## ASCEPT 2016 Abstracts

## A1: The Waitemata MedChart experience

David Ryan

## A2: The Taranaki MedChart experience

Tracey Watson

# A3: Clinical Decision Support in an Electronic Prescribing and Administration System

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Background: There is a large gap between the postulated and demonstrated benefits of clinical decision support (CDS) in electronic prescribing and administration (ePA) systems. CDS in healthcare traditionally aims to provide all potentially relevant information to the user. This leads firstly to alert fatigue with users sometimes missing significant alerts and secondly to users sometimes changing actions inappropriately in response to irrelevant alerts. MedChart® is the ePA system mandated for New Zealand public hospitals. CDS functions in MedChart® are locally configurable.

Aim: To describe the development of CDS for MedChart® at Canterbury District Health Board (CDHB).

Methods: The CDHB CDS project goal is *to reduce patient harm from inappropriate medicines use*. Local data on adverse drug events and published literature were used to identify high risk events, as targets for locally defined alerting and non-alerting CDS. Alerting CDS includes: overdose, drug-drug interactions, and other prescribing and administration rules. Non-alerting CDS includes: *Protocols* of orders sets linked to clinical pathways and *Quick Lists* of preformatted individual drug prescriptions. External references were used to benchmark the CDHB CDS system including validated test scenarios and evidence based audit tools.

Results: Non-alerting CDS was developed based on existing clinical pathways. Alerting CDS with high specificity was developed for overdoses and drug-drug interactions. External benchmarking using an evidenced-based audit tool was valuable for testing design principles and guiding direction of development. There are multiple user requests for more alerts, often based on perceived risk and for reasons other than patient outcomes.

Conclusion: CDS aimed at reducing patient harm and facilitating use of clinical pathways can be developed, but this is resource-intensive and requires a well-designed rules engine and clinical expertise. Despite years of worldwide experience, CDS in ePA software is primitive and there are many lessons to be learned from other industries.

1. The Office of the National Coordinator for Health Information Technology (ONC). *SAFER Guides - Computerized Provider Order Entry with Decision Support* https://www.healthit.gov/safer/guide/sg007 accessed 7 March 2016
1. Schiff GD, Amato MG, Eguale T, et al (2015). *Computerised physician order entry-related medication errors: analysis of reported errors and vulnerability testing of current systems*. BMJ Qual Saf. 24:264-71

# A4: Data extraction and analysis in MedChart

QianYi Chuah

## A5: Drug-drug interaction alerts in an electronic prescribing system

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Introduction. Unintended drug-drug interactions (DDIs) are associated with adverse drug reactions and loss of drug efficacy. Electronic prescribing and administration (ePA) systems can include clinical decision support alerts to warn of potential DDIs. However, proprietary DDI clinical decision support systems are associated with high alert burden (70 to 360 per 1000 prescriptions) and risk of alert fatigue. Consequently, the vendor-defined DDI alerts in MedChart™ have been disabled at Canterbury District Health Board (CDHB). We hypothesised that the alert burden could be minimised by restricting alerts to the DDIs most likely to be a) unintentional and b) cause patient harm.

Aims. To develop evidenced-based rules for DDI alerts in MedChart. To predict the alert rate due to these rules in hospital inpatients.
Methods. A literature search was undertaken and local "trigger tools" data were reviewed to develop DDI alert rules. Pharmacokinetic (PK) DDI alert rules were defined as single drug alerts to identify major perpetrators of DDIs for prescribers. Initial pharmacodynamic (PD) DDI alert rules were defined based on bleeding risk. Alert burden was predicted by applying the DDI alert rules in a test environment to MedChart CDHB data from older persons health inpatients, June-August 2015.
Results. 360 patients were prescribed 4,242 medicines. These generated 193 alerts (PK=123, PD=70), a rate of 45 alerts per 1,000 prescription items and 50 alerts per 100 patients. These included 59 alerts for parenteral anticoagulants co-prescribed with oral antiplatelet drugs that were potentially intentional and/or low risk.
Discussion. The DDI alert rules developed at CDHB have a lower alert burden than most current proprietary systems. Future evaluations should assess the effect on prescribing behaviour and patient outcomes.

Polasek, T.M., Lin, F.P.Y., Miners, J.O. et al (2011). *Perpetrators of pharmacokinetic drug–drug interactions arising from altered cytochrome P450 activity: a criteria-based assessment*. Br J Clin Pharmacol. 71: 727–36.

# A6: Use of MedChart™ generated lorazepam administration time data as a marker of agitation/anxiety

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Background: Benzodiazepines are commonly used as a pharmacological strategy to reduce agitation or anxiety in an acutely disturbed patient, often in combination with antipsychotics. Lorazepam is the first line benzodiazepine for these indications within the Canterbury District Health Board's (CDHB) Specialist Mental Health Services (SMHS), and is often prescribed and administered as 'as required' (PRN) dosing. Administrations of PRN lorazepam could be used as a marker of agitation and anxiety in these patients and the timings of these administrations as periods of disturbance on the ward.

Aim: To examine the times of day of administrations of PRN lorazepam across the Specialist Mental Health Services (SMHS) as a marker of agitation or anxiety.

Method: Medicines administrations data for all SMHS inpatients from June to December 2015 were extracted from the electronic prescribing and administration database (MedChart™) using a locally developed (currently still under development) administrations report. Times that PRN lorazepam was administered were 'binned' in two hour bands. Data were analysed using Microsoft Excel™ and Tableau™.

Results: A total of 4656 PRN doses of lorazepam were administered to 211 different patients. Times of lorazepam administrations are shown in the figure below. When examined in 2 hour blocks the 4pm to 6pm block had the highest number of administrations (749/4656, 16%), while the 4am to 6am block had the lowest number (78/4656, 2%).

Conclusion: Overnight use was less than day time use with a 'peak' in the late afternoon. Although literature is sparse this corresponds with reports on the time of greatest agitation or anxiety. There are potential confounding factors such as nurse handover occurring just prior to the block of time with the highest number of administrations. A nurse survey is now proposed to investigate nurse behaviour alongside analysis of sedatives and antisychotics administration data.

## A7: Adverse Drug Reactions in an Electronic Prescribing and Administration System

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Background: Adverse drug reactions (ADRs) cause morbidity and mortality for patients and add unnecessary costs to the health system. Between 5 and 10% of hospital admissions and emergency department visits are attributable to ADRs. Electronic prescribing and administration systems (ePAs) have the potential to reduce harm from ADRs by alerting prescribers to previously recorded ADRs at the time of prescribing.

Aim: To describe the use of MedChart™ (an ePA system) to record, and alert prescribers to, potential ADRs.

Methods: ADRs recorded, drugs prescribed, and ADR alert data for May to October 2015 were extracted from the Canterbury District Health Board instance of MedChart™ using locally written SQL queries. The data were analysed in Microsoft Excel® and GraphPad Prism®. The ADR records were compared with local guidelines.

Results: Over six months, 2,852 ADRs were recorded. 22% (618) were recorded by class name, 17% (389) by brand name. 9% (260) had no description of the reaction. During this time there were 59,509 prescriptions for 2,747 patients (median 18 per patient). At least one ADR was recorded in 44% (1,210) of these patients. An ADR alert was triggered by 2% (1,169) of prescriptions, and 93% (1,091) of these were overridden. Areas of ambiguity and inaccuracy were found in the ePA affecting utility of ADR recording.

Conclusion: Many users do not record ADRs according to local policy. The ADR alert rate and subsequent override proportion were comparable to the established literature. There is potential for alert fatigue as the majority of alerts were overridden. Changes to MedChart™ and to local processes could reduce this risk and improve the accuracy of ADR recording.

## A8: Use of Clinical Decision Support in ePrescribing to Facilitate Generic Prescribing

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Background: Electronic prescribing and administration (ePA) is being rolled out in Australasian hospitals. ePA systems include clinical decision support (CDS) tools that can be used to influence clinician behaviour. Canterbury District Health Board (CDHB) policy is that medicines should be prescribed by generic name, rather than trade name. We hypothesized that a CDS rule would increase the rate of generic prescribing and be acceptable to prescribers.

Aim: To compare the rates of generic and trade name prescribing pre and post implementation of a CDS rule to encourage generic prescribing.

Methods: For selected medicines, a CDS rule was implemented in MedChart™ to alert CDHB prescribers, when prescribing by brand. Prescribing data for the selected medicines in the 3 months before and 3 months post implementation of the rule were extracted from Medchart™ using locally developed SQL queries. The generic prescribing rates before and after alert implementation were compared using a Fisher's exact test.

Results: Pre-implementation 86% of prescriptions (3675/4257) were by generic name and post-implementation 98% (6565/6668) were prescribed by generic name, a 12% increase in generic prescribing (95%CI 11-13% $p < 0.0001$). This corresponds to a 88% decrease in trade name prescribing. There were no negative comments received about this alert.

Conclusion: Generic prescribing increased and trade name prescribing decreased markedly, after the implementation of the generic prescribing rule. The rule is specific, only firing after users attempt to prescribe by trade name, which minimizes false alerts and alert fatigue. CDS rules can be safely used to encourage generic prescribing in ePA systems.

## A9: Clinical use of monoclonal antibody drugs

Lisa Stamp

## A10: Pharmacokinetics and modelling issues for monoclonal antibodies

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Monoclonal antibodies (mAbs) have had a huge clinical impact on the management of a wide variety of diseases with generally low toxicity[1]. Their pharmacokinetic (PK) characteristics are markedly different and more complicated when compared to small molecules. mAbs are administered intravenously, intramuscularly or subcutaneously. Oral administration is precluded by the molecular size, hydrophilicity and gastric degradation of mAbs (generally, oral bioavailability < 1%). Distribution into tissues is slow because of the large molecular size of mAbs, and the volume of distribution is generally low. mAbs are eliminated from the body by circulating phagocytic cells (catabolism, by the same mechanism as for endogenous immunoglobulins (IgG)) or by target-mediated clearance which is more common with biologics including mAbs. Due to the contribution of a target based elimination pathway the half-lives of mAbs often depend on the amount of the target (often correlated with disease activity) as well as their exposure (i.e. dose amount and concentration of mAbs). As is done for endogenous IgG, mAbs are protected from elimination by binding to the neonatal Fc-receptor (FcRn), which explains their long elimination half-lives (~weeks). Since the binding affinity for FcRn is species specific, the elimination of non-human (e.g. murine) mAbs is relatively rapid in humans[2], which means half-lives of mAbs also depend on the type of mAbs. However, considering the half-lives of small molecules, the elimination of mAbs is still slow in most cases.

Population pharmacokinetic analyses have been applied to characterize PK properties of mAbs, and to assess influential factors (covariates) in the disposition of mAbs. Both linear and nonlinear elimination have been considered for the PK modelling of mAbs, the latter due to target-mediated disposition. Possible factors influencing elimination of mAbs include patient characteristics as well as their immunogenicity i.e. formation of anti-drug antibodies (ADA) which may enhance the clearance of mAbs. Body size is generally related to the volume of distribution and clearance of mAbs, but clinical relevance is often low.

In conclusion, the non-oral administration, slow tissue distribution and long elimination half-life are the most important PK characteristics of mAbs.

1. Inumaru, S. *Introduction to advanced biologics*. Vet. Immunol. Immunopathol., 2012, 148(1-2), 126-128.
2. Ober, R.J., Radu, C.G., Ghetie, V. & Ward, E.S. *Differences in promiscuity for antibody-FcRn interactions across species: implications for therapeutic antibodies*. Int. Immunol., 2001, 13, 1551–1559.

## A11: Measurement of anti-TNF biologics and anti-drug antibodies in the clinical laboratory

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Clinical laboratories are now providing tests that allow individualised assessment of patient response to anti-TNF biologics to guide therapeutic strategies. Higher circulating drug level, when measured at drug trough, is associated with longer duration of clinical effect while the presence of neutralising anti-drug antibody (ADA) is associated with treatment failure. There is no standardised assay format and the methods applied range from radioimmunoassay, enzyme linked immunoassays (ELISA), homogenous mobility shift assays, liquid chromatography tandem mass spectrophotometry to reporter gene assays. Many of these methods require specialised equipment with ELISA being the favoured commercial format. Canterbury Health Laboratories (CHL) provides an ELISA based method to measure drug level and its unique ADA assay specifically detects the clinically relevant neutralising ADA. The assays are available to clinicians within New Zealand and are used in treatment decisions.

# A12: Monitoring of monoclonal antibody drugs

Murray Barclay

## A13: An evaluation of warfarin dose prediction methods

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There are a large number of published dosing algorithms designed to predict warfarin maintenance dose requirements. We have recently proposed that these algorithms may exhibit poor predictive performance in patients who require higher than average daily doses.[1] We conducted a meta-analysis of warfarin dosing algorithms to determine if there exists a systematic under- or over-prediction of dose requirements for patients requiring ≥7 mg/day across published studies and algorithms. We searched Medline and Embase databases for studies that evaluated the predictive performance of warfarin dosing algorithms. Studies were included if they (1) provided a scatterplot of the observed and predicted maintenance dose, and (2) the predicted dose requirements were evaluated against an external (validation) dataset. Studies were excluded if (1) the published scatterplot was of insufficient resolution to allow data to be extracted, and (2) there were less than five patients requiring doses ≥7mg/day. We quantified the proportion of over- and under-predicted doses in patients requiring ≥7 mg/day. A null proportion of 0.5 was used assuming that there would be an equal distribution around the line-of-identify when no bias was present. A random-effects model was used to pool the proportion of over- and under-predicted doses across studies and algorithms.

Fifteen publications met our inclusion criteria, representing 22 different warfarin dosing algorithms. Note that nine algorithms were evaluated in more than one study. The meta-analysis included data from 1116 patients who required warfarin doses of ≥7 mg/day. Twenty-one of the 22 algorithms under-predicted warfarin dosing requirements in patients who required ≥7 mg/day by an average of 2.5mg/day. The pooled proportion of under-predicted doses was found to be 92.5% (95% CI 90.2 - 94.5, $I^2$ = 26.2%). Overall, our study does not support the use of warfarin dosing algorithms to predict the maintenance dose.

1. Saffian SM et al. (2015) *Methods for Predicting Warfarin Dose Requirements*. Therapeutic Drug Monitoring. 37(4): 531-8.

# A14: Quantifying the influence of vitamin K on warfarin dosing requirements (Part 1)

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The aim of this research is to quantify the influence of vitamin K (VK) on warfarin dose requirements. The first part of this project is to understand the quantitative influence of warfarin on the time course of VK-dependent clotting factors and anticoagulation proteins. Nine blood samples from each of 17 patients with atrial fibrillation who were initiated with oral daily warfarin were assayed for factors II, VII, IX, X, protein C, and protein S. Warfarin pharmacokinetic data were not available. The factor data were modelled in a stepwise manner using NONMEM v.7.2. In the first stage, each of the clotting factors and anticoagulation proteins were modelled independently using a kinetic-pharmacodynamic (K-PD) model. In the subsequent step, the six K-PD models were combined into a single joint model whereby the six clotting factors and anticoagulation proteins were modelled simultaneously. Individual K-PD models consist of two parts: (a) a one-compartment model with first order absorption and elimination for warfarin in the biophase; and (b) an inhibitory Emax model linked to a turnover model for clotting factors and anticoagulation proteins in the response compartment. In the joint model, the estimated degradation half-life of VK-dependent clotting factors and anticoagulation proteins were in agreement with previous published values. The joint model provided an adequate description of the observed data. The model developed represents the first work to quantify the influence of warfarin on VK-dependent clotting factors and anticoagulation proteins simultaneously. The current model provides an initial framework for subsequent incorporation of the VK cycle as an intermediary step between warfarin exposure and response. This will be useful for predicting the coagulation kinetics in response to exogenously administered VK in warfarinised patients.

## A15: Determination of post-mortem clozapine levels in coronial autopsy cases

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Clozapine-associated myocarditis and cardiomyopathy are fatal if undetected. Currently, these cardiotoxicities are diagnosed by non-specific signs and symptoms and the underlying mechanism(s) are unknown. There remains a paucity of studies into the underlying causes of these adverse reactions. A type-I drug hypersensitivity reaction has been proposed. This may be dependent on the biotransformation of clozapine to form a chemically-reactive metabolite that damages cardiac protein(s) and attracts inflammatory infiltrate. However, this has only been investigated in the mouse heart.

Routine clinical assays used for clozapine quantification have the ability to detect the biotransformation products (metabolites) N-desmethylclozapine and N-oxide, however these are typically not quantified. Thus it is not known if decreased biotransformation of clozapine (e.g. ratio of clozapine to metabolites) or increased formation of a minor, yet toxic metabolite is a risk factor.

We are investigating if there is a role for altered drug metabolism in clozapine-associated myocarditis and/or cardiomyopathy in coronial autopsy cases where patients died from or with these cardiotoxicities. Clozapine and its major metabolites were quantified in whole blood and compared with the concentrations found in patients who died whilst taking clozapine but did not have myocarditis and/or cardiomyopathy.

We determined that post-mortem levels of clozapine and its major metabolites in whole blood are not suitable for investigating altered clozapine metabolism due to post-mortem redistribution. Further, post-mortem redistribution may lead to misclassification of the manner of death in coronial investigations.

# A16: Modulation of multidrug resistance protein 2 (MRP2) by RNA interference (RNAi) increases the chemo-sensitivity of HepG2 cells to oxaliplatin

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Gastrointestinal (GI) cancer is one of the main cause of cancer mortality in New Zealand. Oxaliplatin-based chemotherapy has greatly contributed to improving patient outcomes from GI cancers[1,2]. However, some patients fail to response to this therapy due to the development of resistance during treatment. A member of the ATP-binding cassette (ABC) transporter super-family, multidrug resistance protein 2 (MRP2) has been suggested to confer oxaliplatin resistance by pumping oxaliplatin out of cells[3]. The aim of this study was to determine whether silencing MRP2 by small interfering RNA (siRNA) reversed oxaliplatin resistance in HepG2 cells.
HepG2 cells were transfected with siRNA of ABCC2 and negative control. The expression of ABCC2 mRNA in transfected cells was determined by quantitative real-time PCR (qPCR) using Roche LightCycler 480 system. Thereafter, cellular accumulation and cytotoxicity studies were undertaken in knockdown and control cells. According to qPCR, transfection of HepG2 cells with 20 µM ABCC2 siRNA reduced target mRNA expression by 30% to 50% with negligible off-target effects. The cellular accumulation of a specific MRP2 substrate, 5(6)-carboxy-2', 7'-dichlorofluorescein (CDCF) was measured by flow cytometry and its accumulation in MRP2-silencing cells increased by 175% ± 5% ($n=3, p < 0.05$) compared with control. In cytotoxicity assays, two MRP2 siRNA sequences caused significant increase in the sensitivity to oxaliplatin compared with control cells. These results suggested that silencing of MRP2 increased oxaliplatin sensitivity in HepG2 cells and may reverse multidrug resistance in GI cancers.

1. Ryan DP, Hong TS and Bardeesy N. *Pancreatic adenocarcinoma.* The New England journal of medicine. 2014; 371: 2140-1.

2. Stein A and Arnold D. *Oxaliplatin: a review of approved uses*. Expert opinion on pharmacotherapy. 2012; 13: 125-37.

3. Myint K, Li Y, Paxton J and McKeage M. *Multidrug Resistance-Associated Protein 2 (MRP2) Mediated Transport of Oxaliplatin-Derived Platinum in Membrane Vesicles*. PloS one. 2015; 10: e0130727.

# A17: Diagnosing and recording adverse drug reactions in general medical patients, a cross-sectional study.

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Background: Adverse drug reactions (ADRs) are a significant cause of patient morbidity and mortality. Hospitals have policies and guidelines for staff to record patients' ADR histories. In practice, a patient's ADR history is assimilated via several sources, of variable quality, on multiple occasions. The absence of a standard diagnostic process for ADRs, and a single record, creates uncertainty for clinicians. Recording ADRs has been previously demonstrated to be substandard, but the validity of ADR documentation in New Zealand is not known.
Aim: To determine the validity of ADR documentation for patients admitted to the general medical service at Canterbury District Health Board (CDHB)
Methods**:** Two hundred consecutive patients admitted to general medicine at CDHB were recruited. A reference list of ADRs for each patient was established by patient interview and review of records and assessed using the Naranjo Score by a study doctor. The ADRs recorded in each source document were entered into a database and compared with the reference ADR list.
Results: Of the first 25 patients, 15 had a history of definite or probable ADRs (average 3.5 /patient). The GP electronic record had a true positive rate of 63%, with 2% false positive rate, and a 35% false negative rate. The resident doctor review had a true positive rate of 67%, with 0% false positive rate, and a 32% false negative rate. The pharmacist review had a true positive rate of 90%, with 6% false positive rate, and a 4% false negative rate. The drugs most commonly associated with ADRs were antibiotics (25%).
Conclusion: ADR documentation is inaccurate but improves with each subsequent clinical review. Processes to diagnose and record ADRs at the time of the original event are needed. Assessing ADRs retrospectively is difficult because there is usually insufficient information to make a diagnosis. A single valid ADR list is needed to inform prescribing decisions.

2. Cook, M. & Ferner, R.E. 1993, "Adverse drug reactions: who is to know?", *BMJ (Clinical research ed.),* vol. 307, no. 6902, pp. 480-481.

1. Shenfield, G.M., Robb, T. & Duguid, M. 2001, "Recording previous adverse drug reactions--a gap in the system", *British journal of clinical pharmacology,* vol. 51, no. 6, pp. 623-626.

# A18: A Mathematical Model for Urate Transport in a Proximal Tubular Cell.

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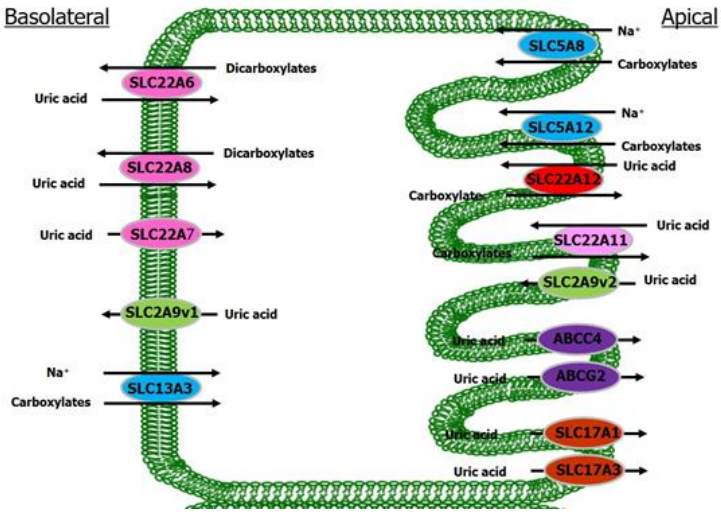
Urate is a breakdown product of purine nucleotide degradation in humans.[1] The under-excretion of urate, largely due to reduced renal clearance, is believed to be the most important cause of hyperuricemia and gout.[1] Our understanding of renal urate handling remains rudimentary. An improved comprehension of this process would facilitate further investigation into the effects of transporter polymorphisms or medications on serum urate concentrations. Thus the aim of this project was to develop a mathematical model to simulate urate transport across the proximal tubule in order to study these effects *in silico*.

Known urate transporters expressed in the proximal tubules of the nephron were identified as well as their respective urate transport kinetic parameters (Vmax and Km). These were expressed as ordinary differential equations in order to describe the bidirectional flux of urate across the proximal tubular cell, and were coded in MATLAB® (ver R2013b). The initial estimates of Vmax and Km were set to values from the literature. The parameter values were calibrated heuristically to achieve steady state urate concentrations in the blood and urine that align with known average values. The system was then used to simulate the effects of probenecid in order to compare steady state urate predictions with and without a competing ligand.




Future development of this model is expected to provide a basis to examine agents that affect urate transport and disposition and provide the basis for understanding genetic changes in transporter function.

1. Anzai N, Kanai Y, Endou, H. *New insights into renal transport or urate.* Curr Opin Rheumatol. 2007;19(2):151-7.

## A19: Introduction

Hesham Al-Sallami

# A20: Predicting Dose Differences Between Patients: The Impact of Maturation

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Rational dosing requires that we target concentrations in the patient that are associated with the desired drug effect. This is done by knowledge of pharmacodynamics and pharmacokinetics. Biological variability is often large which means that concentration may be outside the acceptable range of safe and effective concentrations.

Body size is the quantitatively most important covariate that accounts for variability in pharmacokinetics. However size alone is insufficient to predict clearance in neonates and infants, in whom maturation of pathways responsible for drug metabolism and excretion is incomplete.[1, 2] Age can be used to describe how maturation progresses as a function of time.

By 2 years of age, most systems have reached 100% of size equivalent adult values. Maturation often follows a sigmoidal relationship with post-menstrual age.[3] By accounting for size, maturation and renal function we can explain almost 85% of variability in clearance in humans.

1. Holford N.H, Heo Y.A, Anderson B.J. *"A pharmacokinetic standard for babies and adults*". *J Pharm Sci.* 2013 Sep;102 (9):2941-52. doi: 10.1002/jps.23574
2. Van den Anker J.N, Schwab M, Kearns G.L. Developmental Pharmacokinetics. In: Rosenthal W, Barrett JE, Flockerzi V*, et al.*, eds. *Pediatric Clinical Pharmacology Handbook of Experimental Pharmacology*. Berlin Heidelberg: Springer-Verlag, 2011.
3. Rhodin M. M, Anderson B.J, Peters A.M et al. *"Human renal function maturation: a quantitative description using weight and postmenstrual age." Pediatr Nephrol*. 2009 Jan;24(1):67-76. doi: 10.1007/s00467-008-0997-5

## A21: Proof is in the pudding: Body size and body composition really works

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The magnitude of response to a drug is a function of what concentration can be attained at the desired site of action, this is linked to the theoretical volume of distribution of the drug. Volume of interstitial and intracellular compartments is related to body mass, weight has a significant impact on quantifying drug effects. In general, apparent volume of distribution is directly proportional to total body weight. Normal practice is to adjust a drug dose to the patient's weight, i.e. give more to heavier patients, less to lighter patients in order to produce the desired therapeutic effects. This approach may be suitable when the patients weight is normal for their height and age, but when there is biologic variation such those who are anorexic or obese, dosing needs to be adjusted to account for changes in body water to body mass ratios. The incidence of obesity among young children is increasing. This has led to questions regarding appropriate dose for weight adjustments. The effect of an unusual body composition such as those with morbid obesity can lead to situations where a highly lipophilic drug accumulates in fat and does not distribute to the target site. Changes in body composition can alter drug disposition and, consequently, generates uncertainty for drug dosing. However, pharmacometric techniques can be used to address the uncertainty and complexity of drug dosing related to changes in body composition. Predicting the pharmacokinetic profile of a drug yields improved efficacy and safety in dosing regimens. Neonates offer a particularly challenging set of variations associated with body size and body composition, including small for gestational age (SGA) and extremely low birth weight (ELBW) vs term neonates (>38 weeks gestation) and Intrauterine growth restriction (IUGR) and the Barker hypothesis (1). Thus, pharmacometrics offers a means to enhance the safety and efficacy of drug utilization among the youngest patients.

(1) D J Barker *The fetal and infant origins of adult disease*. BMJ: 1990, 301(6761);1111

# A22: Predicting Dose Differences Between Patients: Organ Function Variability

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**Predictable PK variability**

Renal Function: Most widely used predictors of renal function are based on prediction of glomerular filtration rate using serum markers such as creatinine and cystatin C. Methods may be theory based e.g. Cockcroft and Gault [1], Schwartz [2] or empirical e.g. MDRD [3]. No useful independent predictors of tubular function. Renal function accounts for ~ 10 fold variability in clearance.

Hepatic Function: Clinical "liver function tests" are poorly correlated with useful predictions of hepatic drug elimination. Disease severity scales e.g. Child-Pugh, only reflect changes in drug elimination with severe hepatic disease [4]. Clinical tests of liver function account for ~ 2 fold variability in clearance.

Genotype: Genotype predictions have little clinical impact with the exception of the rare thiopurine methyltransferase (TPMT) homozygous genotype (~ 10 fold variability in clearance of 6-mercaptopurine in acute lymphatic leukemia [5]). TPMT activity is a better predictor than genotype of azathioprine clearance [6].

Common CYP2C9 genotype variants predict small (<20%) decreases in S-warfarin clearance [7].

Age: Ageing in adults accounts for minor predictable changes e.g. 20% decrease in S-warfarin clearance in a 50 year period [8].

Muscle Mass: May predict differences in digoxin volume of distribution but not of clear clinical importance (~ 50%).

**Predictable PD variability**

Organ Disease: Maximum bronchodilator response is impaired in chronic obstructive airways disease compared with asthma. Hypertension associated with renal artery stenosis is more sensitive to ACE inhibitors and angiotensin receptor blockers – especially first dose hypotension.

Genotype: Common VKORC1 and CYP4F2 genotype variants predict small (<30%) increases in warfarin potency (C50)[7].

Age: There is no detectable effect of age on the turnover of prothrombin complex activity or warfarin potency (C50)[7].

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## A23: There and back again: understanding GPCR ligand binding pathways to design better drugs

Angela Finch

## A24: Understanding Adverse Drug Reactions Using Genome Sequencing (UDRUGS): A focus on statin induced myalgia.

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The UDRUGS study is an initiative from the Carney Centre for Pharmacogenomics to bio-bank DNA and store associated clinical data from patients who have suffered adverse drug reactions (ADRs). The aim is to provide a genetic explanation of drug-induced ADRs using methods ranging from Sanger sequencing to exome and whole genome sequencing.

Statins are drugs that reduce the risk of cardiovascular disease. A proportion (up to 25 %) of patients prescribed statins report a spectrum of muscle aches and pains ranging from myalgia to myopathy, and very rarely, rhabdomyolysis. The milder and more common muscle myalgia is limiting to both quality of life and adherence to statin therapy. While statin-associated muscle pain is reported to be dose-dependent, some patients experience muscle aches and pains at relatively low doses and across various brands and types of statins. Therefore excluding dose as a factor, a number of gene variants, have been associated with an increased risk of statin-induced muscle ADRs. However, we suspect that there may be additional and/or different genes that pre-dispose a patient to be statin-intolerant. To assess this, we collected blood samples from a group of highly selected patients who have trialled various statins, but have suffered muscle myalgia on at least two re-challenges. These patients were defined as statin-intolerant (n=8). We then conducted exome sequencing to seek genetic variants that predispose to statin-intolerance. Genetic variation identified was analysed using standard bioinformatic methods to identify rare variants i.e. variants that are reported to occur in less than 1% of the population, as well as using existing (PharmGKB, CLINVAR) and user-created candidate gene lists. Variants of note were identified in the *CYP2C19*, *CYP2D6, UGT, CYP2A6* and *SLCO1B1* genes. This work and further analysis, will support our goal to identify genetic variants that may predispose to statin-intolerance, and to then apply this information clinically to identify those patients who may benefit from alternative medication.

## A25: Population pharmacokinetics of OZ439 in healthy volunteers and patients with *falciparum* and *vivax* malaria

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Artemisinin-based combination therapies are the recommended first-line treatment for *falciparum* malaria. Artemisinin derivatives, containing the peroxide pharmacophore, are the most potent and rapidly acting antimalarial drugs available. OZ439 is a novel synthetic trioxolane with a similar pharmacophore but with improved pharmacokinetic (PK) properties of prolonged elimination half-life and therefore prolonged antimalarial activity [1]. The aim of this work was to characterise the population PK properties of OZ439 in healthy volunteers and patients with *falciparum* and *vivax* malaria.

Healthy volunteers (n=52) and patients with acute, uncomplicated *falciparum* or *vivax* malaria (n=81) were enrolled in two separate clinical trials. Subjects were assigned to receive OZ439 50, 100, 200, 400, 800, 1200 or 1600 mg. Drug concentration-time data were pooled and evaluated using NONMEM v.7.3. One-, two- and three-compartment disposition models were evaluated. Zero-order, first-order with and without lag-time and transit compartments were explored as absorption models. Covariates tested included formulation (suspension or capsule), fasted or fed condition, total body weight, lean body weight, age, sex, race, dose amount, healthy or infected, and infection (*falciparum* vs *vivax*). Model evaluation was performed using likelihood ratio testing (OFV) and visual predictive checks (VPCs).

The PK properties of OZ439 were best described by two transit compartments in the absorption phase followed by two distribution compartments with first-order elimination. OZ439 exposure increased with concomitant food intake, and the exposure was higher for the suspension compared to the capsule formulation. Lean body weight was a significant covariate on clearance and volume of distribution. The PK properties of OZ439 were well described by the developed population PK model. Final PK parameter estimates had high precision and the final model

showed a high predictive performance, suggesting it to be suitable for further optimal trial design simulations. The developed model will be expanded to include all measured OZ439 metabolites.

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## A26: Contribution of organic anion transporters (OAT) to renal secretion of the gout medication oxypurinol

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Oxypurinol is the major active metabolite of the gout medication allopurinol used to lower serum uric acid (SUA). Oxypurinol is secreted via the kidneys. Recent studies have suggested that the uric acid transporters URAT1 and ABCG2 may be involved in renal oxypurinol secretion. However, conclusive evidence about the involved transporters for the renal elimination of oxypurinol, and how this dictates drug-drug interactions, pharmacokinetics of allopurinol and gout treatment regimes is still lacking. Therefore, the aim of this study was to investigate the interactions and kinetics of human organic anion transporters (hOATs), hOAT1, hOAT3 and hOAT4, with oxypurinol in order to determine the molecular mechanisms of renal oxypurinol secretion, and to aid in developing a pharmacokinetic profile for the drug.

6-carboxyfluorescein (6-CF) was used as a substrate in *cis*-inhibition and *trans*-stimulation assays employing 1mM oxypurinol and probenecid (as a control for *cis*-inhibition studies) and glutarate as a control for *trans*-stimulation studies in stably transfected HEK293-OAT cells. hOAT1 could be identified as a low affinity basolateral transporter of oxypurinol with an $IC_{50}$ value of 321µM, indicating basolateral uptake of oxypurinol via hOAT1. Oxypurinol showed a significant inhibition of hOAT3-mediated 6-CF transport, however, no *trans*-stimulation was observed suggesting possible drug-drug interactions for hOAT3-mediated drug secretion. Investigating the luminal exit of oxypurinol via hOAT4, we could not detected any inhibition of 6-CF transport by hOAT4, reflecting also the asymmetric nature of hOAT4 and a lack of apical reabsorption of oxypurinol by hOAT4. Studies are underway to further determine the contribution of hOAT4 and other OATs such as the basolateral hOAT2 or luminal hOAT10 and UART1, alongside OAT1, to determine the transporters involved in renal elimination of oxypurinol.

**Implications:** deciphering the molecular mechanisms of renal oxypurinol secretion could be of therapeutic benefit as a specific pharmacogenetic profile would support a more individual SUA-lowering regime.

## A27: Predicting oxypurinol exposure in patients receiving intermittent haemodialysis

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The aims of this study were to characterise the population pharmacokinetics of oxypurinol in patients receiving haemodialysis and to compare oxypurinol exposure in dialysis and non-dialysis patients. Oxypurinol plasma concentrations from 6 patients with gout receiving intermittent haemodialysis and 19 non-dialysis gout patients were available for analysis. In the dialysis patients, 14 oxypurinol plasma concentrations were measured over two dosing intervals, one of which included a dialysis cycle. A population analysis was conducted using NONMEM v.7.2. Deterministic simulations from the model were used to predict the steady-state area under the oxypurinol plasma concentration time curve over 1 week () for dialysis and non-dialysis patients. The pharmacokinetics of oxypurinol were best described by a one compartment model with a separate parameter for dialytic clearance. Allopurinol 100mg daily produced an  of 279 µmol/L*hr in dialysis patients, a value 50-75% lower than the  predicted for patients with normal renal function taking standard doses of 200 to 400mg daily (427-855 µmol/L*hr). Dosing pre-dialysis resulted in about a 25-35% reduction in exposure compared to post-dialysis. We have developed the first population pharmacokinetic model for oxypurinol in haemodialysis patients. Oxypurinol is efficiently removed by dialysis. Our results suggest that if the combination of low dose allopurinol and haemodialysis does not result in sustained urate lowering below treatment targets (serum urate ≤ 0.36 mmol/L) then allopurinol doses may be increased to optimise oxypurinol exposure.