. For a standard oral dose of 75mg/m^2, the concentration of 6-thioguanine nucleotide (6-TGN) in RBC is about 30 and 2 times higher for the no activity and intermediate activity groups compared to the high activity groups respectively.

Conclusion: A PBPK model that can predict concentrations in different tissues has been developed and this can be used for dose optimisation. This model could help to improve clinical outcome in the use of 6-MP through better dosing.

In Even the Simplest of Cases, Deconvolution May Not Give Exactly What You Might Expect: Analysis of IVIVC Applied to a Simplified Absorption and Transit Model

A. Margolskee, A. Galetin, A. Rostami, L. Aarons

University of Manchester

Purpose

Deconvolution methods have been used extensively in in vitro-in vivo correlation (IVIVC) of oral formulations to derive in vivo dissolution profiles for comparison with in vitro dissolution data for different formulations. These point by point comparisons, termed Level A IVIVC, are the recommended level of IVIVC by the FDA. Traditional methods of deconvolution estimate oral absorption by removing disposition, or the system's response to IV administration, giving an estimate of the cumulative drug entering systemic circulation. However, this is not a pure representation of in vivo release/dissolution since it includes intestinal permeation and first pass extraction, among other processes. Using an oral solution instead of IV during deconvolution removes permeation and first pass extraction. However, intestinal transit and varied dissolution, absorption, and gut wall metabolism along the intestinal tract further complicate the interpretation of the deconvolved input.

Methods

A simplified version of a typical compartmental absorption and transit model was used to compare the results of deconvolution with what might be reasonably expected. Parameter values for transit, dissolution, and absorption were varied across a range of realistic values obtained from the literature and the deviation between expected and deconvolved input were analyzed.

Results

The result of deconvolution is not exactly what is expected. The most important factor is the transit rate, followed by absorption, and dissolution. The deviation is most profound for rapid transit rates, and for slow absorption and dissolution rates. Thus for compounds and formulations where absorption and dissolution are rate limiting, the deviation will be more noticeable.

Conclusion

The deviation between expected and deconvolved inputs occurs due to violation of one of the basic assumptions of deconvolution: the unit impulse response and unknown input are administered in the same location. Though technically an oral formulation will release/dissolve in the same location (the intestines) as an oral solution, intestinal transit and varied gut physiology along the length of the intestinal tract complicates the interpretation of the deconvolved input. Traditional methods of deconvolution may need to be replaced by more physiologically meaningful models to expand the application of IVIVC to low solubility/permeability compounds and exotic formulations.

Translation from pre-clinical to clinical effects of a drug that prolongs the QRS complex

Linnéa Bergenholm[1,4], Teresa Collins[2], Joanna Parkinson[3], Neil Evans[4], Michael Chappell[4]
[1]Discovery Safety, Drug Safety and Metabolism, iMED, AstraZeneca, Mölndal, Sweden
[2]Translational Safety, Drug Safety and Metabolism, iMED, AstraZeneca, Alderley Park, UK
[3] Early Clinical Development, Quantitative Clinical Pharmacology, iMED, AstraZeneca, Mölndal, Sweden
[4]Systems Modelling and Simulation, School of Engineering, University of Warwick, Coventry, UK
This work is funded through the Marie Curie FP7 People ITN European Industrial Doctorate (EID) project No. 316736, IMPACT (Innovative Modelling for Pharmacological Advances through Collaborative Training)

Background: Cardiovascular parameters are routinely analysed in drug discovery and development. In the past decade, methods for prediction and translation of the QT interval (an important ECG parameter) from pre-clinic to clinic have been developed. In particular, PKPD modelling has been utilised to translate pre-clinical *in vivo* animal telemetry studies to clinical results [1]. Another important ECG parameter is the QRS duration, which corresponds to the spread of ventricular depolarisation that precedes contraction. Drug-induced prolongation of the QRS complex has been shown to increase cardiovascular risk. Pre-clinical QRS risk assessment includes *in vitro* ion channel (NaV1.5) and *in vivo* telemetry studies. However, the translation of QRS effects from *in vivo* animal studies to quantitative clinical effect is largely unknown.
Aim: To investigate the quantitative translation of drug-induced QRS prolongation from *in vivo* conscious dog telemetry to clinical effect for an anti-arrhythmic AstraZeneca compound.
Methods: Conscious dog and clinical telemetry data were analysed in a sequential population pharmacokinetic-pharmacodynamic (PK-PD) modelling approach using Matlab and Monolix. The first step was population PK modelling for interpolation of exposure over the measured time points. Exposure data consisted of plasma concentrations sampled during 24 hours after oral and/or iv administration in beagle dogs and healthy volunteers, adjusted for plasma protein binding measured *in vitro.* In the second step, individual PK parameters were used for modelling the drug-induced effect on QRS duration. The continuous telemetry data was binned and averaged at pre-defined time points before and up to 24h after drug administration. The binned data was then normalised to percent of baseline, where the baseline was defined as pre-dose QRS duration. Tested PD models include linear, power and emax direct effect/link models with constant or oscillating baseline. Model selection was based on performance plots, AIC value, precision in estimated parameters and visual inspection. For the translational analysis, confidence intervals for the population-predicted drug effects in dog and human were generated using parameterised Monte Carlo sampling. Then, the quantitative relationship between the pre-clinical and clinical models were analysed.
(Preliminary) Results: Conscious dog and clinical telemetry PKPD data of the discontinued anti-arrhythmic compound AZD1305 was analysed according to the described scheme. In dog, a linear model could describe the data adequately. The drug-induced effect was estimated to be 4.0±1.2 %/uM free AZD1305. In human, inclusion of occasion variability in baseline value improved model performance, and a power model could adequately describe the data. The drug-induced effect was estimated to be 10.1±0.7 *c^0.80±0.05 %/uM.
(Preliminary) Conclusion: This initial analysis suggests that dogs are less sensitive to QRS prolongation by AZD1305, as 4 % QRS prolongation in dog corresponds to 10 % in human.
References: [1]. Parkinson J, Visser SAG, Jarvis P, Pollard C, Valentin J-P, Yates JWT, and Ewart L. Translational pharmacokinetic-pharmacodynamic modeling of QTc effects in dog and human. *Journal of pharmacological and toxicological methods*. 2013

Dose-response-time data analysis of nicotinic acid-induced changes in non-esterified fatty acids in rats

Robert Andersson[1,2], Mats Jirstrand[2], Johan Gabrielsson[3],
[1] School of Engineering, University of Warwick, Coventry, CV4 7AL, [2] Fraunhofer-Chalmers Centre, Chalmers Science Park, 412 88, Göteborg, Sweden, [3] Swedish University of Agricultural Sciences, 750 07, Uppsala, Sweden.

Background: The traditional pharmacokinetic/pharmacodynamic modelling approach, where plasma concentration data and pharmacological effect data are analysed to elucidate the pharmacological properties of a substance, is inadequate in studies where systemic exposure data are sparse or absent. This involve situations where the pharmacological response precedes the systemic exposure (e.g. pulmonary drug administration) or when the drug is locally administered (e.g. ophthalmics). Dose-response-time data analysis act as a surrogate to general pharmacokinetic/pharmacodynamic modelling in these cases.
Aim: To challenge the utility of dose-response-time data analysis.
Methods: We have conducted an analysis on a large preclinical biomarker dataset on the nicotinic acid (NiAc) and non-esterified fatty acids (NEFA) interaction. Data were collected from different rates, routes and modes of NiAc provocations on the NEFA time course.
All information of the exposure to NiAc was excluded in order to challenge the utility of a dose-response-time model. Special emphasis was placed on the selection process of a nonlinear input biophase model. An inhibitory Imax-model, driven by the biophase amount, was used to inhibit the turnover rate of NEFA. A second generation NiAc/NEFA turnover model, which encompasses integral control (slow) and moderator (rapid and oscillatory) feedback, was used.
Results: The dose-response-time model was successfully fitted to all time courses in normal rats. The integral control feedback process allows complete adaptation (return to baseline) when 72 hrs constant-rate infusion protocols of NiAc is used. Finally, new numerical algorithms were successfully applied in the non-linear mixed effects modelling which are more accurate and faster than the conventional techniques used in *e.g.* NONMEM.
Conclusion: The results obtained show the potential of dose-response-time data analysis as a modelling tool in pharmacological studies.

EARLY ESTIMATION OF CLINICALLY EFFICACIOUS DRUG DOSE USING SYSTEMS PHARMACOLOGY APPROACHES; APPLICATION TO THE NERVE GROWTH FACTOR PATHWAY.

Neil Benson[1],
[1] Xenologiq Ltd, Canterbury Innovation Centre, University road, Canterbury, Kent. CT2 7FG. UK.

[Background]Arguably, the major challenge currently facing drug discovery is attrition [1]. In order to address this problem, improvements in the level of understanding of the complexity of human disease biology are required. This presentation will discuss why a mathematical systems pharmacology approach can add value in the pursuit of this improved knowledge, exemplified with the Nerve Growth Factor (NGF) pathway. The NGF pathway has been studied extensively and systems biology models of some of the signaling processes have been published [2, 3]. It is also a pathway of interest in drug discovery, for example for pain [4].

[Aim] To produce a tool using the published systems biology models of the NGF pathway and integrating cross membrane signaling, together with realistic physiological context. This tool could be used for exploring the likelihood of efficacy and identifying optimal targets and dose regimens.

[Methods] A mathematical ordinary differential equation (ODE) model of the NGF biology was constructed and via sensitivity analysis, the targets in the known pathway rank ordered with respect to a biomarker of pain response, the di-phosphorylated extracellular signal regulated kinase concentration in the nucleus. Once selected the concentrations of drug required to inhibit signaling through the pathway were explored. Using a simplified version of the model, lacking the interactions downstream of NGF binding to its receptor, the impact of the additional complexity on inhibition of signaling was investigated. Finally, in order to explore dose regimens that may result in maximal efficacy, a systems pharmacology model was constructed incorporating appropriate physiological context [5]. In order to enable this, cross membrane signaling was required and this was modeled assuming rapid transfer of receptor mass between neuronal and interstitial compartments [6].

[Results] It was concluded that NGF was the most sensitive druggable target in the known pathway, although TrA kinase and Ras signaling may also be of interest. It was found that the negative feedback loops in the pathway attenuate expected inhibitor potency at NGF and TrkA kinase and that non-intuitively high multiples of equilibrium binding constant were required to fully block signaling. These results were concordant with subsequent clinical data. Introducing appropriate physiological context into the model enabled quantitative study of drug dose and regimen.

[Conclusion] Systems pharmacology approaches can have had clear impact on drug discovery at the early research and clinical stages. Systematic application of systems pharmacology will become an important tool in tackling attrition.

REFERENCES

1. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J: Clinical development success rates for investigational drugs. *Nature biotechnology* 32(1), 40-51 (2014).
2. Sasagawa S, Ozaki Y, Fujita K, Kuroda S: Prediction and validation of the distinct dynamics of transient and sustained ERK activation. *Nature cell biology* 7(4), 365-373 (2005).
3. Fujioka A, Terai K, Itoh RE *et al.*: Dynamics of the Ras/ERK MAPK cascade as monitored by fluorescent probes. *The Journal of biological chemistry* 281(13), 8917-8926 (2006).
4. Lane NE, Schnitzer TJ, Birbara CA *et al.*: Tanezumab for the treatment of pain from osteoarthritis of the knee. *The New England journal of medicine* 363(16), 1521-1531 (2010).
5. Benson N, Matsuura T, Smirnov S *et al.*: Systems pharmacology of the nerve growth factor pathway: use of a systems biology model for the identification of key drug targets using sensitivity analysis and the integration of physiology and pharmacology. *Interface focus* 3(2), 20120071 (2013).
6. Benson N, Van Der Graaf PH, Peletier LA: Cross-membrane signal transduction of receptor tyrosine kinases (RTKs): from systems biology to systems pharmacology. *Journal of mathematical biology* 66(4-5), 719-742 (2013).

Interplay between α-, β-, and γ-Secretases Determines Biphasic Amyloid-β Protein Level in the Presence of a γ-Secretase Inhibitor

Fernando Ortega
Affiliation: Centre for Applied Pharmacokinetic Research. School of Pharmacy and Pharmaceutical Sciences. The University of Manchester, Stopford Building, Oxford Road. Manchester M13 9PT, UK
e-mail: fernando.ortega@manchester.ac.uk

Amyloid precursor protein (APP) is processed by β- and γ -secretases producing pathogenic β-amyloid (Aβ) and by α-secretase precluding the Aβ formation. Paradoxically, it has been shown that low to moderate concentrations of γ-secretase inhibitor (GSI) cause a rise in Aβ in different scenarios from cell lines to man. A mechanistic understanding of the Aβ rise remains elusive.

Herein, we show that the fate of Aβ rise is not determined by γ-secretase alone but that the interplay between the three secretases decides Aβ production rate when a GSI is added. Aβ rise is displayed if β- and γ-secretase operates in the linear kinetic region and α-secretase displays saturation kinetics. Furthermore, we build a mechanistic model that rationalizes a series of experimental results that spans from in vitro to in vivo and to man. This has important implications for the development of drugs targeting Aβ production in Alzheimer's disease (AD).

Input estimation in nonlinear dynamical systems for model-based drug discovery using optimal control techniques

Magnus Trägårdh[1], Michael J. Chappell[1], Neil D. Evans[1], Mats Jirstrand[2], Johan Gabrielsson[3], Peter Gennemark[4]

1. School of Engineering, University of Warwick, Coventry CV4 7AL, UK
2. Fraunhofer-Chalmers Research Centre for Industrial Mathematics, SE-412 88 Gothenburg, Sweden
3. Swedish University of Agricultural Sciences, Dept. of Biomedical Sciences and Veterinary Public Health, Division of Pharmacology and Toxicology, SE-750 07 Uppsala, Sweden
4. CVMD iMED DMPK AstraZeneca R&D, SE-431 83 Mölndal, Sweden

Background: In many pharmacokinetic (PK) applications, it is of interest to determine the input to a dynamical system, based only on sparse and noisy measurements. One typical case is when a drug is administered orally, and where there is a known PK model, but the absorption process is not well understood. When the model of the system is linear and time-invariant, input estimation is referred to as deconvolution. Traditional deconvolution methods based on regularised regression can easily be solved in closed form for linear models. However, many PK models are nonlinear, e.g. as a result of saturable elimination. Therefore, being able to handle only the linear case is a severe restriction. Besides, input estimation methods have a much wider applicability than PK, and can be used in any pharmacodynamic (PD) or disease modelling problem where the input to a linear or nonlinear model needs to be determined. As an example, these methods are being considered for use in body-weight modelling, estimating the energy intake from body weight measurements.

Aim: To investigate, implement and benchmark techniques for input estimation (deconvolution) for the case when the underlying dynamical system is nonlinear.
Methods: Key techniques from optimal control theory were applied: multiple shooting and collocation in combination with sensitivity analysis and automatic differentiation. The techniques were benchmarked on a previously published dataset measuring the plasma concentration of eflornithine in 26 rats after oral administration. Two choices of regularisation functions were used: Tikhonov (ridge regression) and Maximum Entropy.

Results: The investigated methods worked robustly on the benchmark dataset, even when starting from very poor initial guesses. The multiple shooting methods needed 15 seconds on a standard workstation for a typical dataset, while collocation methods needed about 5 seconds.
Conclusion: Optimal control methods make it possible to use traditional deconvolution methods even when the system is nonlinear.
Acknowledgements: This work is funded through the Marie Curie FP7 People ITN European Industrial Doctorate (EID) project, **IMPACT** (Innovative Modelling for Pharmacological Advances through Collaborative Training).

Tumour Growth Inhibition Model and Survival Analysis in Patients with Second-Line Metastatic Ovarian Cancer

Chiara Zecchin[1], Nathan H. Enas[2], Lena Friberg[3] and Ivelina Gueorguieva[1]
[1]Lilly Research Laboratories, Sunninghill Road, Windlesham, Surrey, UK, [2]Lilly Research Laboratories, Indianapolis, Indiana, USA , [3] Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Background: In the scientific community there is growing interest in using Change in Tumour Size (CTS) as a measure of treatment effect and as a primary endpoint, instead of conventional metrics as progression free survival, since it allows earlier evaluation of treatment effects, ultimately resulting in more timely regulatory approvals of cancer treatments.
Aim: The aim of this work is to develop a modelling framework to quantify the anti-tumour effect of Carboplatin alone and Carboplatin in combination with Gemcitabine treatments and to investigate the relationship between CTS and Overall Survival (OS) in second line metastatic ovarian cancer.
Methods: Data from a multicenter, Phase III, randomized study designed to compare the efficacy and safety of Gemcitabine plus Carboplatin versus Carboplatin monotherapy in patients with recurrent ovarian cancer were analysed. A drug dependent model to describe tumour growth dynamics was developed and parametric models for the prediction of new lesions appearance and of survival probability are currently under investigation.
Results: The tumour growth inhibition (TGI) model incorporated different shrinkage efficacy by both Carboplatin and Gemcitabine with common resistance to the two drug effects. A preliminary visual analysis shows that appearance of new lesions, ECOG status at baseline and tumour size at baseline are predictive of OS. Future work will further investigate these relationships, together with metrics related to tumour size time course and relative change over time, incorporating them in a parametric time-to-event model for predicting OS probability.
Conclusions: A modelling framework was established to quantitatively describe the promoting effects on tumour death of Carboplatin monotherapy and Gemcitabine plus Carboplatin combotherapy. Future work will formalize the effect of the model predicted tumour size time course on survival probability in second line metastatic ovarian cancer.

Application of a physiologically-based population pharmacokinetic model for simvastatin and its active metabolite simvastatin acid to predict clinically relevant drug-drug interactions

Nikolaos Tsamandouras[1], Amin Rostami-Hodjegan[1,2], Aleksandra Galetin[1], Leon Aarons[1].

[1] Centre for Applied Pharmacokinetic Research, University of Manchester, UK, [2] Simcyp Ltd, Sheffield, UK

Background: Simvastatin (SV), a commonly used HMG-CoA reductase inhibitor, is a prodrug with complex pharmacokinetics due to the inter-conversion between the parent drug and its main active metabolite, simvastatin acid (SVA). Both SV and SVA undergo oxidative metabolism mainly by CYP3A4/5 and therefore are subject to clinically important drug-drug interactions (DDIs) and associated risk of myopathy.

Aim: Use a physiologically-based population pharmacokinetic model for simvastatin and its active metabolite simvastatin acid to predict clinically relevant drug-drug interactions.

Methods: In the current study a model with physiologically realistic compartmental structure was developed allowing inter-conversion between the lactone (SV) and acid (SVA) form of the drug in different tissues. The model was developed with nonlinear mixed effects software (NONMEM 7.2) using SV and SVA plasma concentrations from 34 healthy volunteers. The ability of the developed model to predict DDI effects was assessed by evaluating the model's predictive performance using a range of CYP3A inhibitors, namely clarithromycin, itraconazole, erythromycin and diltiazem. The concentration-time profiles of inhibitors in the sites of interaction were generated in Simcyp v13 and were used as forcing functions in the small intestinal wall and liver tissue compartments of the developed SV/SVA mechanistic model.

Results: For each of the DDI investigated, the model-predicted changes in SV and SVA Cmax and AUC were compared to the observed values from reported clinical DDI studies. Overall, the developed model predicted the increase in both SV and SVA AUC and Cmax within 2-fold of the observed values for the evaluated DDIs. The best model performance was observed in the case of clarithromycin DDI. Specifically, the model predicted an increase in plasma SV AUC and Cmax by 10.02- and 6.49-fold respectively and 11.46- and 8.97-fold increase in SVA AUC and Cmax respectively, following a week of co-administration of 40mg simvastatin with twice-a-day 500mg clarithromycin. The respective observed values were 9.95, 7.14, 12.17 and 10, respectively [1]. A significant advantage of the developed mechanistic model is that it can predict the DDI effect on the SV/SVA concentrations in the clinically relevant tissues such as the liver (site of action) and muscle (site of toxicity). Our model predictions indicate that the evaluated DDIs cause a significant increase in the muscle exposures of both SV and SVA, which is concordant with the clinically observed cases of rhabdomyolysis.

Conclusion: The presented model-based approach can be of significant use during the drug development for assessing DDI risk of compounds likely to be co-administered with simvastatin.

[1]. Jacobson, T.A., Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. The American journal of cardiology, 2004. 94(9): p. 1140-6.

A population pharmacokinetic model for AZD1152 and AZD1152hqpa in the rat following intravenous dosing of either AZD1152 or AZD1152hqpa

Mike Walker
AstraZeneca Oncology iMED: DMPK Modelling & Simulation

Background and Objective

AZD1152 was developed as an intravenous treatment of solid and haematological cancers and is a prodrug of the active drug AZD1152hqpa. The aim of this work is develop a model for both compounds that adequately predicts the plasma concentrations of AZD1152hqpa in the rat for use in pk/pd modelling. Data was available following iv bolus dosing of both compounds and infusion dosing of AZD1152. In total 2402 quantified observations were available from 616 rats. There were also 575 observations below the assay limit of quantification. Data was available from both males and females and from the nude and Han Wistar strains.

Pharmacokinetic Model

The final structural model linked a 2 compartment model for AZD1152 to a 3 compartment model for AZD1152hqpa with all of the clearance of the prodrug forming active drug. The model was built using data from rats with at least 4 observable data points. The final parameters were estimated using the full data set, including the observations below the limit of quantification. A 100 sample bootstrap with sampling stratified by strain and sex was run to generate estimates of the variability of each parameter.

Both sex and strain were tested as categorical covariates for all of the fixed effect parameters. No significant covariate effects were found.

Discussion and conclusions:

The size of the inter-individual errors and the shrinkage values for the compartment volumes and the inter-compartmental flow of AZD1152 show that these parameters are highly variable and maybe poorly quantified. However, comparison to models with these terms removed indicated that these terms should remain in the final model. It is felt that this reflects both the lack of individuals with rich data and the fact that the terminal phase of AZD1152 following intravenous bolus dosing is in the range where many of the concentrations fall below the assay limit of quantification. The model provides a good prediction of the pharmacokinetics in the rat of the active drug AZD1152hqpa after intravenous bolus dosing and following intravenous bolus or infusion dosing of the prodrug AZD1152.