Annual scientific meeting
1st—3rd September 2015

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Abstract and Programme Booklet

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A word from some of our sponsors

AFT Pharmaceuticals

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.

General Information

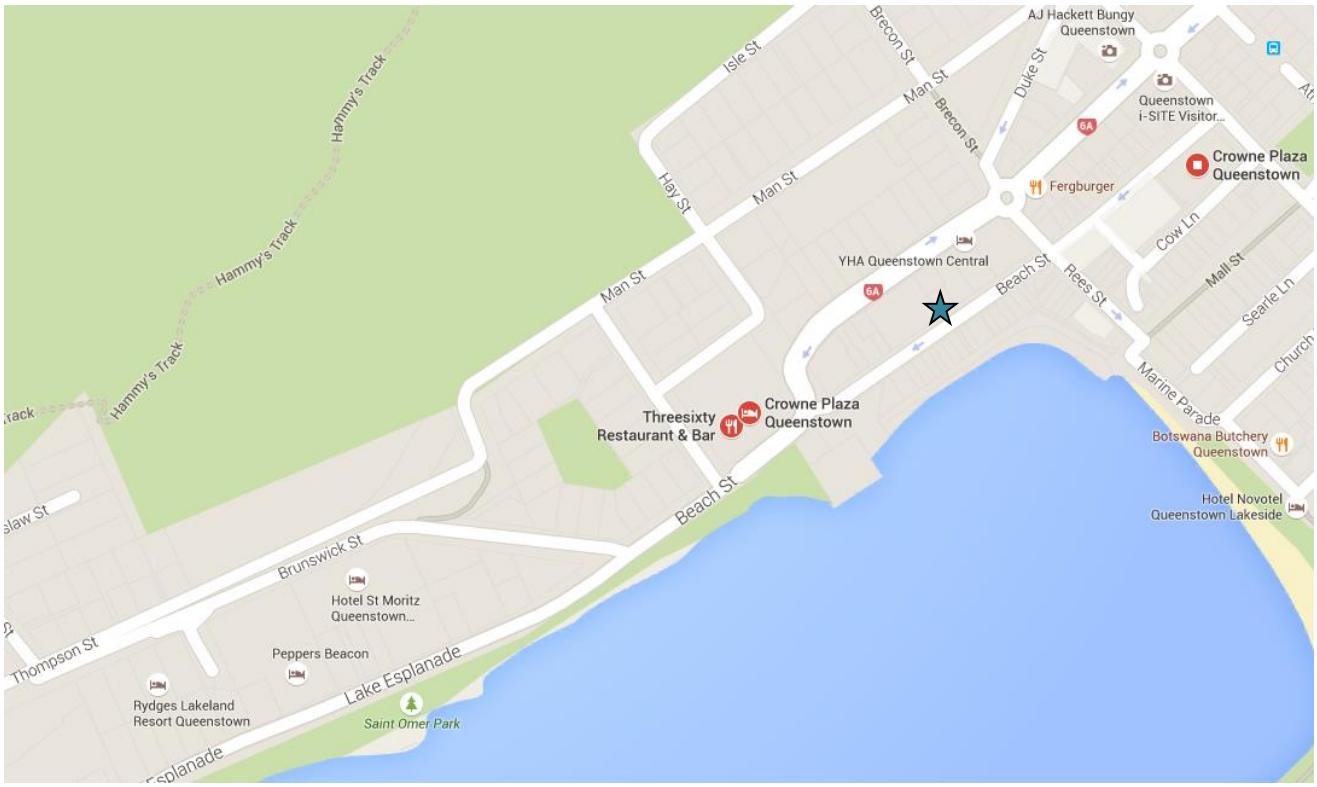
Welcome to the 2015 ASCEPT NZ meeting as part of Queenstown Research Week. On behalf of the organising committee we hope that you have an enjoyable, informative and educational meeting.

Organising Committee Members:

Daniel Wright (chairperson) – University of Otago, Dunedin
David Reith (treasurer) – University of Otago, Dunedin
Chris Cameron (secretary) – Capital and Coast District Health Board
Michelle Glass – University of Auckland
Pam Buffery (convenor) – Canterbury District Health Board

Venue:
Crowne Plaza Hotel
93 Beach St,
Queenstown 9300

Conference dinner:
Flame Bar and Grill
61 Beach St,
Queenstown 9300



Invited Speakers

Distinguished Professor Richard Faull (Faculty of Medical and Health Sciences, University of Auckland)

With a research career spanning over 35 years, Professor Richard Faull is recognised internationally as a leading expert on the workings of the human brain and the neurodegenerative diseases that can affect it including Alzheimer's, Parkinson's and Huntington's diseases. In 2007, his research group provided the first evidence that the diseased human brain can repair itself by the generation of new brain cells, overturning the long-held view that the adult brain can only degenerate.

Professor Faull's contributions to neuroscience were recognised by the University of Auckland in 1993 with the award of a Personal Chair in Anatomy. In 2002 he was awarded the Inaugural Peter Gluckman Medal and Distinguished Faculty International Lecturer at the University of Auckland. In 2005 he was awarded the Liley Medal by the Health Research Council and in 2007, New Zealand's top science honour, the Rutherford Medal, which is administered by the Royal Society on behalf of the New Zealand Government. In 2010, Professor Faull was the Supreme Winner of the World Class New Zealand Awards.

Professor Faull is founder and director of the Neurological Foundation Human Brain Bank based at the University of Auckland. Established in 1994, the brain bank now houses an extensive collection of human brain tissue from over 400 brains, including normal brains and those from nine different neurological diseases. Research using this tissue provides vital insights into neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's diseases, motor neurone disease, and epilepsy and schizophrenia.

Tissue from the Neurological Foundation Human Brain Bank is a crucial resource for researchers at the Centre for Brain Research, and at research institutions and universities throughout New Zealand. The Human Brain Bank has also provided opportunities for valuable international collaborative studies with leading research scientists in England, Switzerland, Sweden, USA and Japan.

Dr Bruce Russell (Faculty of Medical and Health Sciences, University of Auckland)

Following registration as a pharmacist, Bruce completed a PhD under the supervision of Professor Dick Laverty in the Dept. of Pharmacology at the University of Otago. He was Professor Laverty's last PhD student. Bruce's PhD investigated the mechanisms underlying amphetamine-induced neurotoxicity. This provided him with a very strong foundation in the underlying pathophysiology and neuropharmacology of mental health disorders and drug-induced changes in behaviour. He then undertook post-doctoral research at the University of Edinburgh followed by work as a specialist pharmacist in Scotland before returning to NZ. During that time he became an active team member involved in the diagnosis and treatment of people with severe mental illnesses such as treatment-resistant schizophrenia, depression, bipolar affective disorder and the addictions. This experience complemented his PhD and subsequently provided a focus for his research career. Since 2005 he has worked at the University of Auckland successfully establishing a new stream of research by working with patients who suffer from severe mental health disorders using MRI, EEG and neurocognitive testing. Next year he is taking up a new post at the University of Otago.

Professor Mike Dragunow (Faculty of Medical and Health Sciences, University of Auckland)

Mike is a neuropharmacologist and his research focuses on studying the causes of brain disorders and on developing novel drug treatments for these disorders. He completed a PhD at the University of Otago under the supervision of Professors' Dick Laverty and Graham Goddard, and undertook post-doctoral studies in Canada and the University of Auckland. His is now a Professor of Pharmacology (Personal Chair awarded 1999) at the Centre for Brain Research, University of Auckland Medical School. He has taught brain pharmacology to 1000's of science and medical students at Auckland University over 25 years and has supervised over 50 graduate students in brain research. He was awarded the New Zealand Association of Scientists Research Award in 1996 and a Fellowship of the Royal Society of New Zealand in 2000, has published over 260 research papers which have been cited over 20,000 times (Google Scholar Search, H-index of 75), has worked for Biotech as a consultant and Scientific Advisory Board member and has been awarded over $30M in research grants over his career. He currently directs a Health Research Council Programme Grant and also established and directs the Centre for Brain Research Biobank, a facility for growing human brain cells to study mechanisms of brain disease causation and to test and develop novel treatments.

Dr Yiwen Zheng, (Department of Pharmacology and Toxicology, University of Otago, Dunedin)

Dr Yiwen Zheng completed her undergraduate study majoring in Pharmacology at Shanghai Medical University, China before undertaking a PhD study in the Department of Pharmacology and Toxicology, University of Otago under the supervision of Professor Dick Laverty in 1994. Dr Zheng is currently a Senior Research Fellow and a co-director of the Vestibular and Auditory Research Group in the Department of Pharmacology and Toxicology, University of Otago leading active research in two areas: 1) tinnitus treatment and underlying mechanisms of tinnitus generation and 2) the contribution of vestibular information to higher cognitive function. Using two animal models of tinnitus, the research group is the only one in New Zealand that has induced and assessed tinnitus in animals with a focus on understanding how tinnitus develops, how it is maintained and evaluating different drug treatments. She has published 3 book chapters and 75 journal articles. Dr Zheng was awarded a HRC Sir Charlies Hercus Research Fellowship in 2007 and a Jean Cathie Bequest/AMRF Senior Research Fellowship in 2015. She is on the editorial board for Frontiers in Neuro-Otology and an Academic editor for PLOS One. She also serves as a reviewer for national and international granting bodies and international journals.

Professor Carl Kirkpatrick (Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia)

Professor Carl Kirkpatrick is the Director of the Centre for Medicines Use and Safety and Director of Pharmacy Education, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University. He is recognized for building population models, of medicines, disease progression and systems biology via pharmacometrics. The application of this methodology has made impact in the following clinical areas: anti-infectives, obesity, cancer, diabetes and aged care.

Associate Professor Adam Patterson (ACSRC, University of Auckland)

Associate Professor Adam Patterson obtained his degree in Biochemistry from the University of Oxford, before completing a PhD jointly at the Institute of Molecular Medicine (John Radcliffe Hospital, Oxford) and the MRC Radiobiology Unit (Harwell, Oxford). He completed his post-doctoral studies at the University of Manchester (Pharmacy) before emigrating to New Zealand in 2000. He currently leads the Translational Therapeutics Team at the Auckland Cancer Society Research Centre, an internationally recognised academic drug development laboratory based at the University of Auckland, New Zealand. He is also Principle Investigator of the Maurice Wilkins Centre for Molecular Biodiscovery. His research is largely focused on exploiting the tumour microenvironment as a therapeutic target, including both small molecules and biological agent based platforms. He is co-inventor of TH-4000, a first in class hypoxia-activated tyrosine kinase inhibitor currently in Phase 2 clinical trials.

Professor Mark McKeage (Department of Pharmacology and Clinical Pharmacology, University of Auckland)

Professor Mark McKeage (School of Medical Sciences) is an academic clinician and scientist with interests in translational oncology and clinical trial research. Passionate about finding new approaches to cancer treatment, Mark has led over 15 phase I oncology drug trials to date, facilitating the early stage clinical evaluation of promising anticancer agents. These include DMXAA, PR104 and PR610, which all originated from the Auckland Cancer Society Research Centre. Currently, he leads initiatives establishing large-scale high-throughput profiling of tumour somatic mutations, primarily in lung cancer patients, to support genotype-directed cancer treatment and clinical trials. Understanding mechanisms and developing treatments for irreversible nerve damage induced by platinum anticancer drugs is another area of research for which he is known.

Mark is also a Consultant Medical Oncologist at Auckland City Hospital and Co-Director of the Auckland Cancer Society Research Centre. Prior to joining the academic staff of the University of Auckland in 1996, he acquired qualifications in clinical medicine (MBChB Otago), medical oncology (FRACP) and postgraduate research degrees (MMedSc Auckland; PhD London), and gained professional and research experience abroad in the United Kingdom and in Australia. While at the University of Auckland, Mark has made significant contributions to teaching, acting as the main supervisor for over 25 postgraduate research students, including nine PhD students. Mark also serves in a demanding clinical role and contributes research leadership at a national and international level as a member of various research committees and advisory panels and as editor of BMC Cancer and other journals.

Dr Matthew Strother (Department of Medicine, Christchurch, University of Otago)

Matthew Strother practices as a medical oncologist in Christchurch. He trained at Indiana University (USA) in Internal Medicine, Clinical Pharmacology, and Medical Oncology, with research focused on early phase cancer clinical trials, pharmacokinetics, and pharmacogenetics. After joining the faculty of Indiana University, he spent two years living in Kenya establishing a cancer care program as part of a larger academic collaboration. He moved to Christchurch in 2012, and his present research interests include lymphoma in low-resource countries, chemotherapy in special populations, pharmacokinetic optimization of chemotherapy, and adverse drug events.

Programme

DAY 1 – Tuesday 1 September 2015 – WELCOME FUNCTION

18.30 – 18.35	**Welcome** Dan Wright *Chair of ASCEPT NZ*
18.35 – 19.30	Registration opens. Drinks, nibbles, poster viewing and networking function

DAY 2 – Wednesday 2 September 2015 – ANNUAL SCIENTIFIC MEETING

08.30 – 09.30	Registration opens. Tea and coffee available

Welcome – Dan Wright

Emeritus Professor Dick Laverty Symposium

09.30 – 09.40	Introduction
09.40 – 10.00	Richard Faull *Faculty of Medical and Health Sciences, University of Auckland*
10.00 – 10.30	**Morning tea**
10.30 – 10.50	Bruce Russell *Faculty of Medical and Health Sciences, University of Auckland*
10.50 – 11.10	Mike Dragunow *Faculty of Medical and Health Sciences, University of Auckland*
11.10 – 11.30	Yiwen Zheng *Department of Pharmacology and Toxicology, University of Otago, Dunedin*

ASCEPT Guest Speaker – Chair: Dan Wright

11.30 – 12.30	**ASCEPT Invited Speaker:** Carl Kirpatrick *Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia.*
12.30 – 12.35	**QRW Sponsor presentations**
12.30 – 13.30	**Lunch and Poster Viewing**

Oral Communications Session 1 – Chair: David Reith

13.30 – 13.45	Hesham Al-Sallami The influence of body composition on the dose-response of heparin in children *School of Pharmacy, University of Otago, Dunedin*

13.45 –14.00	Phil Drennan Is it bad to take flucloxacillin with food? *Department of Clinical Pharmacology, University of Otago, Christchurch*
14.00 – 14.15	Hartley C Atkinson Phenylephrine Related Adverse Events – Population Modelling and Simulation Studies *AFT Pharmaceuticals Ltd, Auckland*
14.15 – 14.30	Dan Wright Predicting allopurinol response in patients with renal impairment *School of pharmacy, University of Otago, Dunedin*

Oral Communications Session 2 – Chair: Pam Buffery

14.30 – 14.45	Matthew Doogue RAPID Pharmacovigilance in Palliative Care *Department of Clinical Pharmacology, University of Otago, Christchurch*
14.45 - 15.00	Simran Maggo Understanding Adverse Drug Reactions Using Genome Sequencing (UDRUGS): Recent cases on SSRIs and SNRIs. *Department of Pathology, University of Otago, Christchurch*
15.00 – 15.15	Ailsa McGregor Varenicline and Huntington's Disease: A case series *School of Pharmacy, University of Auckland*
15.15 - 15.45	**Afternoon tea**

Student Oral Communications Session – Chair: Chris Cameron

15.45 - 16.00	Brandi Bellisma* Clozapine Associated Myocarditis and Cardiomyopathy in Auckland *Department of Pharmacology and Clinical Pharmacology, University of Auckland*
16.00 - 16.15	Isabelle Kuan* Are conventional methods for measuring isotopic GFR really the gold standard? *School of Pharmacy, University of Otago, Dunedin*
16.15 – 16.30	Shamin Saffian* Warfarin dosing tools do not accurately predict maintenance doses in patients who require >7mg daily *School of Pharmacy, University of Otago, Dunedin*
16.30 – 16.45	Emma Salis* Extremely premature neonates exhibit insulin resistance. *School of Pharmacy, University of Otago, Dunedin*
16.45 - 17.00	Fang Yu* Exploring the influence of patient covariates on the dose-response of vitamin D supplementation in pregnant women and their infants *School of Pharmacy, University of Otago, Dunedin*
17.00 – 18.00	**ASCEPT AGM**
19.00	**Conference dinner** Flame 61 Beach Street, Queenstown

DAY 3 – Thursday 3 September 2015 – ANNUAL SCIENTIFIC MEETING

Oncology Symposium – Chair: Nuala Helsby

09.00 – 09.15	**Symposium introduction:** Nuala Helsby *Molecular Medicine and Pathology, University of Auckland*
09.15 – 10.15	**Symposium Speakers** Adam Patterson Pharmacokinetically guided development of TH400 an irreversible EGFR inhibitor *ACSRC, University of Auckland*
10.15 – 10.45	**Morning tea**
10.45 – 12.45	**Symposium Speakers** Mark McKeage Oxaliplatin chemotherapy: bench to bedside *Department of Pharmacology and Clinical Pharmacology, University of Auckland* Matthew Strother Does size matter? The weight of the evidence in chemotherapy dosing in obese patients. *Department of Medicine,* Christchurch, University of Otago.
12.45 – 13.00	**15 minute panel discussion**

Conference Close and Prize Giving

13.00 – 13.15	Dan Wright *Chair of ASCEPT NZ*

*eligible for student prize

Abstracts - Oral

The influence of body composition on the dose-response of heparin in children

Al-Sallami, HS[1], Newall, F[2,3,5], Monagle, P[2,3,5], Ignjatovic, V[2,3], Cranswick, N[2,4], Duffull, SB[1]
School of Pharmacy, University of Otago[1], Dunedin; Department of Paediatrics, University of Melbourne[2], Melbourne; Murdoch Children's Research Institute[3], Melbourne; Department of Pharmacology, University of Melbourne[4], Melbourne; Clinical Haematology, Royal Children's Hospital[5], Melbourne.

Introduction. Unfractionated heparin (UFH) is the anticoagulant of choice in paediatric patients undergoing a variety of cardiac procedures. The ability to predict the dose-response relationship of UFH is essential in order to optimise its dosage. There are currently no population pharmacokinetic-pharmacodynamic (PKPD) models for UFH in paediatrics.
Aims. To develop and evaluate a PKPD model to predict the dose-response relationship of UFH in paediatrics. Also, to explore the use of fat-free mass (FFM) to guide dose-individualisation of UFH in this population.
Methods. Data from 64 infants and children who received 75-100 IU/kg of UFH during cardiac angiography were analysed. Four plasma samples were collected at baseline and at 15, 30, 45, and 120 minutes post-dose. UFH concentration (231 measurements) was quantified using a protamine titration assay. UFH effect (164 measurements) was quantified using activated partial thromboplastin time (aPTT). A PKPD model was fitted to the data using the non-linear mixed effects modelling (in NONMEM v7.2). Various patient covariates such as age, weight (Wt), and FFM were tested. The final model was evaluated using the likelihood ratio test and visual predictive checks (VPCs).
Results. A one-compartment model with linear elimination provided the best fit for the dose-concentration data. Wt and FFM had substantial influence on model fit; FFM was preferred statistically. A linear model provided the best fit for the concentration-effect data using the PPP&D sequential estimation method. Censored PD data (above the upper limit of quantification) were accounted for using likelihood estimation. The PKPD model performed well using visual predictive checks.
Discussion. A PKPD model to describe the time-course of UFH effect was developed in a paediatric population which received a high single prophylactic bolus dose. FFM was shown to describe drug disposition well and can potentially be used in dose calculation after appropriate evaluation.

Phenylephrine Related Adverse Events – Population Modelling and Simulation Studies

Atkinson, HC[1], Anderson, BJ[2]
AFT Pharmaceuticals Ltd, Takapuna, Auckland, New Zealand[1], Department of Anaesthesiology, University of Auckland, New Zealand[2]

Introduction. A pharmacokinetic interaction between acetaminophen and phenylephrine has recently been reported[1-3]. Phenylephrine is a sympathomimetic agent with welldefined dose dependent effects on blood pressure. The effective doubling of phenylephrine concentration, when administered in combination with acetaminophen increases the blood pressure, but the magnitude of such an effect has yet to be defined.
Aims. To use pharmacokinetic and pharmacodynamics data of phenylephrine to predict changes in mean arterial pressure (MAP).
Methods. Population parameter estimates were obtained using non-linear mixed effects modelling (NONMEM 7.3). MEDLINE and EMBASE databases were also searched for papers discussing or describing an adverse effect, hypersensitivity, or safety concerns related to phenylephrine alone or in combination with other drugs. Phenylephrine concentration was linked directly to MAP using an E_{max} model to describe drug effect.
Results. Phenylephrine doses over 15 mg increase the blood pressure and decrease the heart rate. The model predicts a 20 mmHg increase in systolic blood pressure after an oral dose of 45 mg phenylephrine in normotensive healthy people and a modest increase in MAP when an oral dose of 10 mg phenylephrine is co-administered with 1000 mg paracetamol (4.2 vs 12.3 mmHg).
Discussion. Oral co-administration of phenylephrine with paracetamol more than doubles the bioavailability of phenylephrine and reduces the absorption half-time by 50%. This is of particular concern in those with cardiovascular compromise.

1. Atkinson HC, Stanescu I, Anderson BJ. *Increased Phenylephrine Plasma Levels with Administration of Acetaminophen.* N Engl J Med. 2014 Mar 20;370(12):1171–2.
2. Atkinson HC, Stanescu I, Salem II, Potts AL, Anderson BJ. *Increased bioavailability of phenylephrine by co-administration of acetaminophen: results of four open-label, crossover pharmacokinetic trials in healthy volunteers.* Eur J Clin Pharmacol. 2015;71(2):151–8.
3. Atkinson, Hartley C., Potts, Amanda L., Anderson, B. J. *Potential Cardiovascular Adverse Events when Phenylephrine is combined with Paracetamol: Simulation and Narrative Review.* Eur J Clin Pharmacol. 2015 May 29 (Epub ahead of print)

Is it bad to take flucloxacillin with food?

Begg ,E[1,2], Gardiner, S[1,2], Drennan, P[2], Green, J[2], Isenman, H[2,] Begg, R[1], Chambers, S[1,2], Zhang, M[1,2], Everts, R[3]
University of Otago, Christchurch[1], Christchurch Hospital[2], Nelson Hospital[3]

Background: Flucloxacillin, given orally, is recommended to be taken on an empty stomach, based on early studies that showed that AUC and Cmax were reduced when flucloxacillin was taken with food. Recent knowledge suggests that β-lactams have 'time-dependent' efficacy, with the target end-point for mild to moderate infections, of free drug concentrations exceeding the MIC of the infecting organism for at least 50% of the dose interval.
Aim: We aimed to examine the detailed pharmacokinetics and pharmacodynamics of flucloxacillin (free and total) given orally with and without food, to see if food compromises likely efficacy.
Methods: Flucloxacillin 1 g orally was given to 12 healthy volunteers on an empty stomach and after a FDA recommended high fat breakfast, on two separate days, one week apart. Blood was sampled for 12 hours following flucloxacillin ingestion, and total and free plasma concentrations of flucloxacillin measured by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The fed vs fasting pharmacokinetics and pharmacodynamics were assessed.
Results: Food decreased the AUC of free flucloxacillin by 0.8-fold and the Cmax by 0.5-fold, as a result of decreased oral availability. However, the T_{max} was prolonged 2.2-fold, resulting in a concentration-time profile that was more in keeping with the time-dependent kill-rate of flucloxacillin. For dosing q6h or q8h, the free concentrations of flucloxacillin at which the time above that concentration was 0.5 of the dose interval were bioequivalent (q6h) and not inferior (q8h) in the fed state.
Discussion: Taking flucloxacillin with food was at least 'bioequivalent', at usual oral dosing intervals. With the likely compliance benefits, these results have profound importance for flucloxacillin dosing world wide.

Predicting allopurinol response in patients with renal impairment.

Wright, DFB[1], Duffull, SB[1], Merriman, TR[2], Dalbeth, N[3], Barclay, ML[4], Stamp, LK[4].
School of Pharm, University of Otago[1], Dunedin; Depart of Biochem[2], University of Otago, Dunedin, Department of Medicine, University of Auckland[3], Auckland, Department of Medicine, University of Otago[4], Christchurch;

Introduction. Allopurinol is used to manage gout and works by reducing plasma urate concentrations. Daily doses recommended by the current renal dosing guidelines [1] have been found to result in an inadequate response, failing to achieve the clinical target for plasma urate of <0.36 mmol/L in the majority of patients [2-4].
Aim. 1) To explore factors that predict allopurinol response, 2) To determine the probability of achieving a plasma urate of <0.36mmol/L under the current renal dosing guideline, 3) To determine the dosing regimen that results in treatment success across different levels of renal function.
Methods. Data were sourced from five studies (summarised in [5]). A population analysis was conducted using NONMEM v.7.2. Covariates analysed included renal function, body size, sex, race, concomitant drugs, and renal transporter genotype. The final PKPD model was implemented in MATLAB (2014a). Stochastic simulations were performed under two scenarios; 1) doses recommended by the current renal dosing guideline, and 2) daily doses sufficient to achieve target plasma urate concentrations in >75% of patients.
Results. A total of 1105 oxypurinol and 1162 urate plasma concentrations from 133 patients were available for analysis. A one compartment PK model with first-order absorption and elimination was the best fit to the oxypurinol data. The urate response was best described by a direct effects Emax model. Renal function (CL), diuretic use (CL, Emax, baseline urate), and body size (CL, V) were found to be significant covariates. Applying the maximum allopurinol doses from the current guidelines for renally impaired patients, the probability of achieving plasma urate concentrations <0.36 mmol/L for a 70kg patient was 64%, 29% and 12% for CLCR values of 100mL/min, 40mL/min and 20mL/min, respectively. Dose requirements were found to increase approximately 2-fold over a 3-fold range of weights and were 1.25-2 fold higher in those taking diuretics. Renal function had a relatively modest impact on allopurinol dose requirements. Dose predictions to achieve the clinical target for plasma urate were found be substantially higher than the current guideline and were largely based on weight and diuretic use.
Discussion. A population PKPD model for allopurinol was developed. Simulations from the model support the contention that the current guideline using CLCR-based dosing for allopurinol will result in suboptimal treatment. A revised dosing guideline, accounting for differences in body size and diuretic use, is proposed.

1. Hande KR, et al. Am J Med 1984; 31:667-673
2. Dalbeth N, et al. J Rheumatol 2006; 33:1646-1650.
3. Vazquez-Mellado J, et al. Ann Rheum Dis 2001; 60:981-983.
4. Stamp LK, et al. Aust NZ J Med 2000; 30:567-572.
5. Wright DFB, et al. Eur J Clin Pharmacol 2013; 69: 1411-1421

RAPID Pharmacovigilance in Palliative Care

Doogue, MP[1,2], Rowett, D[3], Devilee, L[4], To, T[4,5], Currow, D[4]
Department of Clinical Pharmacology[1], Christchurch Hospital, Christchurch, NZ. Department of Medicine[2], University of Otago, Christchurch, NZ. Drug and Therapeutic Information Service[3], Repatriation General Hospital, Daw Park, Australia. Discipline of Palliative and Supportive Services[4], Flinders University, Daw Park, Australia. Department of Rehabilitation and Aged Care[5], Repatriation General Hospital, Daw Park, Australia.

Background: Adverse drug reactions (ADRs) cause morbidity and mortality for patients and add unnecessary costs to the health system. ADRs cause 5% to 10% of all hospital admissions and emergency department (ED) visits. The most vulnerable patients are routinely excluded from clinical trials. Palliative care services care for patients at high risk of ADRs but little is known about the safety of medicines in palliative care. Further the most effective medicines have potential to help or harm. Harms from medicines(ADRs) need to be considered together with benefits to establish net benefit to patients.The Palliative Care Clinical Studies Collaborative (PaCCSC) has established a process for consecutive cohort studies on effects of medicines with RAPID turnaround of results.
Aim: To prospectively evaluate safety and efficacy of medicines commonly used in palliative care.
Methods: De-identified data collected through a secure web-server from cohorts each studying one medicine for one indication. Three time points (chosen for the medicine) are assessed: baseline, a time at which clinical benefits should be experienced, and a time by which short-term harm should be apparent. In addition, harms can be recorded at any time. The time impost on clinicians is minimal (3 mins per patient at each data collection point).
Results: A diverse group of sites are participating (100+ sites across 20+ countries). Studies to-date include metoclopramide for nausea, haloperidol for delirium, gabapentin for neuropathic pain and pregabalin for neuropathic pain. Common findings include high rates of benefit, high rates of harm and discontinuation, and clinically significant net benefit.
Conclusion: Palliative care patients are vulnerable to ADRs but can gain rapid symptom relief from commonly used medicines. Frequent monitoring of response, early clinical review, dose titration to responses and early discontinuation in the event of harm can increase the net benefit of pharmacotherapy in vulnerable patients.
1. Currow, DC, Rowett, D, To THM, et al. An International Initiative To Create a Collaborative for Pharmacovigilance in Hospice and Palliative Care Clinical Practice. J Palliat Med 2012; doi.org/10.1089/jpm.2012.9605
2. Sanderson C, Quinn SJ, Agar M, et al. Pharmacovigilance in hospice/palliative care: net effect of gabapentin for neuropathic pain. BMJ Support Palliat Care 2014; pii: bmjspcare-2014-000699. doi: 10.1136/bmjspcare-2014-000699. [Epub ahead of print)

Understanding Adverse Drug Reactions Using Genome Sequencing (UDRUGS): Recent cases on SSRIs and SNRIs.

Maggo, SDS[1], Foulds, J[2], Luty, SE[2], Miller, AL[1], Kennedy, H[3], Doogue, M[4], Kennedy, MA[1]
Department of Pathology[1], University of Otago, Christchurch, NZ, Department of Psychological Medicine[2], University of Otago, Christchurch, NZ, Department of Molecular Pathology[3], Christchurch Hospital, Christchurch, NZ, Department of Clinical Pharmacology[4], University of Otago Christchurch & Christchurch hospital, NZ.

A multitude of factors can affect drug response in individuals. It is now well established that variations in genes, especially those coding for drug metabolising enzymes, can alter the pharmacokinetic and/or pharmacodynamic profile of a drug, impacting on efficacy and often resulting in drug-induced toxicity. 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 rare and/or serious 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.
Herein we describe a series of patients with severe and/or “abnormal” ADRs to antidepressant medication (SSRIs: citalopram, fluoxetine, sertraline or SNRIs: venlafaxine), identified through their referring clinicians. We genotyped patients for common single nucleotide polymorphisms (SNPs) associated with altered pharmacokinetic response and/or associated with ADRs to the above medications. Cytochrome P450 (CYP450) enzymes are associated with up to 60 % of all drug-induced toxicity, and polymorphic enzymes, CYP2D6 and CYP2C19 are the primary route of metabolism for the anti-depressants mentioned above. To evaluate any polymorphisms in these enzymes, genotyping by Sanger sequencing was conducted for eight common CYP2D6 SNPs and seven common CYP2C19 SNPs. The variants were chosen based on literature recommendations and when available, guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Of the six patients referred, we identified two poor metabolisers (PMs), two intermediate metabolisers (IMs) and two extensive metabolisers. Genotyping classification was based on an algorithm[1] described in Gaedigk *et al* (2008). The presence of commonly reported reduced function and/or non-functional alleles in these patients may account for their reported ADRs. We are currently in the process of performing exome analysis on these patients which will allow us to look for rare variants, not previously documented.
1. Gaedigk A, Simon SD, Pearce RE, et al. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clin Pharmacol Ther 2008; 83(2): 234-42.

Varenicline and Huntington's Disease: A case series

McGregor, AL[1], Tingle, MD[2], Russell, B[1], Kydd, R[3], Dysart, J[4], Finucane, G[4]
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Changes in cognitive function precede impairments in motor function in both animal models and human patients with Huntington's Disease (HD)[1,2]. Cognitive dysfunction is progressive and includes impairments in executive function, perception, visuospatial and psychomotor skills, memory loss and problems learning new skills. Nicotinic cholinergic systems play a well-documented role in attention, learning and memory[3] and our experimental studies have shown administration of the nicotine analogue, varenicline (Champix®) improves delay-dependent and short term recognition memory in the YAC128 transgenic mouse model of HD.

While recent evidence suggests no increased risk of neuropsychiatric events in varenicline users[4], we performed an open label study to determine the tolerability of varenicline (1 mg twice daily) and its effect on cognitive function in three patients with early HD. Cognitive assessment was performed before and after treatment with varenicline for 4 weeks using a touch screen computer-based neurocognitive test battery (IntegNeuro, Brain Resource Company). Cognitive testing assessed manual dexterity, impulsivity and attention and basic emotion recognition, in addition to a measure of premorbid intelligence. The frequency, intensity and burden of side effects were recorded weekly, in addition to self-reported cigarette use.

Prior to treatment all participants displayed significant deficits in motor tapping, maze navigation and emotional identification compared to matched controls. Four weeks after treatment, two participants showed improved performance in executive function and emotion recognition tasks compared to baseline values. These participants displayed a single episode of aggression which did not require clinical management. No other side effects commonly associated with varenicline administration (nausea, headaches, problems sleeping and abnormal dreams) were reported. One participant stopped smoking.

Our preliminary investigation indicates that varenicline was well tolerated in these patents and improved aspects cognitive function. A randomised control trial is now underway to further investigate the effectiveness of varenicline in the symptomatic treatment of patients with HD.

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Clozapine Associated Myocarditis and Cardiomyopathy in Auckland

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Clozapine-associated myocarditis usually presents within the first 18 weeks of clozapine therapy and is acute in nature whereas cardiomyopathy may take far longer to manifest. Despite the fact that they are long recognised as problematic and careful clinical management and monitoring of patients is required, neither the true incidence of these cardiotoxicities nor the relationships with clozapine exposure are known. Myocarditis and cardiomyopathy present with non-specific signs and symptoms. Typically the causative role of clozapine is determined by way of exclusion given the lack of standardisation for the criteria used to diagnose clozapine-associated cardiotoxicity.
This study undertakes a series of clinical investigations to assess the incidence of clozapine-associated cardiotoxicity and to determine the potential risk factors associated with these life-threatening adverse drug reactions in patients currently taking clozapine and in patients who have died whilst taking clozapine.
A clinical review of patient records was conducted to determine the incidence of the development of myocarditis using recommended ADHB criteria. Approximately 2% of patients initiating clozapine were diagnosed with myocarditis. However, many more patients had clozapine therapy stopped due to increases in laboratory markers for cardiotoxicity, although myocarditis was not recorded as a diagnosis. The Coronial autopsy database in ADHB was searched between the years 2001-2015 using the word search parameters cardiomyopathy, myocarditis and clozapine. Each autopsy report was reviewed and available clinical laboratory results for clozapine levels, lipid profile, liver enzyme profile and diabetes markers were collated. Our initial data suggests that patients on clozapine die several years younger than individuals who die from cardiotoxicity with the same co-morbidities. Additionally high levels of clozapine in our cases at the time of death may be misleading and most likely represent post-mortem redistribution.

Are conventional methods for measuring isotopic GFR really the gold standard?

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Introduction. The current Gold Standard for determining glomerular filtration rate (GFR) involves the administration of a radioisotope, such as ^{51}Cr EDTA, and the measurement of plasma concentrations in the terminal elimination phase. We propose that current methods over–simplify the disposition of ^{51}Cr EDTA and may lead to biased results.
Aim. (1) To develop and test a population pharmacokinetic (PK) model for the disposition of ^{51}Cr EDTA, (2) to compare predictions of GFR from the PK model to those estimated by conventional methods, and, (3) to determine if differences in predicted GFR could change dosing decisions in the clinic.
Methods. Data from 40 individuals who received 2 mL (~3.7 MBq/mL) of ^{51}Cr EDTA were available for analysis [1]. Four plasma concentrations were measured at approximately 2, 4, 6 and 24 hours after the dose. Participants included 26 males and 14 females, with a median age of 69.5 (range: 21-88 years). The median serum creatinine concentration was 89 µmol/L (range: 66-217 µmol/L). A population analysis was conducted using NONMEM® v.7.2. Covariates analysed included weight, sex, age, creatinine clearance, total body weight and fat free mass. Predictions of GFR from the PK model were compared to conventional methods using mean prediction error (MPE) and root mean square error (RMSE).
Results. A total of 159 ^{51}Cr EDTA plasma concentrations from 40 patients were analysed. A two compartment PK model with first-order elimination was the best fit for the data. Significant covariates included creatinine clearance on ^{51}Cr EDTA clearance and actual body weight on the central volume compartment. Conventional methods used to estimate clearance from radioisotope data (i.e. UV/P, AUC and slope-intercept method) were found to produce biased estimates of GFR compared to the PK model ((MPE -7.5 mL/min/1.73m^2 (95% CI -12.3,-2.6), 56.6 mL/min/1.73m^2 (95% CI37.8, 75.4) and 12.2 mL/min/1.73m^2 (95% CI2.8, 21.5), respectively). Commonly used equations for estimating GFR in the clinic (eGFR) (e.g. Cockcroft Gault, MDRD and CKD-Epi) led to negatively biased estimates compared to the PK model (MPE -19.5 mL/min/1.73m^2 (95% CI -26.0, -12.9), -20.6 mL/min/1.73m^2 (95% CI -27.8, -13.3) and -16.9 mL/min/1.73m^2 (95% CI -23.4, -10.4), respectively). Carboplatin doses for a 40 year old male who weighs 83kg, calculated by the Calvert formula [2], were over-predicted by 116 mg when GFR was determined using the conventional slope-intercept method for Cr-EDTA versus the PK model (988 mg versus 871 mg, respectively). Relative to the PK model, commonly used equations for estimating GFR (eGFR) (i.e. Cockcroft Gault, MDRD and CKD-Epi) led to under-predicted doses of 737 mg, 649 mg and 715 mg, respectively.
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Current warfarin dosing tools do not accurately predict maintenance doses in patients who require > 7mg daily

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Introduction. Several methods for predicting warfarin maintenance dose requirements have been proposed, including equations that incorporate *CYP2C9* and *VKORC1* genotype information. We have previously proposed a Bayesian method as a means of predicting warfarin maintenance doses without the need for genetic information [1]. We have shown that the Bayesian method provided unbiased dose predictions overall, however, observed doses greater than ~7mg/day were found to be over-predicted. The source of this bias was not obvious, nor was it known if it had been observed in other warfarin dose prediction studies. A post-hoc analysis of the data suggested that over-prediction may be associated with the *VKORC1* GG genotype (-1639G>A) [2].

Aims. 1) To determine if evidence exists in the published literature for biased warfarin dose predictions in patients requiring doses above 7 mg/day, and, 2) To explore the influence of *CYP2C9* and *VKORC1* genotype on warfarin dose predictions produced by a Bayesian doing method.

Methods. A literature search of published warfarin dose prediction tools was conducted. Studies were included if they provided a scatter plot of the observed vs predicted dose. The proportion of dose predictions above and below the line of identity in each study was compared using a chi-squared test. For aim 2, observed dose and INR data from 140 patients initiating warfarin therapy at Dunedin Hospital and the Royal Infirmary Hospital, Glasgow were retrospectively analysed using a Bayesian dosing tool. The predicted warfarin doses were compared to the observed doses using mean prediction error [MPE] across different CYP2C9 and VKORC1 genotypes.

Results. Twenty-one studies met the inclusion criteria. All studies were found to under-predict warfarin dose requirements in patients requiring >7mg/day ($p<0.001$ in all cases). By contrast, the Bayesian method was found to over-predict doses in patients who require > 7mg daily. Dose predictions were also found to be positively biased in patients with *VKORC1* and *CYP2C9* *1*1 (MPE [95% CI], 0.53 [0.21, 0.86] and 0.36 [0.12, 0.61] respectively) however this was only obvious at higher daily doses and appears unlikely to be an independent genotype effect.

Discussion: Current warfarin dosing methods do not appear to accurately predict the maintenance dose in patients requiring above 7mg/day. We propose that the current methods do not adequately capture the complexity of the coagulation network at higher warfarin doses.

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Extremely premature neonates exhibit insulin resistance.

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Introduction. Preterm birth disrupts normal timing of physiological adaptation of insulin secretion [1] putting premature neonates at risk of abnormal glucose homeostasis [2]. The insulin/C-peptide (I/CP) ratio gives an indication of insulin clearance [3] but has not been reported in neonates. Premature neonates have significantly higher fasting levels of GLP-1 than adults that increase even further with feeding [4].

Aims. To determine I/CP and insulin/blood glucose level (I/BGL) ratios in neonates and the effect of postmenstrual age (PMA) on these measures. To determine GLP-1 concentrations in never-fed versus fed neonates.

Methods. Plasma samples were obtained from 102 neonates admitted to Dunedin Hospital NICU. Plasma was analysed for insulin and C-peptide using chemiluminescent kits (Invitron, UK), GLP-1 and glucagon using ELISA (BioCore Pty Ltd, Australia). Statistical analyses were performed using Stata/IC (v11.2).

Results. The PMA range was 24-51.3 weeks. The median I/CP ratio was 0.44, 95% CI (0.44, 0.61). The median I/BGL ratio was 9.3, 95% CI (8.2, 10.6). Linear regressions of ln-transformed data were performed. I/CP and I/BGL ratios were significantly affected by PMA ($p<0.01$). Negative correlations were found ($r= -0.21$ and -0.35 for I/CP and I/BGL respectively, $p<0.01$) and I/CP changed around 34 weeks. Insulin concentrations were negatively correlated ($r= -0.38$, $p<0.01$) with increasing PMA. ANOVA showed higher GLP-1 concentrations ($p=0.011$) in fed vs. never-fed neonates.

Conclusions. These findings indicate insulin resistance in premature neonates prior to 34 weeks gestation. The significantly higher GLP-1 concentrations in fed neonates confirm that GLP-1 increases with the establishment of feeding.

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Exploring the influence of patient covariates on the dose-response of vitamin D supplementation in pregnant women and their infants

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Introduction. Vitamin D deficiency during pregnancy is associated with an increased risk of pre-eclampsia and gestational diabetes in the mother and an increased risk of rickets in the infant. Supplementation of vitamin D during pregnancy is advocated but the recommended doses of existing regimens vary four-fold and are not individualised. This can potentially result in treatment failure or hypervitaminosis D.

Aims. To explore the influence of patient covariates (e.g. age, sex, size) on the dose-concentration relationship of vitamin D supplementation.

Methods. Data were obtained from 260 pregnant women and their infants (n=260) who enrolled in the PIVID trial.[1] Mother-infant pairs were randomised to either placebo (0 IU, 0 IU), low dose (1000 IU, 400 IU), or high dose (2000 IU, 800 IU) vitamin D. Serum concentrations of 25(OH)D were obtained from mothers in two occasions and from infants in five occasions. Several PK models were fitted to the data using non-linear mixed effects modelling and the influence of patient covariates was explored. The final model was evaluated using the likelihood ratio test and goodness-of-fit plots.

Results. A one-compartment model with first-order elimination was found to provide the best fit for the mothers' data. Similarly, a one-compartment model with first-order elimination provided the best fit for the infants' data. No patient covariates were found to have a significant effect on the parameters of either model.

Discussion. PK models for vitamin D supplementation in pregnant women and their infants were developed. Patient covariates were found to have no significant influence on model parameters. It is uncertain whether this lack of covariate effect on the drug's disposition is real or whether the design (models and data) was inadequate to detect covariate effect. However, based on this study, there is no evidence to support dose-individualisation of vitamin D based on patient covariates tested here.

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Abstracts - Posters

Drug Utilisation Analysis from MedChart™ data

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Introduction: MedChart™ is an electronic inpatient prescribing and administration (ePA) software product adopted for use within New Zealand Public Hospitals which is currently being implemented by Canterbury District Health Board (CDHB). Reporting of detailed drug prescribing and administration data is under development and may enhance drug utilisation understanding.
Aim: To describe the development of drug utilisation reports from ePA data at CDHB. *Methods:* Reports were generated through the reporting module of the software and locally developed SQL-query-generated reports which were then further analysed. Reports generated for mental health (first to switch to MedChart™) include: top administered drugs by patient numbers; mean dose of a drugs administered; times of administration; comparison of antipsychotic class prescribed; comparison of types of prescribers of a particular drug over time. These reports are fed-back to the clinicians regularly.
Results: Top administered drugs: paracetamol 79/156 patients (51%), lorazepam 59/156 (38%), docusate+sennosides 50/156 (32%) and zopiclone 46/156 (29%). Mean doses administered: zopiclone 9 mg, temazepam 15 mg. Administration times: zopiclone, 0.3% before 8pm, 18% between 8-9 pm, 50% 9-10 pm and 20% 10-11 pm. Class comparison: antipsychotics, 177/207 (86%) of prescriptions were for atypicals vs 30/207 (14%) for typicals. Prescribers - nicotine, which is prescribed by doctors and nurses, was prescribed by doctors 37/86 (43%) of the time in March 2015 vs 15/54 (27%) in May 2015. Dissipation of these reports to clinicians has led to initiation of changes in practice.
Discussion: ePA-generated data analysis is in its early stages at CDHB but has shown potential to inform clinicians and to support change in practice. Substantial technical and clinical resources are required to develop useful and clinician-friendly reports from these complex data. A robust infrastructure for extracting and analysing ePA-generated data is need to support safe and effective use of medicines in New Zealand hospitals.

A pilot study of transport of mitoxantrone by human OCT1, OCTN2 and OATP-C

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Mitoxantrone (MXR) is an antineoplastic drug which improves the survival of children suffering from first relapse of acute lymphoblastic leukaemia [1]. As an organic cation under physiological conditions, MXR is supposed to be taken up into cells by Solute Carrier (SLC) transporters. Although MXR has recently been suggested to inhibit human organic cantion transporter 1 (OCT1), the cellular uptake mechanisms of MXR remain unknown. This project aims to identify the organic cation transporter(s) for MXR uptake.
HEK293/PcDNA3.1 (HEK/mock), HEK293/OCT1, HEK293/OCTN2 and HEK293/OATP-C cells were used in this study. MXR uptake was initiated by incubating 1 ml of cells (in HBSS) in 15 ml conical tubes by the addition of MXR (5 μM). After an incubation period of 1, 3, 5 min, the reaction was stopped by adding 3 ml of ice-cold PBS. Cells were resuspended in ice-cold PBS with 1% paraformaldehyde for cell fixation. The intracellular level of MXR was detected by a BD FACSVerse flow cytometer at excitation and emission wavelengths of 635 and 670 (bandpass) nm, respectively. Cellular uptake of MXR was also investigated in poly-L-lysine coated plates and cellular MXR level determined by a validated HPLC assay.
The best model to describe the uptake of MXR in HEK/Mock cells was delineated as a saturable process (a Michaelis-Menten model) with a Km value of 33.3 ±19.3 μM. In the presence of quinidine (500 μM), the cellular uptake of MXR in HEK/mock cells decreased by 50% ($p < 0.05$). Cellular uptake of MXR by HEK/OCTN2 was 65% higher ($p < 0.05$) than that by HEK/Mock cells. In the presence of an OCTN2 substrate quinidine (500 μM), cellular uptake of MXR by HEK/OCTN2 decreased by 22% ($p < 0.05$). Our preliminary results suggest a quinidine-sensitive transporter endogenously expressed in HEK293 cells may be involved into the active uptake of MXR.
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