A laboratory perspective on substance harm reduction

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Introduction. This presentation is based on the recent involvement of the clinical laboratory at the Centre for Addiction and Mental Health in Toronto, Canada with substance harm reduction initiatives requiring drug testing expertise. Previous harm reduction programs, such as methadone maintenance for opioid (heroin) addiction, originated on facts showing that complete elimination of substance/drug misuse is difficult, regardless of the socio-economic factors and/or enforcement approaches.

Aim and Methods. The harm has lately been aggravated by illicit heroin products adulterated to various degrees with fentanyl and/or fentanyl analogues that lead to side effects, overdoses and/or deaths of epidemic, public health proportions worldwide, including Canada. The actual testing of the products provided voluntarily by the users can be instrumental in raising public awareness of their content; at the individual level, the available information can motivate the user to avoid consumption and prevent unwanted harm. However, the identification of novel/unknown illicit drugs can pose analytical challenges at multiple levels.

Results and Discussions. Using high resolution mass spectrometry technology our laboratory developed a ‘suspect’ screen/confirmation algorithm which was validated with commercially available standards and applied for the retrospective analysis of untargeted/unknown designer drugs. We, thus, demonstrated the exposure of our patient population to multiple fentanyl analogues, alone or in combination, all related to the current opioid-crisis, including but not limited to carfentanil, furanyl-, valeryl- and butyryl fentanyl. Caffeine, lidocaine and dextromethorphan were identified in a heroin product used intravenously by a patient experiencing repeated seizure episodes of unknown cause.

Conclusions. In order to raise public awareness and ultimately protect the public health the direct involvement of the clinical laboratories in the surveillance of the misused substances (also referred to as ‘drug checking’) has merits.
101 Ethanol, the opioid/drug epidemic and substance abuse involvement in completed suicides

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Drug addiction has long plagued U.S. society, but has more recently reached epidemic proportions. The attendant co-occurring morbidities have greatly challenged federal, state and local governments, and fuel a very significant percentage of crime at all levels of U.S. society. The incidence of “despair deaths” (drug- and alcohol-induced fatalities, and suicide from same) has markedly escalated, more recently impacting racial and ethnic minorities in a disproportionate manner. While the official mortality derived from “despair deaths” numbered 142,000 in 2016, the unofficial tally is likely far greater. One primary driver of this epidemic is the prevalence of mental illness in the U.S., with individuals suffering from the spectrum of mental illness far more likely to develop co-occurring substance abuse disorders. An analysis of the 215 completed suicides during the three years of 2015-2017 within the Delaware County Medical Examiner’s Office is discussed. Questions arising from this analysis are addressed, and selected literature addressing the co-occurring morbidities of substance abuse in some of its varied forms and suicidality is presented. Of particular note is the increasing frequency of suicide amongst women and the prevalence of illicit and prescription drug abuse with completed suicides.
Pharmacogenetics, the bedrock of Personalised Medicine, explains why one person develops toxicity on a drug or combination while others do not. Most drugs used in psychiatry are metabolised by Cytochrome P450, a highly polymorphic, gene-encoded enzyme system. When enzymes are missing, defective, or inhibited, drug toxicity may follow. In 2017, the Australian Bureau of Statistics reported that, in 2011, 14.8% of the population had been dispensed one or more of five drug groups: antidepressants, antipsychotics, benzodiazepine sedatives, non-benzodiazepine sedatives and psychostimulants. This 14.8% accounted for 49.6 of the deaths and 52% of Australian suicides in the age range 15 to 75 years. Psychiatric drugs may have caused or contributed to up to 75,000 unnecessary deaths every year. Many drugs cause akathisia, a fluctuating, can’t-sit-down restlessness, with toxic delirium, suicidality and aggression right up to mass homicide. Non-recovering, neurotoxic patients need disability pensions, filling hospitals and prisons, generating enormous costs to the taxpayer. The cost of Mental Health has reached $200 billion, quintupling since new generation drugs were introduced in 1990. Forensic pathologists, toxicologists, pharmacologists, pharmacists, and physicians can assist in civil and criminal litigation. Drug companies pay damages to survivors of violence. Medication-induced suicide committed in a state of involuntary intoxication is classified as an accident for insurance purposes. Homicide committed in a state of involuntary intoxication may attract a defence of non-insane automatism - involuntary intoxication from chemical lobotomy. The medical examiner needs the manner of death; blood toxicology ASAP, genetic profile, medication history, and the order drugs were prescribed. Records and survivors may confirm reasons for prescription and identify behavioural changes that ante- or post-dated the first prescription and may confirm organ toxicity. A psychological autopsy records observations of behaviour for correlates of brain toxicity: restlessness, insomnia, paroniria, irritability, hostility, (homicidal ideation), and emotional lability (suicidal ideation).
Antiepileptics and hypersensitivity syndrome: Role of ethnicity and epigenetics

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Hypersensitivity-syndrome-reactions (HSRs) to anti-epileptic drugs (AED) are associated with Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced liver injury (DILI).

Aims 1-To assess HSRs with in vitro lymphocyte toxicity assay (LTA); 2-To correlate HLA allele with the HSRs in Han-Chinese population.

Methods: HSRs patients had manifested fever, cutaneous eruptions and organ involvement within 8 weeks of exposure to lamotrigine (LTG), carbamazepine (CBZ), phenytoin (PHY). Controls were on AEDs without HSRs. We studied: 98 HSR-PHY (23 that presented DILI), 28 control-PHY; 32 CMZ-HSR (13 DILI), 24 controls-CZM, 12 HSR-LTG (2 DILI) and 28 control-LTG. There were 10 Han Chinese in our cohort.

Results: 1-A perfect correlation was observed between the LTA positive and the clinical diagnosis in DILI and SJS/TEN. 2-HLA-*B1502 positivity in Han-Chinese is a predictor for CMZ and phenytoin-HSR. In HLA-*B1502-negative Han receiving only CMZ, tolerated the drug presenting LTA-CMZ negative had LTA-LTG: 38%, 28% and 25%. 3 patients had LTA positive to both PHY and CBZ, 3 had LTA positive to PHY and LTG and had HSR to both drugs.

Conclusions: The LTA technique is sensitive for DILI and TEN. HSR-prediction will prevent AED-induced morbidity. In Han-Chinese, HLA *B1502 positivity in is a predictor for CBZ and PHY-HSR. Its negativity does not predict a negative LTG-HSR.
Myths abound in clinical toxinology, and there is always intrigue about venomous creatures. Australia has the deadliest snakes in the world; snakes attack their victims; spider bites cause ulcers; antivenom is a magical cure for envenomation. Amongst the fear, the fascination and the stories, there is a major health issue. Snake envenomation has been defined a neglected tropical disease by the World Health Organisation. Investigating the true epidemiology of venomous creature injuries and providing evidence for effective treatments will allow us to provide better treatments, where they are required. The Australian Snakebite Project (ASP) has collected data on snakebites across Australia for the last 12 years, including blood samples to confirm the type of snake involved and the efficacy of antivenom therapy. The study has demonstrated that severe snake envenomation is uncommon, one vial of antivenom is sufficient for all cases of snake envenomation in Australia, and most deaths are pre-hospital and early cardiopulmonary resuscitation is life-saving. The measurement of snake venom in patient’s blood was essential to defining the efficacy and dose of antivenom. A large study of definite spider bites found that the majority of bites cause minor effects, and spider bite does not cause ulcers or necrotic lesions in Australia. The Redback AntiVenom Evaluation (RAVE-II) study was a placebo randomised controlled trial that showed that the addition of antivenom to standardized analgesia in redback spider envenomation, did not significantly improve pain or systemic effects. Future studies of venomous creature injuries must include authenticated cases and the measurement of venom/toxin concentrations to assess the efficacy of antivenom treatment.
The evidence supports dosing of mycophenolic acid (MPA) to a target concentration: interpreting the literature and research priorities

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The need to adjust MPA to a target concentration, as opposed to empiric dosing, remains contentious. This is in part due to imprecision when based upon single concentration-time points. However, it is also due to an apparent conflict in the data supporting benefit of a therapeutic drug monitoring (TDM). Much of this data is from the kidney transplantation literature, where the ongoing prevalence of immune-mediated graft loss and life-limiting toxicities of immunosuppression highlight the need for greater precision in dosing.

Through critical interrogation of the available randomised concentration-controlled data, and systematic review of exposure-effect data involving estimated area under the concentration-over-time curve (AUC), it will be shown that

a) the data is clearly supportive of a causative association between plasma MPA exposure and drug effect, and benefit of TDM in cyclosporine co-treated graft recipients, and
b) that empiric dosing in tacrolimus co-treated kidney transplant recipients leads to both underexposure associated with rejection, and overexposure associated with serious toxicities, clearly highlighting a role for TDM.

Nevertheless, there remain important knowledge gaps. There is a need to better define the optimal target concentration of MPA in contemporary drug regimens, and critically in the maintenance-phase of transplant immunosuppression. The best strategy for TDM of MPA: single concentration-time point, AUC estimation or a combination of the two; and the choice of AUC estimation technique, requires elaboration. The utility and exposure target of unbound MPA needs better definition, in the setting of altered plasma protein binding seen with severe renal impairment, hypoalbuminemia and hyperbilirubinemia. Finally, application of MPA TDM in other fields of transplantation and autoimmune diseases, to which the pharmacokinetic-pharmacodynamic evidence from kidney transplantation should also apply, would benefit from better definition of optimal exposure targets.
106 Using different analytical methods and matrices to assess the exposure of mycophenolic acid: what is the evidence?

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Total plasma concentration of mycophenolic acid (MPA), the active moiety of mycophenolate mofetil (MMF), and mycophenolate sodium (MPS, enteric-coated formulation), is the recommended target analyte to be used in pharmacokinetic strategies for monitoring of the therapy with these drugs in routine patient care. This recommendation is based on a large body of evidence generated over more than 20 years of drug use. Additional pharmacokinetic measurants, such as the concentration of the free (unbound) MPA concentration or the concentration of the MPA metabolites (a phenolic glucuronide (MPAG, inactive) and an acyl glucuronide (AcMPAG, with a low pharmacological activity)) have been investigated particularly in research projects. Within blood, MPA is largely distributed in plasma and therefore plasma is the material of choice for its therapeutic drug monitoring (TDM). However, particularly during the most recent years, analysis of drug concentrations in alternative matrices (blood cells, tissue biopsies, saliva) became available due to the introduction of highly sensitive analytical techniques and fostered the research on their potential application for issues related to TDM. For determination of MPA concentrations chromatographic (HPLC with either ultraviolet-, fluorescent- or with mass-spectrometric detection) and automated assay are available. The group of the automated methods includes an inosine monophosphate dehydrogenase (IMPDH) inhibition assay as well as several immunoassays. The choice of assay usually depends on local circumstances including the apparatus and expertise available in the laboratory, the sample load, or the required analytical sensitivity.

This talk will summarize the most relevant analytical aspects related to the TDM of mycophenolates; will critically discuss advantages, disadvantages and caveats of currently available instrumental techniques as well as the appropriateness of their application to the analysis of the above mentioned pharmacokinetic measurants and to various sample matrices.
107 The interpretation of mycophenolic acid concentrations, considerations to be made

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The immunosuppressive drug mycophenolic acid (MPA) is an inhibitor of inosine monophosphate dehydrogenase (IMPDH). MPA can be administered as enteric coated mycophenolate sodium (ECMPS) or as the prodrug mycophenolate mofetil (MMF). The drug has a complicated pharmacokinetic profile (see figure) as it undergoes enteroheptic recirculation and is highly bound to plasma proteins, for which it competes with its glucuronide metabolite. For therapeutic drug monitoring of MPA certain aspects should be taken into consideration when interpreting the measured concentrations. Most frequently the total MPA trough concentration or AUC is used as therapeutic target. However, the unbound concentration, IMPDH activity or the intracellular MPA concentration could give more information about the immunosuppressive effect. The therapeutic range can differ between patients as a result of different indications and the comedication used.

A practical and suitable method to determine the MPA AUC is an abbreviated AUC measurement, for which the $\text{AUC}_{0-12h}$ is estimated based on several time points in the early period after dose administration. Several methods using multiple regression or Bayesian estimation are used to estimate the AUC based on these concentrations.

All these considerations should be taken into account for the interpretation of MPA concentrations. Dose adjustments should be based on the concentrations and these factors to improve therapeutic drug monitoring of MPA.
108  Clinical implementation of MPA monitoring, in transplant and beyond

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A lot has been written about the need for TDM of mycophenolate. At fixed-dose treatment, there is considerable between-patient variability in MPA-AUC. Low MPA plasma concentrations have been found to correlate with a higher incidence of rejection after kidney transplantation, especially in patients at higher risk of rejection. The logical next step would be to perform TDM and to adjust the dose in order to reach the therapeutic window. This strategy was found to reduce the incidence of BPAR in a French randomized controlled trial in patients treated with MMF [APOMYGRE study]. Also in the field of auto-immune disease there is support for TDM for mycophenolate.

It is often argued that in patients who are treated with 3 or 4 immunosuppressive drugs concomitantly, the MPA exposure may be less important. However, several studies have shown that despite the presence of corticosteroids and CNI therapy the MPA concentrations were still predictive of the risk of rejection. In whom and when to measure MPA concentrations, and whether predose concentrations or AUC measurements are to be preferred for TDM purposes will be discussed in this symposium.
109 Monoclonal antibodies monitoring: Clinical relevant aspects

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The clinical pharmacology of therapeutic monoclonal antibodies (MoAb) is dependent on both the structure of the antibody and the physiological system that it targets. Therapeutic MoAb are drugs with a complex dose–concentration–effect relationship.

The interindividual variability in clinical response to MoAb may partly be explained by pharmacokinetic (PK) variability. The PK of MoAb and the sources of interindividual variability in clinical is very different from that of “conventional” drugs. MoAb generally have different and potentially more complex PK profiles that are often associated with non-linear distribution and elimination. MoAb can be administered by intravenous or subcutaneous routes and are much more slowly transported to the target tissue than small molecule drugs, which is reflected in slow PK. The binding to plasma or tissue targets can influence antibody distribution, but the density and expression of the target antigen or, alternatively, active transport processes such as uptake by neonatal Fc receptor (FcRn) may also impact antibody biodistribution. MoAb are eliminated by catabolic degradation, which usually leads to a longer half-life. The PK and PD of MoAB are often inter-related.

The PK of several MoAb are often similar despite differences in their pharmacological targets and the fact that they are investigated and used in different patient populations and disease states. Therapeutic drug monitoring has been proposed as a means to understand and respond to the variability in clinical response and remission.

PNPLA3 gene polymorphism is associated with predisposition to and severity of Alcoholic Liver Disease (ALD)

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Introduction. Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH) share similar histopathological sequelae, progressing through fatty liver, hepatitis and cirrhosis. Genome-wide association studies (GWAS) identified PNPLA3 polymorphism (rs738409), C to G substitution resulting in I148M at a highly conserved codon, associated with NAFLD/NASH1. The G allele associated with higher hepatic fat content, liver transaminases and as an independent risk for liver dysfunction in fatty liver diseases. In ALD, candidate gene approaches replicated the association of rs738409[G] with increased disease severity2,3. The only GWAS in a retrospective cohort also showed an association of this variant with alcohol related cirrhosis4.

Aims. To investigate the genetic risk factors that influence the progression of cirrhosis in heavy chronic drinkers.

Methods. Our multinational GenomALC Consortium performed a case-control GWAS in a prospective and retrospective cohort of thousands of heavy chronic drinkers with and without cirrhosis (Cases and Controls, respectively). Heavy chronic drinking was defined as consuming 50/80 grams (female/male) of alcohol per day for at least 10 years. Extensive phenotype data was collected and blood drawn for DNA. Genotyping was performed using Illumina Infinium iSelect 24x1 HTS Custom Beadchip Kit. Well defined QC thresholds were used to clean data. Preliminary analysis used logistic regression for covariates (age, sex, drinking years, lifetime alcohol use).

Results. A total of 6710 participants were recruited from multiple sites worldwide. The Case and Control groups were well-matched for sex, age, ethnicity and lifetime alcohol exposure. A total of 5,533 (of 6528) samples and 503,625 SNPs (of 700,078 SNP targets) passed the QC. Our preliminary data show genome wide significance for PNPLA3 rs738409 (OR=1.9, p-val 6.2 x10^{-35}) as the top association with cirrhosis.

Discussion. This study confirmed association of PNPLA3 rs738409 variant with alcoholic cirrhosis in line with related phenotypes, such as NAFLD and previous reports in ALD.

111 Moderation of baclofen response by a GABA<sub>B</sub> Polymorphism.

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Background and aims: Baclofen has been shown to reduce alcohol consumption in alcohol-dependent individuals, but there is marked heterogeneity in response. An association between GABBR1 rs29220 and alcohol dependence has been demonstrated previously. The present study evaluated whether the response to baclofen is moderated by a single nucleotide polymorphism (rs29220) in the GABAB receptor subunit 1 gene (GABBR1). Previous research has identified similar associations between naltrexone response and the OPRM1 gene. Similarly, a GRIK1 polymorphism (rs2832407) moderated improved response to topiramate.

Design: Double-blind, placebo-controlled study.

Participants: Seventy-two alcohol-dependent men and women receiving 12 weeks of 30 mg/day of baclofen, 75 mg baclofen or placebo.

Measurements: Primary outcomes included time to lapse (any drinking) and relapse (> 5 drinks per day in men and > 4 in women). We also examined alcohol consumption at follow-up (drinks per drinking day, number of heavy drinking days and percentage days abstinent).

Findings: We observed significant medication × genotype interaction effect for time to relapse (P = 0.049) and a near-significant interaction effect for time to lapse (P = 0.055). For the CC genotype group, the relapse hazard ratio for baclofen versus placebo was 0.32 [95% confidence interval (CI) = 0.14-0.75] and for the G- group it was 1.07 (95% CI = 0.43-2.63). There was also a significant medication × genotype interaction for follow-up alcohol consumption (drinks per drinking day, heavy drinking days and days abstinent) (P = 0.02). Covarying for baseline levels of craving, aspartate aminotransferase and abstinence before enrolment reduced the medication × genotype effect for time to lapse and relapse but not for alcohol consumption at follow-up.

Conclusions: The GABBR1 rs29220 polymorphism may influence treatment response and possibly predict adverse effects to baclofen in the treatment of alcohol dependence. When combined with previous observations, the present findings demonstrate an evolving personalised medicine approach to pharmacotherapy for alcohol use disorder.
112 B cell Activating Factor (BAFF) and its Receptor (BAFF-R) in kidney transplantation

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B-cell activating factor (BAFF) is a member of the TNF family which supports B cell survival and proliferation. It binds to three receptors, the BAFF receptor (BAFF-R), the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), and the B-cell maturation antigen (BCMA). BAFF is produced by monocytes, macrophages, dendritic cells, as well as activated T lymphocytes. Increased BAFF expression has been linked to the development of autoimmune diseases. BAFF can be proteolytically cleaved from the cell surface and can be measured in its soluble form SBAFF by ELISA in blood. This is also true for its receptor BAFF-R which is required for complete B cell maturation.

In kidney transplantation (KTx) BAFF has been associated with B cell activation and rejection, BAFF-R with loss of graft function. Elevated pre-transplant SBAFF concentrations have been observed in sensitized KTx patients. In addition, KTx patients with high SBAFF concentrations have been shown to have an increased risk of developing de novo donor-specific antibodies (dnDSA). Therefore, BAFF and BAFF-R concentrations in plasma may reflect the degree of B cell activation in KTx patients and could be predictive biomarkers for the risk of developing dnDSA and antibody mediated rejection, as well as kidney graft dysfunction.
113 Immunotoxicity associated with herbal-induced liver injury

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Background and aims: Liraglutide (Saxenda™) is a glucagon-like-peptide-1 analogue that increases insulin secretion through beta cell receptors. We report a patient with drug-hepatotoxicity (DILI) and a case of herbal-induced liver injury (HILI) due to Herbalife tea and protein-shake. We aim to present clinical and laboratory evidence implicating mitochondrial toxicity and an immune response leading to DILI and HILI.

Case Report 1: A 52 year-old (BMI 31.2 kg/m²) woman was given subcutaneous liraglutide (0.6 mg to 3 mg daily for 3 months. aminotransferase: ALT of 547 IU/L, AST of 268 IU/L; alkaline phosphatase of 390 IU/L gamma-glutamyl-transferase (GGT) of 427 IU/L, 1.3 mg/dL, anti-histone-antibodies 52 IU/mL. Liraglutide was discontinued with clinical and laboratory normalization.

Immuno-Mechanism: Lymphocyte toxicity assay demonstrated liraglutide-toxic response. The mitochondrial markers (M65 and M30) revealed a high necrotic score. The pro-inflammatory cytokines (x control) in serum were as follow: TNF (tumor necrosis factor alpha) x26; IL1 beta (interleukin) x5; IL6 x3; IL8 x6. Vascular endothelial growth factor was 3x upper normal limits (UPN). Adipokine levels were: leptin x6, adiponectin x0.5, gherelin x2. Dysregulation of nuclear factor KB (NFKB) signal transduction pathway x 3 (UPN) in our patient, can be associated with autoimmune disease.

Case Report 2: A 65 year old lady was hospitalized due to progressive jaundice and hepatocellular injury. Ingestion of Herbalife tea and protein-shake was noted. Liver biopsy revealed necrotizing granulomatous hepatitis, apoptotic cells. Immunohistochemistry demonstrated bile duct loss. Discontinuation of the Herbalife products and treatment with both prednisone and ursodeoxycholic acid resulted in resolution of her complaints. ALT decreased from 1096 U/L to 69U/L and GGT decreased from 899 to 218 U/L. A lymphocyte toxicity assay (LTA) was performed. LTA (% toxicity) was: protein alone 20; tea alone 44; protein+ tea 66. The cytokines (x control) in serum were: TNF x40; IL1 x12; IL13-x3; IL8-x5. Vascular endothelial growth factor was 5106 pg/mL (x46). Mitochondrial markers M30 and M65 revealed a predominant level of necrosis process versus apoptosis. Herbalife products were discontinued with clinical and laboratory normalization.

Conclusions: In susceptible individuals, drugs and herbs might produce mitochondrial toxicity and a strong T-lymphocyte-1 response.
114  Protein binding and the interpretation of drug concentrations

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Introduction. The total drug concentration in plasma or serum is the sum of the bound and unbound concentrations of the drug. Unbound drug is in equilibrium with the site of action at steady state. Hence, the bound drug concentration is a potential source of bias and imprecision in TDM. In healthy people unbound and total concentrations are closely correlated but the relationship changes as patients become sicker with consequent changes in the concentrations of binding proteins and drug affinity. This relationship also applies to endogenously active molecules (hormones), where production (dose) is endogenously regulated. Some endogenous molecules are also administered as drugs, for example cortisol (hydrocortisone), testosterone and 25-hydroxyvitaminD (cholecalciferol).

Aims. To describe protein binding issues in TDM using the examples of cortisol (hydrocortisone) and 25-hydroxyvitaminD (cholecalciferol).

Methods. Total and measured unbound cortisol concentrations in the three trimesters of pregnancy were compared with healthy volunteers taking and not taking the oral contraceptive pill. Total and calculated unbound 25(OH)D concentrations in intensive care patients were compared with healthy volunteers.

Results. A progressive rise in total plasma cortisol and cortisol binding protein was demonstrated during pregnancy (mean 3-fold rise compared with controls). Plasma free cortisol increased 1.6-fold by the third trimester. In the OCP group, total plasma cortisol and CBG were 2.9- and 2.6-fold elevated, respectively, whereas plasma free cortisol was not significantly different from controls. Total 25(OH)D concentrations were significantly lower in critically ill patients than controls (37 (95% CI 31 – 43) vs 57 (53 – 60) nmol/L). Calculated unbound concentrations of 25(OH)D were not lower in critically ill patients than healthy controls (26 (22 – 29) vs 19 (18 – 20) pmol/L).

Discussion. The unbound concentrations of endogenously regulated drug molecules (hormones) are maintained. Bound concentrations vary with changes in physiological states. Total concentrations are potentially misleading in critical illness and other altered physiological states (such as pregnancy). In critical illness and pregnancy therapeutic decisions have greater potential consequences for patients than when they are healthy.
115  TDM and protein binding in critical care – flucloxacillin and phenytoin

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Introduction. TDM is an important tool to ensure appropriate drug concentrations are achieved in the critical care setting. Critical illness is associated with alterations to physiology and hence pharmacokinetics. Typically, total drug concentrations are measured as part of TDM, with the assumption that reference values for protein binding facilitate the translation of these into unbound concentrations. However, protein binding may be altered in critical illness. This is expected to particularly affect highly protein bound drugs, such as flucloxacillin ($f_u = 0.04$) and phenytoin ($f_u = 0.10$).

Aims. To examine the protein binding of phenytoin and flucloxacillin in hospitalised and intensive care unit (ICU) patients.

Methods. Hospitalised and ICU patients at a tertiary institution (Christchurch Hospital, New Zealand) who had flucloxacillin or phenytoin concentrations measured were identified using the local laboratory databases. The corresponding protein binding values were calculated, and compared to healthy volunteers and non-ICU hospitalised patients. Flucloxacillin and phenytoin were measured by LC-MS/MS and chemiluminescent microparticle immunoassay, respectively.

Results. For flucloxacillin, the median (range) $f_u$ in hospitalised patients (61 samples) and healthy volunteers (248 samples) was 0.10 (0.05, 0.37) and 0.04 (0.02, 0.07), respectively ($P < 0.001$). Flucloxacillin protein binding was significantly lower in hospitalised patients. For phenytoin, the median (range) $f_u$ in ICU patients (53 samples) and non-ICU patients (217 samples) was 0.26 (0.14, 0.37) and 0.17 (0.09, 0.56), respectively ($P < 0.001$).

Discussion. Protein binding of flucloxacillin and phenytoin, was significantly lower in hospitalised and ICU patients than their healthier counterparts. For each drug, the range of $f_u$ values in our hospitalised/ICU patients was higher than the literature reference $f_u$ values. Direct measurement of unbound drug concentrations, instead of extrapolation using reference $f_u$ values, is an important strategy to overcome the limitation of total drug concentrations in critical care.
The relevancy of drug protein binding in pregnancy

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During pregnancy, maternal physiology changes to favor development of the fetus. These changes often alter the pharmacokinetics of drugs, due to changes in metabolic enzyme and drug transporter expression, increased liver and renal blood flow, decreased gastric acid secretion, delayed gastric emptying, reduced intestinal motility, a decrease in hematocrit and reduced serum protein concentrations, among others.

All these changes together may result in either decreased, unaltered or increased exposure to drugs during pregnancy and these changes may be clinically relevant.

Often, when pharmacokinetics of drugs in pregnancy are studied, total (bound and unbound) pharmacokinetics are assessed. When a drug is highly protein bound and protein binding is limiting for the pharmacodynamics of a drug, measuring unbound concentrations is pivotal to unravel the mechanisms underlying the observed changes in pharmacokinetic exposure and to assess their relevance. Two examples with the antiretroviral drugs efavirenz and darunavir are discussed in this session. The pitfalls and solutions for pharmacometric analysis of these highly protein bound drugs are discussed in the context of pregnancy. Lastly, the similarities of drug protein binding and erythrocyte binding are discussed as well as the impact of altered hematocrit during pregnancy on the interpretation of highly erythrocyte bound drugs like immunosuppressive drugs.
117 Determining unbound drug concentrations

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The plasma protein binding of drugs has been shown to have significant effects on numerous aspects of clinical pharmacokinetics and pharmacodynamics. In many clinical situations, measurement of the total drug concentration does not provide the needed information concerning the unbound fraction of drug in plasma which is available for distribution, elimination, and pharmacodynamic action. Thus, accurate determination of unbound plasma drug concentrations is essential in the therapeutic monitoring of drugs. Many methodologies are available for determining the extent of plasma protein binding of drugs, however, in the clinical evaluation of drug therapy, equilibrium dialysis and ultrafiltration are the most routinely utilised methods. Both of these methods have been proven to be experimentally sound and to yield adequate protein binding data. Furthermore, the characterisation of the interactions between drug and protein molecules is essential for the assessment of the pharmacokinetic implications of drug-protein binding. Due to the speed of extraction, ultrafiltration has become the preferred method, however it is not without it’s issues. Non-specific binding of the unbound drug to both the membrane and holder device must be assessed, along with the temperature the sample must be equilibrated at prior and during centrifugation. Several practical clinical examples will be discussed to demonstrate these problems and how they were overcome.
118 Introduction to Pre-emptive Pharmacogenomic testing, rationale and overview of current approaches for Implementation

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There is a growing interest in identifying the most effective way of integrating pharmacogenomics (PGx) testing into a variety of healthcare environments. Pharmacogenetics or pharmacogenomics involves analysis of an individual's genotypes among a number of genes that dictate various aspects of medication pharmacology and allows for insight into mechanisms that account for increased likelihood for adverse reactions or therapeutic failure. One approach that has been proposed as being both cost effective and enabling rapid and efficient utilization of PGx test results, is to test candidate patients for a panel of PGx genes in a pre-emptive mode that may or may not include a trigger-event. Thus, as opposed to limiting a testing transaction to testing only for genetic variation that is linked to response to a specific medication of interest, for example testing a patient scheduled to receive clopidogrel for genetic variation in CYP2C19, this testing event would include testing for additional PGx genes that have a high likelihood of relevance to the care of this individual going forward and thus eliminate the associated costs and time required by multiple testing transactions.

This session will introduce the rationale and driving forces, (e.g. incidence of polypharmacy) for this concept and provide an overview of the background literature as an introduction. We will then have thought leaders to present their experience with this approach. Study design and results from a large European multi-site study will be presented as well as the experience of a major healthcare center which has adopted this approach into routine care of patients.
119  Implementing Pharmacogenomics in Europe: Design and implementation strategy of the ubiquitous Pharmacogenomics consortium

Professor Henk-Jan Guchelaar

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Pharmacogenomics is the study of genetic variability affecting an individual’s response to a drug. Its use allows personalized medicine and reduction in ‘trial and error’ prescribing, leading to more efficacious, safer and cost effective drug therapy. Technical developments have moved the field from reactive genotyping to a pre-emptive panel approach: in this latter approach patients are tested for a panel of genetic variants even before drug prescribing has taken place. When these data are included in a patient’s electronic medical record, this allows physicians and pharmacists to use this information at time of drug prescribing and medication surveillance.

Due to its highly developed infrastructure, The Netherlands healthcare system is at the forefront of implementing pharmacogenomics into routine clinical practice. Pre-emptive testing of f.e. DPYD before use of 5-fluorouracil or capecitabine and of TPMT before use of 6-mercaptopurine or azathioprine is standard in many centers in The Netherlands and patient’s drug dosages are personalized based upon the pharmacogenomics test result.

Recently, an EU Horizon2020 project Ubiquitous Pharmacogenomics (U-PGx) was funded and investigates the approach of pre-emptive panel testing using a randomized clinical trial design in 7 EU countries and including a total of 8,100 patients. Feasibility, health outcome, especially the reduction of adverse drug events, and cost-effectiveness will be studied. The U-PGx consortium ultimately aims to formulate European strategies for further improving implementation of pharmacogenomics.
120 Implementation of a pre-emptive PGX testing strategy in a large US healthcare system

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Introduction. Clinical implementation of pharmacogenomics is an expanding field. Early adopters have developed a few solutions to the many challenges facing genomic implementations. For the field to expand even more scalable and sustainable solutions must be created.

Aims. Describe how one health system has implemented pharmacogenomics with the goal of improving pharmacotherapy related health outcomes through integration of genomic data into routine care.

Methods. This presentation will review the process for implementation at a community health system in the United States. Highlighting several recently published studies for the institution.

Results. Through an iterative process a robust solution for implementing pharmacogenomics into routine clinical care has been develop. Many challenges have been faced and novel solutions have been developed.

Discussion. Clinical implementation of pharmacogenomics has made great progress of the last 5 to 10 years however the perfect solution has not been created. The presentation focuses on how a single health system in the USA built a team of various experts to implement pharmacogenomics as the first use case for personalized medicine at the institution. This implementation has created solutions that will be used for other personalized medicine projects and has begun to revolutionize routine care at the institution. Keys to success include starting with small manageable project and having a clear strategic and tactical focus for improving care.
Opportunities and challenges in implementing precision medicine into pharmacy practice

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Introduction. The importance of pharmacist leadership in precision medicine (PM) is increasingly being highlighted through development of organizational guidance and practice-based resources. Pharmacists are willing to incorporate PM services into their practices but they face political, institutional and educational challenges. It is important to summarize successful models to help improve PM pharmacy practices.

Aims. To describe the PM practice models implemented in healthcare institutions in USA in the most recent five years, summarize the workflow and roles of pharmacists, and evaluate the opportunities, challenges and resources for implementing PM into pharmacy practice.

Methods. In the Pubmed database, we searched articles about pharmacists’ roles in PM/pharmacogenetics/personalized medicine practice models implemented in US institutions, which were published between January 1st, 2013 and December 31st, 2017. Thirty pertinent articles were found, in which twelve articles were included based on the following inclusion criteria: 1) the workflow of the practice model in a particular institution was described 2) the roles of pharmacists were described. The opportunities, challenges and resources for clinical pharmacists or for institutions were also summarized at the end of the review.

Results. Fifteen models were described in the included articles. They include molecular tumor board, behind-the-scenes EHR decision support, EHR-driven consultation service, ambulatory pharmacogenomics clinic (fee-for-service or insurance billable service), community pharmacy service, medication therapy management, and pre-emptive pharmacogenetics clinical decision support and consultation. Pharmacists are actively involved to perform results explanation, genotype-guided medication selection and dosing adjustment, medication acquisition, medication ADR monitoring and patient education. Institutions who are interested in implementing similar models shall overcome the challenges such as reimbursement issues, informatics, and educational knowledge gap.

Discussion. Some institutions in US have implemented PM/personalized medicine/pharmacogenetics into pharmacy practice and pharmacists are playing active roles. A strong institutional support, well-defined goals, standardized procedures and a strategy to educate clinicians and patients are the prerequisites to integrate, interpret, deliver, and apply the full range of genetic data to medication-related therapy.
Population Pharmacokinetics of Voriconazole and CYP2C19 Polymorphisms for Optimizing Dosing Regimens in Renal Transplant Recipients

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**Introduction.** At present, the research on voriconazole is mainly focused on hematopoietic stem cell transplantation, liver or lung transplantation, and patients in the intensive-care unit. However, the information on pharmacokinetics and refining dosage regimens of voriconazole in renal transplant recipients is still very limited.

**Aims.** To characterize the pharmacokinetics of voriconazole in renal transplant recipients and identify factors significantly influencing its pharmacokinetic parameters, and to explore adequate dosing regimens for patients suffering from invasive fungal infections.

**Methods.** A total of 105 patients (342 concentrations) were included prospectively to conduct a population pharmacokinetic analysis. Nonlinear mixed effect models were developed with Phoenix NLME software. Dosing simulations were performed based on the final model.

**Results.** A one-compartment model with first-order absorption and elimination was fit to characterize the data. Population estimates of the clearance, the volume of distribution and the oral bioavailability were 2.88 L•h⁻¹, 169.3 L and 58%. CYP2C19 genotype had a significant influence on the clearance. Voriconazole trough concentrations in poor metabolizers were significantly higher than in both intermediate metabolizers and extensive metabolizers. The volume of distribution increased with the body weight. The oral bioavailability was substantially lower within 1 month after the operation but increased with postoperative time. Dosing simulations indicated that during the early postoperative period, poor metabolizers could be safely and effectively treated with 150 mg intravenous or 250 mg oral regimen twice daily, intermediate metabolizers with 200 mg intravenous or 350 mg oral regimen twice daily, and extensive metabolizers with 300 mg intravenously twice daily.

**Discussion.** Combining CYP2C19 phenotype with postoperative time to determine the initial voriconazole dosing regimens followed by therapeutic drug monitoring will help improve patients’ clinical outcome and advance individualized treatment.
123  Therapeutic drug monitoring of voriconazole

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Introduction. Voriconazole is used to treat invasive fungal infections (IFIs). It is an ideal candidate for therapeutic drug monitoring (TDM) as it displays non-linear pharmacokinetics, a narrow therapeutic index and large inter-patient variability. The electronic Therapeutic Guidelines\textsuperscript{1} (eTG; Antibiotic Expert Group, 2015) suggest target trough concentrations of 1 to 5 mg/L, independent of indication.

Aims. To examine voriconazole dosing and TDM at St Vincent’s Hospital, Sydney and determine compliance with eTG.

Methods. A retrospective audit (1\textsuperscript{st} January 2016 – 31\textsuperscript{st} December 2016) of voriconazole dosing and TDM was undertaken. Data was collected from electronic and paper medical records. A Bayesian dose prediction software (DoseMe\textsuperscript{®}, Brisbane, Australia) was used to predict voriconazole trough concentrations.

Results. Data were obtained for 132 courses of voriconazole prophylaxis (47%) and proven IFIs (53%) therapy from 94 patients. Patients received oral, IV or mixed (oral and IV) formulations. Overall, guideline compliance was below 44% for intravenous (IV) prophylaxis and proven IFIs therapy. Compliance with oral voriconazole dosing guidelines was also observed to be poor, unless the guidelines recommended dosing at 200 mg – the most commonly prescribed dose (57% of prescriptions). Voriconazole concentrations were obtained for 107/132 therapies. A median of 3 (range: 1 to 27) plasma concentrations were obtained per course of therapy. Marked variability was observed in the timing of the first plasma concentration collection in a course of therapy (median: before 5th dose, range: before 1st to 22nd dose). Of the first plasma concentrations collected, 21% were true trough concentrations (median: 1.7 mg/L, range: 0.1 – 4.3 mg/L). Of these, 30% were sub-therapeutic. No dose adjustments were associated with sub-therapeutic true troughs. DoseMe\textsuperscript{®} accurately predicted voriconazole concentrations regardless of formulation (r\textsuperscript{2}=0.98, p<0.0001).

Discussion. Compliance with eTG for voriconazole was poor. Further, when trough concentrations were outside the guideline recommended therapeutic range no change in dosing was observed. This observation and the observed variability in monitoring highlights the need for improved guidance for clinicians to optimise patient outcomes. Incorporation of Bayesian dose prediction software in voriconazole therapy has the potential to support TDM.

124 Voriconazole for treatment of invasive fungal infection in paediatric patients: Is there need for a more frequent dosing strategy?

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Introduction. Therapeutic drug monitoring (TDM) of voriconazole is recommended to achieve trough concentration of 1 mg/L at steady state. This study describes our experience with voriconazole, focusing on dosing regimens, dose adjustment and TDM.

Aims. To determine whether the current dosing regimen of voriconazole is adequate for pediatric patients.

Methods. This was a prospective, single arm study conducted in pediatric patients aged 1-18 years. All patients received standard dose of voriconazole orally (200 mg) or intravenously (7mg/kg) q12h. The dose was subsequently modified according to TDM results. Two blood samples were obtained at steady state, one at 8th hour and another at 12th hour for determination of plasma voriconazole levels by HPLC.

Results. 42 patients on voriconazole for invasive fungal infection were enrolled in the study. Trough (12th hr) concentration was <1mg/L in 51% patients while the corresponding 8th hr concentration was <1mg/L in only 23% patients. Median dose of voriconazole received by our patients was 8.9 mg/kg (4.7-15) which is significantly higher than the recommended adult dose of 4mg/kg. In spite of high doses being administered, the median trough concentration was 0.93 mg/L, which is less than the threshold concentration (1 mg/L). The median trough concentration in 22 patients who had sub-therapeutic levels was 0.48 (0-0.93) mg/L while in the same cohort median 8th hour concentration was 2.12 (0-6.5) mg/L.

Discussion. Our study highlights that very high doses also could not achieve therapeutic trough levels of voriconazole in >50% of children. In children, this is challenging due to age-related variability in voriconazole pharmacokinetics. Corresponding concentration at 8th hr as compared to 12th hr was well above the therapeutic threshold in majority of patients. Smaller, frequent doses may be a better strategy for administering voriconazole in paediatric patients.
125 Posaconazole monitoring during real-life in haematological patients: Experience from a tertiary care center

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Introduction: Invasive fungal infections (IFIs) are a major cause of life-threatening diseases in immunocompromised transplant or cancer patients receiving chemotherapy, and emerging opportunistic fungal pathogens are significantly prevalent. Posaconazole (POS) is recommended as a first-line prophylaxis during prolonged neutropenia and leukaemia induction treatment. The current guidelines recommend optimal trough plasma concentration (PPC) ≥1mg/L during treatment and ≥0,7 mg/L for prophylactic use and lower concentrations could be associated with breakthrough IFIs.

Aims: To describe in a real life setting of adult hematologic patients POS pharmacokinetics by evaluating the achievement of PPC, its prophylactic efficacy, drug toxicity, and the impact of potential risk factors.

Methods: we retrospectively analyzed 33 unselected adult affected by Acute Myeloid Leukemia, who underwent induction chemotherapy and received POS as prophylaxis for IFIs. PPC were assessed 4 days after POS start and bi-weekly during grade IV CTCAE neutropenia period. POS delayed-release tablets was administered at 300 mg/day, after loading dose of 300x2 mg/day; POS oral suspension was administered at 200x3 mg/day. PPC was measured by LC-MS/MS.

Results: Among the 33 pts (17F/16M), median age 53,3 years, 29 received POS delayed-release tablets and 4 pts oral suspension; POS was administered until neutropenia resolved (PMN >0.5x10⁹/L) for a median of 30,5 days (range 11-97); during this period the median PPC₅₅ was 1,4 mg/L (range 0,2-4,8). The overall rate of PPC ≥ 0,7 and 1,0 mg/L was 80,9% and 61,8%, respectively. Median PPC at the 1st determination (day 4) was 1,1 mg/L (range 0,2-3) and in only 8 cases the level was <0.7 mg/L. Some pts experienced transient drug-related toxicity (8 diarrhea episodes and 4 hepatic toxicity); 7/33 pts (23%) experienced probable/possible pulmonary breakthrough infection that caused switch to L-AmB and their median PPC was 2,0 mg/L (range 0,3-4).

Discussion: Our data collected in a real life setting confirm that PPC increase in a short period ensuring a potential good coverage against fungi. However, the incidence of fungal infections was high although adequate PPC in all breakthrough cases. Other factors impairing the efficacy of antifungal prophylaxis are probably involved. Therapeutic drug monitoring plays an important role in improving efficacy and safety of antifungal prophylaxis, but a comprehensive knowledge of all other clinical risk factors for infections have to be considered in order to better define a successful management of each individual patient.
126 Retrospective analysis of posaconazole dosing strategy in a pediatric haematology-oncology population: single center experience

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Introduction: Posaconazole (POS) is a broad-spectrum triazole with a strong level of recommendation in adults as prophylaxis of invasive fungal infections (IFIs) in high-risk immunocompromized patients (pts) and with a moderate level as second-line therapy of invasive Aspergillosis and Zygomycosis, while it has not been approved in pediatrics. When used as oral suspension it is characterized by inter- and intra-individual PK variability and oral bioavailability, which is improved by delayed-release tablet formulation. Low plasma levels (< 0.7 mg/L for prophylaxis and < 1 mg/L for therapy) might be associated with breakthrough infections and therapeutic failure.

Aims: To evaluate, in a cohort of pediatric pts, the association between POS daily dose and the achievement of optimal trough plasma concentration (PPC) and the impact of potential risk factors on PPC achievement, the efficacy, both for prophylactic and therapeutic purposes and drug toxicity.

Methods: we retrospectively analyzed 26 pediatric hematology-oncology pts, who underwent chemotherapy or HSCT, and received POS as prophylaxis or treatment for IFIs with at least 1 steady-state PPC in the first 6 weeks after POS start. Considering the retrospective nature of the study, where the timing of PPC was not planned in advance by the study protocol, only steady-state levels (PPC<sub>ss</sub>) were used for data analysis; to normalize our data, POS dose was converted to mg/kg per day to enable weight-based dose comparison among pts. PPC was measured by LC-MS/MS.

Results: Among 26 pts (17M/9F), median age 8.2 years (range 0.97-19.3), POS was used as prophylaxis in 23 pts, and in 3 as rescue therapy. All pts received oral suspension, except 3 (aged > 16 years) who received the delayed-release tablet formulation. The median daily dose was 12 mg/kg/day (range 4.9-20) divided in 3 times daily, and the median duration of POS administration was 138 days. Median PPC<sub>ss</sub> was 0.98 mg/L (range 0.15-3.62). The overall rate of PPC<sub>ss</sub> ≥ the threshold target of 0.7 and 1.0 mg/L was 65.5% and 46.5%, respectively. In the prophylactic group no patient developed breakthrough fungal infection; among pts who received POS as therapy, 2 resolved the infection, and one died because of multi organ failure.

Discussion: POS is a safe and well-tolerated drug with few and low-grade site effects in pediatric population. PPC<sub>ss</sub> analysis allowed a comparison of the dose empirically chosen by the physician, the PPC achieved at that dosage, and the desirable recommended PPC for POS optimal efficacy. Further large prospective studies are needed to define the optimal dosage, frequency, target PPC, and management of POS in children.
127 An International survey on the practice of therapeutic drug monitoring of antifungal drugs

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Introduction. Antifungal drugs can reduce morbidity and mortality if provided early and in appropriate doses. Triazoles and flucytosine antifungals show wide inter and intra-patient variation. Though guidelines recommend titration of doses be based on therapeutic drug monitoring (TDM), there are currently no publications which document the global practice of antifungal TDM.

Aims. We aimed to document which countries had antifungal TDM services and its practice and concordance with current antifungal TDM guidelines (BSMM, 2014).

Methods. We conducted a worldwide survey to document the current global practice of antifungal TDM using an online questionnaire. It was sent to 79 validated emails covering 35 countries through the newsletter of GAFFI (Global action fund for fungal infections).

Results. Twenty-four of 35 countries (69%) surveyed had access to a TDM service. Respondents in 52% countries had the laboratories located in their own cities. High performance liquid chromatography was the commonest technique, followed by tandem mass spectrometry, and bioassays. TDM services were not used in clinical practice by 60%, 48%, 20%, and 4% of the countries respectively for flucytosine, posaconazole, itraconazole, and voriconazole. The ideal turnaround time for flucytosine (<3 days), posaconazole, voriconazole and itraconazole (all <7 days) were met in 67%, 55%, 53%, and 38% countries. The laboratories offered clinical advice in TDM results in 50%, 56%, 64%, and 20% countries for itraconazole, voriconazole, posaconazole, and flucytosine respectively. About 50% of the countries used the service as a clinical proxy for efficacy of itraconazole, voriconazole, and posaconazole or to avoid toxicity (29%) for flucytosine. Recognition of unpredictable pharmacokinetics and major drug interactions varied from 17-41.2% by respondents. The average costs of the assays ranged from USD 30-75.

Discussion. We conclude that immediate steps should be taken to expand access to and standardize antifungal TDM across the world. This will go a long way in preventing the health fallout from the global burden of serious fungal infections.
Real-world dabigatran concentration monitoring - Christchurch experience

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Introduction. Dabigatran etexilate is an oral anticoagulant administered at fixed dose, stratified by renal function, with limited clinical monitoring. There is increasing recognition of the utility of using plasma concentrations of dabigatran, the active metabolite, to inform treatment decisions. However, there is limited information about real-world use of this assay. An in-house LC-MSMS dabigatran assay was recently made available clinically at Christchurch Hospital, New Zealand, with samples analysed as a weekly batch.

Aims. To describe the clinical reasons for measuring dabigatran concentrations and subsequent dabigatran etexilate prescribing decisions at Christchurch Hospital.

Methods. Patients with dabigatran concentrations during 2017 were identified from the hospital’s laboratory database. These patients’ health records were reviewed and the dabigatran etexilate prescribing before and after measuring dabigatran concentrations was examined.

Results. There were 34 patients with 41 dabigatran concentrations. The median (range) age of patients was 73 years (<1 – 89). The predominant indications for anticoagulation were atrial fibrillation (17/34, 50%) and venous thromboembolism treatment (16/34, 47%). The most common reasons for measuring dabigatran concentrations were: post-thromboembolic events despite dabigatran (12/41, 29%), uncertainty about concentrations because of renal function and pharmacokinetic drug-drug interactions (9/41, 22%), and post change in dose (8/41, 20%). The median (range) dabigatran concentration was 73 microg/L (0 – 470), reference range 30 – 130 microg/L. After the dabigatran concentration was reported, patient dabigatran etexilate prescriptions changed in 11/41 (27%) including: cessation (6), dose reduction (3) and dose increase (2). Of the remainder, prescriptions were unchanged in 20/41 (49%), and the clinical records did not reveal the dabigatran etexilate prescribing decision in 10/41 (24%).

Discussion. Measurement of dabigatran concentrations in the clinical setting was associated with a subsequent change in dabigatran etexilate prescriptions immediately after 27% of these tests. These data will be used to inform the clinical use of dabigatran concentration monitoring in New Zealand, which may lead to increased assay use, and a justification for shorter turnaround times.
129 Lidocaine infusion for pain management in major surgery patients - pharmacokinetic and therapeutic drug monitoring challenges

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Introduction. Adverse effects of opioid usage can prolong and complicate post-operative recovery, and some patients do not attain adequate pain relief. Intravenous lidocaine (LID) infusion may be used as an opioid sparing regimen. However, as the pharmacokinetics of LID changes over time, possibly due to an accumulation of the active metabolite monoethylglycine xylide (MEGX) and its influence on LID elimination, the dosing of long term intravenous LID infusion is a challenge.

Aims. To describe the pharmacokinetics of LID and MEGX during infusions up to 5 days and develop a limited sampling strategy for individual dose adjustment following major surgery.

Methods. Patients aged 18 years or older and scheduled for major liver-, pancreas- or lung cancer surgeries were eligible for inclusion. LID therapy was initiated with a bolus (1.5 mg/kg i.v) followed by constant infusion (1.5 mg/kg/h i.v) aiming for a target therapeutic range of 2-5 mg/L in serum. In this initial phase of the study, a 24 hour infusion was investigated, with frequent serum samples collected during infusion and the subsequent 48 hours. LID and MEGX serum concentrations were measured using liquid chromatography-mass spectrometry.

Results. Eleven patients have completed the initial phase. No LID related adverse events were observed. Following the bolus a transient LID peak of (mean, range) 4.5 mg/L (2.8-5.4 mg/L) was shown. LID steady-state was not achieved during the 24 hour infusion, resulting in an end of infusion LID concentration of 4.1 mg/L (2.5-5.3 mg/L). Maximum MEGX concentration was 1.6 mg/L (0.8-2.5 mg/L), generally observed at the end of infusion. LID half-life after end of infusion was 7.8 h (3.4-12.9h).

Discussion. The applied regimen resulted in LID serum concentrations within the target range. However, the preliminary data suggest that steady-state is not reached within 24 hours, and individual dose modifications to avoid toxic concentrations during prolonged lidocaine infusions are thus most possibly required. MEGX may be a significant contributor to efficacy and toxicity during lidocaine infusion.
130 A time and motion study of phlebotomists’ work

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Introduction. Therapeutic drug monitoring (TDM) is the cornerstone of clinical practice for drugs with a narrow therapeutic range. Obtaining blood samples at regimented times is critical for TDM. However, due to the busy nature of the clinical setting, TDM samples are often collected at the incorrect time. Phlebotomists play a key role in blood collection. No research has explored phlebotomists’ work and their role in the TDM process.

Aims. To collect time and motion data on the work of phlebotomists and to explore phlebotomists’ perceptions of their work.

Methods. All inpatient phlebotomists (n=5) at St Vincent’s Hospital, Sydney were observed for a total of 45 hours and data on all tasks, interruptions and multi-tasking were collected using the Work Observation Method by Activity Timing (WOMBAT) software. Descriptive statistics were used to determine the proportion of total observed time spent on tasks. Phlebotomists also partook in a semi-structured focus group. Blood collection information was reviewed to determine the proportion of TDM samples collected by phlebotomists.

Results. Phlebotomists predominantly spent time collecting blood (54%) and in professional communication (15%). Phlebotomists spent 14% of their time multitasking and were interrupted, on average, every 19 minutes. Phlebotomists reported a high workload, predominately attributed to understaffing, which contributed to physical fatigue and stress. Phlebotomists conducted 56% of all inpatient TDM blood collections. However, their high workload and workflow practices did not facilitate timely collection of TDM samples.

Discussion. Phlebotomists have a high workload, take few rest breaks, are required to multi-task frequently and are interrupted at high rates. Increasing the number of phlebotomists and/or recruiting a dedicated TDM phlebotomist(s) may assist in reducing workload and allow for the collection of TDM samples at regimented times.
Therapeutic monitoring of antipsychotic efficacy in schizophrenia patients by simultaneous determinations of a panel of biomarkers in plasma

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Introduction. Schizophrenia is long suffering from an absence of adequate biomarkers and laboratory tests. It is difficult to provide diagnostic criteria or to assess the therapeutic outcome using the current standard of behaviour rating scores and/or therapeutic drug monitoring.

Aims. We aim to evaluate the utility of a novel metabolomic model build upon a panel of treatment biomarkers for the diagnosis and therapeutic monitoring of schizophrenia patients.

Methods. Firstly, using metabolomic technologies, we have revealed the efficacy of atypical antipsychotic drugs (AAPDs) by targeting multiple stress-related metabolic pathways as reflected by a panel of treatment biomarkers [Cai et al. Transl Psychiatry. 2017, 7(5):e1130]. Secondly, the fasting plasma samples were collected from a training set consisting of 147 first-episode antipsychotic-naïve or relapsed antipsychotic-free schizophrenia inpatients at baseline and after 4 weeks of AAPD treatment, and from 74 gender- and age-matched healthy controls. The fasting plasma samples at baseline, 3 and 6 weeks were collected from a separate prediction set consisting of 19 schizophrenia patients and 12 controls. Thirdly, a UFLC-MS/MS method was developed to quantify the panel of biomarkers simultaneously. The SIMCA-P 12.0 package was used for model constructions and multivariate analyses.

Results. The metabolic profiles of healthy controls, schizophrenia patients at onset (baseline) and remission stage (4-week) were clearly separated in the scores plot of a partial least square-discriminant analysis (PLS-DA) model, which can classify and discriminate the subjects with a high accuracy of 95.9%. Using principle component analysis (PCA)-Class models, the prediction set was judged by DModXPS+ values and a D-critical line, which can assist the diagnosis of schizophrenia and therapeutic monitoring of antipsychotic efficacy, especially for the patients who showed no response even when their plasma AAPD concentrations are sufficient.

Discussion. This panel of biomarkers is state-like and may potentially serve for therapeutic monitoring of antipsychotic efficacy in schizophrenia patients.
132 Barriers overcome: a case study of deploying model-informed precision dosing across five continents and 50+ sites

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Background. Despite the substantial body of literature evidence for Bayesian dose forecasting or model-informed precision dosing (MIPD) across multiple clinical specialties, until recently, clinical uptake has been slow and is generally limited to centres with in-house scientific expertise deploying in-house developed solutions.

Aims. To present a case study of the widespread deployment of a MIPD tool (DoseMe) across a large number of clinical sites assessed against commonly-raised barriers to implementation.

Methods. The deployment of DoseMe was assessed using the framework identified in a recent qualitative study of the barriers to adoption of clinical decision support software (CDSS; Liberati EG et al. 2017) and the five barriers enumerated in the recent consensus statement on the barriers to MIPD tools (Darwich AS et al. 2017): 1) providing an appropriate tool for clinical rather than scientific users, 2) addressing health economics, 3) clinical and model validation, 4) key therapeutic areas to target, and 5) regulatory issues.

Results. In this case study the barriers identified by Darwich et al. were found to be accurate but surmountable. A focus on clinical usability and workflow required upgrades to DoseMe’s user interface and EHR integration. To address health economics, a return on investment (ROI) calculator for MIPD of vancomycin was developed using pilot US customer data and literature evidence, with projected savings for a 500-bed hospital including assay reductions ($55,695pa), staff time that can be reinvested in other clinical work (up to 1069 hours pa), medication savings from avoiding switching therapy ($219,600pa), and avoiding nephrotoxicity (188 cases pa). A multi-stage clinical and model validation process was cleared through regulators. Finally, multiple therapeutic areas were market-tested, and antimicrobial stewardship and paediatrics were identified as having clinical demand and acceptance of MIPD. After three years, DoseMe has successfully overcome these barriers and deployed MIPD at more than 50 sites.

Discussion. While there remain barriers to implementation of MIPD, these are surmountable within targeted therapeutic areas. Instead, a focus on overcoming healthcare-system and economic barriers is likely to result in increasing clinical update of MIPD and improvement in clinical outcomes and healthcare resource use as a result.
133 Evaluation of the pharmacokinetics of psychotropic drugs in HIV-infected patients: implications for clinical practice

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Introduction. Management of psychiatric illness in HIV-infected patients can pose challenges for clinicians because of the risk of potential drug-drug interactions with antiretroviral drugs. This may result in the selection of inadequate psychotropic drug doses, eventually causing suboptimal clinical response.

Methods. Four-hundred patients treated with psychotropic drugs for at least one month and with at least one plasma trough concentration of antiretrovirals, antidepressants or antipsychotics available.

Results. Sixty patients given concomitant antiretroviral therapies with psychotropic drugs were identified. Boosted antiretrovirals were used in 43% of patients, non-nucleoside reverse transcriptase inhibitors in 38% and integrase inhibitors in 37%. Overall, 58% of the samples resulted below the minimum effective psychoactive drug concentrations, whereas only 7% of the samples exceeded the upper threshold of the therapeutic ranges.

Discussion. Psychotropic drugs are likely be underdosed in HIV-infected patients. The creation of multidisciplinary teams involving different specialists may contribute to an optimal management of these complex patients through a rationale selection of the more appropriate drug dose eventually guided by therapeutic drug monitoring.

<table>
<thead>
<tr>
<th>Psychoactive drug</th>
<th>Patients (n)</th>
<th>Daily drug doses</th>
<th>Trough levels (ng/mL)</th>
<th>Reference ranges (ng/mL)</th>
<th>Subtherapeutic samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>11</td>
<td>20 mg (all patients)</td>
<td>60±64</td>
<td>50 – 100</td>
<td>63%</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>7</td>
<td>60 – 90 mg</td>
<td>33±37</td>
<td>30 – 120</td>
<td>57%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4</td>
<td>20 – 40 mg</td>
<td>204±190</td>
<td>120 – 500</td>
<td>50%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>8</td>
<td>20 – 40 mg</td>
<td>18±22</td>
<td>30 – 120</td>
<td>75%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>6</td>
<td>50 – 100 mg</td>
<td>16±10</td>
<td>10 – 150</td>
<td>33%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>2</td>
<td>150 mg (both patients)</td>
<td>229±88</td>
<td>100 – 400</td>
<td>0%</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4</td>
<td>0.5 – 5.0 mg</td>
<td>1.4±0.7</td>
<td>1 – 10</td>
<td>75%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>7</td>
<td>2.5 – 20 mg</td>
<td>18±17</td>
<td>20 – 80</td>
<td>86%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>8</td>
<td>50 – 200 mg</td>
<td>287±264</td>
<td>100 – 500</td>
<td>50%</td>
</tr>
</tbody>
</table>
134  Two concomitant cases of strychnine poisoning

**Associate Professor Amanda Jenkins**

1 Umass Memorial Medical Center, Worcester, United States

Introduction. Emergency Department [ED] clinicians are challenged with correctly diagnosing and treating poisoned patients. They may utilize urine drug testing to assist in the differential diagnosis. Typical panels are limited to drugs of abuse and not readily adaptable to unusual substances.

Aims. To discuss two concomitant cases of poisoning with strychnine. To describe detection of this compound with a comprehensive general toxicology screen using gas chromatography–mass spectrometry [GC-MS], offered on a STAT basis by the treating hospital clinical laboratory.

Methods. A 39 year old male and 56 year old female, who were acquaintances, presented to the ED with symptoms of agitation, increased muscle tone, increased deep tendon reflex, and increased heart rate. Chemistries were performed using Beckman Coulter LH780 analyzer and Unicel DxI 800; and iQ Sprint 200 instrument. Toxicology testing of a urine specimen consisted of an alkaline liquid-liquid extraction followed by GC-MS analysis, with an Agilent 6890 GC coupled to a 5973 MS. An HP1 0.20 mm ID, 12 m, 0.33 µm film cross linked methyl silicone column was used with a ramped temperature program from 70 to 280°C. The internal standard was clomipramine. The instrument was operated in SCAN mode.

Results. Laboratory testing revealed acidosis, elevated WBC, low calcium, and elevated serum CPK. The GC-MS analysis revealed a peak at 14.7 minutes, with a relative retention time [RRT] of 1.27, electron impact spectrum demonstrated ions [m/z] at 334, 167, 162, 130, 120 and 107. This compound was identified by an in house library and NIST library as strychnine. Another compound detected at 17.9 minutes, RRT = 1.54 and major ions at m/z 394, 379, 203, 197 and 190, was identified as brucine.

Discussion. Both individuals were admitted and treated with activated charcoal. CPK levels continued to rise in both patients, peaking on days 4-5. Supportive measures were provided, the patients recovered and were discharged after 10 days. The source of the strychnine was identified as a herbal remedy from Cambodia which the male used to prepare tea. Brucine [2,3-dimethoxysterchynine] is often present with strychnine in plants of the Strychnine family, such as Strychnos nux-vomica L. This case illustrates the benefit of mass spectrometric testing compared with typical immunoassays used in emergency toxicology.
135 Detection of synthetic opioids using high resolution mass spectrometry: keeping up with the trends

Associate Professor Kara Lynch

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Introduction. The emergence of illicitly manufactured synthetic opioids including fentanyl and analogues represents a significant escalation of the ongoing opioid overdose epidemic in the United States. Synthetic opioids have been identified as adulterants in heroin and counterfeit opioid pills and are often consumed unknowingly. The true extent of the synthetic opioid epidemic is underappreciated due to the lack of routine diagnostic monitoring.

Aims. To validate the detection of 14 predominant fentanyl analogues/synthetic opioids using a high resolution mass spectrometry (HRMS) drug screen and develop a comprehensive suspect analysis approach for the detection of additional emerging synthetic opioids and metabolites, for which analytical standards are not always available.

Methods. Urine samples were diluted 1:5 and chromatographic separation was performed using a C18-column with a 10-minute gradient from 2%-100% organic. Data was collected on a SCIEX TripleTOF®5600 operating in positive-ion mode using a TOF-MS survey scan with IDA-triggered collection of high resolution product ion spectra (20 dependent scans). Limit of detection (LOD) was defined as the lowest concentration for which the drug met scoring criteria for positive identification in duplicate injections and had a signal-to-noise ratio >20:1. Matrix effects were determined using three matrixes tested in triplicate at three concentrations. A library spectrum was collected for each analytical standard using a dedicated product ion scan. The spectra were added to our in-house library for data analysis.

Results. The analytically defined LOD and matrix effects (average for all concentrations) were as follows (LOD ng/mL, % matrix effects): butyryl fentanyl (5, -14%), 3-methyl fentanyl (2.5, -11%), tetrahydrofuran fentanyl (2.5, -10%), acryl fentanyl (2.5, -16%), acetyl fentanyl (1, -26%), carfentanil (2.5, -11%), beta-hydroxythiofentanyl (2.5, -20%), furanyl fentanyl (2.5, -17%), para-fluorofentanyl (2.5, -19%), para-fluorobutyryl fentanyl (2.5, -8%), sufentanil (5, -11%), alfentanil (1, -15%), cyclopropylfentanyl (2.5, -8%) and, U-47700 (10, -33%). An extracted ion chromatogram data analysis list was created containing the extraction mass (M+H) for 157 additional synthetic opioids and metabolites representing 91 unique formula due to isomers. The method described here has been used to identify synthetic opioids, predominately U-47700 and carfentanil, in cases referred to our clinical laboratory from the northern California poison control center. The presentation will discuss the use of this method in these cases.

Discussion. This method had been validated for 14 synthetic opioids and is designed to detect additional emerging synthetic opioids using a suspect analysis method with a curated list of potential synthetic opioids and metabolites.
136 Designer benzodiazepines pharmacological effects: how to find the information?

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¹University hospital of Limoges, Limoges, France, ²Faculty of Pharmacy of Limoges, Limoges, France

Introduction. Designer benzodiazepines (DBZD) have become a rapidly growing class of drugs of abuse. However, their specific pharmacological action and their potentially toxicity have not been studied yet. Web specialized forums are regularly fed with ab/users trip-reports (TR) offering a mine of information for the health professionals and users.

Aims. To analyse in detail and by an approved method the Web fora contents related to the most abused DBZD.

Methods. Key words such as: trip-report, legal highs, research chemicals, designer drugs, NPS, designer benzodiazepines, drug forums... were searched on the surface Web. Seven specialized websites were selected for this study. For each DBZD having a sufficient number of TR, data were analysed by the Empirical Phenomenological Psychological (EPP)[1]. This approach involves a series of sequential steps: (i) reading the TR 3 times to familiarise and create an overview in the absence of any predetermined hypothesis; (ii) sub dividing the text into meaning units (MU); (iii) restating the MUs in objectivised terms (e.g. « I was sleepy, no physical power, no brain power... » is a text with 3 MUs corresponding to hypnotic effect, sedation and low ability to concentrate); (iv) all the MUs for each DBZD were collectivised into coherent categories; (v) qualitative and quantitative analysis were then performed. The intake contexts and modes and the reported effects in relation with the chemical structures were studied for each DBZD.

Results. A sufficient number of TR was obtained for 10 DBZD: clonazolam, deschloroetizolam, diclazepam, etizolam, flubromazepam, flubromazolam, metizolam, nifoxipam and pyrazolam (n= 193 TR). In 60% of cases, DBZD were taken alone. The doses could vary from 1 to 3 folds with effects duration < 5h. The qualitative analysis allowed ranking the DBZD by the principle effects. Diclazepam is reported to be the most anxiolytic, clonazolam the most hypnotic and the most muscles relaxant, flubromazepam and flubromazolam the most sedative and etizolam the most euphoric. Amnesia was the most reported side effect. The structural study of DBZD confirmed the majority of reported effects.

Discussion. Despite the potential weaknesses of the EPP approach, we were able to identify the most abused DBZD and their principal effects. This approach could be applied to other new psychoactive substances.

Utilization of µLC-tandem mass spectrometry for analysis of polypharmacy levels using microsampling technique

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Introduction. There is a risk factor for drug-drug interactions and toxicity for polypharmacy. Studies characterising the blood concentrations of drugs in patients with polypharmacy are limited, with even fewer determining the kinetics in these patients with overdoses.

Aims. To characterise the blood levels of drugs using LC-MS in patients with polypharmacy and investigate interactions and pharmacokinetic of drugs.

Methods. A µLCMS-MS method was developed for 45 drugs and metabolites from different therapeutic classes. We designed and applied a protocol for sample extraction using methanol from the FDA approved Mitra® 20 µL finger prick device. The extract was injected into a µLCMS-MS system. Chromatographic separation was achieved using a gradient flow of 10mM ammonium acetate, pH 2.9 and acetonitrile. The eluate was introduced to ESI-mass spectrometer and scanned using multiple reaction monitoring (MRM).

Results. The method was robust, reproducible and easy to use and was validated with acceptable ranges (<15%). These methods were applied to three patients prescribed metformin, atorvastatin and apixaban. The CV% of extraction efficacies were (8.58, 3.95 and 9.68), lower limit of quantitation (LOQ) were (25, 0.5 and 6.25 ng/mL) and blood concentrations were (310.9 to 885.7, 64.1 to 106.9 and 7.5 to 15.5 ng/mL) respectively.

Discussion. The use of MRM decreases the interference of the matrix and increases the specificity and selectivity of the method. We demonstrate that the microsampling device, Mitra® is volumetrically accurate making it suitable for therapeutic drug monitoring (TDM) for polypharmacy including a wide range of drugs with different polarities. A µLCMS-MS method has been developed and demonstrated to be effective for for TDM and also in overdose cases.
138  Acute intentional self-poisoning with pesticides: presentation of two cases and risk factors for severity

Steeve Rouillon¹,², Dr Souleiman El Balkhi³, Yse Sauvageon¹,², Jeremy Lelong¹,², Dr Bertrand Brunet¹,², Dr Patrick Mura¹,², Dr Nicolas Venisse¹,²

¹Centre d’Investigation Clinique INSERM 1402, CHU Poitiers, Poitiers, France, ²Service de toxicologie et pharmacocinétique, CHU Poitiers, Poitiers, France, ³Service de Pharmacologie et Toxicologie, CHU Limoges, Limoges, France

Introduction. Acute poisoning with pesticides is rare in developed countries, but can be severe and even lethal in 7-8% of cases. A wide variety of substances can be involved.

Aims. To present two cases of acute poisoning with pesticides following massive ingestion and a literature review in order to identify risk factors for severity in such poisonings.

Methods. - Case #1: a 81-year-old man ingested about 0.2 L of kick-off® solution (glyphosate 360 g/L, isopropylamine salt form) at H0. Although he was clinically stable, biological assessment revealed renal insufficiency, hyperleucocytosis and metabolic acidosis. His condition gradually deteriorated, and cardiovascular troubles appeared. A gastroscopy revealed a severe necrotic esophagitis (H16). Blood was collected at H29 and H41 to quantify glyphosate and its metabolite, the aminomethylphosphonic acid (AMPA) using LC-MS/MS. Due to the aggravation of respiratory troubles and anuric renal failure, the patient died at day 10, despite repeated dialysis sessions. - Case #2: a 58-year-old woman was found unconscious with a suicide letter. Neither drugs nor alcohol were found in blood. She presented cholinergic symptoms such as bradycardia and myosis. Clinical examination and biological assessment revealed hypertension and mixed acidosis. An UHPLC-HRMS toxicology screening on blood and urine samples revealed the presence of carbofuran that was quantified using LC-MS/MS. Eventually, the patient recovered and went back home on day 2.

Results. In case #1, the toxicology screening did not reveal any other compounds involved in poisoning. Quantification of glyphosate and AMPA in blood is presented in table 1. Apparent half-life of glyphosate was longer than previously reported, probably because of renal failure. Blood alcohol concentration was 1.23 g/L. In case #2, carbofuran and its metabolite were quantified in blood and urine (table 2).

Discussion. In both cases, measured concentrations were high and compatible with those found in acute poisoning following massive ingestion. Literature review shows that risk factors for severity are: type and amount of ingested substance, concentration measured on admission and patient’s age.

<table>
<thead>
<tr>
<th>Compound (mg/L)</th>
<th>Blood H29</th>
<th>Blood H41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyphosate</td>
<td>36.4</td>
<td>279.2</td>
</tr>
<tr>
<td>AMPA</td>
<td>1.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound (mg/L)</th>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbofuran</td>
<td>2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>3-OH-carbofuran</td>
<td>0.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>
139 Amodiaquine and the reactive metabolite activate inflammasomes leading to amodiaquine-induced liver injury and agranulocytosis

**Ryuji Kato**1,2, Yoshio Ijiri3, Yoshihiko Hirotani3, Kazuhiko Tanaka4, Tetsuya Hayashi1, Jack Uetrecht2

1Osaka University of Pharmaceutical Sciences, Osaka, Japan, 2Faculty of Pharmacy, University of Toronto, Toronto, Canada, 3Faculty of Pharmacy, Osaka Ohatani University, Osaka, Japan, 4Kidney Center, Shirasagi Hospital, Osaka, Japan

Background: There is increasing evidence that most idiosyncratic drug-induced liver injury (IDILI) is immune mediated, and in most cases reactive metabolites appear to be responsible for induction of this immune response. Reactive metabolites can cause the release of damage-associated molecular patterns (DAMPs), and inflammasomes can be activated by DAMPs. This may be a common mechanism by which DAMPs initiate an immune response. In this study, inflammasome activation by reactive metabolite of amodiaquine, which is no longer used for malaria prophylaxis because it is associated with both severe liver injury and agranulocytosis, was evaluated using 3D culture of human hepatocarcinoma functional liver cell-4 (FLC-4) cells and differentiated human THP-1 macrophages.

Methods: The FLC-4 cells were cultured with amodiaquine for 7 days, and then the supernatant was added to differentiated THP-1 cells and incubated for 24 hr. The control was incubation without amodiaquine. IL-1β concentration in the THP-1 culture medium was measured using an ELISA kit. Caspase-1 activity was also measured using the Caspase-Glo® 1 Inflammasome Assay. FLC-4 and THP-1 cells were lysed and amodiaquine covalent binding was determined by western blot using rabbit anti-amodiaquine primary antibody.

Results: The supernatant from the incubation of amodiaquine with FLC-4 cells at therapeutic concentrations led to the activation of inflammasomes in THP-1 cells with release of IL-1β. The pattern of caspase-1 activity was similar to that of IL-1β. However, amodiaquine is bioactivated by THP-1 cells leading to covalent binding to the cells and it directly activated THP-1 cells; therefore, we cannot tell whether it was DAMPs or amodiaquine in the FLC-4 cell supernatant that led to inflammasome activation in THP-1 cells. Amodiaquine requires cytochromes P450 for reactive metabolite formation and is also oxidized to a reactive iminoquinone by myeloperoxidase, which covalently binds to bone marrow cells, and this is presumably why it can also cause agranulocytosis.

Conclusions: Our results are consistent with the hypothesis that the mechanism of amodiaquine induced liver injury and agranulocytosis involves oxidation to a reactive metabolite by hepatocytes and immune cells resulting in the release of DAMPs, and these DAMPs activate inflammasomes leading to an immune response.
140 Impact of therapeutic drug monitoring of antiretroviral drugs in routine clinical management of patients infected with human immundeficiency virus

Dr Dario Cattaneo\(^1\)
\(^1\)Luigi Sacco University Hospital, Milano, Italy

The management of pharmacological therapy in HIV-positive patients is a complex procedure: there is in fact a latency between the onset of therapy and the onset of therapeutic or toxic responses, an incomplete knowledge of the pharmacokinetics of antiretroviral drugs in the atypical patients, and a high risk of drug-to-drug interactions. These conditions, which may limit the optimal response of HIV-infected patients to therapies, both in terms of effectiveness and toxicity, may be eventually handled in clinical practice by therapeutic drug monitoring (TDM).

In our center, TDM of antiretroviral agents has been carried for the optimization of drug dosing in HIV-infected patients for nearly 10 years. As first finding, we observed that a significant proportion of patients treated with conventional drug dose had trough concentrations exceeding the upper therapeutic threshold. These patients may benefit from TDM-driven adjustments in antiretrovirals doses. A second main role of TDM is in the field of drug-to-drug interactions (DDIs). Although practically unavoidable in HIV care, many DDIs can be better managed, reducing the risks to patients and the burden on resources. A third clinical application of TDM relates to antiretroviral safety/tolerability. In fact, significant associations have been reported between the plasma concentrations of some drugs (such as tenofovir, efavirenz, atazanavir and lopinavir) and their toxicity (renal, neurological and metabolic toxicity, respectively), while therapeutic windows for other antiretroviral drugs have not be firmly established yet.

Finally, we have also provided evidence that inclusion of TDM as part of routine clinical optimization of drug dosing in HIV-infected patients is associated with higher adherence to therapy, reduced length of hospitalization stay, and reduced cost of illness.
141  TDM for valganciclovir in patients with poor renal function after transplantation

Prof Teun van Gelder  
Erasmus MC, Rotterdam, The Netherlands

Valganciclovir, the pro-drug of ganciclovir, is the first choice drug in the prophylaxis of cytomegalovirus (CMV) infections after kidney transplantation. Valganciclovir prophylaxis for 6 months is now used in many centers worldwide. Ganciclovir is not metabolized and is eliminated through both glomerular filtration and tubular secretion. As in patients with reduced renal function ganciclovir may accumulate, dose is adjusted based on calculated creatinine clearance. Patients with a creatinine clearance below 25 mL/min typically receive as little as 450 mg valganciclovir twice weekly. In renal transplant patients with delayed graft function (DGF) this may result in prolonged periods of such (very) low dose prophylactic treatment. In some of these patients the reduced dose valganciclovir results in sufficiently high ganciclovir concentrations, leading to an increased risk of failed prophylactic treatment.

A recently published population pharmacokinetic study showed that the probability of reaching the ganciclovir target AUC was insufficient when using the recommended dosing regimens for prophylaxis in patients with impaired renal function. Higher doses of valganciclovir would be needed to achieve adequate oral prophylaxis for CMV infection in kidney transplant recipients. Another possibility would be to monitor ganciclovir concentrations, and adjust the valganciclovir dose accordingly. The advantage of a TDM based approach is that also over-exposure can be prevented. It is not a dosing strategy we have used in our center so far, and we suspect only very few centers routinely adjust doses based on drug levels. However, the analysis on our large database shows an increased failure rate of prophylaxis in patients with DGF, and suggests that TDM may be of added value. Prospective trials are needed to study the impact of novel dosing strategies on drug exposure and clinical outcome.
Hepatitis E virus (HEV) is the most common cause of viral hepatitis, fortunately generally self-resolving. However, it can cause chronic hepatitis and cirrhosis in immunocompromised patients. Reduction of immunosuppression, when possible is the first therapeutic option. Otherwise, ribavirin monotherapy induces a sustained virological response (SVR) in 78–85% of patients, but also anaemia in many. It is recommended that ribavirin therapy be continued until HEV is cleared from plasma and faeces [1], but dose adjustment to compensate for its large pharmacokinetic variability may also be a means to improve its benefit-risk balance and shorten treatment duration.

Ribavirin is used to treat hepatitis C in combination with interferon gamma (although this bitherapy has been replaced by direct antiviral agents in many countries). Two treatment personalization tools are proposed, IL28B gene genotyping for interferon, and TDM for ribavirin. Some groups propose ribavirin CO at weeks 4, 8, 12 or 24 of treatment as exposure index for dose adjustment. With $T_{1/2} \approx 200\text{h}$, ribavirin only reaches steady-state after approx. 6 weeks, while virological response and anaemia, develop earlier. A retrospective study of 59 patients with HEV found no difference in ribavirin concentration at week 1 or month 2 between responders and non-responders [2]. Also, RBV was reported to select resistant HEV mutants. Therefore, early RBV dose adjustment would be preferable.

A PK-PD study in genotype 1 hepatitis C patients showed that those with SVR had a significantly higher $\text{AUC}_{0-4\text{h}}$ and $\text{AUC}_{0-12\text{h}}$ after the first dose [3]. A randomized FD vs. CC trial in genotype 1 HCV in which patients of the CC group were dose-adjusted if RBV $\text{AUC}_{0-4\text{h}}$ after the first dose was $< 1755 \text{µg·h·L}^{-1}$, showed that SVR (but also grade 1 anaemia) was significantly more frequent in the CC group, especially in patients with $\text{AUC}_{0-4\text{h}} < 1755 \text{µg·h·L}^{-1}$ [4].

Whether this TDM strategy is applicable to HEV is not known. More largely, optimal dosing, duration of treatment and the modalities of therapeutic drug monitoring of ribavirin are still to be clarified.

1- de Winter et al. (2018) Pharmacol Res 130:308-315
Educating future clinical toxicologists

Dr Eric Franssen¹
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In this presentation we will discuss the current experience in the multidisciplinary training of hospital pharmacists in Clinical Toxicology in Amsterdam, the Netherlands. The 4-year post graduate training in hospital pharmacy consists of a 1-year specialization. The specialization includes a specific clinical area (ED, ICU), research and/or back-office topics (e.g. clinical toxicology laboratory). We report our experience of a multidisciplinary specialization in “Acute Care and Toxicology”. The course is patient-oriented and focuses on “the patient journey of intoxicated patients” in the hospital. Residents learn skills in different clinical settings, such as the Emergency Department, the Intensive Care Unit, the Hospital Pharmacy and the TDM and Toxicology Laboratory of the Hospital Pharmacy.

The learning objectives include various clinical, pharmacology, laboratory and toxicology skills that will be discussed in this presentation: e.g the ability to give advice on diagnosis and treatment of intoxicated patients based on current toxicology guidelines, the availability and application of antidotes, toxicology assays in the laboratory, the potential and limitations of elimination enhancing techniques and to develop local and national toxicology guidelines. Furthermore, the residents are encouraged to develop themselves in the general skills of a medical expert, according to CanMEDS. Feedback and testing is done and coordinated by a multidisciplinary team of mentors with different clinical and laboratory backgrounds.
144 Importance of multidisciplinary set-up to enable consistent care and optimised TDM practice through broad education

Jennifer Martin1, Assoc Prof Ross Norris1, Assoc Prof Jennifer Schneider1, Dr Catherine Lucas1, Ms Mirjana Radovanovic1, M Williams1, Dr Peter Galettis1
1Discipline of Clinical Pharmacology, University of Newcastle, Newcastle, Australia

Therapeutic drug monitoring (TDM) is a key part of optimising patient care, and is often requested by clinicians across a number of drugs and clinical areas. Nevertheless clinicians are often disappointed that the concentrations recorded have little in the way of interpretation either generally or for their patient, and tend to ‘make do’ using knowledge gleaned from the scientist, pharmacist and clinical pharmacologist. However, this system is inconsistent and tends to fall over when people become overwhelmed with other clinical roles. Key to successful, functioning TDM services appears to be an operational set up in a multidisciplinary team environment, with ongoing multidisciplinary research and education. This is because measurement, interpretation and implementation of drug concentration data can only be easily obtained by education and research collaboration between scientists, clinicians and pharmacists; excellent understanding of the skills and limitations of all areas and frequent communication and shared information is necessary to ensure that best practice in TDM is achieved. Although a few hospitals in some jurisdictions do provide aspects of a TDM service for some drugs only, the true potential of a TDM service that is funded as a flexible and adaptive yet permanent aspect of patient care is rarely seen. However as better shared clinical information, multidisciplinary education tools and new information technology develops, point of care testing improves and robust and clinically relevant cost-effectiveness models develop, TDM services would have a significant impact. We discuss some of the possibilities of improved educational aspects to facilitate multidisciplinary team development and maintenance, despite irregular and inconsistent health system funding and siloed department set ups.
145  Education for vancomycin - what works?

Ms Bethany Van Dort¹,², Dr Jane Carland¹,³, Associate Professor Melissa Baysari³,⁴, Dr Sophie Stocker¹,³, Professor Richard Day¹,²,³
¹Department of Clinical Pharmacology and Toxicology, St Vincent’s Hospital, Sydney, Darlinghurst, Australia, ²School of Medical Sciences, UNSW, Sydney, Australia, ³St Vincent’s Clinical School, UNSW, Sydney, Australia, ⁴Australian Institute of Health Innovation, Macquarie University, Sydney, Australia

Introduction. Dosing and monitoring guidelines are readily available for vancomycin. However, hospital audits consistently show suboptimal vancomycin therapy (Davis et al., 2013). Few studies have examined the types, strengths and weaknesses of educational resources used to support vancomycin prescribing.

Aims. To explore the opinions and experiences of Australian educators on the methods used to educate health professionals about vancomycin in order to identify the most effective approach to education.

Methods. Health professionals involved in delivering antibiotic education to clinical staff were approached via email and invited to participate in a semi-structured interview. Questions focused on the use of educational resources and methods for vancomycin dosing and monitoring practices. Interviews were transcribed verbatim and analysed independently by two researchers for emerging themes.

Results. Pharmacists (n=18) and Infectious Disease physicians (n=6) were interviewed. The most frequent mode of vancomycin education reported was an annual lecture during junior staff orientation. This was in contrast to what educators viewed to be ideal education (one-on-one, case-based, tailored learning). Educators reported that different methods were likely to be effective for different healthcare professionals (e.g. doctors vs. nurses). Access to online resources (such as vancomycin.com.au and Qstream) and dosing calculators were also seen to enhance vancomycin education. Time constraints were a major limitation to clinical education, with development of readily accessible and efficient educational strategies a priority.

Discussion. Effective education was reported to be multimodal, including strategies such as academic detailing and interactive, problem based learning using case studies.

146 Patient Centric Blood Sampling – What is it and where might it be taking us?

Dr Neil Spooner¹
¹Spoonner Bioanalytical Solutions, Hertford, United Kingdom

Patient centric microsampling is a rapidly developing collection of technologies that have the potential to simplify the collection, processing and analysis of blood, plasma and serum samples for the quantitative determination of drugs, metabolites, biomarkers and clinical pathology measurements. Several technologies are currently available, or are on the visible horizon, that have the potential to revolutionise the way we generate high quality data through empowering the patient and consumer. Further, they will enable us to collect samples in previously intractable situations and for hitherto unforeseen applications.

This presentation will outline what patient centric sampling is and what technologies are currently available. It will highlight the benefits and challenges of implementing these technologies and will take a look into the future, speculating around where patient centric sampling might be taking bioanalytical science.
147  Dried blood spot; when will it become standard of care?

Dr Marieke G.G. Sturkenboom
University Medical Center Groningen, The Netherlands

Dried blood spot (DBS) sampling is an attractive patient friendly alternative for venous sampling. Advantages such minimal invasive sampling, sample stability and small blood volume required for analysis have been recognized for a number of years. Methods for the quantitative analysis of many drugs in DBS have been published. However, the available guidelines on validation in bioanalysis do not provide guidance on specific DBS issues, such as haematocrit and volume effects. These hurdles have been recognized and are often manageable nowadays. Clinical validation is needed to provide evidence that capillary DBS is comparable to venous sampling. Once the method has been validated both analytically and clinically, training of the person who samples needs attention, either clinical staff or the patient at home. Lastly, an interlaboratory (external) QC (or proficiency testing) programme is an essential component of quality assurance that provides evidence of laboratory competence for clinicians and researchers. Such a programme is lacking for DBS sampling at the moment. DBS may become standard of care, the moment all these conditions are met.
The application of microsampling to clinical pharmacokinetic studies in critically ill patients

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Introduction. Performing clinical studies can be challenging in critically ill patients, particularly critically ill neonates, infants and children, due to burden of blood sampling. Innovation in the quantitative analysis of samples, led by improved sensitivity of methods such as LC-MS/MS, has reduced blood sample volumes to less than 50 μL or ‘microsamples’. samples can potentially be acquired from a finger or heel prick.

Aims. The aim of the study is to assess the suitability of the implementation of microsampling for clinical pharmacokinetic studies in two stages: an ex-vivo bioanalytical validation and clinical bridging study, in accordance with international regulatory agency guidelines.

Methods. Whole blood and plasma from a critically-ill patient receiving vancomycin was collected as a traditional liquid sample from an arteriovenous catheter and from a finger-prick as both a capillary liquid plasma sample and volumetric absorptive microsample (VAMS). Samples of plasma and whole blood were extracted using zinc sulphate and acetonitrile and analysed for vancomycin concentrations using a Shimadzu LC-MSMS 8030+ [1].

Results. Bioanalytical validation testing met acceptance criteria for linearity, accuracy and precision. The whole blood on VAMS method was suitable across a range of patient haematocrits (19 to 59%). Stability, selectivity and matrix effects testing were acceptable. Figure 1 shows a Bland-Altman plot for the comparison between peripheral and arterial plasma for vancomycin concentrations for critically ill patients. The results of peripheral and arterial whole blood on VAMS met acceptance criteria as an incurred sample reanalysis test.

Discussion. The bioanalytical validation found our methods were suitable for measuring vancomycin in microsamples of liquid plasma and in whole blood using VAMS. The clinical bridging study found whole blood samples collected as VAMS from an arterial line were a valid alternative to peripheral VAMS sampling.

200 Translational TDM – integrating evidence into practice

Prof Jennifer Martin, The University of Newcastle, Australia

Therapeutic Drug Monitoring (TDM) has traditionally been strong in the areas of infectious diseases, cardiology and immuno-suppressant medicine. However over the years, funding for TDM services has been stripped away, leaving the pathology testing predominantly as a cost-recovery and/or privatised service, and clinicians having little support to individualise dose. Gone are the systems that linked clinicians with pathologists, and funded pharmacists, clinical pharmacologists and assay development and quality control of new and old TDM tests in the laboratory. In this era where many new and vastly expensive immunotherapies including cancer therapies are being developed, and old drugs are being restested and repurposed (e.g. cannabinoids as medicines), where drug development and registration has been relatively rapid and incomplete, with resultant dosing being imprecise and non-individualised, a resurgence of not just TDM but TDM systems are urgently needed. Opportunities for Governments, health providers, clinicians and researchers from science, clinical and health services abound but good leadership, strategic partnerships, education and collaboration are pivotal. This session discusses methodologies and opportunities that successfully have taken research into practice.
201 Setting the scene – Australia and the world – current regulation status, agriculture regulations and drug development

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Australian State, Territory and Federal legislation has liberalised access to cannabis plant and extracts to treat specific medical conditions. This has followed many other countries including Israel, Canada, some US states and Netherlands. However, Australia has taken a slightly different route to other countries in that it is pursuing cannabis as a regulated medical therapeutic good, under the regulations of the Therapeutic Goods Agency. This means that standard pharmacological grade product, preclinical and clinical testing will be required to enable registration of medical cannabinoid products. This certification will then enable all doctors including General Practitioners to be able to prescribe. However many growers do not have expertise in the good manufacturing or clinical practice areas, enabling opportunities in the this area of appropriately registered therapeutic goods to be pursued by drug development expertise and clinical experts.

This presentation will discuss the international situation in terms of access and regulation, and some of the challenges this is leading to in terms of standard drug development to enable appropriate, known and consistent drug dosing. As therapeutic drug monitoring (TDM) is helpful to appropriately dose cannabis, the literature supporting this and current guidelines will be referenced.

The presentation will set the scene for the other pharmacology presentations in this Symposium and pose the difficult questions that we with drug and therapeutics training and roles will need to grapple with as this non standard drug development program rolls out.
202 Did medical cannabis programs in some US states pave the way for the legalisation of recreational cannabis use?

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In 2012 citizens in Washington State and Colorado voted to legalise cannabis use by adults. Uruguay decided to legalise cannabis in 2013, Oregon and Alaska did so in 2014 and California, Maine, Massachusetts and Nevada in 2016. Canada will do so in October 2018. In this paper I assess the extent to which these radical changes in cannabis policy were facilitated by citizen-initiated referenda that legalised medical uses of cannabis, initially in California in 1996 and later in 29 other states. I suggest that reformers in some states used medical cannabis laws to introduce a de facto legal market for recreational cannabis. They did so by broadening what counted as medical use and by establishing retail “cannabis dispensaries” that flourished after the Obama administration announced that it would not enforce Federal cannabis prohibition in these states.
203 Issues around taking a plant into clinical practice

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Plants have been used as medicines throughout history. In the last century many medicines have been developed from plant materials. Examples include digoxin, morphine and anticancer agents such as the vinca alkaloids and the taxanes. These medications all underwent standard drug development from anecdotal use in the herbal community, to preclinical testing to Phase I to Phase IV clinical studies, a process that takes many years to produce evidence for safety, dose and efficacy. Recently there has been increasing interest in the use of cannabis for a wide range of medicinal purposes and it is becoming more available by governments due to public pressure, without pre-clinical or clinical studies. However the term medicinal cannabis refers to a number of different products, including Cannabis Flos, Cannabis Oils and THC or CBD extracts from plants. This presentation will discuss several issues around trying to use a plant such as cannabis in clinical practice. Some of the issues that will be discussed in this presentation include; regulation, product selection, quality of product, content of the product, dose selection, product availability and clinician willingness to prescribe.
204 Cannabis contaminants: sources, distribution, human toxicity and pharmacologic effects

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Agricultural grade Cannabis is inherently predisposed to harbouring a variety of biotic and abiotic contaminants, however in many jurisdictions this is the product used for therapeutic purposes. An understanding of these contaminants and subsequent altered cannabinoid profile and effects on pharmacokinetic disposition is required in order to ensure patient safety. We thus aimed to undertake a systematic review to critically appraise the evidence base investigating cannabis contaminants, their human health and pharmacological effects and identify any pertinent gaps in current knowledge.

All indexed biological and biomedical databases and the Cochrane library were systematically searched from inception to December 2017. Filtered results were assessed for eligibility by two independent reviewers. Selected articles were aggregated into a qualitative narrative addressing four domains concerning cannabis contaminants: sources and distribution, human toxicity, the effect of different routes of administration on contaminant bioavailability and potential interactions with phytocannabinoid pharmacokinetic and dynamic profiles.

Microbes, heavy metals and pesticides were commonly reported contaminants of cannabis. Infection, carcinogenicity, reproductive and development effects comprise their known human toxicity with a possible additional contribution from toxins in planta. However, the deficiency of aggregate data prevented adverse event quantification. We described how the various administration routes and dosing formulations of cannabis impact the subsequent transformation and bioavailability of contaminants and carcinogens. Although of key interest to clinicians, this Review could not determine likely effects on important pharmacokinetic and pharmacodynamics interactions between phytocannabinoids and contaminants.

In conclusion, a significant paucity of data and primary research obscures a comprehensive understanding of cannabis contaminants and their human effects. Disseminated legalisation of medicinal cannabis and increasing momentum in its international trade necessitates further investigation into the sources, prevalence and human toxicity of cannabis contaminants, a prominent concern that remains to be addressed.
205 Medicine dose-response in children and the use of algorithms in dose individualisation

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1
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Dose selection in children is challenging as many drugs are developed in adults then scaled down for children. The scaling aspect is complex as children undergo non-linear structural and metabolic maturation before reaching adulthood.

Dose requirements vary between individuals due to variability in pharmacokinetic (PK) and pharmacodynamic (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 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.\[3\]

This talk will cover drug dosing methods given the variability in drug-response between patients. Dosing tools, algorithms, and integration of tools to medical systems will be introduced.

206 Application of decision support tools in hospitals

Dr Stefanie Hennig

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Therapeutic drug monitoring practice, targets and acceptable ranges for a particular medicine vary greatly across hospitals, countries (1). Similarly, application of tools used for decision support vary greatly. Several tools currently used in clinical practice will be presented, illustrating benefits and barriers of adaptation of Bayesian forecasting (BF) programs in particular. Although, BF programs as TDM decision tool have been available for over 30 years (2), we found that widespread adoption of these programs into the clinical setting has been poor, despite local and international guidelines recommending computerised monitoring. Several freeware, accessible from any internet connected computer with a web-browser, and commercial programs with 24-hour support using BF methods are available to support personalised dosing for a variety of drugs, nowadays. We could show that BF methods have the potential to improve patient care by minimising drug toxicity and maximising drug efficacy whilst saving both the hospital and the individual patient time and money by reducing the number of blood samples required and providing flexibility around sample times (3).

207 Development of dosing support tools for paediatric diseases

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In recent years, the application of advanced modelling and simulation techniques have opened new avenues for drug research in children. Because these approaches allow for the utilization of infrequently obtained samples and observations in the real life clinical situation, rather than data from a specific experimental setting, the study of drug effects in patient groups which are otherwise difficult to study, such as young children, is greatly facilitated. Moreover, this approach ensures that information is obtained which can indeed be directly applied in clinical practice and that the burden to the individual patient can be kept to a minimum.

Despite the increasing number of reports on the pharmacokinetics (PK) and pharmacodynamics (PD) of multiple drugs in children of different ages that have been generated in these years, implementation of these type of publications into paediatric clinical practice is hampered. The complexity of the statistical analysis approaches requiring specific expertise, discussions on approaches used and the large number of drugs and age groups seem complicating factors.

In the lecture, examples of clinical and PK-(PD) data analysis studies are presented in which on the basis of advanced population modelling doses for specific drugs can be adjusted. Prerequisites for implementation in pediatric clinical practice such as internal and external validation requirements of these models are discussed together with prospective clinical trial designs that can be used for implementation and to facilitate clinical acceptance. In addition, approaches are discussed on how to generate biological system specific information from specific drug studies that can be used for extrapolation to other drugs taking advantage from both into account empirical population modelling and physiologically-based pharmacokinetic modelling (PBPK). Based on the information that is available today, it seems that it is now time for pharmacometriicians and clinicians to work together to use and apply the available information into ready-to-use guidelines and formularies that are regularly updated with the most recent evidence.
Evaluation and integration dosing tools in special populations

Assoc Prof Catherine Sherwin
University of Utah School of Medicine, USA

Therapeutic Drug Monitoring (TDM) and the application of decision support tools have become a mainstay of management for many drugs including antimicrobials and immunosuppressants to establish initial doses and PK/PD relationships in adults. However, there is a need to understand the impact of TDM dosing tools in paediatrics including how they are evaluated and integrated into practice. The utility of dosing support tools remains relatively understudied and there are subsequently gaps resulting in difficulty in establishing initial doses and PK/PD and pharmacogenetic relationships. There remain a number of issues and challenges associated with paediatric pharmacology/toxicology, and how TDM dosing tools can be applied to this population. There is an urgent need to improve relevant drug research in paediatrics and to enhance the integration between clinical and research areas. There are challenges faced when using TDM support tools to determine clinical endpoints and to make clinical decisions in special populations specifically some disease states and in different paediatric age groups. The application and utility of decision support tools have been adapted from adult guidelines with little consideration to adapt these specially to paediatric patients. There is a need for integration between clinical and research outcomes as well as the Physician-Pharmacist-Patient triad interactions to improve health outcomes when integrating these dosing tools into clinical practice. Applying TDM dosing tools in special populations allows for more accurate dosing, better patient care and better outcomes for selected drugs.
Can we do better? Optimising beta-lactam therapy in *S. aureus* bacteraemia

**Prof Deborah Marriott**

1St Vincent’s Hospital, Sydney, Australia

A significant percentage of blood stream infections are caused by *Staphylococcus aureus*, a pathogen that is feared because of the severity of the infection and mortality rates up to 40%. *Staphylococcus aureus* bacteraemia (SAB) may be community or hospital acquired with the incidence of nosocomial SAB increasing in many centres. Mortality varies significantly with a number of factors such as patient age, clinical manifestations, accompanying illnesses, treatment choice and methicillin resistant *S. aureus* (MRSA) as the causative organism influencing the outcome. In Australia methicillin sensitive *Staphylococcus aureus* (MSSA) accounts for around 80% of cases of SAB.

Standard therapy of MSSA bacteraemia recommended in therapeutic guidelines is treatment with β-lactam antibiotics which include anti-staphylococcal penicillins such as nafcillin, oxacillin or flucloxacillin and the first generation cephalosporins cefazolin or cephalothin. Despite adherence to treatment guidelines mortality remains unacceptably high and few randomized studies of the optimal treatment of MSSA have been undertaken. Management of SAB is complicated by the fact that many patients are critically ill and exhibit clinical features of sepsis with the associated physiological changes including altered volume of distribution and protein binding which have a significant impact on the antibiotic pharmacokinetics. This is particularly important for highly protein bound agents such as flucloxacillin. Like other β-lactam antibiotics the important bacterial kill characteristic is time above the MIC of the organism. Standard bolus doses of 8-12 gm/day of flucloxacillin may not provide adequate exposure in septic patients resulting in treatment failure. Higher antibiotic doses and/or continuous infusion may improve the outcome although good trial data is lacking. Therapeutic drug monitoring remains in its infancy but anecdotal data and single centre studies suggest it may have an important role in improving the outcome of SAB by optimising drug dosing. Randomized studies are urgently required.
Oxazolidinones are synthetic antibiotics with bacteriostatic activity against Gram-positive pathogens. Linezolid, the first marketed oxazolidinone, has shown also activity against Mycobacterium tuberculosis, including multidrug-resistant and extensively drug-resistant strains. Recently, a second agent of this class (tedizolid) has been approved for the treatment of acute bacterial skin and skin structure infections.

According to available literature, the pharmacokinetics of linezolid are significantly affected by renal function, age, body weight and co-medications. Linezolid-related adverse events are more frequent in elderly, in patients with impaired renal function and in those requiring longer linezolid treatment. The incidence of these adverse events can be reduced by TDM-guided linezolid dose adjustments.

Less conclusive evidence is available on the potential role of TDM as a tool to improve LZD efficacy, mainly because the plasma target concentrations necessary to ensure the highest antibiotic activity of LZD are not well defined.

According to the EUCAST rational document based on PK/PD data and Monte Carlo simulations, the defined linezolid susceptible breakpoints are <2 mg/L for streptococci and <4 mg/L for both staphylococci and enterococci. However, it must be remembered that the efficacy of antimicrobials must be correlated to the relationship of pharmacokinetics to pharmacodynamics through the assessment of the minimum inhibitory concentration (MIC) of the infecting organism. For linezolid, an optimal antibacterial effect is achieved when plasma drug concentrations are above the MIC (T>MIC) for at least 85% of length of treatment (for twice daily administration) or when the ratio between AUC and the MIC (AUC/MIC) is >120.

In conclusion, consistent evidence is now available showing that TDM and guided individual dose optimization of linezolid is justified and feasible in clinical practice to improve tolerability and possibly response to therapy. The role of individualized drug dosing regimens for tedizolid remains to be proven.
211 Vancomycin: Innovative approaches to getting it right

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In this presentation we will present a prospective cohort study comparing safety and efficacy of trough-guided vancomycin TDM, vs. Bayesian assisted, AUC-guided TDM with and without optimal sampling.
212 Alternative treatment options for *S. aureus* infection

**Dr Natasha Holmes**

1Austin Health, Melbourne, Australia

This symposium presentation will discuss the merits of therapeutic drug monitoring and implications for clinical use of other antibiotics that are used to treat patients with serious *S. aureus* infection including bacteraemia. These include rifampicin, fusidic acid, co-trimoxazole, and clindamycin.
Impact of recipient and donor pharmacogenetics on acute rejection in kidney transplantation

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Introduction. Therapeutic drug monitoring (TDM) of the immunosuppressant tacrolimus (TAC) is necessary to minimise acute rejection following kidney transplantation. Although pharmacogenetics of its major metabolising enzymes (CYP3A4/5), P-glycoprotein efflux transporter (ABCB1), their expression regulator Pregnane X Receptor (NR1I2), and cytochrome P450 reductase (POR), have been widely studied for their effects on TAC concentrations[1], few studies have addressed their effects on acute rejection[2].

Aims. To investigate the impact of CYP3A4/5, ABCB1, NR1I2 and POR genetic polymorphisms on acute rejection in kidney transplant patients receiving TAC in the first 3 months post-transplant.

Methods. A total of 165 kidney transplant recipients and 129 donors were included. TDM was applied targeting trough blood TAC concentrations (C₀) between 8 to 15 ng/ml in the first 3 months post-transplant. Biopsy confirmed acute rejection, human leukocyte antigen (HLA) mismatch, panel reactive antibody (PRA) peak, induction therapy and number of transplants data were collected from case notes. Genotyping was performed for: CYP3A5*3; CYP3A4*22; ABCB1 61A>G, 1199G>A, 1236C>T, 2677G>T, 3435C>T; POR*28; and NR1I2 8055C>T, -25385C>T, 63396C>T. Recipient and donor genotypes and predicted ABCB1 haplotypes (PHASE 2.1) were tested separately using a generalised linear model (function:: package, glm:: lme4[3]) in R (version 3.4.3), and adjusted for HLA mismatch (0-2/3-4/5-6), PRA peak (≤10/>10), induction therapy (Y/N) and number of transplants (1/≥2).

Results. Forty-seven patients (28%) developed acute rejection with 64% occurring when C₀ was > 8 ng/ml at least 2 days before and on the day of biopsy. No recipient or donor genotypes/haplotypes had a significant effect on the occurrence of acute rejection (P > 0.01), after adjusting for multiple testing (False discovery rate (α=0.05) adjusted P = 0.004).

Discussion. Tacrolimus metabolism and transport-related genetic factors did not significantly affect acute rejection in the first 3 months post-kidney transplant. Most patients benefited from TDM of TAC C₀, however, it cannot prevent all acute rejection episodes. Therefore, other factors (unbound or lymphocyte TAC concentrations) may be worthwhile exploring in the future to better predict acute rejection.

Antipsychotic-Induced Weight Gain is associated with FTO gene variants rs9939609 and rs7185735

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Introduction: Weight gain is a frequent and therapy limiting side effect of second-generation antipsychotic (SGA) therapy, which has been associated with various gene variants. Identifying patients at risk prior to therapy may significantly improve therapy.

Methods: We, therefore, examined the influence of two single nucleotide polymorphisms in the fat mass and obesity-associated (FTO) gene (rs7185735, rs9939609) and their possible association with SGA therapy in a naturalistic study. Results: After 4 weeks of treatment, no significant association of polymorphisms with weight change was observed (n=350 inpatients; p > 0.05). However, a subpopulation of patients which had received clozapine or olanzapine (n=174), both known for their high propensity for inducing weight gain, showed a higher weight gain for rs7185735 G-allele carriers in comparison to homozygous A-allele carriers (2.11 ± 3.2 kg vs. 0.92 ± 3.6 kg; p=0.042). Restricting analysis to a subpopulation, excluding patients that had received additional potentially weight inducing comedication (n=178), also resulted in significant findings. G-allele carriers of rs7185735 gained 3.4 times more weight (1.69 kg ± 3.1 kg; p=0.019) than AA genotypes (0.49 kg ± 3.1 kg). A-allele carriers of rs9939609 gained 3.1 times more weight (1.65 kg ± 3.1 kg, p = 0.029) than TT genotypes (0.54 kg ± 3.2 kg). In previous studies in this population MC4R rs17782313 had been identified as a potential risk factor for weight gain [1,2]. We, therefore, investigated a potential additive effect of the MC4R SNP with the FTO rs7185735 and could show that weight gain was increasing with the combined number of risk alleles (p<0.0134). This result remained significant after adjustment for sex, age, baseline weight and therapy outcome (ANCOVA p<0.009).

Discussion: The findings of this study indicate a potential association of both closely related polymorphisms in the FTO gene not only with obesity in general, but also with SGA induced weight gain. This weight gain seems to be additional to other previously identified associations in the same study population [1,2]. Weight gains of only a few kilograms seem to lack clinical impact at first glance, however, initial weight gain is a good predictor of far more impressive changes of body weight long term [3]. Confirmation in independent samples is mandatory, before the results of this study may influence future clinical decision making. [1] Int J Neuropsychopharmacol. 2013 Oct;16(9):2103-9. [2] J Clin Psychopharmacol. 2013 Feb;33(1):74-9. [3] J Clin Psychiatry. 2015 Nov;76(11):e1417-23.
**Effect of ABCB1 genetic polymorphisms on the transport of rivaroxaban in HEK293 recombinant cell lines**

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**Introduction.** Direct oral anticoagulants (DOAC) are substrates for the ABCB1 transporter. ABCB1 polymorphisms have been previously reported to influence the pharmacokinetics of several drugs such as immunosuppressants and tyrosine kinase inhibitors. Recently, in vivo studies have suggested that genetic variants might contribute to the inter-individual variability in DOAC plasma concentrations.

**Aims.** To evaluate in vitro the effect of the most common coding ABCB1 single nucleotide polymorphisms (SNP), 1236C>T-2677G>T-3435C>T, and the coding ABCB1 1199G>A SNP on the transport activity towards rivaroxaban.

**Methods.** HEK293 cells were transfected to overexpress the ABCB1 wild-type (1236C-2677G-3435C, 1199G) or variant proteins (1236C-2677G-3435T, 1236T-2677T-3435T or 1199A). Cell surface ABCB1 expression was characterized by flow cytometry. Recombinant cells were incubated for 120 min with 5 different concentrations of rivaroxaban (from 50 ng/ml to 1000 ng/ml). The intracellular accumulation of rivaroxaban was quantified by LC-MS/MS analysis.

**Results.** The overexpression of ABCB1 decreased significantly the intracellular accumulation of rivaroxaban, when compared to control cells (Fig 1, p<0.01). This confirms the involvement of ABCB1 in the active transport of rivaroxaban. For both the ABCB1 1236C>T-2677G>T-3435C>T and 1199G>A SNPs, the transport activity towards rivaroxaban was similar between cells overexpressing the ABCB1 wild-type and variant proteins (Fig 1, p>0.05).

**Discussion.** The intracellular accumulation of rivaroxaban was influenced by the overexpression of ABCB1. The ABCB1 coding SNPs that were evaluated in the present study had no significant effect on the efflux of rivaroxaban in HEK293 cell lines. They are unlikely to contribute to the inter-individual variability in rivaroxaban plasma concentrations.
Influence of combined CYP3A4 and CYP3A5 single-nucleotide polymorphisms on tacrolimus exposure in kidney transplant recipients

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Background: Tacrolimus (Tac), an immunosuppressant used for the prevention of graft rejection in kidney transplant patients, is characterized by a high interindividual variability of its pharmacokinetics. It is metabolized specifically by the CYP3A isoenzyme: CYP3A4 and CYP3A5.

The present study investigated in Tunisian renal transplant patients, the genetic polymorphisms of CYP3A4*1B-392A>G, CYP3A4*22 15389C>T and CYP3A5*3 6986A>G, and their influence on tacrolimus pharmacokinetics during early and late post-transplant (PT) phases.

Methods: We included adult Tunisian patients having received Tac for de novo kidney grafts and undergone a therapeutic drug monitoring (TDM) of Tac by C₀ monitoring during early (1 to 90 days) and late (over 90 days) PT phases. The genomic DNA was extracted from peripheral blood mononuclear cells using a salting-out procedure. CYP3A4 and CYP3A5 genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: Seventy-eight patients were enrolled in this study. During the early PT phase, only the CYP3A5*3 and the CYP3A4*22 polymorphisms correlate significantly with Tac dose-normalized C₀ (C₀/D ratio). During the late and all PT phases, only the CYP3A4*1B polymorphism correlates significantly with Tac C₀/D ratio. The mean daily doses (mg/kg) matching therapeutic C₀, regardless of the CYP3A genotypes were 0.68 ± 0.2 and 1.09± 0.17, during early and late PT phase, respectively.

Conclusions: Our data support a critical role of the CYP3A4*1B, CYP3A4*22 and CYP3A5*3 polymorphisms on the variation of Tac exposure during the early and the late PT phase, respectively. The establishment of customized Tac doses, according to CYP3A4/CYP3A5 genotype combination and the PT time, may allow preventing graft rejection and improving the safety profile of this drug.
217 Personalized infliximab dosing in inflammatory bowel diseases: Pharmacokinetic-based therapeutic drug monitoring

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Introduction. Therapeutic-drug monitoring (tdm) using ifx trough concentrations (c\textsubscript{min}) with clinical interpretation is forming an integral part of clinical practice in inflammatory bowel disease (ibd). Our hypothesis is that tdm with a Bayesian prediction approach will improve pharmacokinetic (pk) target attainment in patients who do not initially achieve c\textsubscript{min} target.

Aims. Primary: number of patients with ibd that keep c\textsubscript{min}>3 mg/L after dose adjustment. Secondary: describe differences in pk parameters before and after model-based dosing.

Methods. Prospective study including adult patients with ibd and treated with ifx between July 2013-July 2017. C\textsubscript{min} and antibodies towards ifx (ati) were measured by using an Elisa kit. We implemented tdm in combination with computerised Bayesian forecasting methodology with Nonmem v7.3. Population pk (ppk) model used: Fansamade et al 2011. The individual predicted c\textsubscript{min} and pk parameters were estimated before and after dose optimization.

Results. A total of 103 ifx c\textsubscript{min} from 95 patients were analysed. Ati were detected in 12 samples (11.6%). Tdm-dose adjustment was performed in 56 occasions (49 patients): 31 intensifications, 14 de-escalation and 11 switching. The proportion of patients achieving the target after dose adjustment was 86.4%. Median c\textsubscript{min} before vs after intensification and de-escalation were 1.64 vs 5.13 and 12.65 vs 8.07 mg/L, respectively. Central clearance (cl) decreased 12% and 7.8% after intensification and de-escalation respectively. Cl and elimination rate values before vs after dose-optimization were: 1) intensification strategy: 5.57 vs 5.06 l/h and 0.112 vs 0.09 h\textsuperscript{-1} and 2) de-escalation strategy: 4.38 vs 4.04 l/h and 0.08 vs 0.075 h\textsuperscript{-1}, respectively. Patients that did not achieve the pk target had a cl value before vs after intensification of 5.27 vs 5.45 l/h, respectively (3.4% increase).

Discussion. Model-based dose adjustment kept ifx c\textsubscript{min}>3 mg/L in >85% of ibd patients by implementing a previously developed ppk model using sparse concentration data. While differences in cl values have been observed, dosing regimen should be redefined using upcoming new pk data. We observed decreasing cl values after optimization except in those patients not achieving the pk target. It has been described that higher target antigen expression associated to disease activity may lead to increased ifx elimination and therefore decreased exposure; this association may be responsible of cl increase observed in patients that did not achieve the pk target in this study. Testing how these adaptive dosing regimens influence drug survival rates and effectiveness needs to be performed.
IL28-B genotyping in HCV infected patients. An old marker with new perspectives

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Introduction. Therapeutic-drug monitoring (tdm) using ifx trough concentrations (cₘᵢₙ) with clinical interpretation is forming an integral part of clinical practice in inflammatory bowel disease (ibd). Our hypothesis is that tdm with a Bayesian prediction approach will improve pharmacokinetic (pk) target attainment in patients who do not initially achieve cₘᵢₙ target.

Aims. Primary: number of patients with ibd that keep cₘᵢₙ>3 mg/L after dose adjustment. Secondary: describe differences in pk parameters before and after model-based dosing.

Methods. Prospective study including adult patients with ibd and treated with ifx between July 2013-July 2017. cₘᵢₙ and antibodies towards ifx (ati) were measured by using an Elisa kit. We implemented tdm in combination with computerised Bayesian forecasting methodology with Nonmem v7.3. Population pk (ppk) model used: Fansamade et al 2011. The individual predicted cₘᵢₙ and pk parameters were estimated before and after dose optimization.

Results. A total of 103 ifx cₘᵢₙ from 95 patients were analysed. Ati were detected in 12 samples (11.6%). Tdm-dose adjustment was performed in 56 occasions (49 patients): 31 intensifications, 14 de-escalation and 11 switching. The proportion of patients achieving the target after dose adjustment was 86.4%. Median cₘᵢₙ before vs after intensification and de-escalation were 1.64 vs 5.13 and 12.65 vs 8.07 mg/L, respectively. Central clearance (cl) decreased 12% and 7.8% after intensification and de-escalation respectively. Cl and elimination rate values before vs after dose-optimization were: 1) intensification strategy: 5.57 vs 5.06 l/h and 0.112 vs 0.09 h⁻¹ and 2) de-escalation strategy: 4.38 vs 4.04 l/h and 0.08 vs 0.075 h⁻¹, respectively. Patients that did not achieve the pk target had a cl value before vs after intensification of 5.27 vs 5.45 l/h, respectively (3.4% increase).

Discussion. Model-based dose adjustment kept ifx cₘᵢₙ>3 mg/L in >85% of ibd patients by implementing a previously developed ppk model using sparse concentration data. While differences in cl values have been observed, dosing regimen should be redefined using upcoming new pk data. We observed decreasing cl values after optimization except in those patients not achieving the pk target. It has been described that higher target antigen expression associated to disease activity may lead to increased ifx elimination and therefore decreased exposure; this association may be responsible of cl increase observed in patients that did not achieve the pk target in this study. Testing how these adaptive dosing regimens influence drug survival rates and effectiveness needs to be performed.
219 Proposed strategy to refine the phenotyping approach and its implementation to predict drug clearance

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Introduction. It is well established that many drug-metabolising enzymes (DME) and transporters have high inter-individual variability. The phenotyping approach which enables quantification of DME and transporter activity in an individual and to dose accordingly is important (Hohmann et al, 2016). However, often times this is hampered by lack of adequate correlation between the probe and the drug of interest.

Aims. The aim of this study is to propose a strategy to refine the phenotyping approach and its implementation to predict drug apparent clearance (CL/F).

Methods. The simulation was run in Simcyp Simulator v.17 using healthy population library (10 in silico trials with 20 typical adult subjects each). The correlation between for a probe and drug in different scenarios was constructed.

Results. The CL/F of midazolam was strongly correlated with triazolam ($r^2 = 0.87$) and to lesser extent with nifedipine ($r^2 = 0.56$), but had a poor relationship with alprazolam and simvastatin. The CL/F of aripiprazole and risperidone, both of which are extensively metabolised by CYP3A4 and 2D6, were better predicted by the sum of midazolam and dextromethorphan CL/F. The clearance of atorvastatin and repaglinide had a strong correlation with that of pitavastatin (a SLCO1B1 probe) (Figure 1), far superior than their correlations with CYP probes.

Discussion. There are many parameters including the non-metabolic determinants that have to be considered in selecting a suitable phenotyping probe. Use of multiple probes for drugs that are predominantly metabolised by more than one CYP enzyme should be considered. In a case where hepatic uptake transporters play a significant role, the transporter probe will be more predictive of the drug clearance.

A limited sampling strategy for Bayesian estimation of intracellular everolimus exposure in renal transplant recipients

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Introduction. Therapeutic drug monitoring of everolimus is routinely performed in whole blood. However, the exposure of everolimus at the site of action (within lymphocytes) may be a better marker of therapeutic effect.

Aims. To develop pharmacokinetic population models and Bayesian Estimators based on a limited sampling strategy for estimation of everolimus exposures in both whole blood and peripheral blood mononuclear cells (PBMC) in renal transplant recipients.

Methods. Full whole blood and PBMC concentration-time profiles of everolimus were obtained from 12 stable renal transplants in two occasions. The dataset was treated as 24 individual profiles and split into a development dataset (n=20) and a validation dataset (n=4). The pharmacokinetic model was developed using non-parametric modeling (Pmetrics) and its performances and those of the derived Bayesian estimator were evaluated in the validation set.

Results. A structural two-compartment model with first-order elimination and two absorption phases described by a sum of two gamma distributions best described the data. None of the tested covariates (age, gender, albumin, hematocrit, fat-free mass and genetic variants as CYP3A5*1 and ABCB1 haplotype) were retained in the final model. A limited sampling schedule of two whole blood samples at 0 and 1.5 hours and one PBMC sample at 1.5 hours post dose provided accurate estimates of the area under the curve (AUC) in comparison with the trapezoidal reference AUC (relative bias ±SD= -3.9 ±10.6% and 4.1 ±12.3% for whole blood and PBMC concentrations, respectively).

Discussion. The developed model allows simultaneous and accurate prediction of everolimus exposure in whole blood and PBMC, and supplies a base for a feasible exploration of the relationships between intracellular exposure and therapeutic effects in prospective trials.
A Predictive Model of Ribavirin Pharmacokinetics in Lung Transplant Recipients Providing Guidance for Effective Dosing

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The guanosine analogue ribavirin (RBV) is an established treatment for respiratory viruses in lung transplant recipients. [1-5]. Goals of treatment are prevention of progression of lower respiratory tract viral infection to deadly pneumonitis as well as prevention of the bronchiolitis obliterans syndrome, linked with progressive deterioration of graft function [5-7]. Despite RBV’s common usage, pharmacokinetic data is limited and the difference in relative exposure between oral and intravenous regiments, both of which are used at transplant centres internationally, is unknown. To address this the authors developed a physiological pharmacokinetic model of RBV in the transplant population using data collected from a cohort of lung transplant recipients being treated with RBV for respiratory syncytial virus (RSV), human metapneumovirus (HMPV) or parainfluenza virus infection. Data was collected at St Vincent’s Hospital Sydney and Groningen University Medical Centre, Netherlands. The model was validated using published data from healthy volunteers [8]. Our model established that there is no difference in the pharmacokinetics of RBV in lung transplant recipients in comparison to the general population. It also support PO only regimes for a desired plasma concentration of 1.5-3.0 μg/mL as well as providing a valuable tool for predicting effective dosing in this vulnerable population.
Pharmacokinetic modeling and cardiovascular tolerance of intravenous sildenafil in newborns with congenital diaphragmatic hernia

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Introduction. Congenital diaphragmatic hernia (CDH) is a developmental defect of the diaphragm and lungs that allows the abdominal organs to herniate into the chest cavity. This defect impairs normal lung development, resulting in pulmonary hypertension (PH). CDH is associated with a reported mortality of approximately 27% in live-born patients. Sildenafil is a drug of choice when treating PH. As it is increasingly recognized that PH determines survival in patients with CDH data on the pharmacokinetics and pharmacodynamics of sildenafil are urgently needed.

Aims. To develop a pharmacokinetic model and dosing regimen of intravenous sildenafil and its metabolite and to evaluate its cardiovascular tolerance in high risk newborns with congenital diaphragmatic hernia (CDH).

Methods. An open label study was conducted in 2 referral centres for newborns with CDH in Germany and The Netherlands. Most patients received a standard loading dose of 0.4mg/kg in 3 hours, followed by a continuous infusion of 1.6mg/kg/day to target plasma sildenafil levels of 50-400ug/l. 64 samples were taken at different time points. For pharmacokinetic analysis Non Linear Mixed Modelling (NONMEM®) version 7.2 was used. Inter-individual variation (IIV) and inter-occasion variation (IOV) are tested. Demographic and laboratory parameters were evaluated as covariates. Normalized prediction distribution errors (NPDE) and Visual Predictive Check (VPC) were used as validation steps for the model. The relationship between drug concentration and blood pressure, was tested by means of simulations on different time points of blood pressure measurements.

Results. The model included a two-compartment disposition of sildenafil and a one-compartment disposition for desmethylsildenafil (DMS) with IIV on sildenafil clearance, distribution volume of sildenafil and clearance of DMS. Only postnatal age was a significant covariate resulting in increased sildenafil clearance, which was partly compensated by a higher metabolite concentration, as can be seen in Figure 1. With NPDE and VPC use the final model showed good results. In only one patient hypotension led to a temporarily stop of the sildenafil infusion. No relationship was found between blood pressure and drug concentrations, using simulations.
223 Prediction of CYP3A metabolic phenotype in patients with ziprasidone by blood concentration measurement

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Introduction. With the development of pharmacogenomics in recent years, more and more attention has been paid to the molecular genetic mechanism of pharmacokinetics among different individuals. Gene polymorphisms of drug metabolizing enzymes can affect the retention of drugs in vivo. However, the cost of gene polymorphism of drug metabolizing enzymes determination is high.

Aims. The aim of this study was to investigate the relationship of CYP3A gene polymorphism and plasma concentration of ziprasidone injection.

Methods. The serum concentration of ziprasidone was determined by two-dimensional high performance liquid chromatography (HPLC) and the distribution proportion of CYP3A gene polymorphism in hospital database was calculated. Results. 28 patients of ziprasidone blood concentration results showed that: 14 patients ziprasidone average half-life is 7.92, accounting for 53.57%; 8 patients average half-life is 5.37, accounting for 28.57%; 4 patients average half-life is 2.87, accounting for 14.29%; 1 patients half-life is 1.23, accounting for 3.57%. The CYP3A5 statistical data of 1327 patients in the center showed that the weak metabolic type accounted for 52.60%, the intermediate metabolic type accounted for 40.17%, and the fast metabolic type accounted for 7.23%.

Discussion. The metabolic characteristics of ziprasidone in 28 patients were closely related to the CYP3A5 gene polymorphism in 1327 patients. The plasma concentration could reflect the metabolic type of the patients in some extent.
Evaluation of the predictive performance of population pharmacokinetic models for probabilistic continuous-infusion dosing of meropenem and value of plasma measurements

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Introduction. Meropenem (MEM) is a valuable option in the treatment of severe nosocomial infections. To enhance its efficacy, prolonged infusion regimens -also in combination with therapeutic drug monitoring (TDM)- have been proposed. Depending on the availability of TDM, model-based dosing can be guided based on (i) patient information alone (probabilistic dosing) or (ii) also considering MEM plasma measurements, i.e. individual pharmacokinetics (PK).

Aims. The present work sought to evaluate diverse published population PK models for their ability to predict clinical data on continuously infused MEM in intensive care (ICU) patients a priori and thus to elucidate their adequacy for probabilistic dosing. Furthermore, the utility of 1 TDM sample to improve the predictive performance was assessed.

Methods. We conducted a literature review and selected 15 parametric population PK models for MEM to predict steady-state concentrations measured in adult ICU patients receiving continuous infusion and routine TDM. The first 2 samples per patient (drawn on 2 days) were analysed (n_tot=244): MEM measurements of day 2 were predicted (using NONMEM®7.3) (i) a priori solely based on patient covariates and (ii) additionally considering the MEM measurement of day 1. Model-predicted and observed concentrations were compared by standard goodness-of-fit plots as well as by statistical measures of accuracy and precision (e.g. relative bias rBias, relative root mean squaered error rRMSE).

Results. The selected models covered heterogeneous patients, dosing regimens and covariates, leading to markedly differing accuracy and precision of the MEM predictions (range rBias_mean: -62.4-38.2%, minimum absolute rBias_mean_abs: 0.96%, range rRMSE: 27.8-78.7%). The overall best model (Chung et al. 2017; rBias_mean: 3.57%, rBias_median: -1.39%, rRMSE: 34.8%) included creatinine clearance as a covariate on clearance. Predictive performance substantially decreased for covariate values beyond the range of some models, advising caution against such extrapolations. Predictive performance overall improved if future concentrations (day 2) were predicted considering a previously measured MEM sample (medianallmodels rBias_mean_abs: 23.1±4.28%; medianallmodels rRMSE: 39.1±4.0); In case of low rBias_abs<5% and rRMSE<35% for population predictions, these measures were comparable for individual predictions.

Discussion. Fifteen heterogeneous population PK models for MEM vastly differed regarding their adequacy for probabilistic continuous-infusion dosing in a critically ill population. One TDM MEM measurement already appeared to improve model predictions. Further studies are warranted to assess individual model predictions when considering >1 previously measured MEM concentrations as well as to confirm the findings based on a larger dataset.
The Cost-Effectiveness of Therapeutic Drug Monitoring (TDM) of Generic Imatinib for the Treatment of Chronic Myelogenous Leukemia (CML)

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Introduction. A recent therapeutic drug monitoring study of imatinib mesylate (IM) for the treatment of CML found that cytogenetic response at 12 months was significantly improved with IM TDM. Given that tyrosine kinase inhibitors (TKI) other than IM had previously shown more rapid molecular responses at standard doses, the improvement in IM efficacy with TDM provides new clinical information when selecting CML treatment. A recent cost-effectiveness analysis of TKI for CML found that the pending loss of IM patent exclusivity made first-line IM the most cost-effective treatment option. No studies have considered the cost-effectiveness of IM since the loss of patent exclusivity, nor has the cost-effectiveness of IM TDM been evaluated.

Aims: The study objective was to determine the cost-effectiveness of using generic IM TDM for first-line treatment of CML.

Methods. A peer-reviewed and published TKI cost-effectiveness model in CML was modified to include IM TDM. Efficacy inputs for major molecular response rates were taken from published studies: IM TDM 65%, dasatinib 52%, nilotinib 53%. The Federal Supply Schedule (FSS) and average and lowest wholesale acquisition cost (WAC) as price bases, alternative estimates were used for drug prices including generic IM. The cost of TDM for IM was added to the IM TDM comparator arm at $228 annually (6 tests at $38 each) over the 5-year time horizon. Other input costs were updated to 2016 U.S. Dollars. The model compared first-line IM TDM vs. first-line IM without TDM, first-line dasatinib or nilotinib (D/N) in terms of costs, quality-adjusted life-years (QALYs), and cost-effectiveness. Univariate and multivariate sensitivity analysis was performed on key clinical and economic parameters.

Results. The model found that IM TDM dominates IM alone with $15,452 to $36,940 in savings and 0.25 higher QALYs. Using an FSS price basis, per patient total costs for IM and IM TDM were $270,905 and $233,965, respectively. For WAC average pricing, these costs were $461,657 and $446,205, respectively, and for the lowest WAC pricing, these costs were $366,966 and $350,090, respectively. The results comparing first-line use of IM TDM to D/N found that IM TDM had slightly higher QALYs and lower costs (0.08 QALYs gained, and $117,006 to $172,420 savings per patient. For cost-effectiveness, IM TDM dominates D/N with both lower costs and higher QALYs. The model also found that for each first-line IM TDM patient responding for 5 years $114,577 to $207,564 was saved vs. patients receiving first-line D/N. Sensitivity analysis confirmed that the results are robust.

Discussion. The analysis found that IM TDM dominates IM alone and D/N under a wide range of price scenarios. The analysis suggests that IM TDM is both a clinically and economically viable first-line treatment option for CML.
Establishment of a national Therapeutic Drug Monitoring (TDM) service for the treatment of challenging childhood cancer patient populations

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Introduction. The utility of Therapeutic Drug Monitoring (TDM) represents a remarkably under-used clinical tool in oncology, particularly bearing in mind the small margins between sub-therapeutic and toxic drug exposures associated with many chemotherapeutics. Following several years of conducting clinical pharmacology TDM studies focused on individual anticancer drugs in defined patient populations, publication of key findings and subsequent changes to clinical practice have led to funding from the NIHR to establish a national TDM service in a childhood cancer setting.

Aims. To establish a network of primary treatment centres across the UK actively participating in TDM studies to support treatment individualization for some of the most challenging childhood cancer patient populations, including pre-term infants and neonates, anephric patients, those receiving high dose chemotherapy and obese patients.

Methods. A national TDM programme of work will formally begin in 2018, to generate clinical pharmacology data alongside patient characteristics, outcome and response data in defined patient populations. Funding from the NIHR is in place for an initial 3 year period to support the collection/transport of clinical samples from centres around the UK and real-time sample analysis at the Newcastle Cancer Centre Pharmacology Group (NCCPG) laboratories. The NCCPG have >75 fully validated assays according to EMA guidelines, for the quantification of a wide range of anticancer drugs.

Results. Prior to the opening of the national TDM programme, a total of 35 patients were studied in 2017 following treatment with a range of drugs including carboplatin, cisplatin, dactinomycin, vincristine, doxorubicin, cyclophosphamide and ifosfamide. Based on the data generated, changes to dosing regimens were carried out in >75% of cases, with dose modifications of up to 250% required to achieve therapeutic drug levels, highlighting the potential importance of TDM in a childhood cancer setting. Data generated for carboplatin resulted in the development of national treatment guidelines for neonates (<3 months) incorporating TDM dosing in January, 2018.

Discussion. Establishment of a formal national TDM programme of work to support dosing decisions in defined patient groups in childhood cancer is a much needed service. Based on the numbers of patients currently undergoing real-time TDM as clinical requests, we anticipate that between 50-100 patients per annum will benefit from adaptive dosing treatment approaches. This provides a real opportunity to generate practice-changing data in these challenging patient populations, where current dosing regimens are based on limited understanding of clinical pharmacology.

227 Association of fludarabine exposure and survival after allogeneic cell transplantation: retrospectively estimated and prospectively simulated

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Introduction. Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for a variety of malignant and benign hematological disorders. Fludarabine combined with busulfan and rabbit-anti-thymocyte globulin (rATG) is a commonly used conditioning regimen for HCT. A dramatic influence of busulfan- and rATG- drug exposure on HCT outcomes has recently been found, but for fludarabine this influence is unknown.

Aims. To perform a prospective clinical trial simulation testing the effect of a personalized dosing algorithm and TDM. The primary aim of simulations was to evaluate the expected survival gain of alternative dosing based on either the developed PK-model or therapeutic drug monitoring (TDM).

Methods. A previously developed pharmacokinetic (PK) model for the circulating active metabolite of fludarabine-phosphate (F-ara-A, hereafter referred to as Flu) was used to link the Flu AUC was to primary clinical outcomes of HCT using parametric survival models. The Flu AUC corresponding to a minimal probability of having any of these events, was considered the optimum. Next, alternative dosing strategies to attain this target were evaluated in a clinical trial simulation. To achieve this aim, a database was used of patients in the UMC, transplanted for leukemia or lymphoma. Using baseline characteristics of this cohort, Flu PK and subsequent event probabilities were simulated after each different dosing regimen, with the previously developed PK and survival models respectively. Then, 1000 clinical trials were simulated, where patients were randomized to receive either 160 mg/m², Flu PK-model-based dosing, or TDM-based dosing. 80 patients were included per dosing arm. Events were simulated per dosing arm where computed as cumulative incidence at 1 year after HCT.

Results. The incidence of non-relapse mortality (NRM) increased with increasing Flu AUC (p<0.001), and more graft failures were observed at lower AUC (p=0.03). This resulted in a minimal event probability at a cumulative Flu exposure of 20 mg*h/L. In the trial simulations, NRM cumulative incidence decreased from 24% to 13% and 9% in the PK-model-based and TDM-based-dosing arm, respectively. Graft failure and relapse incidence were similar among treatment arms.

Discussion. These results indicate that a substantial survival benefit can be achieved by individualizing the Flu dose prior to HCT. Furthermore, prospective evaluation is feasible in a clinical trial, when TDM is compared to original dosing.
Paracetamol use prior to HCT conditioning has a significant effect on the within-patient busulfan pharmacokinetics over time.

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Introduction. Busulfan is widely used as conditioning in allogeneic hematopoietic cell transplantation (allo-HCT) and has a narrow therapeutic range (80-100 mg*hr/L).

Aims. Primary objective was to examine potential determinants for within-patient busulfan clearance alterations over time in children adults undergoing alloHCT.

Methods. In this prospective cohort study all children and adults underwent allo-HCT with intravenous busulfan were included (July 2011 – July 2016). Busulfan was administered once daily on four consecutive days and drug levels were measured on days 1 (,2) and 4. Potential determinants of busulfan clearance changes such as age, weight and co-medication were modelled using univariate and thereafter multivariate linear regression analyses.

Results. In the total patient population (n=239), clearance of busulfan on day 4 decreased by 8.1% compared to day 1 (p<0.0001). This was more apparent in patients using paracetamol prior but not during busulfan conditioning, who showed a 9.1 and 5.0 % larger drop in clearance compared to patients not using or continuously on paracetamol, respectively. Concomitant use of clobazam as antiepileptic prophylactic agent was associated with an increase in clearance compared to the use of other or no antiepileptic prophylaxis. Also, patients aged 65 years or older showed a significantly larger drop in clearance over time of 11% compared to paediatric patients.

Discussion. This study showed a significant effect of paracetamol use and age on busulfan clearance over the time course of HCT conditioning. Therefore, we strongly advocate the use of model-aided TDM anticipating a decrease in busulfan clearance. This particularly applies to adults and paracetamol users, given the more pronounced decline in busulfan clearance observed in this subset of patients compared to other populations.
Regorafenib pharmacokinetics and exposure-toxicity relationship in Japanese cancer patients

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Introduction. Regorafenib (REG) is an oral multikinase inhibitor that is currently used for the treatment of patients with metastatic colorectal cancer (mCRC), gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma (HCC). REG is metabolized primarily in the liver by cytochrome P450 (CYP) 3A4 to the active metabolites M$_2$ and M$_5$ and by uridine diphosphate glucuronyl transferase (UGT) 1A9 to the inactive glucuronides M$_7$ and M$_8$. REG shows various adverse reactions that can often cause dose reduction or treatment discontinuation, which is a major clinical problem.

Aims. The aims of this study were to investigate the safety and pharmacokinetic (PK) profile of REG and to clarify the relationship between drug exposure and toxicity in the clinical settings.

Methods. A total of 18 Japanese cancer patients (mCRC, n=10; GIST, n=4; HCC, n=4) were enrolled. Eight patients started REG treatment at the recommended dose of 160 mg once daily (3 weeks on/1 week off, 4-week cycle), while the other patients received a reduced starting dose on the basis of impaired liver function or poor performance status. Blood samples were collected before dose and 2, 4, 8, 24 hours post-dose at 1, 2, and/or 3 weeks in the first cycle. In addition, urine samples were also obtained to evaluate the urinary excretion of REG and its metabolites. Concentrations of REG and M$_2$/M$_5$ were measured by hydrophilic interaction liquid chromatography coupled to tandem mass spectrometry. M$_8$ was determined by conversion to M$_2$ following hydrolysis with b-glucuronidase (abalone). All adverse events were evaluated according to the NCI-CTCAE (version 4.0).

Results. PK data was available from 13 patients. Large interindividual variability in the plasma PK of REG and M$_2$/M$_5$/M$_7$ was observed. In plasma, M$_8$ was almost negligible. Sum of the area under the concentration-time curves of REG and M$_2$/M$_5$ for 24 hours, which would reflect pharmacological activity of the drug, was significantly correlated with sum of their trough concentrations ($r^2=0.91$, p<0.0001). In urine, REG and M$_2$/M$_5$ were not detectable, whereas M$_7$ and M$_8$ were detected in significant amounts (M$_7$>M$_8$). The most common adverse event was hand-foot skin reaction (HFSR, 65%). Higher total exposure to REG and M$_2$/M$_5$ at trough levels was significantly associated with the early development of higher grade of HFSR (p=0.004). Furthermore, there appeared to be a toxicity threshold for the total trough index at around 5 µg/mL to predict occurrence of grade ³2 HFSR.

Discussion. We first clarified the PK profiles of REG and its active and inactive metabolites in Japanese cancer patients. Our preliminary results suggest that dose titration based on TDM of REG and M$_2$/M$_5$ improves safety of REG.
Clinical validation of a DPD functional test in dried saliva sample as predictor of 5-fluorouracil exposure and severe toxicity

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Introduction. The dihydropyrimidine dehydrogenase (DPD) enzyme converts about 80% of 5-fluorouracil (5FU) to its inactive metabolite dihydrofluorouracil (FUH2). DPD is also responsible for the conversion of the pyrimidine base uracil (U) to 5,6-dihydouracil (UH2). Thus, the assessment of the ratio between their concentrations has been proposed as a pre-chemotherapy indicative of DPD activity, as a means to improve 5FU therapy outcomes and reduce toxicity rates. The collection of saliva samples is more patient-friendly, but transportation to specialized laboratories still requires the same precautions as plasma. The use of dried samples can be an attractive alternative to conventional biological specimens, usually very stable due matrix drying, with possibility of postal transportation.

Aims. clinically validate the use of dried saliva spots (DSS) as an alternative sampling for DPD deficiency assessment.

Methods. Pre-chemotherapy plasma, fresh saliva and dried saliva samples were obtained from gastrointestinal patients (N=40) for measurement of endogenous U and UH2 concentrations by LC-MS/MS. A second plasma sample collected during 5FU infusion was used for the determination of 5FU area under the curve (AUC) by HPLC-DAD. Data on toxicity was reported according to CTCAE v. 4.0

Results. 15% of the patients developed severe 5FU-related toxicity, with neutropenia accounting for 67% the cases. U, UH2 and [UH2]/[U] were highly correlated between fresh and dried saliva samples (rs=0.960; rs=0.828; and rs = 0.910, respectively). 5FU AUC ranged from 11.3 to 37.31 mg.h/L, with 46.2% of under-dosed and 10.3% over-dosed patients. The [UH2]/[U] ratios in plasma, fresh saliva and dried saliva samples were moderately correlated with 5FU AUC and adverse events grade, indicating a partial contribution of the variables to drug exposure (r=0.412, rs=0.373, rs=0.377) and toxicity (r=0.363, rs=0.523, rs=0.542). Median metabolic ratios were lower in patients with severe toxicity (P<0.01 for salivary ratios, and P<0.5 for plasma ratios), and 5FU AUC were in average 47% higher in this group than in moderate toxicity. The diagnostic performance of [UH2]/[U] ratios in plasma, fresh saliva and DSS for the identification of patients with severe toxicity were comparable. DPD functional test in DSS samples identified 67% of patients prone to severe toxicity, with a 94% of specificity.

Discussion. This study confirmed the suitableness of saliva as DPD phenotype predictor and demonstrated the applicability of DSS as alternative sampling for evaluating DPD activity, with comparable performance to fresh saliva sample.
Breast milk for the estimation of neonatal and lactational exposure to environmental pollutants

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Introduction. Early life (ante and postnatal) is associated with specific vulnerabilities. In recognition of this there is a need for practical approaches that allow effective assessment of exposure during early life. Systematic sampling and analysis of breast milk provides one such approach. In 2000 we commenced a human biomonitoring program in Australia.

Aims. The aim of this presentation is to discuss analysis of breastmilk as a tool for understanding of exposure to chemicals in early life.

Methods. Breast milk have been collected and archived for the last 2 decades as part of a human biomonitoring program. Samples have been analysed initially for a wide range of persistent organic pollutants using GC-MS techniques. More recently we have commenced analysis of other chemical contaminants in the samples including triclosan, perfluorinated chemicals, pharmaceuticals and personal care products.

Results. A wide range of chemicals can be detected in breast milk. Foremost persistent organic pollutants (POPs) including legacy POPs such as PCBs as well as ‘emerging’ POPs can be readily quantified and due to their long half lives in mothers analysis of breast milk provides insight in pre and postnatal exposure. Many other chemicals can be identified that are less persistent and thus analysis of breastmilk provides an indication of at least temporary exposure.

Discussion. Systematic sampling and analysis of breastmilk is a useful tool to contribute to the understanding of exposure at early life to chemicals. Here we discuss the advantages and limitations of collection and analysis of breastmilk for early life exposure monitoring.
Adipose tissue as a site of environmental pollutants accumulation

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Urine and serum concentrations are widely used in biomonitoring studies to estimate exposure to environmental chemicals but they may be highly dependent on time of exposure depending on the chemical’s half-life. Adipose tissue may play a major role in the storage and accumulation of environmental pollutants due to their lipophilic properties. Therefore, adipose tissue might be a suitable matrix for assessment of long-term exposure to these chemicals.

It has been shown that the octanol-water partition coefficient of a chemical may predict its likelihood to diffuse and accumulate into adipose tissue. Several studies have demonstrated the accumulation of environmental pollutants in adipose tissue. Results from cohort analysis show that some of the determinants of environmental pollutants concentrations in adipose tissue are age, sex, body-mass index, professional status, living area, dietary habits. The role of sampling site remains unclear. Moreover, adipose tissue may serve as a reservoir leading to chronic internal exposure, possibly disrupting endocrine and metabolic functions. Indeed, several human data obtained from studies on drastic weight loss in obese individuals suggest pollutants release from adipose tissue.

Concentrations of pollutants in adipose tissue can be assessed using either GC- or LC-MS/MS. Sample preparation is a critical step requiring sample disruption through blending in an high-speed homogenizer. Analytes are extracted from biological matrix using liquid-liquid extraction alone or followed by solid-phase extraction. Alternatively, simple QuEChERS methods can be used. This latter method has been used for the determination of bisphenol A and its chlorinated derivatives. Since contaminants may also be co-extracted, further purification of the extract is required using a clean-up step.

Concentration of environmental pollutants in human adipose tissue can be reliably measured and provide different information to that obtained from urine and serum samples and may be a useful biomarker for the assessment of long-term exposure to these chemicals.
233  Pesticide residues analysis in food matrices

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Introduction. It is mandatory to demonstrate that there is no significant bioaccumulation of pesticide residues in fruits and vegetables before consumption. Our Lab is involved in the control of many food products and/or fruits and vegetables for which different analytical techniques are employed.

Aims. To illustrate pre-analytical, analytical and post-analytical steps for the handling of food matrices that are usually perform to identify and quantitate potential pesticide residues. For this, the example of strawberries lots is used.

Methods. 10 g of strawberries were weighted and extracted by QuEChERS extraction for screening and determination of pesticides by using 2 LC-MS/MS (180 residues) and a GC-MS/MS (100 residues) methods. For determination of carbon disulfide, residues of dithiocarbamates, 2 g of the sample were weighted and hydrolysed with SnCl2 solution before analysis with HS-GC-MS. All the calibrations were based on standard addition calibrations using a matching matrix.

Results. Several pesticides were found in this strawberry samples, and were at concentrations higher than the maximum residue limit (MRL) admitted by the EU regulations: Bifenazate (3 µg/kg), Boscalid (44 µg/kg), Fenhexamid 83 µg/kg), Spinosad (37 µg/Kg), Phtalimide (52 µg/kg) and Iprodione (120 µg/kg).

Discussion. MRL is the highest level of a pesticide residue that is legally tolerated in or on food when pesticides are applied correctly in respect of good agriculture practices. When residues concentrations exceed these levels, the acceptable daily intake (ADI) could be surpassed with possible negative effects on human health. In addition, the toxicity due to the presence of several pesticides in one sample is not well established. As MRL are sometimes very low, it is mandatory to regularly set and develop analytical strategies to improve methods’ performances and to follow regulatory requirements along with cost/time efficiency. Therefore, standard addition calibrations for the multiple fruits/vegetables matrices have been optimized for all of the analytical methods. This allowed us to respect requirements with minimal constraints comparing to external calibrations.

Conclusion. Measurement of pesticide residues in food matrices necessitates multiple developments in pre-analytical, analytical and post-analytical steps. This implies good relationships between the authorities, the Lab and the industry.
Innovations in antidoping – staying ahead of the cheats

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The battle to stay ahead of people engaged in anti-doping is constant. The need to maintain vigilance and using creative analytical and scientific approaches is paramount when it comes to identifying new substances or approaches being used in doping. Innovative approaches include strategic analyses of long-term metabolite data from athletes with insightful interpretation to reveal doping behavior. The emergence of indirect detection methods and the utility of alternative sampling matrices has also been identified as a strategic approach to reveal anti-doping practices. The importance of sharing international experience and expertise across scientific bodies, antidoping laboratories and organizations is critical to ensure anti-doping can stay ahead of the cheats.
Hormones remain the most potent and widely detected substances involved in about 2/3 of anti-doping rule violations detected by increasingly sophisticated detection methods. The vast majority of adverse analytical findings (so called “positive tests”) are due to a wide variety of androgens, including marketed and illicit (nutraceutical, designer) synthetic androgens as well as exogenous natural androgens, while the peptide hormones (erythropoiesis stimulating agents, growth hormone and its secretagogues) and autologous blood transfusion remain difficult to detect. Sports requiring explosive power are most susceptible to androgen doping through their effect on increasing muscle mass and strength whereas sports that require endurance are most enhanced by haemoglobin (blood) doping which increases oxygen delivering capacity to exercising tissues. Performance in contact sports and those involving intense physical activity or training may also be enhanced by growth hormone and its secretagogues through speeding of tissue recovery from injury. Strategies to detect and deter the use of hormones used in doping remain a critical priority in global efforts to address anti-doping.
236 Innovations and logistics – delivering a modern testing program for the games

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A comprehensive world class anti-doping program is an essential aspect of every modern event, including major sporting events such as the Commonwealth Games. Delivering an anti-doping program for the 2018 Commonwealth Games on the Gold Coast presented a range of challenging logistics that required comprehensive planning and agility in both systems, laboratory resources and staffing.

The major pressure to deliver high quality anti-doping tests according to World Anti-doping Agency specified standards was completed within a tight time frame. Notable challenges included implementing a suite of new testing equipment prior to the Games, optimising laboratory workflows and communications to cope with the larger sample numbers and required shorter turn-around times, managing disrupted sample delivery schedules and completing ad hoc product analyses for investigations.

Collaboration was a critical aspect of the success of the program. This involved working closely with games officials but also anti-doping staff to plan and implement testing missions as well the games medical commission on reporting test findings.
High tacrolimus clearance is associated with development of interstitial fibrosis and tubular atrophy in the transplanted kidney

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Introduction. Patients with high tacrolimus clearance need higher daily doses to achieve the same trough concentration compared to those with low clearance. The high clearance makes them more exposed to transient under-immunosuppression in case of a missed/delayed dose, and intake of the high tacrolimus doses result in higher peak concentrations (Cmax). Both are hypothesized to induce development of interstitial fibrosis and tubular atrophy (IFTA) in the transplanted graft.

Aims. Investigate the association between estimated tacrolimus clearance and development of IFTA in the renal transplant during the first year post-engraftment.

Methods. Data from all patients transplanted between 2009 and 2013 at Oslo University Hospital, Rikshospitalet were included in the analysis. Association between estimated tacrolimus clearance (daily tacrolimus dose [mg] / trough concentration [µg/L]) and development of IFTA, (defined as i+t ≤ 1 and ci+ct ≥ 2) in renal protocol biopsies from 6 weeks to 12 months post-transplantation was investigated.

Results. In total, 510 patients were treated with tacrolimus and had paired protocol biopsies (6 weeks + 12 months) in the time period and were included in the analysis. Patients were divided in four groups according to their estimated tacrolimus clearance. There were no differences in biopsy scores between the groups at 6 weeks. The high clearance group developed significantly more IFTA from 6 weeks to 12 months compared to the low clearance group (50% vs 22%, P<0.007). Of the 233 patients without IFTA in the 6-week biopsies a 1-unit increase in tacrolimus clearance was associated with an odds ratio of 1.88 (95% CI; 1.12-3.27) for development of IFTA after adjusting for donor age and deceased donor.

Discussion. High tacrolimus clearance was significantly associated with development of IFTA within the first year following renal transplantation. The effect may be explained by higher peak concentrations and/or more severe transient under-immunosuppressive episodes in these patients.
Pharmacokinetic differences between morning and evening administration of tacrolimus in renal transplant recipients – described by a double absorption-phase model

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Introduction. Therapeutic drug monitoring (TDM) of tacrolimus (Tac) is based on trough concentrations in most transplant centres. Model-based limited sampling strategies (LSS) with area under the curve (AUC) target is however getting more recognition. Tac is subject to a high inter- and intra individual variability due to a range of different factors, including food consumption and circadian differences. Detailed data including non-fasting situations and circadian rhythm needs to be included in the model in order for it to handle patients’ real life situations.

Aims. We wanted to investigate, in a real life setting, the circadian variation of Tac twice daily dosing in renal transplant recipients eating and taking their medications as they do in real life.

Methods. A total of 45 full 24-hours pharmacokinetic (PK) (26 Tac measurements) investigations were performed in 30 stable renal transplant recipients on Tac, MMF, and prednisolone. Food was ingested according to patients’ individual daily routine (breakfast/dinner times) in ¾ of the investigations and the other ¼ were performed during fasting conditions (no food 2 hours before/after Tac administration). Non-parametric population modeling was performed using Pmetrics. AUC calculated using the developed model was compared between different fasting conditions, and day- and nighttime, using a 2 ways ANOVA.

Results. A one-compartment model with first order elimination, no covariates and a double gamma distribution to describe the absorption fitted the data well, irrespective of fasting- and circadian conditions. The evening dose, both with food and fasting, and the morning dose administered with food, showed a flat-, delayed-absorption profile compared to the morning dose administered during fasting conditions, leading to significant different AUC; morning and evening dose with food = 88±21µg*h/L, morning dose fasting=136 ± 29 µg*h/L (P<0.001).

Discussion. A double absorption phase model described the PK differences well between morning and evening administration of Tac and the food-effect on absorption. The circadian variation was only present during fasting conditions, and dose administrations with food showed a flat-, delayed-absorption profile.
Association of infliximab concentrations with clinical response in psoriasis

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Introduction. Between 20-40% of psoriatic patients are unresponsive to initial infliximab (ifx) treatment, a variable percentage of patients lose response and 21-35% discontinue treatment during the first year. These between-patient response differences may reflect variability of ifx pharmacokinetics (pk) and drug exposure in these patients.

Aims. Primary: to evaluate association between ifx through levels (cₘᵡᵢₙ) and pasi response. Secondary: to identify factors that influence ifx cₘᵡᵢₙ and to determine intra-patient cₘᵡᵢₙ variability (ipv) and its contribution to response.


Results. We collected 155 serum samples from 33 patients. 20 patients (60.6%; 51%, and 88% of obese, overweight and normal weight patients, respectively) achieved and 18 (54.5%) pasi 100. Mean (SD) cₘᵡᵢₙ was 2.4 mg/L (2.2). Ati were detected in 6 (18.2%), resulting in undetectable cₘᵡᵢₙ. Overweight and obese patients presented cₘᵡᵢₙ than those with normal weight (2.68 vs 1.64 mg/L). Pasi score and achievement 100/90 were significantly associated to cₘᵡᵢₙ after adjusting by demographic and characteristics (OR 0.8 [IC95% 0.70-0.92], OR 1.79 [IC95%:1.18-2.71] and OR 1.54 1.14-2.81), respectively) (Figure). Patients with cₘᵡᵢₙ≥7.5 mg/L had a 40%-fold chance achieving pasi 90 or higher. Cₘᵡᵢₙ were significantly associated to ati (OR -2.49; IC95% -3.56 a -1.41) and bmi (OR -0.05; IC95% -0.09 a -0.01). The mean ipv was 49% (28.5). Non-responders showed higher ipv than responders/partial-responders (56.3% [20.8] vs 48.3% [29.5]).

Discussion. Cₘᵡᵢₙ ifx was significantly associated with optimal clinical response (pasi 90/100 responses) and pasi score. Cₘᵡᵢₙ cut off ≥7.5 might be recommended to achieve at least pasi 90 response. Bmi and ati status influenced cₘᵡᵢₙ however, patients with normal weight achieved better treatment response despite lower cₘᵡᵢₙ. This result agrees with the fact that obesity is associated with an elevation of pro-inflammatory cytokines levels. Ifx cₘᵡᵢₙ showed a high intra-patient variability but it was not significantly related with clinical response. More studies are needed to elucidate the fluctuations in cₘᵡᵢₙ over time and determine the clinical relevance of this phenomenon.
Association of pharmacokinetic and pharmacodynamic markers of mycophenolic acid and clinical outcomes in cord blood transplant patients

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Introduction. Mycophenolate mofetil (MMF) is a pro-drug of mycophenolic acid (MPA) and is frequently used to prevent acute graft-versus-host disease (aGVHD) in patients receiving hematopoietic stem cell transplantation (HCT). However, optimal doses of MMF and target MPA concentrations in HCT patients have not been defined.

Aims. To evaluate the association between pharmacokinetic or pharmacodynamic markers of MPA and successful aGVHD prevention and neutrophil engraftment in order to inform individualized MPA treatments in HCT patients.

Methods. We recruited 35 patients undergoing cord blood transplantation (CBT) who were treated with MMF and tacrolimus for GVHD prophylaxis. Blood samples were collected immediately before, and at 1, 2, 4, and 8 h after the morning dose in the first and third weeks after the start of MMF treatments. Concentrations of MPA and its metabolites, MPA glucuronide (MPAG) and MPA acyl glucuronide (AcMPAG), and free MPA were analyzed using the LC-MS/MS methods. Inosine-5'-monophosphate dehydrogenase (IMPDH) activity in peripheral blood mononuclear cells (PBMC) was measured. In addition, single nucleotide polymorphisms (SNPs) in genes which were previously reported associated with MPA pharmacokinetics and pharmacodynamics were identified.

Results. Area under the concentration–time curves from 0 to 24 h (AUC0–24) for free MPA and AcMPAG at one week after the start of MMF treatments were significantly higher in patients with gastrointestinal aGVHD at stage ≥ 1 than those at stage 0. Patients with faster neutrophil engraftment had higher free MPA AUC0–24 at one week after the start of MMF treatments compared with those with slower neutrophil engraftment. IMPDH activity in PBMC and SNPs examined were not independent predictors for the clinical outcomes. Receiver operating characteristic model analyses showed that cut-off values of AUC0–24 for successful prevention of gastrointestinal aGVHD were 0.689 and 15.6 µg·h·mL−1 for free MPA and AcMPAG, respectively. In addition, the cut-off value of free MPA AUC0–24 for neutrophil engraftment by day 25 was 0.405 µg·h·mL−1.

Discussion. The AUC0–24 for free MPA may be a better predictor of the prevention of gastrointestinal aGVHD and neutrophil engraftment compared with that of total MPA in patients receiving CBT. Hence, monitoring of the free MPA AUC0–24 between 0.405 and 0.689 µg·h·mL−1 could be considered informative of individualized MPA treatments in CBT patients.
Evaluation of a volumetric absorptive microsampling device for tacrolimus measurement in routine drug monitoring

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Introduction. The use of tacrolimus for immunosuppression after solid organ transplant requires regular measurement in a sample of whole blood taken from a vein which requires trained staff, and can be painful, difficult, and inconvenient. Volumetric absorptive microsampling (VAMS™) offers an alternative that requires only a finger-prick to sample. VAMS potentially offers all the advantages of dried blood spot sampling without many of the drawbacks.

Aims. To validate and evaluate the use of VAMS for measuring tacrolimus in the routine management of transplant patients.

Methods. Samples received for routine tacrolimus measurement were sampled using VAMS (10 µL, Mitra®) and allowed to dry before measurement by LC-MS/MS. Results were compared with reported values from the established protein precipitation (PPT) method, and with quality control and proficiency testing samples. Precision, accuracy, haematocrit bias and robustness were all evaluated.

Results. Imprecision (as %CV) using VAMS was between 2.0 and 9.0 %, and inaccuracy was -3.5 to 4.9 %. Proficiency testing sample results (n = 59) showed good agreement with assigned values (y = 1.0406x – 0.0551, R² = 0.9907), with a mean difference of 2.7 % (95 % confidence interval of -10.0 % to 16.0 %). In patient samples (n = 114) the mean bias was +5.0 % (95 % confidence interval of -15 % to 25 %). VAMS samples were stable for at least 29 days in ambient conditions with results varying between 6.9 % to 11.5 % (n = 6) between day 1 and day 29. No haematocrit bias was observed.

Discussion. Advantages of DBS sampling include small sample volume, patient self-sampling, and reduced biohazard risk. However problems with the sampling process, the analytical process and paper matrix variability have limited implementation. VAMS allows a fixed volume sample to be obtained and processed without the disadvantages of DBS, and is robust and reproducible. Results from patient samples on VAMS were no different to the PPT method, and since preparation of VAMS tips for analysis followed a similar protocol to the established PPT method, minimal changes to laboratory procedures would be required for implementation. For most patients, sampling should be less traumatic especially in the paediatric population, and more convenient and easier to repeat compared with venepuncture.
305  Determination of cyclosporine A following renal transplantation: CMIA or LC-MS/MS?

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Introduction. Although most of commercially available assays, such as chemiluminescent microparticle immunoassay (CMIA), are declared to be specific for monitoring cyclosporin A (CsA) levels, cross-reactivity could still be seen in all immunological assays. Hence it is necessary to evaluate the existing immunoassay in laboratory.

Aims. Our first objective was to develop an ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method for CsA as well as its main metabolite AM1 in whole blood samples and to compare used CMIA with this method. Secondly, we investigated the clinical impact of between-method quantification differences.

Methods. For UPLC-MS/MS, whole blood samples from 133 kidney transplant patients were extracted by adding a precipitation reagent containing the internal standard ([2H4]-CsA) and zinc sulfate heptahydrate solution. Analysis was performed on an Xevo TQ-S mass spectrometer equipped with an Acquity UPLC I-CLASS separations module. Our method was analytically validated and compared with CMIA from Abbott Architect i1000SR. CsA concentrations were clinically classified as valley (C0) and peak concentration (C2). And the agreement between CMIA and UPLC-MS/MS was evaluated by linear regression and Bland-Altman plot. Beside this, the metabolite AM1 of CsA was determined using UPLC-MS/MS to explore what extent the metabolites cross-react with CMIA.

Results. A novel UPLC-MS/MS method using protein precipitation as sole pretreatment and an analysis time of 5.0 min was developed. The assay had a total imprecision of 3.5-9.6%, a limit of quantification of 5.0ng/mL and an accuracy ranging from 93.2 to 113.0%. Measurements of CMIA and UPLC-MS/MS were weakly correlated ($r^2=0.636$). The majority of C0 results were higher for immunoassay than for LC-MS/MS, whereas C2 showed almost no differences. The average overestimation by immunoassay was 19.8%, but in some cases it was as high as 81%. And concentrations of AM1 in those cases were higher than C0.

Discussion. The application of CMIA may lead to an overestimation of blood trough levels and under-dosage of the drug, increasing the risk of organ rejection and graft loss. Further work must be done on multi-center assessments of metabolites-reactivity for CMIA. Here, we developed an applicable UPLC-MS/MS method for rapid CsA and AM1 quantification in human whole blood. This method exhibited very good performance for broad concentration ranges covering the full therapeutic ranges of CsA. The pretreatment procedures are extremely simple and do not involve time. Therefore, LC-MS/MS techniques should be preferable and commonly used in clinical diagnostics.
A novel activity-based concept to screen biological matrices for the presence of (synthetic) opioids

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Introduction. Highly potent synthetic opioids, are a growing health threat. Detection of these novel opioids remains challenging as new compounds continue to enter the market.

Aim. The objective of this study was to set up a novel bioassay for screening biological matrices for the presence of (synthetic) opioids/opiates, not relying on antibody- or MS-based recognition of the structure of these compounds, but based on their opioid activity.

Methods. The µ opioid receptor (MOR) belongs to the class of G-protein-coupled receptors (GPCRs). Activation of these receptors results in recruitment of the β-арrestin 2 protein. This results in functional complementation of a split NanoLuc luciferase, thereby restoring luciferase activity (see figure).

Results. Sensitivity and specificity of the developed bioassay were evaluated using 107 authentic postmortem blood samples with known presence or absence of the synthetic opioids U-47700 or furanyl fentanyl, as determined by LC-MS/MS and QTOF analysis. A first finding was that in 8 synthetic opioid positive samples no positive signal was obtained. In these samples, Q-TOF analysis revealed the MOR antagonist naloxone, which can obviously also prevent receptor activation in vitro. Hence, evaluation was further based on non-naloxone containing samples. For U-47700 and furanyl fentanyl positives, sensitivity was 100% (8/8), respectively 95% (21/22). The missed furanyl fentanyl positive sample could not be retested for the presence of naloxone. Of the 59 opioid negative samples, 55 samples were correctly scored negative, yielding a specificity of 93% (55/59). An additional 5 samples (found to contain opioids codeine, (nor)buprenorphine or loperamide) were correctly scored positive. In 5 negatively scored samples, Q-TOF analysis revealed presence of alfentanil (1) or sufentanil (1) (both < 1 ng/ml) or dextromethorphan/levomethorphan (2) or dextrophan/levorphanol (1) (for the latter, non-detection could be explained by presence of an inactive form).

Discussion. The MOR reporter assay allows rapid identification of opioid activity in blood samples. Although the co-occurrence of opioid antagonists is currently a (solvable) limitation, the high sensitivity, selectivity and the untargeted nature of the technique may render it a useful first-line screening tool to investigate potential opioid intoxications in clinical and forensic settings, complementing conventional analytical methods which are currently used.
307 Futility of urine salbutamol doping control, demonstrated through pharmacometrics

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Introduction. Salbutamol is used to counteract bronchospasm in asthma, bronchitis and COPD, and is often used by elite athletes. However, it is claimed that high salbutamol (oral) doses may also exert an anabolic effect. Therefore, its dosage is restricted by the World Anti-Doping Agency (WADA) inhalation of 800mcg per 12 hours. Urine is tested to determine violations, threshold limit of 1000 mcg/L, but recent cases have resulted in a debate regarding the validity of this approach.

Aims. To determine whether current approaches are sufficiently able to differentiate approved salbutamol usage from doping violations.

Methods. We collected literature pharmacokinetic parameters of salbutamol and its main metabolite sulphated salbutamol. From these parameters, a semi-physiological pharmacokinetic model was synthesised, validated against literature data, and used to perform clinical trial simulations (N=1000) of possible urine concentrations over time resulting from WADA-allowed dosages.

Results. The synthesised model was able to predict the literature data well, including its variability. Simulations showed a very large spread in urine salbutamol concentrations, with a significant portion of virtual subjects (8.4%) exceeding the WADA threshold limit at 1 hour post-dose.

Discussion. The large spread of urine concentrations indicates the infeasibility of determining the administered dose from a single urine sample, especially considering uncertainty regarding dose administration time. The current threshold inadvertently leads to incorrect assumptions of doping violation, whereas many violations may go unnoticed, especially when samples are taken more than 6 hours after drug administration. These issues, combined with the dubious assertion of salbutamol’s anabolic effect, lead us to conclude that the large effort involved in salbutamol doping testing should be reconsidered.
308  Routine toxicology analysis including NPS using GC/MS and LC-ion trap MS

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Introduction: With the fast emergence of Novel Psychoactive Substances (NPS) such as synthetic cannabinoids and cathinones, and their often harmful effects, it is important to be able to detect these NPS in a laboratory’s routine drug screening workflow. Our laboratory performs both clinical and forensic toxicological analyses, mainly employs GC/MS and a recently validated LC-ion trap MS solution (Toxtyper by Bruker) for the analysis of a wide scope of drugs including anti-epileptics, antidiabetics, analgesics, benzodiazepines, narcotics and antipsychotics in blood and urine specimens.

Aim: To expand the scope of analysis to include some commonly encountered NPS in our region.

Methods: For routine screening, aliquots of antemortem and postmortem biological samples were extracted by liquid-liquid extraction under acidic condition (pH 4 with ethyl acetate) and basic condition (pH 12 with 1-chlorobutane). The dried extracts were reconstituted in methanol and injected into a Bruker LC-ion trap MS (a 11-min run) and an Agilent GC/MS (a 32-min run). An Automated Mass Spectral Deconvolution and Identification System (AMDIS) against our in-house spectral library was used for the automated data analysis of GC/MS data. For Toxtyper, automated peak identification was also achieved based on the matching of the precursor ion, MS2 or MS2/MS3 spectra and retention time against that stored in our customised library. Spectral and retention times data for the new NPS were added to both the GC/MS and Toxtyper libraries using commercial reference materials or seized drugs whose identities were verified against available spectral libraries (e.g. SWGDRUG.L) or published high resolution MS spectra and/or NMR.

Results. With these two complementary techniques, we were able to detect a variety of NPS such as designer benzodiazepines (phenazepam, etizolam), tryptamines (5-methoxy-MiPT, 5-methoxy-DiPT, N,N-dimethyltryptamine, harmaline, harmine), synthetic cathinones (e.g. methylene, ethylene, butylene, dibutylene, N-ethylhexedrone), others (e.g. PMMA, methiopropamine, mitragynine, methoxetamine, 2-oxo-3-hydroxy-LSD). In recent months (Oct-Dec 2017), we also detected 5-Fluoro-ADB and/or its acid metabolite in the samples of 9 subjects, mainly by Toxtyper due to its lower concentration. 5-Fluoro-ADB, a synthetic cannabinoid, was shown to be more potent than cannabis and has been reported to be associated with a few deaths.

Discussion: By constantly adding spectral and retention time data into GC/MS and Toxtyper libraries, our laboratory is able to detect increasing number of toxicologically important drugs such as NPS.
309 Metabolism of new psychoactive substances studied by metabolomic techniques? A proof of concept study

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Introduction. Traditionally, metabolites are identified after in vitro or in vivo experiments and mass spectral (MS) analysis using a targeted search for theoretically possible metabolites. This procedure is error-prone since the prediction of metabolites is done a priori and depends on the experience of the investigator or the power of the used prediction software.

Aims. The aim of this study was therefore to show that untargeted metabolomic techniques offer a reliable and comprehensive approach for the identification of their metabolites.

Methods. Alpha-PBP and alpha-PEP used as model substances were incubated in two different concentrations with pooled human liver microsomes and cofactors for phase I reactions. Samples were analysed by LC-HR-MS/MS (TF Q-Exactive Plus). Detection of possible metabolites was done by automated peak picking after full MS using XCMS in an R environment. Significant features were determined using univariate and multivariate analysis. Finally, tentative metabolite identification was done using parallel reaction monitoring in a separate run and MS interpretation.

Results. Statistical analysis revealed significant features that were subsequently identified as alpha-PBP-M (HO⁻), alpha-PBP-M (di-HO⁻), alpha-PBP-M (Oxo⁻) for alpha-PBP as well as alpha-PEP-M (HO⁻), alpha-PEP-M (di-HO⁻) and alpha-PEP-M (Oxo⁻) for alpha-PEP. Data corresponded well to those described literature (Manier et al., Drug Test Anal. 2018) after traditional metabolite identification and additionally revealed di hydroxylated metabolites.

Discussion. The applied metabolomic techniques offered a statistical rather than an experience-based approach for the identification of metabolites and was successfully applied on the metabolite identification of selected compounds. This leads to more investigator independent results. Nevertheless, systematic variabilities can lead to false positive features and need to be prevented by the design of study, which needs to be investigated further.
310  Heavy metals in herbo-mineral formulations in patients undergoing cancer chemotherapy: A tertiary care cancer hospital experience

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Introduction. It is not unusual for cancer patients in India to resort to complementary and alternative medicine (CAM). Some CAM formulations have high levels of heavy metals including lead, mercury and arsenic.

Aims. To evaluate the heavy metal content in CAM formulations used by patients who experienced unexpected adverse events following cancer chemotherapy.

Methods. Breast cancer patients undergoing chemotherapy who presented with unexplained toxicities (such as nephrotoxicity, seizures) and were found to be using CAM were included in the study. CAM obtained from these patients was tested for the presence of heavy metals using inductively coupled plasma mass spectrometry (ICP-MS).

Results. Eleven patients were enrolled and provided 65 CAM samples (median=5, range 1-12) for analysis. Heavy metals (lead, arsenic, mercury and others) were found in 17/65 (26%) formulations, with 8/11(72%) patients consuming at least one such formulation. The heavy metal content in all 17 samples was above daily human consumption limits. Mercury (7/17), lead (6/17) and arsenic (4/17) were found in CAM samples in concentrations of 216-70,585 μg/g , 28.4-79.7 μg/g and 711.3-16150 μg/g respectively.

Discussion. Unreported use of CAM formulations containing high levels of heavy metals by cancer patients could contribute to unexplained toxicities following chemotherapy.
311 Parabens exposure during pregnancy: determination in urine of pregnant women from the French EDDS cohort study

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Introduction. Parabens are used as conservatives in medicines and food products, but they are mostly found in cosmetics and personal care products. Thus, women, including pregnant women, are likely exposed to parabens. Parabens are suspected to be endocrine disrupting chemicals (EDC) due to their binding ability to estrogen receptors. Therefore pregnancy represents a period of particular vulnerability to these compounds.

Aims. To assess exposure to parabens compounds (methyl-, ethyl- propyl- and butyl-paraben) in a cohort of 164 french pregnant women.

Methods. Urine samples were collected at the second (U2) and third trimester (U3) of pregnancy. They were stored at -20°C until analysis. Assay method was validated according to EMA’s guidelines. It consisted in a simple liquid/liquid extraction, followed by a UHPLC-MS/MS analysis. Limits of detection were defined as three times the standard deviation of the area obtained from 5 blank samples. Limits of quantification were 0.025 ng/mL for all analytes.

Results. 152 U2 and 152 U3 samples were collected and analysed. Detection/quantification frequencies and mean (+/- SD) concentrations are presented in table 1 and 2, respectively.

Discussion. Parabens were found in the majority of U2 and U3. Mean methyl-paraben concentrations were up to 33 times those of the 3 cumulated other parabens. Methyl-paraben is the most frequently detected, according to its wide use in personal care products. This study highlights the importance of informing pregnant women or women planning to have children about EDC, their sources of exposure and the ways to avoid them.
An open-label, multicentre, observational trial to assess teicoplanin levels in critically ill Chinese patients

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Introduction. In Asia and Europe, teicoplanin is widely used in clinical practice for the treatment of infections caused by drug-resistant Gram-positive bacteria. As a glycopeptide antibiotic, teicoplanin has a lower possibility than vancomycin to cause renal toxicity, and causes fewer anaphylactoid reactions. There is a good correlation between trough levels and clinical outcome, therefore therapeutic drug monitoring (TDM) is recommended. However, TDM of teicoplanin is not routine in China, and data of teicoplanin TDM are largely lacking.

Aims. The first objective of this work was to establish a reliable high performance liquid chromatography (HPLC) method of plasma teicoplanin measurement for recruited TDM centres. Secondly, we evaluated results from teicoplanin TDM in critically ill patients in routine clinical practice.

Methods. In this open-label, multicentre, observational study, we recruited 27 TDM centres and 1 quality control centre responsible for room quality evaluation samples’ preparation. C(min) levels for the first 4 days of treatment were collected 15min prior to drug administration. Levels were determined by HPLC. Analysis was performed using a Waters Symmetry C18 column (250mm×4.6mm, 5µm). The mobile phase was NaH₂PO₄(0.01 mol/L): acetonitrile =75:25 (pH 3.3). The flow rate was 1.0mL/min and the detection wavelength was 215 nm. Piperacillin sodium was used as an internal standard.

Results. Teicoplanin and piperacillin sodium had elution times of 7.8 and 9.7 min, respectively. For all TDM centres, linearity of teicoplanin concentration ranges were between 3.125 to 100 µg/mL and linear using least squares regression with a weighting factor of the reciprocal concentration. Intraday and interday precisions ranged from 0.3% to 13.5%. Intraday and interday accuracies (%bias) were within 15%. And those TDM centres all passed inter-room quality assessment evaluated by quality control centre. Then, 458 samples were collected. Patients with sub-optimal (< 10 mg/L) plasma teicoplanin concentrations constituted nearly seventy percent of the total study population. The majority of these patients received the recommended loading and maintenance dose.

Discussion. A stable and specific HPLC method for determining teicoplanin levels was successfully applied to therapeutic drug monitoring in clinical practice for 27 TDM centres. In China, a significant proportion of patients in clinical practice achieved only sub-optimal teicoplanin concentrations, which emphasizes the importance of dose increase and routine therapeutic drug monitoring.
313  Loss of control of HIV viremia with OTC weight-loss drugs: A call for caution?

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Introduction. Improved survival achieved by HIV-infected patients has complicated their medical care as increasing numbers of co-morbidities leads to polypharmacy, which in turn has been associated with increased risk of adverse drug events and drug-drug interactions (DDIs) potentially compromising the efficacy of antiretroviral treatment.

Methods. In September 2016 we have set up a service for the management of polypharmacy in HIV-infected patients. 510 HIV-infected patients on maintenance antiretroviral therapy were screened in the first 15 months of activity.

Results. Four patients experiencing virologic failure related to DDIs were identified. All have a long-term history of optimal adherence to antiretroviral therapy and long-standing HIV viral control. Two patients voluntarily decided to buy over the counter orlistat. The third patient failing antiretroviral therapy had recently started a naringin-containing supplement which inhibits the activity of carrier proteins resulting in impaired drug absorption. The forth patient voluntarily bought a dietary supplement of phytosterols (mainly psyllium) reported to decrease the absorption of calcium. After discontinuation of the weight-loss agents, HIV viral load returned to <37 copies/mL in all patients.

Discussion. Weight-loss drugs should be used with caution in HIV-infected patients treated with lipophilic antiretroviral drugs for the risk of virologic failure. This is particularly relevant considering that these agents are available on the market as OTC medications, thus potentially escaping the control of the physician. Therefore, more restrictive rules for the use of weight-loss drugs are advocated by drug regulatory agencies.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Antiretroviral therapy</th>
<th>Interacting agent</th>
<th>TDM 1</th>
<th>TDM 2</th>
<th>Therapeutic range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, 43 years</td>
<td>ATV/r TDF/FTC</td>
<td>Orlistat 60 mg thrice daily</td>
<td>ATV: 50 ng/mL</td>
<td>ATV: 195 ng/mL</td>
<td>150-800 ng/mL</td>
</tr>
<tr>
<td>Female, 39 years</td>
<td>EFV TDF/FTC</td>
<td>Orlistat 60 mg thrice daily</td>
<td>EFV: &lt;150 ng/mL</td>
<td>EFV: 3795 ng/mL</td>
<td>1000-4000 ng/mL</td>
</tr>
<tr>
<td>Female, 40 years</td>
<td>ATV/r TDF/FTC</td>
<td>Sinetrol 450 mg twice daily</td>
<td>ATV: 85 ng/mL</td>
<td>ATV: 719 ng/mL</td>
<td>150-800 ng/mL</td>
</tr>
<tr>
<td>Male, 44 years</td>
<td>TAF/FTC DRV/cobi</td>
<td>Lipidyum 6.5 g daily</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>

TDM 1: performed during concomitant administration with the interacting agent; TDM 2: after discontinuation of the interacting agent.
The effectiveness and safety of individualized vancomycin dosing via pharmacokinetic monitoring in critically ill patients

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Introduction. Pharmacokinetic parameters can be significantly altered for critically ill patients because of altered Vd and creatinine clearance. In this case, pharmacists’ intervention with pharmacokinetic monitoring to individualize vancomycin dosing may be necessary.

Aims. The objective of the study was to evaluate vancomycin’s therapeutic goals and safety of a consult-to-pharmacy service in critically ill patients.

Methods. This single-arm cohort study included patients receiving intravenous vancomycin and consult-to-pharmacy service. Consult-to-pharmacy service included designing initial vancomycin regimen based on PPK model and adjusting dosing with TDM and bayesian prediction. The consult-to-pharmacy service concerning vancomycin dosing has become a part of the routine clinical care in intensive care unit, Peking University Third Hospital since April, 2016. The primary endpoint was target trough concentration attainment rate defined as 10-20 mg/L. Secondary endpoints included clinical failure rate and nephrotoxicity (KDIGO criteria). Descriptive statistics were used to describe the characteristics of the included patients and endpoints.

Results. Eight-two consecutive critically ill patients were involved in this study from April, 2016 to January, 2018. Fifteen of them were collected retrospectively and 67 prospectively. The mean age of the patients was 58.7±20.8 years. Sixty (73.2%) of the patients were surgical critically ill patients and 12 of them were commitment with continuous veno-venous hemofiltration therapy (CVVH) therapy. Thirty-one (37.8%) of them had gram-positive proven infections. Loading dose was given to 14 (17.1%) patients. The mean initial dosage was 1614.8 ± 629.8 mg/d. Thirty-eight (46.3%) initial concentrations attained goal range and 47 (57.3%) patients had repeat TDM. The overall target trough concentration attainment rate was 68.3%. Concerning the clinical endpoint, 11 (13.4%) patients experienced clinical failure and nephrotoxicity rate was 10.0%, which was slightly lower than the incidence rate published before.

Discussion. Pharmacists’ service with pharmacokinetic monitoring possibly increases the target trough concentration attainment rate and decreases the clinical failure and nephrotoxicity risk. Further quality improvement study with control group should be designed to confirm the benefit of pharmacists’ service with pharmacokinetic monitoring.
315 Vancomycin – Improving prescribing practices

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Introduction. Vancomycin is an antibiotic used to treat infections caused by methicillin-resistant Staphylococcus aureus. Therapeutic drug monitoring (TDM) is advocated for vancomycin due to its narrow therapeutic index. Dosing guidelines suggest target trough concentrations of 15-20 mg/L or an AUC0-24/MIC ≥ 400 mg.h.L⁻¹

Aims. To assess vancomycin prescribing according to guidelines, evaluate the attainment of therapeutic targets and identify factors associated with nephrotoxicity.

Methods. Vancomycin dosing history, patient demographics, pathology and incidence of acute kidney injury (AKI) and associated risk factors were collected retrospectively over a 9-month period from patients receiving vancomycin (>48 hours). Loading and maintenance doses and collection of drug concentrations were evaluated against guidelines. A Bayesian dose prediction software (DoseMe®) was used to estimate vancomycin drug exposure. It was assumed that the MIC was 1 mg/L. Vancomycin-associated AKI was defined according to van Hal et al. (2013).

Results. Plasma vancomycin concentrations (n=1043) were collected from 163 patients during 179 courses of therapy. The first dose prescribed was concordant with the guideline defined loading dose in only 24% of courses, while 72% were lower than guideline recommendations. In 42% of courses the initial maintenance dose was guideline concordant, while 24% exceeded the guidelines. Further, only 14% of blood samples were trough samples collected after the appropriate dose. Approximately 30% of the predicted trough concentrations were within 15-20 mg/L. Regardless, an AUC0-24/MIC≥400 h was achieved at least once in 83% of courses. Patients who received doses (loading and maintenance) concordant with guidelines were twice as likely (71% vs. 36%, p=0.004) to achieve target drug exposure by 48 hours of therapy compared to those who did not. Vancomycin-associated AKI was observed in 9% of patients.

Discussion. Poor compliance with vancomycin guidelines was observed. Utilisation of dose prediction software provides an opportunity to correctly interpret all drug concentrations and individualise therapy to optimise patient outcomes.

316 Development of f%T>MIC Calculation Model and its Application in Individualized Medication Optimization of Carbopenems in Critical Care Patients

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Introduction. Imipenem/cilastatin and meropenem widely used in the treatment experience of severe bacterial and as time-dependent antibiotics, the time the free concentration exceeds the minimum inhibitory concentration (f%T>MIC) is the main pharmacokinetics/pharmacodynamics (PK/PD) index to evaluate the clinical antibacterial effect.

Aims. To develop the f%T>MIC computing model of carbapenems based on intravenous infusion one-compartment model at steady state and to adjust dose strategy according to measured drug concentrations.

Methods. Pharmacokinetic equations within one time interval were deduced at steady state after multiple intravenous infusion. f%T>MIC calculator was compiled using EXCEL software and used for evaluation of antibiotic effect based on the concentrations at 0.5h and 3h before administration of imipenem or meropenem at steady state.

Results. The calculation model can be used for f%T>MIC evaluation and dosage optimization. The model has been used to determine f%T>MIC level of 107 ICU patients receiving imipenem or meropenem treatment.

Discussion. PK equations during infusion phase at steady state after multiple intravenous infusion were hardly obtained from articles or publications, which made the evaluation of f%T>MIC inaccurate. The present calculation model can provide a reasonable tool for the evaluation and optimization of dosage strategy, and it can be applied to other time-dependent antibiotics.
Beta-lactam concentrations inadequate? Try a gout drug! A case series of probenecid boosting of flucloxacillin 24 hour infusions

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1Pharmacy Department, St Vincent’s Hospital, Sydney, Sydney, Australia, 2Microbiology and Infectious Diseases, St Vincent’s Hospital, Sydney, Sydney, Australia

Introduction. Intravenous (IV) flucloxacillin is used to treat serious infections caused by gram-positive bacteria. Probenecid (PBC), commonly prescribed to treat gout, increases renal excretion of uric acid by blocking tubular resorption; however its use to increase the duration of action of oral penicillins is well recognised. In the inpatient setting, PBC “boosting” for IV flucloxacillin therapy is rarely required as doses can be increased to achieve therapeutic targets with no set maximum dose. In Australia, IV flucloxacillin administration using an elastomeric pump may facilitate treatment at home. However, device concentration stability limitations cap IV flucloxacillin therapy at a maximum dose of 14 grams per day.

Aims. To analyse flucloxacillin therapeutic drug monitoring (TDM) and safety of adding PBC to patients prescribed IV flucloxacillin therapy.

Methods. Medical records of patients prescribed PBC in addition to IV flucloxacillin therapy at St Vincent’s Campus, Sydney between 2015 and 2017 were reviewed. Patient total flucloxacillin serum levels were analysed, as well as liver function tests (LFTs) and serum creatinine.

Results. Seven patients were prescribed PBC during IV flucloxacillin therapy. Therapy doses and administration were variable. In two patients, steady states on 14g infusion + PBC were similar to those observed on 18g infusions alone. In the remaining four, increases in steady state flucloxacillin concentrations of between 5 and 15 mg/L were observed after addition of PBC during flucloxacillin infusions at a stable dose. In one patient, no obvious effect of PBC addition was observed. No patients had a substantial increase in LFTs or serum creatinine. One developed an allergic rash which may have been due either to PBC or to flucloxacillin.

Discussion. While PBC boosting of oral beta-lactams is well accepted, this practice has rarely been applied to IV therapy. This is one of the first case series to demonstrate the effect of PBC on serum concentrations of flucloxacillin when administered intravenously. Despite its small sample size, this cohort study suggests that the addition of PBC is an effective and safe intervention to facilitate dosing limitations of IV flucloxacillin in an outpatient setting.
318 Adaptive Feedback Control (& TDM) need NOT just be based on PK data

Dr Gauri Rao
University of North Carolina, USA

Abstract coming soon.
Clinical application of population pharmacokinetic models of antibiotics

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Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, Netherlands

As a consequence of increasing antimicrobial resistance and the shortage of new antibiotics, there is a need to optimize the use of antibiotics. Modelling of the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of antibiotics can support the optimization of dosing regimens. Antimicrobial efficacy is determined by susceptibility of the drug to the microorganism and exposure to the drug, which relies on the PK and the dose. Population PK models describe relationships between patients characteristics and drug exposure. To attain a specific PK/PD target, the exposure to the antibacterial agent should be adequate. Simulations with PK/PD models can be used to calculate the probability of target attainment (PTA) of several dosing regimen (figure 1A).

Three clinical applications of these models apply to antibiotics will be discussed: 1) dosing evaluation of old antibiotics, 2) setting clinical breakpoints (figure 1B) and 3) dosing individualization using therapeutic drug monitoring (TDM). For each clinical application, challenges regarding interpretation can be made. An important challenge is to improve the understanding of the interpretation of modelling results for good implementation of the dosing recommendations, clinical breakpoints and TDM advices.
320 Overcoming obstacles to practical, model-based prescribing

Dr Michael Neely

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In this presentation we will cover common barriers to model-based, computer-assisted therapeutic drug management and individual dose optimization, as well as possible solutions.
Evidence of and barriers to TDM-based precision dosing of oncology drugs

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Keio University School of Medicine, Tokyo, 〒160-8582

Introduction. A great deal of attention has been paid to individualized therapy of oncology drugs particularly for molecular targeting agents and immune-checkpoint inhibitors. A number of clinical studies confirmed that individualized cancer therapy using genetic markers significantly improved treatment outcome, for example selection of tyrosine kinase inhibitors based on mutation status of EGFR of non-small cell lung cancer. Companion diagnostics is an important tool to choose a right drug for a right patient. In the field of oncology, individualized (or personalized) drug therapy becomes a quite common concept but it mostly limits to select a right drug, not to select right dose. Although choosing right dose for every patient is also important component of individualized drug therapy, oncology community are not aware or even reluctant to changing dose.

Evidence. Exposure-response or exposure-toxicity relationships have been demonstrated for many oncologic drugs including chemotherapeutic agents and targeting agents. In addition, pharmacokinetic variability produces a large difference in drug exposure among patients with different pathophysiological backgrounds such as renal and hepatic functions, advanced age, performance status and so on. Therefore, flat dose is not optimal for each patient, and dose individualization based on TDM plays an important role for personalized cancer therapy. The scientific committee of IATDMCT, TDM in Oncology is working hard to assemble existing evidence showing that TDM is beneficial to improve efficacy and safety in cancer treatment. The committee is developing consensus guidelines on TDM for various oncology drugs. The TDM guideline for 5-FU has been recently published (Beumer et al. (2018) Clinical Pharmacology Therapeutics) and subsequent imatinib and busulfan projects are underway.

Barriers. A flat dose therapy (or simply standardized by body surface area) called as ‘standard treatment’ has been a tradition in oncology for long years and the standard treatment is believed a best option in oncology community. Current treatment guidelines do not mention dose adjustment but guide drug selection according to the decision tree. Therefore, oncologists simply optimize drug selection but are not familiar to adjust dose for individual patient. To open their eyes and change their practice, we need further evidence. There are little strong evidence to demonstrate the clinical benefit of TDM by prospective RCT studies. Observational or case-series studies seems not sufficient and we need prospective RCT evidence to change the oncology practice.
322 Widespread TDM implementation - You can lead a horse to water...

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¹Department of Clinical Microbiology and Infectious Diseases, St. Vincent’s Hospital, Sydney, ²Department of Clinical Pharmacology, St. Vincent’s Hospital, Sydney

Observational data suggests that therapeutic drug monitoring (TDM) may improve the efficacy, safety and cost of health care, especially for drugs with a narrow therapeutic index. Despite this, successful implementation of TDM processes is complex, institution/individual specific and often performed sub-optimally. Literature and case examples from our experience at a tertiary teaching hospital will highlight barriers and facilitators to the successful implementation of a TDM service and identify key features of a sustainable service.
323  Novel psychoactive substances in the Netherlands and beyond: Challenges for clinical toxicology and pharmacology

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Introduction: Novel psychoactive substances (NPS) have been increasingly introduced to the European Union as (legal) substitute for existing traditional illicit substances, like 3,4-methylenedioxymethamphetamine (MDMA) or cannabis. Most NPS are produced in small commercial laboratories and follow similar molecular scaffolds as their illicit counterparts, belonging to chemical classes such as phenethylamines, synthetic cathinones or arylcyclohexylamines. Despite chemical resemblance, marked differences between the numerous NPS and well-known illicit drugs may result in increased toxicity or unexpected adversity.

Method: A retrospect of many recent toxicological case reports and pharmacological studies was created to give an overview of the potential toxicity of a number of representatives of NPS chemical classes as they occur throughout the globe.

Results: Several NPS are associated with adverse effects and toxicity, in some cases even clearly elevated toxicity as compared to widely used and well-known illicit substances. Some NPS, like methylenedioxypyrovalerone (MDPV), are directed towards the stimulant users, but lead to severe tachycardia, hyperthermia and psychosis at relatively modest doses. Other NPS, like the NBOMe-molecules, are directed towards hallucinogen users but lead towards palpitations, extreme anxiety and fear, dosing these substances is often problematic. In the Netherlands, gamma hydroxybutyrate (GHB) is a popular recreational drug, but its narrow dose-effect margin often leads to visits to the emergency departments and it has rapid dependence potential. Finally, synthetic cannabinoids lead to a level of intoxication that is quite dissimilar to intoxications following use of natural cannabis.

Conclusions: NPS form a heterogeneous group of substances. Although some might resemble existing illicit substances, chemical differences and unfamiliarity with their dosing might lead to much more severe intoxications. The rapid evolution of chemical modification of former NPS into new ones faces society and policy with an enormous challenge for the future, with pharmacology and clinical toxicology positioned at the centre of it.
How to detect Novel Psychoactive Substances in a clinical setting?

Dr Eric Franssen
Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands

This presentation will deal with state-of-the-art analytical techniques that can detect drugs of abuse including Novel Psychoactive Substances (NPS) in patients. These techniques may shorten turnaround times and make toxicology screening in clinical situations feasible. Further, we will address what skills are needed to obtain relevant results with these techniques and how to interpret the data to select the best treatment of intoxicated patients.

What laboratory techniques and toxicology screening should be available in our hospitals and toxicology laboratories? For instance, the emergency departments (ED) of OLVG hospital in Amsterdam are the busiest ED’s in the Netherlands. The ED’s of OLVG hospital in the Centre of Amsterdam receive approximately 95,000 patients annually. For a proper diagnosis and treatment in the ED, it is important to know whether the patient’s condition is caused by drugs of abuse (DOA) or other substances. The clinical presentation of the patient may be the result of unintended (over)use of medicines. These cases can lead to serious adverse effects [1, 2].

In most hospitals in the Netherlands the hospital pharmacy is available for toxicological testing in blood and urine. At the ED’s of OLVG hospital a rapid triage is facilitated by a point-of-care test for drugs of abuse. Apart from the POCT, traditional laboratory methods are available at the central laboratory for confirmation analysis and/or quantification in blood/serum. Laboratory methods are important for the treatment of patients with potentially serious intoxications [1].

We present an overview of laboratory methods for blood and urine that should be available for the care of poisoned patients in the Amsterdam hospital setting. We discuss in which cases these methods may be optimally used. Furthermore, a distinction can be made between assays which should be available in all hospitals 24/7 and assays where other measures may be taken.

We conclude that several laboratory tests should be available 24/7 in hospitals, because they may change patient management [2]. Other tests may be postponed until working hours the next day and possibly sent out to an external laboratory. Toxicological screening of recreational drugs seems most meaningful in a clinical setting in patients, who are unconsciousness and in patients with psychiatric and neurological symptoms. The tests are less informative in patients who already admitted their drug abuse at ED presentation. With this information ED physicians may use these tests more effectively.

GC and LC-MS toxicology screening methods enable high quality rapid, extensive and cost-effective toxicology analyses. The LC-MS procedure has proven its value already in various clinical and post mortem cases showing sometimes unexpected results. However, toxicologists should still be aware of false negative findings. In this regard, validation of negative findings should get more attention.

NPS enter the market. In the Netherlands, gamma hydroxybutyrate (GHB), a central depressant drug and 4-fluoroamphetamine (4-FA, a stimulant drug) become more and more popular. It is often unclear whether these drugs can be detected by drugs tests. We present clinical cases and comment on laboratory tests to detect these NPS [3].

Post mortem toxicology screening in a forensic setting

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Toxicology can come in three domains. 1. Clinical toxicology: Patients with a possible intoxication need a clinical diagnosis and treatment in hospital. 2. Post mortem investigations are required in cases of suspicious deaths. The toxicologist may help to establish whether death might be caused by an intoxication. 3. When the intoxication is induced in a criminal act, it becomes real Forensic Toxicology and police and public prosecutor are involved.

It can be very advantageous treating these 3 domains as 3 phases in one sequence. Doing so there is less chance that information from an earlier phase will be lost before the next phase is entered. Of course, in real case work not all 3 phases will be clearly visible or will be present all three at all.

At the basis of all toxicology lie screening techniques from analytical chemistry. Were it colour- or crystal- tests in the 19th and early 20th century; via thin layer chromatography we reached the availability of large GC/MS and LC/MS spectral libraries. Lately they have become financially affordable for toxicologists working in all 3 phases described above. One thing has not changed: It is essential that these kinds of libraries, the toxicologist’s main toolboxes, are kept up to date continuously. Since they constitute the possibilities but also the limitations of the analytical toxicologist. Special attention is necessary to detect Novel Psychoactive Drugs (NPS). This market is quickly changing and these substances are important in at least clinical toxicology (phase 1). So phase 2 and 3 will follow soon after. These broad screening procedures, will not always cover the need in case work. E.g. substances like insulin and carbon monoxide are still not included in such screening procedures and even the probably most frequently encountered substance (ethanol) needs separate testing.

Speed is essential in phase 1 and 2. High quality of information is required in all phases, and phase 3 has it extra judicial aspects. For example, the chain of custody for all materials(samples) under investigation in a forensics case, is essential. Despite differences in working processes between clinicians and layers it can be surprisingly easy with small adjustments in processes to let information from an earlier phase be admissible for a court of law or available to a court at all!
This presentation aims at providing an overview of the current state-of-the-art of dried matrix sampling, with particular focus on the promises and perils of dried blood spot (DBS) sampling. It will start from a historical perspective and will provide a bird's-eye-view on what has been achieved in recent years, to end with future prospects.

Currently, major DBS applications include newborn screening for metabolic disorders, epidemiological surveys (e.g. HIV monitoring), therapeutic drug monitoring (TDM), as well as toxicology. Analytes being covered can be therapeutic drugs, drugs of abuse, environmental contaminants, toxins, as well as (trace) elements.

Implementing dried blood microsamples in an analytical workflow offers several advantages, such as simplification of the sample collection, transport, storage and processing. Furthermore, it enables collection of representative samples by non-medically trained persons in remote areas. However, the implementation of a DBS approach also brings along several challenges, amongst which the need for sensitivity and even more extensive method validation. In addition, quantitative DBS analysis also suffers from several issues, which are still limiting its breakthrough in routine bioanalysis. Amongst these issues are the effect of the volume of blood spotted onto the filter paper cards, spot inhomogeneity, as well as the influence of hematocrit. Several approaches allowing to cope with the distinct issues will be discussed, along with their potential and limitations.
Matrix effects and ion suppression are well-known phenomena mainly observed during LC-MS and can affect performance specifications such as detection limits, precision and linearity. Despite the terms matrix effects and ion suppression/enhancement are often used in the same context, they do not necessarily describe the same fundamental incidents. Suitable examples are selected to elucidate commonalities and differences.

Moreover, the influence of set-up, sample preparation, chromatography, and ionization of an LC-MS procedure on the occurrence and extent of matrix effects and ion suppression will be shown in multiple examples.

Methods for detection and evaluation of matrix effects will be presented and discussed. The establishment of a new bioanalytical method based on LC-MS should include an assessment of matrix effects, which poses an important component in method validation. In order to circumvent matrix effects (ion suppression/enhancement) in the course of method development a so-called post-column infusion experiment could be a useful tool for method optimization.

In special regard to therapeutic drug monitoring (TDM) and clinical toxicology (CT), a high variability of sample matrices due to alterations affected by diseases and comedication should be taken into consideration. In both CT and TDM multi-analyte procedures are gaining popularity but they were also shown to be more susceptible for matrix suppression/ionization effects. Therefore, systematic studies on matrix effects including those altered matrices should be conducted.
Dr Dennis Hesselink

*Erasmus MC, Rotterdam, The Netherlands*

Dennis Alexander Hesselink (1973) is an internist-nephrologist at the department of internal medicine of the Erasmus MC, Rotterdam, the Netherlands. In 2011, he won the Victor Armstrong young investigator award. In this talk, I will explain my personal career, the meaning of winning the young investigator award, and will give career advice to young scientists.
329 Monitoring adherence to cardiovascular agents with LCMSMS: a valuable and objective screening tool

Dr Erik van Maarseveen¹
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Adherence to antihypertensive agents is of importance to attain blood pressure targets and thereby prevent short and long term cardiovascular events. Recently, LC-MS/MS technology has gained interest for compound screening in medication adherence assessment. Consequently, screening for antihypertensive agents in serum using LC-MS/MS in patients suffering from cardiovascular diseases is currently explored and has successfully been implemented as standard of care in various centers worldwide. The results of recent studies and data from clinical practice by our and other research groups show that screening and/or concentration monitoring of antihypertensive drugs with LC-MS/MS is a valuable tool for a detailed and objective assessment of adherence in patients suffering from cardiovascular diseases. This lecture will cover the clinical relevance of monitoring adherence to cardiovascular agents with LC-MS/MS, illustrated by results from recent studies and unpublished data. Next, bioanalytical and clinical challenges are addressed. Finally, implementation of adherence monitoring of cardiovascular drugs in clinical practice will be discussed.
330  Tackling antibiotic resistance by targeting virulence not viability

Prof Jennifer Martin  
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Every year, more than 700,000 people die from drug-resistant infections. Without immediate action, that number is expected to soar to 10 million deaths each year by 2050. We urgently need new medicines to treat drug-resistant superbug infections. If not, we face a post-antibiotic future where simple infections will kill, and routine procedures - caesarean sections and hip replacements - will carry an intolerable risk of infection. To tackle this problem we need innovative new approaches.

Traditional antibiotics kill bacteria and this creates the strong selection pressure that leads to bacterial resistance. Our research aims to discover potential new drugs, with a novel mechanism of action, targeting bacterial virulence. Anti-virulence drugs won’t kill bacteria but they will disarm bacteria so they won’t cause infection. This presentation will describe the process of identifying, characterising and validating a virulence target and how our team finds chemicals with anti-virulence activity that will disarm rather than destroy bacteria.
Part 1: Basic Concepts

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Bayesian-based therapeutic drug monitoring (TDM) enables the individualization of dosing regimens using sparsely collected pharmacokinetic (PK) samples and pharmacometrics. Moreover, this method allows for more personalized dose adjustments compared to traditional TDM, which can lead to improved efficacy and decreased toxicity. In addition, these benefits can be obtained through the use of fewer PK samples than ordinarily required for traditional TDM, thus saving time, money, and patient discomfort. Vancomycin, a glycopeptide antibiotic, is often monitored through traditional TDM practices such as trough concentration monitoring. A vancomycin simulation exercise will be utilized to demonstrate how Bayesian-based TDM programs work.

For a patient of interest, various initial vancomycin regimens will be explored using Bayesian-based simulation and the known vancomycin pharmacokinetic-pharmacodynamic targets for efficacy and toxicity. An optimal vancomycin dose will be selected and administered to the patient. Then, a trough concentration will be collected and the Bayesian-based TDM program will determine updated PK parameters for the patient. Using this information, additional vancomycin dosing regimens will be explored through simulation-based exercises. This process will be repeated iteratively as new PK samples become available. The same patient will have vancomycin dosing regimens selected using a traditional vancomycin trough-based TDM algorithm. The results will be compared to the results obtained using a Bayesian-based approach.

This session will demonstrate how Bayesian-based TDM programs integrate population PK models, patient demographic information, and PK samples to optimize drug exposures in patients.
Introduction: Tacrolimus is the backbone of most immunosuppressive protocols for renal transplant recipients around the world. Tacrolimus has a narrow therapeutic window and hence therapeutic drug monitoring (TDM) is commonly used. However, a high intra- and inter individual pharmacokinetic variability makes dose individualization challenging. We have previously shown that utilizing pharmacokinetic population models for Bayesian based dosing significantly improves concentration target achievement compared to experienced transplant physicians [1]. Such models are dependent on accurate information on dose intake, drug concentrations and model-specific covariates; e.g. body weight, haematocrit etc. Due to practical reasons, drug concentrations are often limited to only trough concentrations and dosing times set to standard time such as 09:00 and 21:00.

Aims: The effect of novel micro sampling methods and smartphone applications on predictive accuracy of Bayesian based dose optimization in renal transplant recipients will be discussed.

Discussion: Correct dosing times are often not implemented in population models used in outpatients due to logistic reasons. With smartphone applications the patient can easily deliver the exact time every time he/she takes a dose simply by clicking in the app. This is an easy method to improve the quality of data inputs in these models. Bayesian estimates of pharmacokinetic population models are significantly dependent on reliable information of drug exposure. Clinical practice limits the number of blood samples applicable for TDM; e.g. time at hospital, blood volume etc. Dried blood spot techniques have been used for some drugs but haematocrit variation limits its use for tacrolimus. Novel finger prick sampling techniques using inert polymer tips that drawn small (10-20 µL) accurate volumes of blood may provide rich data without that patients needs to come to the hospital.

333 The way to and lessons from >100,000 online Bayesian dose adjustments of immunosuppressants

Prof Pierre Marquet\textsuperscript{1,2,3}

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Therapeutic drug monitoring is mandatory or strongly recommended for most immunosuppressive drugs and is currently based on the measurement of trough levels (C\textsubscript{0}), except for mycophenolate mofetil where the interdose area under the curve (AUC) is the only reliable exposure index. However, consensus conference reports also recommended the use of AUC for other drugs. Accurate AUC estimation, using the classic trapezoidal rule, requires a large number of blood samples, but alternative methods compatible with a limited sampling strategy (LSS) have been proposed, including maximum a posteriori Bayesian estimation (MAP-BE). Bayesian methods based on population PK (POPPK) models and limited individual PK information can reliably estimate individual patient PK parameters, hence the AUC. Since two decades, our group has developed PK models for most maintenance immunosuppressive drugs in various transplant populations, owing to multiple PK studies that we as well as other academic institutions or pharmaceutical companies have conducted. These PK models have been developed with different types of modelling software, using parametric, iterative two-stage modelling (ITSIM) or non-linear mixed-effects modelling (NONMEM), or non-parametric (Pmetrics) modelling. Limited sampling strategies and Bayesian estimators have been defined so as to best estimate the interdose AUC. These tools (currently >150 different Bayesian estimators) are used in several clinical trials and above all for routine dose individualization in transplant patients, through an expert system accessible online. Over the past 13 years, we have received >110,000 requests from all continents.
334 Integrating pharmaco and bacterial dynamics and immunology into optimizing antibiotic therapy

Dr Gauri Rao
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Abstract coming soon.
335 Part 3: Moving Forward

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Here we reinforce some aspects from the other workshop presenters that are particularly future oriented, as well as introduce some additional concepts like optimal sampling for clinical use in individual patients. At conclusion, there will be a 30 minute discussion with audience participation.
336  Cannabis and other drug interactions – usefulness of TDM

**Associate Professor Jennifer Schneider**

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With changes in cannabis access regulations around the world, it is increasingly likely patients will use a cannabis product, either recreationally or as a prescribed medication, as part of their treatment regimen for a range of conditions. Given that the public perceive cannabis as not being harmful, patients may not think to, or even want to, tell their health practitioner that they are co-administering cannabis with prescribed medications. As has been seen with co-administration of other ‘natural’ therapies such as St John’s Wort, there is a very real potential for significant drug interactions to occur. Even when a practitioner is aware that a patient is using a cannabis product, there is a lack of definitive data to help the clinician identify significant interactions as these types of medicines and products have not been through the usual Phase I to III studies and are entering at what would be Phase IV for any other new medication. Current databases which collect adverse drug reaction information may not yet be designed to capture important information about drug interactions with cannabis products. Adding to the complexity is the fact that cannabis products contain many different phytocannabinoids and other compounds such as terpenoids and flavonoids. The blend of constituents will vary between and within products. This presentation will provide an overview of current information available on potential drug-drug interactions and will discuss the role that therapeutic drug monitoring can play in identifying potentially significant interactions between cannabis products and other pharmacological agents.
Introduction. There is increasing interest in the use of cannabinoids for disease and symptom management, but limited information available regarding their pharmacokinetics and pharmacodynamics to guide prescribers.

A wide variety of chemical compounds contribute to the pharmacological and toxicological properties of cannabis, including the cannabinoids delta-9-tetrahydrocannabinol (THC), which is psychoactive, and the non-psychoactive cannabidiol (CBD). There is a need for pharmacological knowledge of the whole plant compared with these individual chemicals. Cannabis use is associated with both pathological and behavioural toxicity and accordingly, is contraindicated in the context of significant psychiatric, cardiovascular, renal or hepatic illness.

Pharmacology. The pharmacokinetics of cannabinoids and effects observed depend on the formulation and route of administration, which should be tailored to individual patient requirements. Pharmacokinetic processes are dynamic and may change over time, affected by frequency and magnitude of drug exposure, and disease state.

Both THC and CBD are hepatically metabolised, hence potential exists for pharmacokinetic drug interactions via inhibition or induction of enzymes or transporters. Their active metabolites have pharmacodynamics effects. Pharmacodynamic interactions may occur if cannabis is administered with other CNS depressant drugs and cardiac toxicity may occur via additive hypertension and tachycardia with sympathomimetic agents.

Discussion. Efficacy and toxicity are not consistent across all patient groups. More vulnerable populations such as older patients may benefit from the potential symptomatic and palliative benefits of cannabinoids, but are at increased risk of adverse effects. The limited availability of applicable pharmacokinetic and pharmacodynamic information highlights the need to initiate prescribing cannabis medicines using a "start low and go slow" approach, carefully observing for desired and adverse effects. Further clinical studies of appropriate cannabinoid and dose in the patient populations for whom prescribing may be considered are needed to derive better understanding of these drugs and enhance safe and optimal prescribing.
Synthetic cannabinoids are a class of Novel Psychoactive Substances. These compounds were originally investigated for their activity in the endocannabinoid system with a view for medicinal applications for conditions such as epilepsy, nausea, and appetite disturbances. However, the research was abandoned due to adverse effects and lay dormant for many years. Recently these compounds were found in smokable blends sold for the primary purpose of producing a cannabis like high whilst remaining undetectable.

Here we present a validated method for the detection of 19 synthetic cannabinoids in Oral Fluid. Oral fluid was chosen as many workplaces, due to union pressure are limited to this matrix. In response to legislative pressure the actual drug found in these smokable blends changes rapidly thus it is quicker to update a method for the detection of parent compounds, found in oral fluid, rather than the metabolites, most likely found in urine. This method demonstrates chromatographic separation in 4 minutes with a linearity from 2.5ng/mL to 500ng/mL and LOD of 1ng/mL. The accuracy was 90.5% - 112.5% of the target concentration and precision was 3% - 14.7%. This method was applied to genuine samples collected for drugs of abuse testing though no synthetic cannabinoids were found. Overall the method provides for rapid detection of multiple synthetic cannabinoids and is suitable for the routine laboratory.