Welcome to the Pharmacokinetics UK 2006 Meeting

Wednesday 15\textsuperscript{th} November – Friday 17\textsuperscript{th} November

Sheffield Marriott Hotel

Kenwood Road

Sheffield, S7 1NQ

Programme and Abstract Book
Wednesday 15th November

12.00  *Arrival and luncheon*

*Welcome & Session 1: Contribution of Modelling to Clinical Pharmacology*

14.00  Welcome: Steve Toon

14.05  Introduction to the First Session: Geoff Tucker and Alison Thomson

14:10  Henry Elliott  Relevant clinical pharmacological analysis is essential for optimal therapeutic outcome

14.45  Jean-Louis Steimer  Population PK model of balicatib, a cathepsin K inhibitor and a PKPD model for changes in bone turnover biomarkers

15.20  Sir Colin Dollery  Pharmacokinetics: master or servant?

16.05  *Coffee break*

16.20  Kim Rainsford  What pharmacokinetics can teach us about adverse reactions from coxibs and the NSAIDs

16.50  Simon Davis  Technical and process obstacles to effective integration of modelling in clinical pharmacology decision making

17.20  Petra Jauslin  Simultaneous modelling of 14-hour glucose and insulin profiles in type 2 diabetics

17.50  *Break*

18.30  *Poster Session (upstairs) – Free Bar (downstairs)*

20.00  *Dinner*

Thursday 16th November

*Session 2: Intracellular Pharmacokinetics*

09:00  Introduction to Second Session: Amin Rostami and Peter Milligan

09.05  Mike Roberts  Intracellular pharmacokinetic modelling

09.50  Raimund Peter  *In vitro-in vivo* correlation of mechanism-based P450 inhibition: complications for kinetic modelling

10.35  *Coffee break*  *Viewing Posters*

10.55  Per Artursson  Role of different transport routes during drug absorption and distribution

11.40  Jiansong Yang  *In vitro* and *in vivo* kinetics of mechanism-based inhibition

12.30  *Lunch*

*Session 3: Systems Biology: What is in it for us?*

14.00  Introduction to Third Session: Atholl Johnston and Leon Aarons

14.05  Erik Mosekilde  Mechanism based modelling of biomedical systems

14:50  Bill Jusko  Modelling pharmacogenomic effects of corticosteroids

15.35  *Coffee break*  *Viewing Posters*

15.50  Sean Ekins  Combining quantitative structure activity relationships and systems biology approaches for *in silico* ADME/Tox

16.35  Bob Leipold  Biosimulation in translational medicine

17.20  *Break & free bar*
17.45 Bob Powell The Peter Coates Lecture, with an introduction by Steve Toon

18.45 Break

20.15 PKUK Banquet

Friday 17th November

Session 4: Open Session

09.00 Introduction to Open Session: Mike Walker and Steve Toon

09.05 Jeff Barrett Design and implementation of a paediatric knowledgebase: a decision support interface to guide patient pharmacotherapy

09.45 Amy Cheung Validation and reparameterisation of a cardiovascular PKPD model

10.15 Iona Macdonald Evaluation of an interacting multiple model approach to the analysis of gentamicin data from clinically unstable patients

10.45 Coffee break Viewing Posters

11.00 James Yates Analysis and application of distinguishable parent-metabolite pharmacokinetic models

11.30 Anthe Zandvliet Optimization of the indisulam-carboplatin regimen using a PKPD model of myelosuppression

12.00 Alison Thomson Population pharmacokinetics of teicoplanin in outpatient home parenteral antibiotic therapy (OHPAT)

12.30 Final conclusions and Closing remarks, Buffet Lunch
Session 1: Contribution of Modelling to Clinical Pharmacology

1. Relevant Clinical Pharmacological Analysis is Essential for Optimal Therapeutic Outcome

Henry L Elliott, Henry L Elliott Consulting Ltd

There are many different methods for exploring and defining pharmacokinetic-pharmacodynamic (PK-PD) relationships but therapeutic practice is littered with examples where relevant PK-PD information has been ignored (or, possibly, misused!).

For example, consider the recent recommendation that atenolol should no longer be considered to be a routine first line antihypertensive drug. This almost certainly has a simple PK-PD basis: atenolol is not suitable for its recommended once daily dosing because it has a relatively short half life and duration of action. The relevant information, albeit from a simplistic PK-PD study, has been available for more than 25 years. Similar information has been overlooked about dosage regimens for ACE inhibitor drugs (e.g. enalapril - twice daily produces a significantly better 24-hour effect than once daily) and dose ranges for statins (e.g. simvastatin - 10, 20 and 40 mg all occupy the middle range of the dose-response relationship).

Furthermore, the clinical pharmacological literature contains the overlooked PK-PD answers to many of the issues implicated in the 1990s debate about the safety of dihydropyridine CCBs e.g. that not all such CCBs are dangerous but the short-acting, rapid-onset agents might well be … and also to the more recent cost-motivated debate about the therapeutic equivalence of different long-acting CCBs e.g. that amlodipine and felodipine ER are not therapeutically equivalent.

The majority of these examples reflect the results of relatively unsophisticated PK-PD studies but they underline the importance and relevance of appropriate pharmacokinetic and PK-PD analyses for the design of optimal drug dosing regimens… provided that the information is applied to the development of optimal treatment regimens without short-term commercial or cost implications used properly.

2. Population PK model of balicatib, a cathepsin K inhibitor, and a PKPD model for changes in rapid and slow bone biomarkers

Jean-Louis Steimer1, Nick Holford2, Nitin Kaila1, Goonaseelan (Colin) Pillai1

1Modeling & Simulation, Novartis, Basel & East Hanover, Switzerland
2Dept of Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand
Background: Registration of drugs for the treatment of osteoporosis requires the demonstration of clinical benefit against fractures. In the course of clinical development, biomarkers may be used, such as serum telopeptide (CTx) and lumbar spine bone mineral density (BMD) to define concentration and dose response relationships. Cathepsin K is a key enzyme for the breakdown of collagen during bone resorption. Balicatib inhibits cathepsin K and has been shown to reduce bone turnover in preclinical experiments and has the potential as a new treatment for osteoporosis. We report a modeling and simulation (M&S) analysis of balicatib studies performed during Phase 1 and 2 of clinical development.

Methods: Pharmacokinetic data in healthy subjects and patients with post-menopausal osteoporosis were obtained after single oral doses of 5 to 400 mg and multiple oral daily doses of 5 to 50 mg up to 12 weeks. CTx, a fast biomarker (time-course of days) of bone resorption, was observed over up to 3 months in 140 patients (Phase 2A) and 12 months in 675 patients (Phase 2B). Daily doses of 5 to 50 mg were administered for 12 months in a randomized parallel group, placebo controlled double blind Phase 2B study. BMD, a slow biomarker (time-course of months) of bone mineralization, was observed up to the end of the Phase 2B study. Drug concentration measurements were not available in the Phase 2B study. NONMEM Version V 1.1 was used for analysis of balicatib PK and the CTx and BMD biomarker data.

Results: A two compartment disposition model with zero-order input and first-order elimination described plasma balicatib concentrations. Renal clearance was predicted by assuming a linear relationship to predicted creatinine clearance (CLcr) and accounted for 13% of total clearance. The variability in balicatib total clearance was unexpectedly small for a CYP3A substrate (apparent CV 12.2%). Inhibition of cathepsin K by balicatib was assumed to drive formation of CTx in the model using a turnover model of collagen. The data showed an initial rapid fall following the first dose of balicatib reaching 70-80% change vs baseline for the 50mg dose. This was well described by the model. CTx concentration data gradually increased over subsequent weeks with a rebound above baseline after stopping the treatment at 12 weeks. The rebound of CTx could be described adequately by proposing a model with accelerated turnover of bone formed during cathepsin K inhibition. The BMD time course was modeled using a linear disease progress model with an Emax offset effect. An empirical effect compartment model was used to account for the slow increase in BMD over several months, driven by the average steady state plasma concentration of balicatib. Clearance was individualized using weight and renal function from the previously developed PK model. This model was adequate to describe the dose-exposure-biomarker relationship over the set of doses (placebo, 5, 10, 25, 50 mg). According to the model, a dose rate of 50 mg/d of balicatib over one year achieves about 75% reduction on CTx and close to the maximum possible effect on BMD. As already demonstrated in the past for bisphosphonates, serum telopeptides act as very rapid and sensitive bone turnover biomarkers, suitable for initial learning studies (e.g. dose-finding) of short duration. Model-based analyses provide early quantitative data for guiding decision making about choice of dose in osteoporosis drug development, which is typically of several years duration.
Acknowledgements: The authors acknowledge the help of Florilene Bouisset, Vincent Buchheit, Williams Collins, Serge Cremers, Aurelie Gautier, Sandip Roy, Andrej Skerjanec, Ulrich Trechsel who all contributed to this project.

3. Pharmacokinetics. Master or Servant?

Colin T Dollery.

The origins of pharmacokinetics lay in a desire to better understand clinical responses by measuring drug concentration in blood. Improving analytical techniques made it possible to measure drug concentrations much more easily and accurately than pharmacodynamic effects. A small industry sprang up describing and modelling the curves of plasma concentration against time. The best work made very valuable contributions, for example developing the concept of clearance, but much of the work on modelling paid no attention to the physiological modelling espoused by Teorell in 1937 and used models that had only a hazy connection to physiological parameters. I have rather unkindly labelled this as membership of the exponential strip club.

Pharmacokinetics can be very important alone, for example in understanding the variability of drug absorption and metabolism, but its greatest value is realised when it is used in conjunction with other information. Part of my lecture is a debate between two characters, a gentleman called NOAEL and a lady called MABEL. Can you guess why they disagree?

All joking apart pharmacokinetics has a very important part of to play in therapeutics, particularly in the analysis of PK/PD relationships. But the real world situation is very much more complex than some theoreticians imagine. The application of pharmacokinetics requires a multi-disciplinary approach and a knowledge of the medical problem is a key requirement – which is where it all started when Friedrich Dost, a paediatrician, coined the work pharmacokinetics.

Looking ahead I see the development of systems biology applied to organs and whole organisms as the key to the application of pharmacokinetics in physiology, pharmacology and medicine. I use Systems Biology ‘modelling’ to refer to predictive modelling of the underlying process that generates the experimental data, rather than simply modelling the data itself.

4. How has the Pharmacokinetics of NSAIDs, Including the Coxibs, Helped in Understanding their Adverse Effects

K. D. Rainsford, Biomedical Research Centre, Sheffield Hallam University, SHEFFIELD, S1 1WB, UK
Adverse reactions from NSAIDs are a major health problem and contribute to appreciable morbidity and, rarely, mortality from these drugs, especially in the elderly arthritic patient who is dependent on these drugs for relief of pain and joint symptoms. Variability in their pharmacokinetics [PK] (especially with age, gender, race and possibly cytochrome and other drug detoxifying polymorphisms), drug-drug and drug-disease interactions are major factors contributing to the development of their toxic reactions. In some cases mechanisms based pharmacology (or toxicology) can be invoked to understand the mechanisms of action of NSAIDs (e.g. inhibition of COX-1/COX-2 in the development of GI and renal effects). The historical term “idiosyncratic” reactions which are used to describe some of these reactions actually disguise ignorance of the understanding of the mechanisms.

Historically, the earliest reactions observed with the NSAIDs were upper gastrointestinal bleeding and ulceration from the salicylates during the mid-late 19th C., and aspirin shortly after its introduction at the beginning of the 20th C. It is now known the factors affecting the GI mucosal uptake and metabolism of these drugs are central to understanding their adverse reactions in the GI tract. In the 1920’s severe liver reactions were observed with cinchophen which probably relate to the development of reactive metabolites from this drug. Accumulation of phenylbutazone in bone marrow coupled with its long plasma T1/2 was thought to underlie the development of blood dyscrasias. Liver and hepato-renal reactions are now legend with many NSAIDs; the most celebrated cases were those from (a) ibufenac, the precursor to ibuprofen, the former being found to accumulate in the liver and the latter developed to avoid this; and (b) that of the long plasma T1/2 drug, benoxaprofen, in the early 1980’s having a complex PK aetiology. Diclofenac is now well-known to cause hepatitis and this is thought to be due to formation of the quinine-immine type reactive metabolite similar to that which is invoked in paracetamol hepatotoxicity. Little direct clinical evidence is available to support this suggestion although there is good evidence from studies in laboratory animal models. Studies on the hepatic reactions attributed to the COX-2 preferential NSAID, nimesulide (not available in the UK) have invoked formation of nitroso- or hydroxylamine reactive metabolites. However, this is difficult to reconcile with the very low production of amino metabolites through the pathway of their formation. Case reports have implicated concomitant intake antibiotics and other hepatotoxic drugs in the development of hepatic reactions form nimesulide. This may also occur with other NSAIDs, thus leading to either drug-drug (e.g. with antibiotics or paracetamol) or drug-disease reactions (such as seen in patients with severe RA or SLE consuming salicylates or other NSAIDs). Acyl glucuronides of salicylates and propionates have been implicated in the formation of covalent derivatives that may be important in hepato-renal reactions. Other reactive metabolites include epoxides of alclofenac and fenclofenac that have been thought to be involved in skin reactions. These few examples highlight the diversity of metabolic reactions that are associated with NSAID toxicities. Mitochondrial accumulation of acidic NSAIDs with subsequent effects in depleting ATP and caspase activation may account for reactions in the liver, kidney and GI tract form these drugs.

Recently, there has been much concern about the occurrence of MI and other serious cardiovascular (CV) effects from the coxibs, a class of drugs developed specifically to
overcome the COX-1 dependent GI ulceration and haemorrhage that frequently occurs with conventional NSAIDs. While rofecoxib (now withdrawn because of these reactions) and valdecoxib were found to be associated with severe CV reactions the occurrence of these events with other coxibs and some NSAIDs has been a subject for debate. The role of selective COX-2 inhibition of vascular prostacyclin has been implicated though in much dispute. Rofecoxib has a long $T_{1/2}$ and this coupled with its potential for systemic drug accumulation and recent identification of covalent binding to vascular cells may underlie the CV reactions from this drug. The issue of reduction in the anti-platelet effects of aspirin due to PK interactions from concomitant intake of ibuprofen is also debatable although it may be circumvented by separating the intake of these drugs. The complex CYP2C9 and 2C19 metabolism of celecoxib [which does not occur with rofecoxib] has been implicated in adverse reactions from this drug. Studies on the oral clearance of NSAIDs in subjects bearing various CYP2C9 genetic variants have implicated their propensity in development of clinically-significant adverse reactions, though the clinical data supporting these interesting suggestions is wanting.

Thus, there are many examples of how the patterns of PK and their perturbation or variation in various clinical states have perforce given support to the importance of PK in development of adverse reactions form the NSAIDs.

### 5. Technical and Process Obstacles to Effective Integration of Modeling in Clinical Pharmacology Decision Making

*Simon Davis, Pharsight*

Many in the pharmaceutical industry share FDA's concerns about the slow translation of scientific discoveries into new and better medical treatments. The Critical Path Initiative, originally published in 2004, has now been supplemented by the 'Critical Path National Opportunities List' Both documents advocate the increased use of modeling and simulation as a means to evaluate the safety and effectiveness of new medical products in faster time frames, with more certainty, and at lower costs. This talk addresses the reasons why widespread adoption of PK modeling continues to be a challenging management objective in most drug development organizations. It will cover the basic limitations on PK/PD modeling including scarce staff with the skills to do it, poor productivity caused by absence of integrated data storage and analysis tools, poor data availability caused by outmoded study designs and antiquated data management procedures, poor predictability of modeling project timelines. Also reviewed will be steps pursued by some cutting-edge organizations to install better-integrated analysis tools and modern data management that leverage staff by making them more productive and shortening learning curves.

### 6. Simultaneous modelling of 14-hour glucose and insulin profiles in type 2 diabetics

*PM Jauslin (1, 2), N Frey (2), MO Karlsson (1)*

*PM Jauslin (1, 2), N Frey (2), MO Karlsson (1)*
Objective. The purpose of this work was to develop a model to describe and predict glucose and insulin profiles during the course of a day following repeated meal tests.

Data. Placebo data of a study investigating an oral antidiabetic were used for analysis. 18 type 2 diabetic patients participated in the study. Samples for the determination of plasma glucose and insulin concentrations were collected in short intervals up to 14 hours after intake of a standardised breakfast. Standardised lunches and dinners were ingested 5 and 10 hours after breakfast, respectively. The three meals were identical in composition.

Methods. Simultaneous analysis of glucose- and insulin data was performed through non-linear mixed effects modelling in NONMEM version VI\(^\beta\). A model previously presented at PAGE 2005\(^1\) was used as a starting point. This model consisted of a two-compartment disposition submodel for glucose with endogenous production and two pathways of elimination, one of them being dependent on insulin, and of a one-compartment submodel for insulin with endogenous production and linear elimination. Glucose absorption was described by a flexible chain of transit compartments. Feedback loops were incorporated for the regulation of insulin secretion stimulated by elevated glucose concentrations, and for the regulation of glucose elimination depending on insulin concentrations. The delay of action of these regulations was mediated through effect compartments. In addition, the incretin effect was taken into account by introducing a pharmacodynamic link between the glucose absorption rate and insulin secretion. Parameter differences between meal tests at different times of the day were investigated to detect possible circadian patterns.

Results and Discussion. In most subjects, higher glucose concentrations were observed after breakfast than after lunch and dinner, despite identical meal composition. Insulin levels, on the other hand, were comparable after all three meals. Similar trends have been described in the literature, and different explanations for these observations have been proposed. Both circadian variations in the glucose-insulin system, such as a higher hepatic glucose production in the morning, and a residual insulin action from previous meals during the day have been hypothesized. The model was able to adequately describe glucose and insulin profiles during 14 hours without any adjustments for circadian patterns. An accumulation of insulin in the effect compartment was able to account for the hypothesized persistent insulin action. However, additional analyses are ongoing to investigate whether the inclusion of circadian variations on different parameters may further improve model performance. Preliminary results indicate that these circadian differences mainly affect the interactions between glucose and insulin: both the magnitude and the rate of the interactions were reduced towards the evening. In particular, an apparent decline in glucose-triggered insulin secretion and a longer delay in the insulin effect on glucose elimination were observed after dinner.

\(^1\) PM Jauslin, Silber HM, Frey N, Gieschke R, Simonsson USH, Jorga K, Karlsson MO. A Disease Model Describing the Regulation of the Glucose-Insulin System in Diabetic Patients after IVGTT and OGTT
Session 2: Intracellular Pharmacokinetics

7. Intracellular Pharmacokinetic Modelling

Michael S Roberts, School of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane, Australia

Intracellular pharmacokinetics seeks to describe the kinetics associated with the transport, binding, sequestration and detoxification of drugs within cells. Our work has emphasised the role of solute physicochemical properties, the underlying organ physiology, biochemistry and pathology, and the differences between organs as determinants for solute pharmacokinetics. Most of our work has been based on the results of multiple indicator dilution studies, whereby drugs and space markers are injected simultaneously as an impulse into a single pass perfused organ and the outflow profiles for these compounds and the drug metabolites are measured. Microdialysis has also been used for human studies.

The work has shown that cellular pharmacokinetic processes differ between organs and solutes with pathology playing a key role in drug disposition kinetics. Of particular note is the role of membrane permeability, organelle ion-trapping, binding and cellular transport as determinants of hepatic clearance. Organs studied to date include the liver, lung, head, pancreas, skin, placenta and limb. Our work with diseased livers has shown that there are differential effects of conditions such as arthritis, cholestasis, steatosis, cirrhosis and partial hepatectomy. A number of physiologically based pharmacokinetic models have been used in the analysis the data obtained.


Raimund Peter, AstraZeneca

Irreversible inhibition of drug-metabolizing CYPs can be observed for a number of marketed drugs in various therapeutic classes (e.g. oral contraceptives, macrolide antibiotics). Predicting the extent of these drug-drug-interactions in vivo based on in vitro experiments still presents a major challenge for drug discovery and development. This presentation aims to discuss the problems encountered in this approach, such as experimental study designs and pharmacokinetic parameters (e.g. dilution factor, protein half-life). A critical evaluation of the different factors influencing in vitro-in vivo correlations should provide us with improved PK predictions for these drugs.

9. Role of different transport routes during drug absorption and distribution
Per Artursson, Uppsala University

Abstract not received.

10. In Vitro and In Vivo Kinetics of Mechanism-Based Inhibition
Jiansong Yang, Simcyp Limited

The increased number of published reports on mechanism-based inhibition (MBI) indicates a growing awareness of the potential impact of MBI in drug development. MBI may cause more serious interactions compared with reversible inhibition, as the inactivated enzyme has to be replaced by newly synthesised enzyme. Although quantitative prediction of the in vivo auto-inhibition and MBI from in vitro data is possible, the accuracy of such predictions will clearly depend on the accuracy of the in vitro estimates of the relevant kinetic parameters.

The conventional experimental protocol (CEP) developed by Silverman 15 years ago is based on several assumptions. These assumptions are often violated in practice, leading to biased estimates of the kinetic values of MBI. Based on the in vitro kinetics of MBI, a mechanistic experimental protocol (MEP) has been developed. The MEP was theoretically assessed by the simulation on 16 reported mechanism-based inactivators. Compared to the CEP, the MEP provides simpler experimental design and more accurate results. Implications to the prediction of in vivo MBI from in vitro data will be discussed.

Session 3: Systems Biology: What is in it for us?

11. Mechanism-Based Modelling of Biomedical Systems

Erik Mosekilde, Department of Physics, The Technical University of Denmark, 2800 Lyngby, Denmark

The BioSim Network: BioSim is an EU sponsored Network of Excellence in “Biosimulation – A New Tool in Drug Development”. The Network brings together researchers from 26 university departments, nine small and medium sized enterprises, one large pharmaceutical company, and four national regulatory agencies in order to promote the use of mathematical modelling in health care and drug development. Five of the university departments are engaged in the development of new treatments for cancer, diabetes, depression, and tremor. Several of the other groups perform experimental research on various biochemical, cellular, pharmacological, or macrophysiological problems. In parallel with physiologically-based pharmacokinetic models and population models, the Network also promotes a mechanism-based modelling approach that takes its starting point in a detailed description of the biological processes of relevance to a given problem.
**Mechanism-based modelling:** Among the basic aims of the mechanism-based modelling approach are (i) to test the consistency of existing hypotheses and data by subjecting them to a quantitative evaluation that considers, for instance, time scales and the relative magnitudes of regulatory mechanism, fluxes, energy consumptions, etc. (ii) to develop a modelling structure that represents the physiological processes in such a manner that changes in behaviour under different conditions can be predicted by parameter adjustments, (iii) to bridge phenomena at various physiological levels such that, for instance, tissue properties can be predicted from cellular behaviours and interactions, and (iv) to establish an effective framework for accumulation of knowledge about a given biological system. This is obviously a major challenge, and it will only be gradually met over the coming decades. The immediate challenge to BioSim is to demonstrate that even the initial steps in this process can be of value to the pharmaceutical industry as well as to the health care system.

**Examples:** The talk will discuss some of the main concepts of the mechanism-based modelling approach including the relation between structure and parameters, the model evaluation process, and the role of unstable regulatory mechanisms and complex dynamic phenomena. These concepts will be illustrated by two examples. The first example considers how modern techniques of nonlinear time-series analysis can be used to reveal the coexistence of many oscillatory processes in nerve cells and to determine the mutual interactions between these processes. The second example demonstrates the development of a mechanism-based model of nephron pressure and flow regulation, and nephron-nephron interaction. The first work represents our initial steps towards a better understanding of nerve-cell interactions in relation, particularly, to the treatment of depression. The second is considered relevant in connection with the treatment of hypertension.

**Conclusion:** Mechanism-based models should be developed through a continuous interaction of experimental work and data analysis with model validation, model predictions and definition of new critical experiments. In several cases our models have pointed to the existence of phenomena that have subsequently been observed experimentally. Most importantly, however, the models have served as an extremely useful tool to integrate a variety of complex physiological phenomena into a consistent framework. At a number of occasions, our analyses have shown that initial hypotheses based on physiological intuition or generally accepted beliefs failed when subjected to a more quantitative analysis.

12. Modelling Pharmacogenomic Effects of Corticosteroids

*William J. Jusko, PhD, Department of Pharmaceutical Sciences, University at Buffalo, New York USA*

Our operative hypothesis is that pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic (PG) modeling can be escalated from a focus on major rate-limiting steps (receptor binding, turnover of receptors, genes, proteins, biomarkers) to integrated
in vivo systems analysis where drug effects on multiple genes, pathways, and functions can be considered in assembling global models of drug action.

Previous efforts from our laboratory based on animal and human studies of corticosteroid PD have firmly established the importance and broad relevance of indirect response models, clarified the key role of receptor binding and occupancy, evolved means of dealing with time-dependent transduction, applied Fourier analysis for irregular circadian input of cortisol and corticosterone, characterized cell trafficking, and demonstrated receptor depletion and gene-mediated feedback as tolerance mechanisms. Detailed mechanistic studies of several steroid-sensitive biochemical systems in normal and adrenalectomized rats has provided a substantive base for integrated modeling. We have explored, rationalized, and validated gene microarray measurements of mRNA expression as a PD/PG biomarker. Efforts to advance PK/PD modeling of corticosteroids (CS) and methylprednisolone (MP) include the following:

• Generation of an extensive gene array database in normal rats demonstrating which genes exhibit circadian behaviors and how many are under the direct and indirect control of corticosteroids.
• Comparison of acute versus chronic dosing effects of MP reveals how CS initiate myriad effects at the genomic level and how the physiologic system copes by various homeostatic mechanisms.
• Supplementation of PG studies of specific metabolic systems which include enzymatic, biochemical, and functional dynamics with gene array studies that depict companion genomic processes that may or may not change simultaneously and play a role in the measured endpoints.
• Examination of multiple genes in several tissues to seek commonalities in the time-course of gene expression with the goal of finding general principles of how drugs alter receptors, transcription factors, and secondary biosignals to control the time-course of gene expression after single and chronic doses. For example, the general model at the right indicates processes with serial regulation and may explain why there are such numerous gene expression profiles showing biphasic behaviors.

The various studies build upon an experimental paradigm that we have established involving treating groups of rats with CS and using destructive sampling methods to examine the time-course of drug exposure, receptor binding, mRNA expression, enzyme activity, and systemic physiological measurements to assess comprehensive in vivo determinants of drug response after single-dose or chronic administration of drugs. This ‘systems pharmacologic’ approach allows the evaluation of multiple determinants of drug effects under strictly controlled conditions but where all biological functions can occur in reasonably natural fashion. The doses, numbers of animals, time-points, treatments, and experimental conditions are typically selected by consideration of profiles and variability found in previous studies, literature evaluation, pilot studies, and utilization of model-based simulations.
Our general goal is to utilize our measurements of the myriad types of steroid effects to advance our conceptualization and development of innovative PK/PD models to quantitate complex drug responses. This research seeks to integrate knowledge generated at the theoretical, molecular, cell, organ, and whole body basis based on the view that studying one level alone will not be sufficient for understanding the complex physiological and pharmacologic processes governing in vivo mammalian drug responses.

Supported by NIH Grants GM 24211, GM57980, and GM67650 and by NASA.

13. Combining Quantitative Structure Activity Relationships and Systems Biology Approaches for In Silico ADME/Tox

Sean Ekins, ACT LLC, NY, and School of Pharmacy Department of Pharmaceutical Sciences, University of Maryland.

The challenge of predicting the ADME/Tox properties of a drug in humans has been approached independently using multiple experimental technologies and more recently computational approaches (e.g. computational quantitative structure activity relationships (QSAR)) and high content data. Understanding the complexity of biological systems requires a broader perspective rather than focusing on just one method in isolation for prediction. From experience of developing computational models for specific ADME/Tox targets such as the pregnane X receptor, human Ether-a-Go-Go-Related Gene potassium channel (hERG), drug transporters and cytochrome P450s to developing a software suite integrating many models, metabolite prediction, human cell signaling networks, metabolic pathways and and toxicogenomic data, the potential for understanding toxicity of small molecules computationally has greatly expanded. Recent work has included applying multiple computational methods to predict hERG inhibition and understanding the applicability of these methods. Further work has applied a systems approach, predicting potential small molecule interactions and visualizing these molecules as networks that can be compared to microarray or other high content data to show the networks of genes that are affected. This represents an example of how the combination of QSAR models, applicability methods and systems biology approaches may provide data mining opportunities for both pharmaceutical and environmental toxicology.

14. Biosimulation in translational medicine

Jeff Trimmer, Entelos

Abstract not received.

*Jeff Barrett, The Children's Hospital of Philadelphia*

Pediatric pharmacotherapy can be challenging due to developmental changes that may alter drug kinetics, pathophysiologic differences that may alter pharmacodynamics, disease etiologies that may be different from adults, and other factors that may result in great variation in safety and efficacy outcomes. The situation becomes more convoluted when one considers critically ill children and the paucity of well-controlled pediatric clinical trials. We are developing a paediatric knowledgebase (PKB) at the Children's Hospital of Philadelphia (CHOP) in attempt to address these issues. The PKB has four overall aims: 1) provide dosing guidance consistent with formulary standard of care, 2) examine patient pharmacotherapeutic indices with respect to individual agent performance relative to historical controls derived from the hospital data warehouse, 3) explore treatment * diagnoses * drug correlation in conjunction with utilization and 4) educate physicians on clinical pharmacologic principles specific to population and drug combinations of interest. Static compendial information (Lexicom, PDR, etc) is searched, indexed and summarized for easy viewing; forecasting of relevant drug exposure or clinical markers (lab values, pharmacodynamics, adverse events) is made available in the "Drug Dashboard" module. Drug dashboards are designed for and by the physician therapeutic area in collaboration with clinical pharmacology and IT collaboration. The prototype methotrexate (MTX) dashboard permits forecasting of plasma concentrations at select time points consistent with the clinical protocol used to manage renal toxicity. The forecasting tool permits dosing scenarios to be explored via a user-friendly interface that front-ends a paediatric population-based PK/PD model. The compilation of dashboards for the PKB will be possible through external collaborations. This environment accumulates clinical outcomes including adverse events in a HIPAA-compliant informatics system. Additional institutions in the US are now collaborating in this endeavor and it is hoped that this will eventually assume a global effort. A fully-functional PKB should yield a dynamic, in silico signature of paediatric pharmacotherapy beyond basic PK/PD.

Jeffrey S. Barrett, Ph.D., FCP  
Research Associate Professor, Pediatrics Director, Laboratory for Applied PK/PD Clinical Pharmacology & Therapeutics Abramson Research Center, Rm 916H

email: barretj@email.chop.edu

**16. Validation and Reparameterisation of a Cardiovascular PK PD model**

*Sau Yan Amy Cheung, James W. T. Yates, Oneeb Majid, Leon Aarons:*
A linear two-compartment PK model with first order absorption describes the distribution of an alpha 1A/1L partial agonist. The regulation of the side effects of the increased peripheral resistance, induced by the constriction of the blood vessels, was modelled by adapting a previous cardiovascular PKPD model [1]. The model has 12 unknown parameters; certain of them were found to be not well determined from parameter estimation; these parameters were also found to have little influence in the sensitivity analysis. Such phenomenon suggested a potential unidentifiability status of the model. In order to verify this, structural identifiability [2] of the model was sought to identify the cause of the phenomenon.

The goal of structural identifiability analysis is to get an insight into the internal structure of a mathematical model based purely on the input-output responses, with the assumption of perfect noise free data. If all the unknown parameters in the model may be uniquely determined, then the model is globally uniquely identifiable. If one of the parameters in the parameter set may take more than one of a finite number of values then the model is locally identifiable. If there is one unidentifiable parameter in the model, then the model is unidentifiable; this means there are infinite sets of parameters values that will fit to the model equally well. In this situation, redesign, reparameterisation or model reduction of the model is necessary.

Generally, different methods are available for structural identifiability analysis of nonlinear model such as the Taylor series expansion [3] and the similarity transformation approach [4]. The nonlinear similarity transformation approach is less straightforward as a non-linear mapping is involved in the analysis; therefore a modified nonlinear similarity transformation approach was used. The new modified version makes used of the theorem [5] stating that if the differential equations of the model are polynomial in the state variables and the observation function is linear in terms of state variables, then it is sufficient to consider a linear map in the analysis. Therefore, to simplify the analysis, the PD model was rewritten into polynomial form. After the analysis using the MATHEMATICA software, the model was confirmed to be unidentifiable. The model was then reparameterised to obtain a globally identifiable model.

17. Evaluation of an Interacting Multiple Model Approach to the Analysis of Gentamicin Data from Clinically Unstable Patients

Macdonald I\textsuperscript{1}, Staatz C\textsuperscript{2}, Thomson AH\textsuperscript{2,3}
Pharmacy Depts, \textsuperscript{1}Western Infirmary & \textsuperscript{2}Gartnavel General Hospitals and \textsuperscript{3}SIPBS, University of Strathclyde, Glasgow.

Patients who have recently undergone cardiothoracic surgery often have varying organ function and this can present a challenge when optimising drug therapy, especially if the drug has a narrow therapeutic range. This study evaluated the ability of the nonparametric Interacting Multiple Model (IMM) software, which is contained within the USC*PAK package [1] and allows “jumps” from one set of parameters to another, to describe the pharmacokinetics of gentamicin in this patient population.

Data from 135 patients who had received gentamicin following cardiothoracic surgery were available from a previous population analysis using NONMEM [2]. These data were analysed individually using no multiple model (no MM), multiple model (MM) and IMM options within the USC*PACK package [1]. A range of probabilities were investigated using the IMM function: 0.001%; 0.1%; 3%; 10%; and variable (0.0001 – 50%). The abilities of each method to predict the measured concentrations were compared with each other and with IPRED results from the NONMEM analysis (MAPNM) [2] by examining individual and patient-averaged prediction errors and percentage prediction errors. Bias was examined by unpaired t-test (p<0.05) and relative precision by non-parametric ANOVA.

Concentration measurements (n = 550) were available from 135 patients. MAPNM was unbiased and IMM minimally biased when all data were analysed but comparison of precision identified IMM with 3% probability as the most precise setting and no MM as the least precise. Some practical problems were identified when using the IMM program, particularly with the dose recommendation function.

The IMM program provided a good fit of gentamicin concentration data collected from clinically unstable patients but the 3% probability setting was the best. Further investigation of the practical value of using the IMM program regularly in routine clinical care is required.

References
1. Technical Note: MMUSC*PACK user guide. Laboratory of Applied Pharmacokinetics, University of Southern California, 2001
18. Analysis and application of distinguishable parent-metabolite pharmacokinetic models

James Yates, Mike Walker and Sarah Kearney. AstraZeneca, Alderley Park, UK.

In this presentation the application of model analysis to build up a wider picture of pharmacokinetics is demonstrated for the case of a drug and a metabolite. Models explaining the two-compartmental disposition after dosing of the parent and the metabolite in separate experiments are examined.

Pharmacokinetic data from an IV bolus dose experiment showing bi-phasic behaviour may have three different 2-compartmental models fitted to it; however, they will fit equally well and so the point of elimination cannot be distinguished. This raises a very interesting point that is the philosophical ‘bedrock’ of this presentation; even though a given model may give a unique parameter fit to experimental data, it does not mean there is not an alternative model structure giving an equally good fit, which is parameter unique. We should explore the other possibilities.

The problems of model indistinguishability are considered from a deterministic and statistical viewpoint. Two experimentally distinguishable models of parent-metabolite kinetics are considered that are also shown to be structurally identifiable. Importantly, this identifiability is as a result of dosing the metabolite in a separately.

The distinguishability of the models is also evident in the fit to data produced during an industrial drug discovery project. The major difference between the two fits is the peripheral model’s ability to capture the different terminal half-lives of the metabolite when it has been dosed iv or produced through metabolism of the parent. This model suggests distribution to the liver, or metabolism itself, is rate limiting.

The reported results demonstrate the impact that incorporating model design into experimental design can have on the conclusions and outcomes of an experimental investigation. By investigating alternative, distinguishable compartmental models to those that are used as ‘standard’ greater insights might be gained into the pharmacokinetics of compounds.

19. Optimization of the indisulam-carboplatin regimen using a PKPD model of myelosuppression

Anthe S. Zandvliet1, Christian Dittrich2, Margit Gneist2, Jantien Wanders3, Jos H. Beijnen1, Jan H.M. Schellens4, Alwin D.R. Huitema1

1Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, Amsterdam, The Netherlands, 2LBI-ACR VIEnna and ACR - ITR
INTRODUCTION: Indisulam and carboplatin showed superadditive activity in preclinical studies and both had single agent activity in non-small cell lung cancer (NSCLC) patients. A dose escalation study was performed to identify a safe dose of indisulam in combination with carboplatin in patients with solid tumors. This study demonstrated that a 3-weekly schedule of the combination was not feasible, because a treatment delay of retreatment was frequently required to allow recovery from myelosuppression from previous cycles.

AIMS: The aims of this study were 1) to develop a semi-physiological PKPD model describing the pharmacokinetics of indisulam and carboplatin and the time profiles of neutrophils and thrombocytes after treatment with the combination and 2) to use this model for optimization of the indisulam-carboplatin treatment regimen.

PATIENTS AND METHODS: Sixteen patients were treated at 4 different dose levels of indisulam (1-hour infusion on day 1) and carboplatin (30-min infusion on day 2). Pharmacokinetic data were analyzed with NONMEM using the previously developed population pharmacokinetic model for indisulam and a two-compartment model for carboplatin. A semi-physiological model describing chemotherapy-induced myelosuppression was applied to characterise the relationship between the pharmacokinetics and the haematological toxicity of indisulam and carboplatin. A simulation study was performed to evaluate 3-weekly and 4-weekly treatment regimens.

RESULTS: The semi-physiological PKPD model adequately described the pharmacokinetic profiles of indisulam and carboplatin and their combined myelosuppressive effect. Both drugs were cytotoxic for proliferating neutrophils and thrombocytes. The sensitivity of patients for thrombocytopenia and the sensitivity for neutropenia co-varied (correlation coefficient 0.59). Results of the simulation study showed that indisulam exposure had a large impact on the risk of neutropenia, while exposure to carboplatin highly influenced the risk of thrombocytopenia. Table 1 lists the predicted risks of dose limiting toxicity and dose delay due to thrombocytopenia and/or neutropenia.

<table>
<thead>
<tr>
<th>Dose indisulam (mg/m²)</th>
<th>Target dose carboplatin (mg·min/ml)</th>
<th>Risk of dose limiting myelosuppression during first cycle</th>
<th>Risk of dose delay at cycle 2 due to myelosuppression 3-weekly regimen</th>
<th>Risk of dose delay at cycle 2 due to myelosuppression 4-weekly regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>350</td>
<td>6</td>
<td>15.4% 10.8%</td>
<td>49.3% 40.5%</td>
<td>5.1% 3.5%</td>
</tr>
</tbody>
</table>
DISCUSSION: These results demonstrate that the risk of dose delay due to haematological toxicity was unacceptably high in a 3-weekly regimen and much lower in a 4-weekly schedule. The 4-weekly regimen seems feasible for future studies. Clinical results were well supported by these predictions. Seven out of 10 patients, who received a second treatment cycle, required a dose delay due to persistent haematological toxicity. All of these patients could be retreated after four weeks. The risk of dose limiting toxicity was predicted to be acceptable at all dose levels in the current analysis. However, in the clinical study ≥ 2 out of 6 patients had dose limiting myelosuppression at the 600/6 and 600/5 dose levels. Therefore, the combination of indisulam 500 mg/m² and carboplatin 6 mg·min/ml was selected as the recommended dose for further evaluation of the indisulam-carboplatin regimen.

CONCLUSION: The 4-weekly schedule of indisulam 500 mg/m² in combination with carboplatin 6 mg·min/ml is safe and feasible for future studies.

REFERENCES:

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

_E Lamont¹, AH Thomson²,³, M Macpherson⁴, L Semple⁵, E Bell⁵, RA Seaton⁵_

¹Pharmacy, ²Brownlee Centre, Gartnavel General Hospital, ³Pharmacy, Western Infirmary, ⁴SIPBS, University of Strathclyde, Glasgow, ⁵Present address AstraZenica.

**Background.** The Outpatient Home Parenteral Antibiotic Therapy (OHPAT) service allows patients who require longterm intravenous antibiotic therapy to be treated at home or as outpatients rather than in hospital. Teicoplanin is a glycopeptide antibiotic which has a long elimination half-life, which allows thrice weekly administration. This is ideal for OHPAT use but there are no established dosage guidelines for this regimen.

**Aim.** The aims of this study were to determine the population pharmacokinetics of teicoplanin from data collected from the OHPAT clinic and to develop dosage guidelines for clinical use.
**Methods.** Patients received loading doses of 15-25 mg/kg/day for three days then thrice weekly. Teicoplanin trough concentrations were measured once weekly and the dose adjusted to maintain troughs of 20–30 mg/L (deep seated infections) or 10-20 mg/L (bacteraemia or cellulitis). Population pharmacokinetic analysis was performed using NONMEM. One and two compartment structural models were compared and the influence of a range of clinical factors was investigated. The final model was used to develop dosage guidelines. A separate data set was then collected and used to validate the population model and the proposed guidelines.

**Results.** The model building data set comprised 95 patients, aged 15 to 94 years (median 59 years) and weighing 43 to 146 kg (median 73 kg). Estimated creatinine clearance ranged from 17 to 195 (median 66) ml/min and there were 471 teicoplanin concentration measurements ranging from 6.7 to 58.3 mg/L. The data were adequately described by a one-compartment model with proportional residual error and covariate analyses identified a relationship between clearance and CrCL. The validation data set comprised 36 patients aged 35 to 79 years (median 62 years) and with estimated creatinine clearance of 9.4 to 178 ml/min (median 69 ml/min). Population predicted concentrations for the validation set were unbiased and had clinically acceptable precision. Preliminary results indicated an improvement in the distribution of concentrations with the new dosage guidelines compared to empirically determined doses.

**Conclusions.** This study has established a population pharmacokinetic model and developed dosage guidelines to achieve target concentrations of teicoplanin in patients who are receiving thrice weekly dosing.
Poster Session Titles (Wednesday 15\textsuperscript{th} November)

Application of a balanced truncation model reduction technique to a PBPK model
Aris Dokoumetzidis, Centre for Applied Pharmacokinetic Research, University of
Manchester, Coupland III, Manchester M13 9PL.

A Microdosing Study to Assess the Oral Absorption of 14C-EM 1421 in Healthy
Male Subjects
L. Stevens\textsuperscript{1}, N. Frazer\textsuperscript{2}, S. Dueker\textsuperscript{3}, A. Church\textsuperscript{1}, M. Gaido\textsuperscript{2}
\textsuperscript{1}Pharmaceutical Profiles Ltd, \textsuperscript{2}Erimos Pharmaceuticals Inc, \textsuperscript{3}Vitalea Sciences Inc

The robustness of predicted/observed ratio in reflecting erratic adherence to drug
therapy.
Yan Feng, Marc Gastonguay, Bruce G. Pollock, Rob Bies

Financial Support: National Institute for Biomedical Imaging and Bioengineering
(NIBIB) Grant # P41 EB001975-06; ACISR Late Life. MH65376 (E.Frank, PI)

PopDes – An Optimal Experimental Design Program for Individual and Population
Uniresponse and Multiresponse Models
Kayode Ogungbenro, Ivelina Gueorguieva, Gordon Graham and Leon Aarons
Centre for Applied Pharmacokinetics Research, School of Pharmacy and Pharmaceutical
Sciences, The University of Manchester, Manchester, UK

Prediction of the oral clearance of tolbutamide in individuals with different
CYP2C9 genotypes using \textit{in vitro} enzyme kinetic data
LM Almond, K Rowland-Yeo, GL Dickinson, EM Howgate, GT Tucker and A Rostami-
Hodjegan