Annual scientific meeting
30th August-1st September 2016

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Abstract and Programme Booklet

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Contents

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Working to improve your health

AFT is a Pharmaceutical sales and development company with operations in Australia, Malaysia, New Zealand and Singapore. AFT began with a $50,000 start-up investment in Dr Hartley Atkinson's home garage in 1997 and last year had turnover of over NZ$66 million. AFT has numerous products listed on Australia's Pharmaceutical Benefits Scheme (PBS) and New Zealand's Pharmaceutical Schedule, sells medicines in public and private hospitals and OTC medicines across Australia and New Zealand. The Company has recently opened offices in Kuala Lumpur and Singapore to accelerate sales in those and nearby countries across the ASEAN region.

It has successfully out-licensed its analgesic development, *Maxigesic*® to over 40 countries. *Maxigesic*® was invented, developed and patented by AFT, a privately-owned Australasian pharmaceutical based in Auckland and Sydney. AFT also has development programs in cold & flu medicines under the tradename *Maxiclear*®, whose first clinical results were recently published in the world's leading medical journal, *The New England Journal of Medicine*.

Further developments involve a patented drug delivery system using ultrasonic mesh nebuliser technology which will enter clinical trials this year for both treatment of chronic sinusitis and delivery of various drugs by the intranasal delivery route.

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- Stelara (ustekinumab) psoriatic arthritis and psoriasis
- Simponi (golimumab) for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

General Information

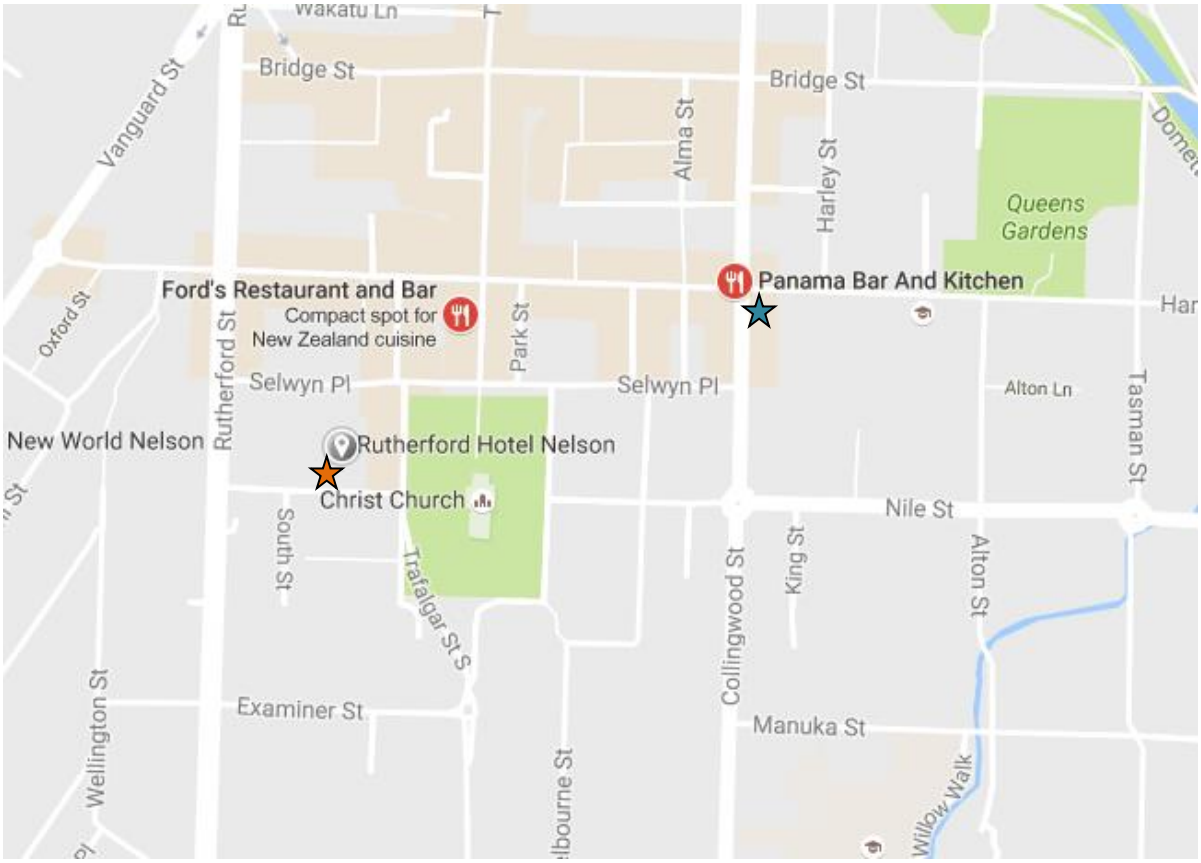
Welcome to the 2016 ASCEPT NZ meeting as part of Queenstown Research Week. On behalf of the organising committee we hope that you have an enjoyable, informative and educational meeting.

Organising Committee Members:

Murray Barclay (chairperson) – Canterbury District Health Board
David Reith (treasurer) – University of Otago, Dunedin
Chris Cameron (secretary) – Capital and Coast District Health Board
Michelle Glass – University of Auckland

Venue:
Rutherford Hotel
27 Nile Street West
Nelson 7010

Conference dinner:
Panama Bar & Kitchen
112 Collingwood Street
Nelson 7010



Invited Speakers

Angela Finch (University of New South Wales)

Angela is a Senior Lecturer in the School of Medical Sciences at UNSW Australia. Her research focus throughout her career has been the understanding of the structure and function of membrane proteins and the design and development of new drugs to modulate these proteins in disease states. Her current research focus is the activation and regulation of G-Protein Coupled Receptors (GPCR) by drugs. The mechanisms of GPCR activation are being explored via: (i) investigating the role of the extracellular region in regulating the binding and activation of GPCRs by endogenous ligands and as a site of interaction with allosteric modulator drugs in adrenergic, inflammatory (C5aR) and taste receptors and (ii) the discovery of novel allosteric ligands for these receptors.

Hesham Al-Sallami (University of Otago)

Hesham Al-Sallami is a lecturer of clinical pharmacy at the School of Pharmacy, University of Otago. He obtained his BPharm degree in 2000 through the University of Otago. He worked as a rotational then a clinical pharmacist around New Zealand while doing his PGDip and Master's degrees in Clinical Pharmacy. His Master's thesis was on the risk factors of enoxaparin-induced bleeding.

He joined/rejoined the School of Pharmacy at Otago as a lecturer in 2008 while doing a PhD in clinical pharmacology/pharmacometrics. His PhD thesis was on dose-individualisation of heparins in adults and children

His current area of research is paediatric pharmacology and the influence of body composition on drug dose-response

Murray Barclay (Canterbury DHB, University of Otago)

Murray is a Clinical Pharmacologist and Gastroenterologist at Christchurch Hospital, Canterbury District Health Board, and a Clinical Professor with University of Otago Christchurch. His areas of research include thiopurine drugs, pharmacogenetics, pharmacokinetics, immunodulators, inflammatory bowel disease, therapeutic drug monitoring, on-line interactive learning in medicine, and doctor wellbeing. With Lisa Stamp, he facilitated the development of assays for biologic agents in Christchurch, which are available for use throughout New Zealand, and has studied the relationship between disease control and concentrations of biologics and antidrug antibodies in IBD.

Paul Chin (Canterbury DHB, University of Otago)

Paul Chin is a Clinical Pharmacologist. His research interests include pharmacokinetics and therapeutic drug monitoring.

Qian Yi Chuah (Canterbury DHB)

QianYi Chuah joined the Department of Clinical Pharmacology as a Pharmacist to work as a Medicines Use Review and eMedicines Pharmacist. She has previously worked as a Clinical Pharmacist in various DHBs in New Zealand. She holds a strong interest in clinical informatics, data analytics and helping making data more accessible to clinicians.

QianYi currently holds a BPharm and Postgraduate Diploma in Clinical Pharmacy from the University of Otago.

Matt Doogue (Canterbury DHB, University of Otago)

Matt Doogue is a consultant Physician at Christchurch Hospital with particular responsibilities in medicines governance and "eMedicines". He is a member of the Department of Medicine, University of Otago, Christchurch and co-ordinates Clinical Pharmacology teaching. His research interests include adverse drug reactions, drug concentration monitoring, drug interactions, pharmacogenetics and pharmacokinetics in particular patient groups, and clincial decision support.

Jacqui Hannam (University of Auckland)

Jacqueline completed her Ph.D. in 2013 with the Department of Anaesthesiology, University of Auckland, during which she studied the clinical pharmacology of anaesthetic and analgesic combinations. Following this she spent six months working with the pharmacometrics team at the University of Navarra, Pamplona, as a Postdoctoral Fellow. She now works at the School of Medicine, University of Auckland. Her research interests include pharmacometrics, anaesthesiology, patient safety and simulation in healthcare. She is currently involved in investigating the pharmacokinetics of commonly used antibiotics in neonates, babies and children for better dosing in this group.

Chihiro Hasegawa (University of Otago)

Chihiro Hasegawa received his PhD in Clinical Pharmacokinetics from Kyushu University, Japan. He has been working in Ono Pharmaceutical Co., Ltd. (Japan) as a PK-PD scientist since 2007 and contributed to more than ten projects as a clinical pharmacology lead. Now he is also a Visiting Researcher in the School of Pharmacy, University of Otago.

Paula Keating (Canterbury Health Laboratories)

Paula is a Scientific Officer in Immunology at Canterbury Health Laboratories (CHL). CHL provides the anti-TNF Biologic drug assays developed with Murray and Lisa. Assays to measure both drug levels and anti-drug antibodies are available to clinicians throughout New Zealand. Paula has a Ph.D. in Immunology from the University of Edinburgh and has worked in both academia and industry.

David Ryan (Waitemata District Health Board)

David is the Pharmacy Operations Manager at Waitemata DHB, and has overseen the implementation of multiple eMedicines initiatives – including the Pyxis Medstation System, smart pumps, eMedicines reconciliation, electronic Prescribing & Administration, and more recently eVitals.

Catherine Sherwin (University of Utah)

Dr Catherine Sherwin is currently an Assistant Professor and Chief of the Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine. She is also the Director of Pharmacometrics in the Clinical Trials Office, Salt Lake City, Utah, USA. She earned her PhD at the University of Otago, Dunedin School of Medicine, New Zealand in Paediatric Clinical Pharmacology in 2007. She then completed one year of Postdoctoral training in the Women's and Children's Health in Dunedin and then a two year T32 Fellowship training program in the Divisions of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Ohio. She received board certification from the American Board of Clinical Pharmacology in 2011. Dr. Sherwin has expertise and experience in the development of quantitative pharmacometric (PK/PD/PG) models in special populations including pediatric and neonatal patients.

Lisa Stamp (University of Otago)

Professor Lisa Stamp is a Rheumatologist at the University of Otago, Christchurch and Christchurch Public Hospital. Lisa completed her rheumatology training in New Zealand and Adelaide and subsequently completed her PhD at the University of Adelaide in Australia. She is Director of the Canterbury Rheumatology Immunology Research Group. Her research interests include individualization of drug treatments in rheumatic conditions, including dosing of allopurinol and the role of oxypurinol concentrations in gout, use of methotrexate in rheumatoid arthritis and the role of intracellular methotrexate polyglutamates in disease activity and drug toxicity. She also has an interest in inflammatory pathways in rheumatoid arthritis in particular interleukin-17. Prof Stamp has been awarded an Early Career Research award and the Carl Smith Medal for research by the University of Otago. In 2016 she was awarded as The Arthritis New Zealand National Researcher Award.

Tracey Watson (Taranaki District Health Board)

Tracey Watson has over 20 years' experience in hospital as a clinical pharmacist at Taranaki DHB, one of the designated national pilot sites for electronic Medication Management (eMM). For the past 4 years she has been the Clinical Lead of the eMM team and sits on several national Committees as an expert user of MedChart, ePharmacy, eMedRec & Pyxis.

DAY 1 – Tuesday 30th August 2016 – WELCOME FUNCTION	
18.30 – 18.35	**Welcome** Murray Barclay *Chair of ASCEPT NZ*
18.35 – 19.30	**Registration opens.** Drinks, nibbles, and networking function
DAY 2 – Wednesday 31st August 2016 – ANNUAL SCIENTIFIC MEETING	
08.30 – 09.30	**Registration opens.** Tea and coffee available
Welcome – Murray Barclay	
ePrescribing Symposium – Chair: David Reith	
09.30 - 09.50	**David Ryan (A1)** Waitemata DHB *The Waitemata MedChart experience*
09.50 - 10.10	**Tracey Watson (A2)** Taranaki DHB *The Taranaki MedChart experience*
10.10 - 10.30	**Matt Doogue (A3)** Canterbury DHB/University of Otago *Clinical Decision Support in ePrescribing*
10.30 - 11.00	**Morning tea**
11.00 - 11.20	**QianYi Chuah (A4)** Canterbury DHB *Data extraction and analysis in MedChart*
11.20 - 11.30	**Panel discussion**
ePrescribing Oral Communications Session 1 – Chair: Chris Cameron	
11.30 – 11.45	**Paul Chin (A5)** Canterbury DHB/University of Otago *Drug-drug interaction alerts in ePrescribing*
11.45 - 12:00	**Jane Vella-Brincat (A6)** Canterbury DHB *Use of MedChartTM generated lorazepam administered time data as a marker of agitation/anxiety*
12.00 – 12.15	**Matt Doogue (A7)** Canterbury DHB/University of Otago *Adverse Drug Reactions in an ePrescribing and Administration System*
12.15 – 12.30	**QianYi Chuah (A8)** Canterbury DHB *Use of Clinical Decision Support in ePrescribing to facilitate generic prescribing*
12.30 - 13.30	**Lunch**

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Monoclonal Antibodies Symposium – Chair: Nuala Helsby	
13.30 - 13.50	**Lisa Stamp (A9)** University of Otago *Clinical use of monoclonal antibody drugs*
13.50 - 14.10	**Chihiro Hasegawa (A10)** University of Otago *The pharmacokinetics of monoclonal antibody drugs*
14.10 - 14.30	**Paula Keating (A11)** Canterbury Health Laboratories *Assays for measuring monoclonal antibody drugs*
14.30 - 14.50	**Murray Barclay (A12)** Canterbury DHB/University of Otago *Monitoring of monoclonal antibody drugs*
14.50 - 15.00	**Panel discussion**
15.00 - 15.30	**Afternoon tea**
Student Oral Communications Session – Chair: Evan Begg	
15.30 – 15.45	**Shamin Saffian (A13)** University of Otago *An evaluation of warfarin dose prediction methods*
15.45 – 16.00	**Qing Xi Ooi (A14)** University of Otago *Quantifying the influence of Vitamin K on warfarin dosing requirements*
16.00 – 16.15	**Brandi Bellissima (A15)** University of Auckland *Determination of post-mortem clozapine levels in coronial autopsy cases*
16.15 – 16.30	**Riya Biswas (A16)** Auckland University of Technology *Modulation of multidrug resistance protein 2 (MRP2) by RNA interference (RNAi) increases the chemo-sensitivity of HepG2 cells to oxaliplatin*
16.30 – 16.45	**Niall Hamilton (A17)** Canterbury DHB *Diagnosing and recording adverse drug reactions in general medical patients*
16.45 – 17.00	**Natalie Fleming (A18)** University of Otago *A mathematical model for urate transport in a proximal tubular cell*
17.00 - 18.00	**ASCEPT AGM**
19.00	**Conference dinner**

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DAY 3 – Thursday 1st September 2016 – ANNUAL SCIENTIFIC MEETING

Predicting Dose Differences Between Patients "Variability is the law of life…so no two bodies are alike.." Osler 1903 – Chair: Dan Wright	
09.10 - 09.30	**Hesham Al-Sallami (A19)** University of Otago, Dunedin *Drug dosing and between-subject variability*
09.30 – 09.50	**Jacqui Hannam (A20)** University of Auckland *Maturation models*
09.50 - 10.10	**Catherine Sherwin (A21)** University of Utah *Body size and body composition*
10.10 – 10.40	**Morning tea**
10.40 - 11.00	**Stephen Duffull** University of Otago, Dunedin *Organ function*
11.00 - 11.30	**Panel discussion**
ASCEPT Guest Speaker – Chair: Murray Barclay	
11.30 - 12.30	**ASCEPT Invited Speaker:** **Angela Finch (A23)** University of New South Wales ***"There and back again: understanding GPCR ligand binding pathways to design better drugs"***
12.30 – 13.30	**Lunch**
Oral Communications Session 2 – Chair: Ivan Sammut	
13.30 – 13.45	**Simran Maggo (A24)** University of Otago, Christchurch *Understanding Adverse Drug Reactions Using Genome Sequencing (UDRUGS): A focus on statin induced myalgia*
13.45 – 14.00	**Piyanan Assawasuwannakit (A25)** Mahidol University, Bangkok, Thailand *Population pharmacokinetics of OZ439 in healthy volunteers and patients with falciparum and vivax malaria*
14.00 – 14.15	**Andrew Bahn (A26)** University of Otago, Dunedin *Contribution of organic anion transporters (OAT) to renal secretion of the gout medication oxypurinol*
14.15 – 14.30	**Dan Wright (A27)** *University of Otago, Dunedin* *Predicting oxypurinol exposure in patients receiving intermittent haemodialysis*
Conference Close and Prize Giving	
14.30 - 15.00	**Murray Barclay**

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Abstracts

A1: The Waitemata MedChart experience

David Ryan

Waitemata District Health Board

Over the past 4 years, we have progressively implemented electronic Prescribing & Administration across approximately 970 beds across the three main hospital sites at Waitemata DHB. The benefits of achieving an integrated system are compelling, and with the initial implementation of ePrescribing we have taken important steps towards achieving this goal. Clinicians now have basic decision support, including interactions, dose ranges, allergies and targeted rules at the point of prescribing, as well as a large number of pre-defined orders and order sets that help guide appropriate prescribing. However, the amount of clinical and technology change required is significant, and implementing such a complex system is fraught.

A2: Implementation Learning's from an Adhoc Evaluation of the Taranaki District Health Board (TDHB) Electronic Prescribing Pilot

Watson TJ[1]

[1] electronic Medication Management, Pharmacy Department, Taranaki District Healthboard, New Plymouth, NZ

Evidence demonstrates that electronic prescribing (ePA) systems eliminate administrative prescribing errors and if implemented well, will reduce clinical errors. However they also introduce new types of errors. Some of these are related to the system itself, while others are related to changes in workflow or other contextual factors. "System-related" errors are not well defined. They vary in type and nature depending on the system and how that system is configured and/or implemented. Furthermore most are not detected by users. Hence while unintended consequences of ePA are to be expected, they are not well defined, are context dependant & are poorly detected.

TDHB first implemented electronic prescribing and administration software (MedChart) in an Assessment and Rehabilitation ward in 2012. In order to ensure patient safety, five different sources of medication event information were monitored to identify prescribing and administration errors in the TDHB context, to mitigate associated risks and inform future roll-out.

For the MedChart ward 24 months baseline data was compared to 12 months post-implementation data, with this also being compared to data for 5 non-MedChart wards.

Administrative type prescribing errors were almost eliminated, but new types of errors were also introduced. Audit enabled better definition of these errors and identification of patterns. Areas of concern included withholding, inadequate checking of administration history, increase in events associated with high risk or error prone drugs, increase in transcribing errors and an increase in the proportion of "incorrect dose regimen", "wrong drug" and "duplicate errors".

Better definition of errors has enabled implementation of strategies to either eliminate them or minimise the associated risks. This work also informed implementation in other areas & an ongoing evaluation strategy at TDHB. It also includes important implementation learning's for other hospitals as MedChart is rolled out nationally.

Notes

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

Doogue MP[1,2]. Chin P[1,2], Strother RM[1,2], Lodge C[2], Dean K[2], Hamilton N[2].

[1]Department of Medicine, University of Otago, Christchurch, NZ. [2]Canterbury District Health Board Christchurch, NZ.

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. 24:264-7

Notes

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

Drennan, P.[1], Chin, P.[1,2], Strowther, M.[1,2], Lodge, C[1], Dean, K.[1], Doogue, M.P.[1,2]

[1]Department of Clinical Pharmacology, Christchurch Hospital, Christchurch, New Zealand. [2]Department of Medicine, University of Otago, Christchurch, NZ.

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

Notes

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

Vella-Brincat, J.[1], McKean, A.[2], Doogue, M.[1], Chin, P.[1], Chuah, Q.[1], Strother, M.[3]

[1]Department of Clinical Pharmacology, Christchurch Hospital, Canterbury District Health Board (CDHB), Christchurch, NZ, [2]Department of Pharmacy, Hillmorton Hospital, Canterbury District Health Board (CDHB), Christchurch, NZ [3]Department of Oncology, Christchurch Hospital, Canterbury District Health Board (CDHB), Christchurch, NZ.

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.

Notes

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

Wareing T.R.[1], Chin P.[1,2], Strother R.M.[1,2], Vella Brincat J.[2], Chuah Q.[2], & Doogue M.P.[1,2].

[1]Department of Medicine, University of Otago, Christchurch, NZ. [2]Department of Clinical Pharmacology, Christchurch Hospital, Christchurch, NZ.

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

Chuah, Q. [1], Vella-Brincat, J. [1], Chin, P.[1,2], Barclay, M.[1,2], Doogue, M[1,2].

[1]Department of Clinical Pharmacology, Christchurch Hospital, Canterbury District Health Board (CDHB), Christchurch, NZ. [2]Department of Medicine, University of Otago, Christchurch, NZ

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.

Notes

A10: Pharmacokinetics and modelling issues for monoclonal antibodies

Hasegawa, C.[1]

[1]School of Pharmacy, University of Otago, Dunedin, NZ

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

Keating, P.[1], Zhang, M.[1, 2], Hock, B.D.[3]

[1]Canterbury Health Laboratories, Christchurch, NZ, [2] Clinical Pharmacology, Department of Medicine, University of Otago, Christchurch, NZ, [3]Haematology Research Group, Christchurch Hospital, Christchurch, NZ.

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.

Notes

A12: Monitoring of monoclonal antibody drugs

Barclay, M.L.[1-3]

Departments of Clinical Pharmacology[1] and Gastroenterology[2], Christchurch Hospital, and [3]Department of Medicine, University of Otago, Christchurch, New Zealand.

Monoclonal antibody drugs (Mabs) are used increasingly in many areas of medicine due to their design versatility and long half-life of elimination. However, they are also prone to antidrug antibody formation, which results in increased clearance and failed efficacy. In recent years, clinicians and researchers have begun to measure concentrations of both Mabs and their antidrug antibodies to explore the reasons for variable drug response and secondary non-response, and to help predict treatment outcome. The most experience so far is with the antagonists of tumour necrosis factor alpha, infliximab and adalimumab, in inflammatory bowel disease (IBD). Many studies show a good correlation between drug response and trough concentrations of drug and antidrug antibodies. There appears to a reliable threshold trough drug concentration above which efficacy is more likely, in the order of 3-10 mg/L. Furthermore, reduction of dose in patients with high concentrations has potential for substantial cost savings. However, prospective studies of therapeutic drug monitoring in IBD have given mixed results so far and more research may be required to clarify the precise role of therapeutic drug monitoring of TNFα drugs in IBD. The research so far suggests a role for more widespread application of therapeutic drug monitoring for Mab drugs to both optimise patient outcome and improve cost-efficacy.

A13: An evaluation of warfarin dose prediction methods

Saffian, S.M.[1], Duffull, S. B.[1], Wright, D.F.B.[1]

[1]School of Pharmacy, University of Otago, Dunedin

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

Notes

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

Ooi, Q.X.[1], Wright, D.F.B.[1], Tait, R.C.[2], Isbister, G.K.[3], Duffull, S.B.[1]

[1]School of Pharmacy, University of Otago, Dunedin, New Zealand, [2]Glasgow Royal Infirmary, Glasgow, Scotland, [3]School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia

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

Bellissima, B.L.[1], Garavan, F.[2], Tingle, M.D.[1]

[1]Department of Pharmacology & Clinical Pharmacology, University of Auckland, Auckland, NZ, [2] Miami-Dade County Medical Examiner Department , Miami, Florida, USA.

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.

Notes

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

Riya Biswas[1], Fabrice Merien[1, 2], Jun Lu[1], James Paxton[3], Mark McKeage[3] and Yan Li[1]

[1]School of Science, Auckland University of Technology, Auckland, NZ, [2]AUT-Roche Diagnostics Laboratory, Auckland, NZ, [3]Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, NZ.

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.

Notes

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

Niall Hamilton[1], Murray L Barclay[1,2], Matthew P Doogue[1,2]

[1]Department of Clinical Pharmacology, Canterbury District Health Board, [2]Christchurch. Department of Medicine, University of Otago, Christchurch

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.

Notes

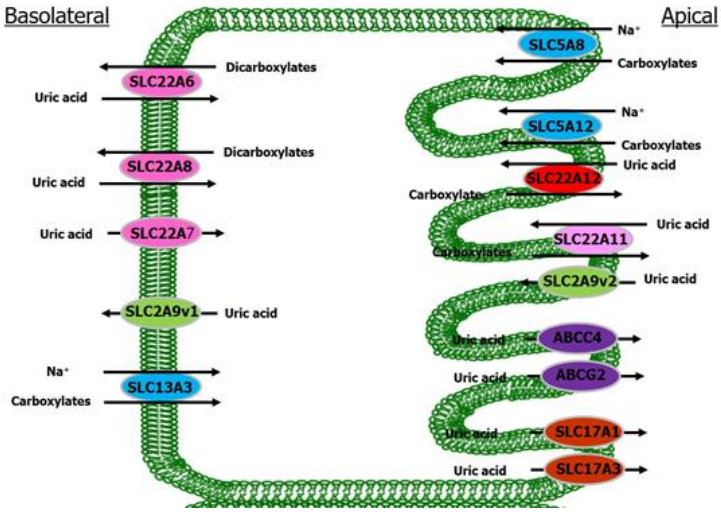
A18: A Mathematical Model for Urate Transport in a Proximal Tubular Cell.

Fleming, N.G.[1], Wright, D.F.B.[1], Duffull, S.B.[1]

[1]School of Pharmacy, University of Otago, Dunedin, NZ.

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.

Notes

A19: Drug dosing and between-subject variability

Hesham S Al-Sallami. School of Pharmacy, University of Otago, Dunedin.

Dose requirements vary between individuals due to variability in pharmacokinetic (PK) and pharmacodyanmic (PD) parameters across a population. This between-subject variability (BSV) is comprised of predictable (BSVp) and unpredictable or random (BSVr) components. BSVp can be reduced by accounting for influential covariates on parameter estimates. For instance, the parameter clearance (CL) is influenced by three covariates: body size, functional maturation, and organ function.[1]

Of note, variability in the parameters across a patient population still remains even after accounting for patient covariates. In a recent review of the reported BSV in PK parameters (quantified using the coefficient of variation percentage), the average CV% for clearance was 40%[2]. Although this refers to PK variability, which is a key source of variability in drug response, complex PD responses (e.g. coagulation) can present significant BSV in PD parameters.[3] In this case the concept of safe and effective variability (SEV) becomes useful.[4] SEV can be used to identify a therapeutic range where a range of target concentrations (e.g. steady state drug concentration) is considered optimal. Based on that, if the achieved concentration in an individual lies within this range, the treatment in the population may be considered safe and effective.

This talk will cover current drug dosing methods given the variability in drug-response between patients. Covariate-based dose-individualisation will be discussed in light of target-concentration intervention (TCI). Finally, the talk will introduce the three influential covariates used currently to account for between-subject variability in drug CL. These covariates will be individually discussed by the symposium speakers.

1. Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008; 47(4):231-43.
2. Al-Sallami HS, Cheah SL, Han SY, Liew J, Lim J, Ng MA, Solanki H, Soo RJ, Tan V, Duffull SB. Between-subject variability: should high be the new normal? Eur J Clin Pharmacol. 2014; 70(11):1403-4.
3. Duffull SB. Is the ideal anticoagulant a myth? Expert Rev Clin Pharmacol. 5(3):231-6.
4. Holford NH, Buclin T. Safe and effective variability-a criterion for dose individualization. Ther Drug Monit. 2012; 34(5):565-8.

Notes

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

Jacqueline A. Hannam

Department of Anaesthesiology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand.

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

Catherine MT Sherwin

Division of Clinical Pharmacology, Department of Paediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA

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

Notes

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

Catherine MT Sherwin

Division of Clinical Pharmacology, Department of Paediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA

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.

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

Notes

A22: Predicting Dose Differences Between Patients: Organ Function Variability

Nick Holford

Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

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].

1. Cockcroft, D.W. and M.H. Gault, *Prediction of creatinine clearance from serum creatinine.* Nephron, 1976. **16**: p. 31-41.
2. Schwartz, G.J., *Does kL/PCr estimate GFR, or does GFR determine k?* Pediatr Nephrol, 1992. **6**(6): p. 512-5.
3. Levey, A.S., et al., *A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group.* Ann Intern Med, 1999. **130**(6): p. 461-70.
4. European Medicines Agency *Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function*. 2005.
5. Relling, M.V., et al., *Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing.* Clin Pharmacol Ther, 2011. **89**(3): p. 387-91.
6. Gardiner, S.J., et al., *Thiopurine dose in intermediate and normal metabolizers of thiopurine methyltransferase may differ three-fold.* Clin Gastroenterol Hepatol, 2008. **6**(6): p. 654-60; quiz 604.
7. Xue, L., N.H.G. Holford, and L. Miao, *Warfarin PKPD – Theory, Body Composition and Genotype.* PAGE, 2016. **25 Abstr 5759 [www.page-meeting.org/?abstract=5759]**.
8. Jensen, B.P., et al., *Influence of adult age on the total and free clearance and protein binding of (R)- and (S)-warfarin.* British Journal of Clinical Pharmacology, 2012. **74**(5): p. 797-805.

Notes

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

Finch, A.M., Campbell, A.P., Leonar, E., Chen J., Urmi, K.F., Noh W-J., Xu, K., Wilkins, B.P., So, S.S., Griffith, R.

Department of Pharmacology, School of Medical Science, UNSW Australia, Sydney, Australia

The classical parameters that are determined for compounds in the drug development process are potency, affinity and efficacy. Until recently, little attention has been devoted to the kinetics of the binding process and influence of residence time on drug efficacy. Molecular dynamics studies suggest that small molecule neurotransmitters such as adrenaline and acetylcholine first associate with an extracellular region (vestibule) of the β_2 adrenoceptor (β_2AR) and muscarinic M_3 receptor respectively, before traversing down a narrow pathway and adopting their final position in the orthosteric pocket (Dror *et al*., 2011). This proposed vestibule region has also been shown to be the site of allosteric modulation on the muscarinic acetylcholine receptors (Kruse *et al*., 2012).

Using mutagenesis, we have demonstrated the role of this vestibule formed by residues at the top of (extracellular side of) transmembrane helices 5, 6 and 7 and the second extracellular loop (ECL2), not only for orthosteric but also allosteric interactions at the β_2AR. Utilizing bitopic ligands as 'molecular rulers' we have similarly identified an allosteric binding site on the α_{1A}-AR that is formed by residues at the top of helices 2,3 and 7 and that also plays a role in the orthosteric ligand transit in and out of the orthosteric binding pocket. This suggests that the location of the vestibule is not shared across adrenergic receptors. Using homology modelling and complex based pharmacophores, based on the α_{1A}-AR vestibule, to perform *in silico* screening, we have identified three novel allosteric modulators of [^{3}H] prazosin dissociation from the α_{1A}-AR.

By further developing our understanding of adrenoceptor ligand binding kinetics and the control of this process by allosteric modulators it is hoped that selective therapeutics will result from improved drug design.

1. Dror, R.O., et al.,(2011) *Pathway and mechanism of drug binding to G-protein-coupled receptors*. Proc Natl Acad Sci U S A. 108(32):13118–13123
2. Kruse, A.C., et al.,(2012) *Structure and dynamics of the M3 muscarinic acetylcholine receptor*, Nature. 482(7386):552-6

Notes

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

Maggo, S.D.S.[1], Young, J.[2], Lehnert, K.[3], George, P[4], Kennedy, M.A.[1]

[1]Department of Pathology, University of Otago, Christchurch, NZ, [2]Lipid and Diabetes Research Group, Christchurch Hospital, [3]Biological Sciences, Faculty of Science, University of Auckland, [4]Canterbury Health Laboratories, Department of Molecular Pathology, Christchurch Hospital, Christchurch.

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.

Notes

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

Assawasuwannakit, P.[1], Phyo, A.P.[1,2,3], Jittamala, P.[4], Nosten, F.H.[1,2,3], Pukrittayakamee, S.[5], Imwong, M.[6], White, N.J.[1,3], Duparc, S.[7], Macintyre, F.[7], Baker, M.[7], Möhrle, J.J.[7], van Giersbergen, P.L.M.[8], Snoeijer, B.[9], Siethoff, B.[10], Tarning, J.[1,3]

[1]Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, [2]Shoklo Malaria Research Unit, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Tak, Thailand, [3]Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK, [4]Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, [5]Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, [6]Department of Molecular Tropical Medicine and Genetics, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, [7]Medicines for Malaria Venture, Geneva, Switzerland, [8]Van Giersbergen Consulting, Wuenheim, France, [9]OCS Biometric Support, Leiden, The Netherlands, [10]Swiss BioQuant, Reinach, Switzerland.

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.

1. Phyo, A.P. *et al.* (2016). *Antimalarial activity of artefenomel (OZ439), a novel synthetic antimalarial endoperoxide, in patients with Plasmodium falciparum and Plasmodium vivax malaria: an open-label phase 2 trial*. Lancet Infect Dis. 16: 61-9.

Notes

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

Cooper, A. and Bahn, A.

Department of Physiology, University of Otago, School of Medical Sciences, Dunedin, New Zealand

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

Daniel F.B. Wright[1], Matthew P. Doogue[2,3], Murray L Barclay[2,3], Peter T Chapman[2,4], Nicholas B Cross[2], John H Irvine[2], Lisa K Stamp[2,4].

[1]School of Pharmacy, University of Otago, Dunedin, NZ, [2]Department of Medicine, University of Otago, Christchurch, NZ, [3]Department of Clinical Pharmacology, Christchurch Hospital, Christchurch, NZ, [4]Department of Rheumatology Immunology and Allergy, Christchurch Hospital, NZ

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.

Notes