

Scientific Spring Meeting
Friday April 12, 2019

Dutch Society for Clinical Pharmacology and Biopharmacy
Nederlandse Vereniging voor Klinische Farmacologie en Biofarmacie



PROGRAMME of the SCIENTIFIC MEETING
Friday April 12, 2019
Rotterdam

SCIENTIFIC MEETING OF THE DUTCH SOCIETY FOR CLINICAL PHARMACOLOGY AND BIOPHARMACY (NVKFB)
together with THE DUTCH SOCIETY FOR PHARMACOLOGY (NVF)

- 09.00 h **Registration (coffee & tea available)**
- 09.30 h **Plenary session (Dreamliner)**
- 09.30 h *Jeffrey Beekman (Utrecht): Organoids for research in cystic fibrosis*
- 10.00 h *Erwin Kompanje (Rotterdam): Ethics of organoids and precision medicine in general*
- 10.30 h **Coffee break**

- 11.00 h **Two parallel sessions**
- 1. Circle of life: from prenatal to end of life (Dreamliner)**
- Moderators: Bram Valkenburg & Anton Roks**
- 11.00 h *P. Mian, K. Allegaert, S. Conings, P. Annaert, D. Tibboel, M. Pfister, K. van Calsteren, J.N. van den Anker, A. Dallmann (Rotterdam):* Characterization of acetaminophen pharmacokinetics in the fetus through integration of placental transfer in a physiologically based pharmacokinetic model
- 11.15 h *Gaby Eliesen (Nijmegen):* Assessing placental exposure to TNF inhibitors in vivo and via ex vivo placenta perfusions
- 11.30 h *Aline Engberts (Leiden):* Dose optimization for preterm neonates: what we learned from the DINO study
- 11.45 h *T. de Kluis, S.C. Goulooze, M. van Dijk, E.H.J. Krekels, I. Ceelie, S.N. de Wildt, D. Tibboel, C.A.J. Knibbe (Leiden):* Item response theory modelling to define the concentration-effect relationship of morphine in preverbal children after major noncardiac surgery
- 12.00 h *G.A. Kalkman, C. Kramers, R.T.M. van Dongen, W. van den Brink, A.F.A. Schellekens (Nijmegen):* Trends in use and misuse of opioids in the Netherlands
- 12.15 h *B.T.G.M. Sallevelt, C.J.A. Huibers, I. Wilting, W. Knol, E.P. van Puijenbroek, A.C.G. Egberts (Utrecht):* Evaluation of clarity of the stopp/start criteria for clinical applicability in patient care for older people
- 2. Cardiovascular disease & metabolism (Arrow)**
- Moderators: Sanne Kloosterboer & Ben Janssen**
- 11.00 h *Jorie Versmissen (Rotterdam):* TDM for adherence of antihypertensive drugs
- 11.15 h *L.C. Hendriksen, B. Koch, B.H. Stricker, L.E Visser (Rotterdam):* Women experience a greater reduction in heart rate while using metoprolol than men
- 11.30 h *Estrellita Uijl (Rotterdam):* SiRNA against angiotensinogen as an antihypertensive treatment

- 11.45 h *J.V Koomen, J. Stevens, H.J.L. Heerspink* (Groningen): Exposure and response analysis of aleglitazar on cardiovascular risk markers and safety outcomes: an analysis of the AleCardio trial
- 12.00 h *Mariska van den Berg* (Groningen): Arginase inhibition in allergic asthma
- 12.15 h *J. Woudstra, M. de Boer, L. Hempenius, E.N. van Roon* (Leeuwarden): Effectiveness and tolerability of urea as second-line treatment for hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion
- 12.30 h **General Meetings, NVKFB (Dreamliner), NVF (Arrow)**
- 12.30h **Pharmaquiz PhD students/trainees: intense knowledge quiz on pharma and more (Sports bar)**
- 13.15h **Grab your lunch and take it to the poster session!**
- 13.30 h **Moderated poster session**

POSTER PRESENTATIONS (NVF posters not included yet)

Circle of life: from prenatal to end of life

S. de Hoogd, S.C. Goulooze, A.J. Valkenburg, E.H.J Krekels, M. van Dijk, D. Tibboel, C.A.J. Knibbe (Nieuwegein): Efficacy of morphine maintenance and rescue analgesia for postoperative pain after cardiac surgery in children: an analysis using repeated time-to-event analysis

S.C. Goulooze, E.H.J. Krekels, M. van Dijk, T. Hankemeier, D. Tibboel, E. Ista, C.A.J. Knibbe (Leiden): Mechanism-based modelling of iatrogenic withdrawal from analgesics and sedatives in critically ill children

C.Y. Ng, S.C. Goulooze, E.H.J. Krekels, M.Y.M. Peeters, D. Tibboel, A.J. Valkenburg, C.A.J. Knibbe (Leiden): Predicting oversedation in children in the intensive care using a logistic PK/PD model for midazolam and morphine

N.J.L. Smeets, B.D. van Groen, J. Pertijs, M.J. Wilmer, B. Smeets, R. Verdijk, S.N. de Wildt (Nijmegen): Ontogeny of human kidney OCT2 expression across the paediatric age range

B.D. van Groen, M.G. Mooij, E. van Duijn, C.A. Knibbe, K. Allegaert, A.D. Windhorst, J. van Rosmalen, N.H. Hendrikse, D. Tibboel, W.H.J. Vaes, S.N. de Wildt (Rotterdam): Pharmacokinetics and metabolism of an oral [¹⁴C]midazolam microdose in 46 critically ill children

C.J.A. Huibers, B.T.G.M. Sallevelt, D.A. de Groot, M.J. Boer, J.P.C.M. van Campen C.J. Davids, J.G. Hugtenburg, A.M.A. Vermeulen Windsant-Van den Tweel, H.P.J. van Hout, R.J. van Marum, M.C. Meulendijk (Utrecht): Conversion of STOPP/START version 2 into coded algorithms for software implementation: a multidisciplinary consensus procedure

G.H.M. Ponjee, H.W.P.C. van de Meerendonk, M.J.A. Janssen, F. Karapinar-Çarkit (Amsterdam): Implementation of a geriatric stewardship reduced post-discharge patient-reported adverse drug events by half

P.J. Upadhyay, N.J. Vet, S.C. Goulooze, E.H.J. Krekels, S.N. de Wildt, C.A.J. Knibbe (Leiden): Preliminary results on the study to identify the relation between midazolam concentrations and level of sedation in critically mechanically ventilated children

Cardiovascular Disease & Metabolism

L.E.J. Peeters, L. Feyz, E. Hameli, T. Zwart, S. Bahmany, B. van der Nagel, J. Daemen, T. van Gelder, J. Versmissen, B.C.P. Koch (Rotterdam): A clinical validation study of a dried blood spot assay for eight antihypertensive drugs

N. van Rein, U. Heide-Jørgensen, W.M. Lijfering, S.C. Cannegieter, H. Toft Sørensen (Aarhus): Major bleeding rates are similar in patients who use DOACs with interacting antiarrhythmics as compared with DOAC monotherapy

N. Vazirpanah, A. Ottria, M. van der Linden, C. Wichers, M. Schuiveling, E. van Lochem, A. Phipps-Green, T. R. Merriman, M. Zimmermann, M. Janssen, T.R.D.J. Radstake, J.C.A. Broen (Utrecht): mTOR inhibition by metformin impacts monosodium urate crystal induced inflammation and cell death in gout: a prelude to a new add-on therapy?

L.C. Hendriksen, K.M.C. Verhamme, B.H. Stricker, L.E Visser (Rotterdam): Women are started on a lower daily dose of metoprolol than men irrespective of dose recommendations

J.V Koomen, J. Stevens, H.J.L. Heerspink (Groningen): Exposure-response relationships of dapagliflozin on cardiovascular risk markers and adverse events

M.Y.A.M. Kroonen, J. Stevens, D. de Zeeuw, H.J.L. Heerspink (Groningen): Association between individual cholesterol and albuminuria response and exposure to atorvastatin or rosuvastatin

D. Mitrovic, R. Folkeringa, N. Veeger, E. van Roon (Heerenveen): The reasons for discontinuation of NOAC therapy in atrial fibrillation patients treated in NOAC clinic

N.J.L. Smeets, M. Dalinghaus, S.N. de Wildt (Nijmegen): Metabolomics in children with heart failure using ACE-inhibitors, an exciting opportunity?

Infectious diseases

B.G.J. Dekkers, M.S. Bolhuis, L. ter Beek, W.C.M. de Lange, T.S. van der Werf, J.W.C. Alffenaar, O.W. Akkerman (Groningen): Reduced moxifloxacin exposure in patients with tuberculosis and diabetes

E.M. Gieling, D.W. de Lange, E. Wallenburg, R. ter Heine, T. Frenzel, J. ten Oever, R.P. Pickkers, D.M. Burger, E. Kolwijck, J.A. Schouten, R.J.M. Brüggemann (Nijmegen): The impact and extent of renal function on the clearance of ciprofloxacin in ICU patients using different makers for renal function

R.A. Wijma, Th. ten Doesschate, A. Plomp, J.W. Mouton, M.J.M. Bonten (Rotterdam): Unregistered use of fosfomycin-trometamol in the Dutch health care setting

R.S. Nannan Panday, M. Schinkel, N. Alam, P.W.B. Nanayakkara (Amsterdam): The effect of pharmacological antipyresis on mortality in patients with sepsis

A. Sobels, L. Binkhorst, D. van Lammeren-Venema, E. Wilms (Den Haag): Therapeutic drug monitoring of posaconazole in patients with haematological malignancies

F.M. Keij, R.F. Kornelisse, N.G. Hartwig, B.C.P. Koch, I.K.M. Reiss, K. Allegaert, G.A. Tramper-Stranders (Rotterdam): A pharmacokinetic evaluation of oral clavulanic acid in term newborns

S. Hartman, L. Orriëns, N. Dia, M. Schreuder, R. Brüggemann, S.N. de Wildt (Nijmegen): Pharmacokinetics and target attainment of antibiotics in critically ill children - A systematic review of current literature

Immunology & Oncology

K.G.A.M. Husaarts, D.P. Hurkmans, E. Oomen-de Hoop, L.J. van Harten, S. Berghuis, R.J. van Alphen, L.E.A. Spierings, Q.C. van Rossum-Schornagel, M.B. Vastbinder, R.H.N. van Schaik, T. van Gelder, A. Jager, R.W.F. van Leeuwen, R.H.J. Mathijssen (Rotterdam): Impact of curcumin with or without piperine on the pharmacokinetics of tamoxifen

S.L. Groenland, R.A.G. van Eerden, R.B. Verheijen, A.D.R. Huitema, R.H. J. Mathijssen, N. Steeghs (Amsterdam): Boosting pazopanib exposure by splitting intake moments – a prospective pharmacokinetic study in cancer patients

M.A. Kuijvenhoven, A.J. Wilhelm, E. Meijer, J.J.W.M. Jansen, E.L. Swart (Amsterdam): Trough vs. AUC Monitoring of ciclosporine: A randomized comparison of adverse drug reactions in allogeneic stem cell recipients (TRAM study)

F.M. de Man, K.G.A.M. Husaarts, M. de With, E. Oomen-de Hoop, P. de Bruijn, H.K. van Halteren, N.C.H.P. van der Burg-de Graauw, F.A.L.M. Eskens, T. van Gelder, R.W.F. van Leeuwen, R.H.J. Mathijssen (Rotterdam): Influence of the proton pump inhibitor esomeprazole on the bioavailability of regorafenib: a randomized cross-over pharmacokinetic study

S.C.F.A. Huijberts, L. Wang, H. Rosing, B. Nuijen, J.H. Beijnen, R. Leite de Oliveira, R. Bernards, J.H.M. Schellens (Amsterdam): Proof of concept study with the histone deacetylase inhibitor (HDACi) vorinostat in patients with resistant BRAF^{v600e} mutated advanced melanoma

F.E. El-Khouly, S.E.M. Veldhuijzen van Zanten, M.H.A. Jansen, G.J.L. Kaspers, D.G. van Vuurden (Utrecht): Preliminary results of a phase I/II study of bevacizumab, irinotecan, and erlotinib in children with progressive diffuse intrinsic pontine glioma

F.M. de Man, G.D.M. Veerman, E. Oomen-de Hoop, M.J. Deenen, D. Meulendijks, C.M.P.W. Mandigers, M. Soesan, J.H.M. Schellens, E. van Meerten, T. van Gelder, R.H.J. Mathijssen (Rotterdam): Comparison of toxicity and effectiveness between fixed-dosed and body-surface area (BSA)-dosed capecitabine

R.W. Meijboom, H. Gardarsdottir, M.L. Becker, A.C.G. Egberts, H.G.M. Leufkens, T.J. Giezen (Utrecht): TNF α inhibitor treatment patterns in patients with rheumatic diseases and those with inflammatory bowel disease

Toxicology/ drug safety

L.M. Moss, M.H. Algera, M. van Velzen, J. Heuberger, S. Strafford, F. Gray, R. Dobbins, A. Dahan, G. Groeneveld (Leiden): High therapeutic buprenorphine levels reduce IV fentanyl respiratory depression

A. van Rongen, I.T. Vleut, C. Bethlehem, B.C.P. Koch (Rotterdam): Be aware of a barbiturate intoxication

J.K. Bekema, R.F. Mahomedradja, D.J. Brinkman, K.C.E. Sigaloff, M.A. Kuijvenhoven, M.A. van Agtmael (Amsterdam): The pharmacotherapy team: a novel multidisciplinary strategy using participatory action research to reduce in-hospital prescribing errors

M.M.E.A. Plantaz, B.A.J. Veldman, A.C. Esselink, H.W.H.A. Fleuren, C. Kramers (Nijmegen): Co-trimoxazole induced hyperkalemia and potassium monitoring in hospitalized patients

A.T.M. Wasylewicz, R.J.E. Grouls, E.H.M. Korsten T.C.G. Egberts (Eindhoven): Clinical rule guided pharmacists' intervention in hospitalized patients with hypokalemia: a time series analysis

S. Bakker, N. van Rein, M.J.H.A. Kruip, W.M. Lijfering, F.J.M. van der Meer (Leiden): The association between the use of SSRIs and the occurrence of INR ≥ 5 and major bleedings during treatment with VKAS – what is the underlying mechanism?

L.E.J. Peeters, C.A. den Uil, MD, L. Feyz, P.M.L.A. van den Bemt, J. Daemen, J. Versmissen (Rotterdam): Calcium channel blocker withdrawal-induced cardiac arrest in a patient with vasospastic angina

Neurology & Psychiatry

T.Q. Ruijs, J.A.A.C. Heuberger, A.A. de Goede, M.J.A.M. van Putten, G.J. Groeneveld (Leiden): TMS-EMG and TMS-EEG as a biomarker for pharmacological effects on cortical excitability

M.A.A. Saleh, J. Ellassais-Schaap, E.C.M. de Lange (Leiden): A comprehensive CNS PBPK model: extension with PH effect and brain binding

R. Pandit, D. Cianci, A.D.R. Huitema, J.J. Luykx (Utrecht): Unemployment is associated with amisulpride-induced weight gain

M.E. Cloesmeijer, R.A.A. Mathôt, M.E.L. Arbouw, M. Zeeman, H.L.A. van den Oever (Amsterdam): Optimizing dosing regimens of clonidine in intensive care unit patients with population pharmacokinetics

L.M.A. Favié, F. Groenendaal, M.P.H. van den Broek, C.M.A. Rademaker, T.C.G. Egberts, A.D.R. Huitema (Utrecht): Pharmacokinetics of lidocaine as anti-epileptic drug in term and preterm neonates

S.M. Kloosterboer, B.C.M. de Winter, M.H.J. Hillegers, G.C. Dieleman, K.M. Egberts, M. Gerlach, T. van Gelder, B. Dierckx, B.C.P. Koch (Rotterdam): Pharmacokinetics and clinical effect of pipamperone in children and adolescents

C.L. Berends, L.M. Moss, E.M.J. van Brummelen, I.M.C. Kamerling, V. Ville, V. Juarez-Perez, A.C. Benichou, G.J. Groeneveld (Leiden): A FIH clinical trial to assess safety, tolerability, PK and PD of STR-324, a dual enkephalinase inhibitor and therapeutic candidate for pain management

A.J. Valkenburg, M.Y. Peeters, S.C. Goulooze, C.V. Breatnach, R.A. Mathot, D. Tibboel, M. van Dijk, C.A.J. Knibbe (Rotterdam): Need for additional sedation after cardiac surgery in children with and without Down syndrome: a pharmacodynamic and pharmacokinetic analysis of midazolam

Education

E. Donker, D. Brinkman, M. Hessel, J.V. Smeden, A. Maassen Van Den Brink, B. Janssen, W. Knol, R. Goorden, L.E.J. Peeters, I. de Waard-Siebringa, G. Dumont, P. Jorens, A. Dupont, T. Christiaens, M. Richir, M. Van Agtmael, C. Kramers, J. Tichelaar (Amsterdam): Development of prescribing knowledge and skills of junior doctors in the first year after graduation

M.J. Bakkum, J. Tichelaar, K.C.E. Sigaloff, M.C. Richir, M.A. van Agtmael (Amsterdam): The efficacy of a mobile clinical decision support application compared to usual care: A proof of concept study among prescribers in different stages of training

F. van Rosse, L. Peeters, T. van Gelder, A. Maassen van den Brink (Rotterdam): Implementation of the national medication safety test at Erasmus MC. is a 'licence to prescribe' easily obtained or not?

M.M.M. Wilhelmus, B. Drukarch (Amsterdam): Success rate of test questions concerning pharmacokinetics is lower compared to pharmacodynamics in clinical pharmacology teaching in a health and life sciences curriculum

Pharmacogenetics and ...(miscellaneous?)

M. van der Lee, W.G. Allard, R.H.A.M Vossen, R.F. Baak-Pablo, H.J. Guchelaar, J.J. Swen, S.Y. Anvar (Leiden): Exploring the impact of long-read sequencing combined with a neural network predictive model to improve the prediction of CYP2D6 enzyme activity

T. Qin, D-J. van den Berg, Robin Hartman, Martin van Royen, E. de Lange (Leiden): Critical assessment of yield and variability in isolation and characterization of extracellular vesicles from human plasma using different methodologies

D.M. van Heteren, W.M. Lijfering, P.H. Reitsma, J.J. Swenn, M.H.A. Bos, N. van Rein (Leiden): Major bleeding rates are high in patients with a high INR combined with a G1639A SNP in the VKORC1 gene

14.30 h **Second parallel session**

1. Infectious diseases (Arrow)

Chairs: Paola Mian & Tom Schirris

14.30 h *Coen van Hasselt (Leiden): Quantitative translational pharmacology of antibiotics*

14.45 h *Birgit Koch (Rotterdam): TDM of antibiotics in critically ill patients*

15.00 h *Laurens Verscheijden (Nijmegen): PBPK model in meningitis*

15.15 h *R. Stemkens, C.H.C. Litjens, S. Dian, A.R. Ganiem, V. Yunivita, R. van Crevel, L.H.M. te Brake, R. Ruslami, R.E. Aarnoutse (Nijmegen): Pharmacokinetics of pyrazinamide during the initial phase of tuberculous meningitis treatment*

15.30 h *Agi Smolinska (Maastricht): Exhaled breath and gut microbiome as biomarkers for gastrointestinal diseases*

15.45 h *L. Verrest, M. Wasunna, F. Alves, T.P.C. Dorlo (Amsterdam): Population pharmacokinetic modeling of paromomycin in East African visceral leishmaniasis patients*

2. Immunology & Oncology (Dreamliner)

Moderators: Anne van Rongen & Hjalmar Bouma

14.30 h *Linda Henricks (Amsterdam): Why EMA recommends DPYD genotyping*

14.45 h *D.R. Geel, S.L. Groenland, J.A. Burgers, J.H. Beijnen, A.D.R. Huitema, N. Steeghs (Amsterdam): Exposure-response analysis of alk-inhibitor crizotinib in non-small cell lung cancer patients*

- 15.00 h *Tamara Mocking (Amsterdam): Light on photopharmacology*
- 15.15 h *M. van Nuland, J.A. Burgers, H. Rosing, A.D.R. Huitema, S. Marchetti, J.H. Beijnen (Amsterdam): Pilot study to predict the pharmacokinetics of a clinically relevant gemcitabine dose from a microdose*
- 15.30 h *A.S. Strik, S.E. Berends, D.R. Mould, R.A. Mathôt, C.I. Ponsioen, J. van den Brande, J.M. Jansen, D.R. Hoekman, J.F. Brandse, M. Löwenberg, G.R. D'Haens (Amsterdam): Dashboard driven versus conventional dosing of infliximab in inflammatory bowel disease: the precision trial*
- 15.45 h *Linette Willemsen (Utrecht): Oligosaccharides in prevention of allergies*
- 16.00 h **Prize ceremony with pitches by winners (Dreamliner):**
- ‘NVKFB’-Thesis Award 2018
- ‘NVF’-Thesis award 2018
- ‘NVKFB’-TOP Publication Award 2018
- ‘NVKFB’-Education Award 2018
- ‘NVF’ best poster prize
- ‘NVKFB’ best poster prize
- 16.30 h **Drinks and networking in the Sports bar; Certificates Clinical Pharmacologists**
- Drinks offered by the Erasmus MC Rotterdam

Characterization of acetaminophen pharmacokinetics in the fetus through integration of placental transfer in a physiologically based pharmacokinetic model

P.Mian^{1,2}, K. Allegaert^{1,3,4}, S. Conings³, P. Annaert^{5,6}, D. Tibboel¹, M. Pfister^{2,7}, K. van Calsteren^{3,8}, J.N. van den Anker^{1,2,9}, A. Dallmann²

¹ Intensive Care and Department of Paediatric Surgery, Erasmus MC, ² Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel (UKBB)³ Department of Development and Regeneration, KU Leuven, ⁴ Department of Pediatrics, Division of Neonatology, Erasmus MC, ⁵ Drug Delivery and Disposition, KU Leuven, ⁶ Department of Pharmaceutical and Pharmacological Sciences, KU Leuven ⁷ Certara LP⁸ Department of Obstetrics and Gynecology, University Hospitals Leuven,⁹ Division of Clinical Pharmacology, Children's National Health System.

Introduction: Little is known about fetal acetaminophen (paracetamol) pharmacokinetics and its potential for toxicity, despite the frequent use of acetaminophen during pregnancy. The aim of this study was to develop a feto-maternal physiologically based pharmacokinetic model (f-m PBPK) to predict placental transfer and PK of acetaminophen and its metabolites in fetus at term pregnancy.

Methods: Previously, a pregnancy PBPK model was developed for prediction of maternal PK of acetaminophen and its metabolites. This model was structurally extended with the fetal liver, and quantitative information on the maturation of relevant enzymes was integrated. Three different approaches (ex vivo placenta perfusion experiments, scaling of passive diffusion transfer rates, and the Mobi® default method) to describe placental drug transfer were tested.

Predicted maternal and fetal acetaminophen concentrations were compared with those observed in the literature.

Results: The 3 different approaches to predicted acetaminophen PK in the umbilical vein were found to yield broadly similar results. Acetaminophen exposure was similar in maternal blood compared to venous umbilical cord blood. Prediction of the median dose fraction of acetaminophen converted to its metabolites (f_m) revealed higher maternal acetaminophen-glucuronide formation clearance and sulphate formation compared to that in the fetal liver ($f_{m_glucuronide}$ 52.2 vs 0% and $f_{m_sulphate}$ 30.4 vs 0.8%, respectively) and higher fraction of acetaminophen converted to the reactive metabolite N-acetyl-*p*-benzoquinone-imine (f_{m_NAPQI} , 6.5 vs 0.06%) in pregnant women compared to their fetus. and higher fraction of acetaminophen converted to the reactive metabolite N-acetyl-*p*-benzoquinone-imine (f_{m_NAPQI} , 6.5 vs 0.06%) in pregnant women compared to their fetus.

Conclusion: No differences were observed in the 3 approaches for integration of placental drug transfer. Differences in acetaminophen biotransformation to its metabolites between pregnant women and their fetuses were quantitatively predicted.

Disclosure: Paola Mian received a Short term Minor (STM-2017) grant from the Stichting Sophia Kinderziekenhuis fonds to conduct this research.

ITEM RESPONSE THEORY MODELLING TO DEFINE THE CONCENTRATION-EFFECT RELATIONSHIP OF MORPHINE IN PREVERBAL CHILDREN AFTER MAJOR NONCARDIAC SURGERY

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Introduction: Despite the wide use of morphine to treat postoperative pain in children, a quantitative understanding of its concentration-effect relationship in this population is still lacking. Research on this topic is complicated by the fact that pain in preverbal children cannot be measured directly, but is derived from observational scales, such as the validated COMFORT-behavior (COMFORT-B) scale¹.

Methods: Data from 2667 COMFORT-B assessments were collected within 40 hours after major non-cardiac surgery from 217 children between 0 and 3 years old during two prior clinical studies.^{1,2} First, an item response theory (IRT) model was developed to estimate a latent variable representing the level of pain and distress, from the item-level data of COMFORT-B assessments³. A pharmacokinetic-pharmacodynamic model was then developed in NONMEM 7.3 to characterize the effect of morphine and other predictors on this latent variable.

Results: The PKPD model identified a population of non-responders to morphine (39.1% of patients), a lower expected COMFORT-B score in children below 14 days of age, and a recovery effect related to time after surgery with high inter-individual variability. In simulations of children older than 14 days, the analgesic effect of morphine at concentrations below 15 ng ml⁻¹ was limited, while adequate COMFORT-B scores (between 11 and 17) are seen in most patients when morphine concentrations are around 30 ng ml⁻¹ (Figure 1).

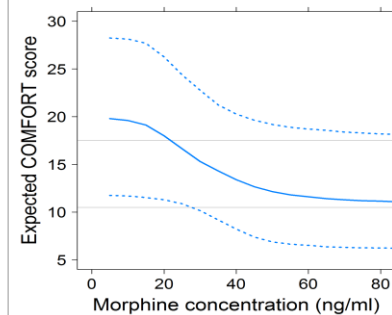


Figure 1: The median and 90% prediction interval for expected COMFORT-B scores, at 4 hours after surgery, in morphine-responsive children older than 14 days versus morphine concentrations.

Conclusion: In a considerable number of pediatric patients higher morphine concentrations were not associated with lower COMFORT-B scores (i.e. non-responders). While this could suggest a lack of analgesic effect of morphine in these children, a more likely explanation is that high COMFORT-B scores in these children were caused by distress or undersedation rather than pain. In addition, it seems that the often-cited morphine target concentrations of 10–20 ng ml⁻¹ might be too low for the treatment of pain¹ after major non-cardiac surgery in children older than 14 days.

1. van Dijk et al. Pain (2000) 84(2-3) 367-377
2. Ceelie et al. JAMA (2013) 309(2) 149-154
3. Väitalo et al. PAIN (2016) 157(8) 1611-1617

TRENDS IN USE AND MISUSE OF OPIOIDS IN THE NETHERLANDS

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Introduction: The United States is currently facing a serious opioid-use epidemic that started with increased sales of oxycodone and eventually resulted in massive overdose mortality. In Europe, including the Netherlands, the medical use of opioids also increased over the past decade but no increase in opioid-related deaths has yet been observed. Given the situation in the United States, we evaluated trends in the number of opioid prescriptions, proxies for misuse and (fatal) overdoses in the Netherlands.

Methods: The number of prescription opioid users was based on healthcare reimbursement data from the Dutch National Health Care Institute. Opioid-related hospitalizations were obtained from the Dutch National Hospital Care Basic Registration. Information on opioid addiction treatment was

obtained from the National Alcohol and Drugs Information System. Opioid related mortality was obtained from Statistics Netherlands. Each database covered all or most of the population of the Netherlands.

Results: Between 2008 and 2017 the overall number of prescription opioid users increased from 4.109 per 100.000 inhabitants to 7.489 per 100.000 inhabitants. This was mainly driven by the number of oxycodone users, which increased from 574 to 2.568 per 100.000 inhabitants in the same period. The number of hospitalizations due to opioid intoxication increased from 2,8 per 100.000 inhabitants in 2008 to 8,7 per 100.000 inhabitants in 2017, and the number of patients in addiction care for opioid use disorders other than heroin and methadone/buprenorphine substitution therapy increased from 3,1 per 100.000 inhabitants in 2008 to 5,1 per 100.000 inhabitants in 2015. Finally, opioid related mortality increased from 0,24 per 100.000 inhabitants in 2008 to 0,65 per 100.000 inhabitants in 2017.

Discussion: Opioid prescribing increased substantially in the past decade and several proxies for misuse show an increasing trend. However, the Netherlands is not experiencing opioid misuse at the same scale as the United States, which has an opioid related mortality of 15 per 100.000 inhabitants (Scholl et al., 2018). Nevertheless, our focus should be to implement safe opioid prescribing guidelines to prevent further escalation of a potential public health threat.

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EVALUATION OF CLARITY OF THE STOPP/START CRITERIA FOR CLINICAL APPLICABILITY IN PATIENT CARE FOR OLDER PEOPLE

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Introduction: Safe and effective prescribing for older people is challenging. STOPP and START criteria are explicit drug screening tools that have been developed to reduce problems associated with over- and underprescribing in older people. Clear formulation of such drug prescribing recommendations is crucial for successful implementation. The aim of this study was to evaluate the clarity of STOPP/START criteria for clinical applicability.

Methods: For each of the 114 STOPP/START recommendations version 2, the parts describing the action (what/how to do), condition (when to do) and explanation (why to do) were identified. Next, clarity rates of these three categories were determined using tools provided by the Appraisal of Guidelines for Research & Evaluation (AGREE) consortium. (Brouwers *et al.* 2010; Brouwers *et al.* 2015) Median and interquartile ranges of clarity rates were determined per category for both STOPP and START criteria. Recommendations with the lowest ($\leq Q1$) and highest ($\geq Q3$) clarity rates per category were analyzed in more detail to identify factors that either positively or negatively affected clarity most. Additionally, the nature of the category 'condition' was further classified into five descriptive

components: disease, sign, symptom, laboratory finding and medication.

Results: 13 out of 80 STOPP criteria and 4 out of 34 START criteria reached a clarity rate $>70\%$ for the three categories action, condition and explanation. The median clarity rate for STOPP related actions, conditions and explanations, were 67% (IQR 50%-77%), 58% (IQR 33%-83%) and 75% (IQR 58%-83%), respectively. The median clarity rates for START criteria related actions and conditions were 67% (IQR 50%-73%) and 50% (IQR 50%-73%), respectively. No clarity rates could be assessed for the explanation category for START criteria, as no explanations were present to substantiate the prescription of potential omissions.

Conclusion: Although the STOPP/START criteria are internationally renowned as 'explicit' drug screening tools to detect under- and overprescribing in older people, our results show that their clarity of presentation can still be improved. The definition of the target population (condition) was identified as the least explicit category in both START and STOPP. To increase the clarity of this category, laboratory findings and signs have the highest potential to be optimized by adding clear cut-off levels. Actions were considered unclear in case recommendations were based on inconclusive drug classes rather than specified on an individual drug level. For future development of explicit drug optimization tools, such as STOPP/START, these findings provide directions to improve clarity of drug recommendations and therefore enhance clinical applicability.

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WOMEN EXPERIENCE A GREATER REDUCTION IN HEART RATE WHILE USING METOPROLOL THAN MEN

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Introduction: In an experimental study plasma levels of metoprolol were analysed in healthy men and women after administration of 100 mg twice daily. Women had a two times higher C_{max} and a significantly higher AUC than men. Women had a greater reduction in heart rate. However, this greater PD effect appeared to be the result of the higher plasma concentration (1). Our objective was to evaluate if sex influences the association between plasma concentration and heart rate in patients using metoprolol.

Method: This study was performed within the Rotterdam Study (RS), a prospective cohort study of adults aged 45 years and older living in the Ommoord municipality of Rotterdam, the Netherlands. A detailed description of the Rotterdam Study methodology is described elsewhere (2). A random sample of 2000 patients from the RS was taken. From this sample, plasma levels were assessed in all 119 users of metoprolol on the sampling date. Participants using metoprolol in whom the plasma level did not exceed the lower level of quantification were excluded. ECGs were digitally stored and analysed. The clinical effect on heart rate was analysed using a linear regression model with metoprolol plasma level (µg/l), sex, age (year), BMI (kg/m²), time difference between blood sampling and ECG (sec), time difference between dose intake and blood sampling, and daily dose (mg) as co-variables.

Results: In total 47 women and 46 men had both a metoprolol plasma level and measured heart rate. In men the effect of metoprolol on heart rate was independent of all co-variables (Daily dose: 0.041, p=0.344. Age: 0.221, p=0.384. BMI: -0.197, p=0.745. Time difference between dose intake and blood sampling : 0.000, p=0.381. Time difference between blood draw and ECG: 0.000, p=0.612. Plasma level: -0.010, p=0.711). In women a higher plasma level was significantly associated with a lower heart rate. With every microgram per litre increase in metoprolol plasma level the heart rate decreased with 0.026 beats per minute (p=0.029). The heart rate was independent of the other co-variables (Daily dose: -0.019, p=0.437. Age: 0.031, p=0.852. BMI: -0.162, p=0.612. Time difference between dose intake and blood sampling: 0.000, p=0.748. Time difference between blood draw and ECG: 0.000, p=0.156).

Conclusion: In women there was a significant association between the plasma concentration of metoprolol and the heart rate. A higher plasma concentration correlated with a lower heart rate.

Reference:

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Exposure and response analysis of aleglitazar on cardiovascular risk markers and safety outcomes: An analysis of the AleCardio trial

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Introduction: Aleglitazar is a dual agonist of the PPAR- α - and $-\gamma$ receptors (PPAR $\alpha\gamma$) and has been shown to improve glycaemic parameters and lipid profile in patients with type 2 diabetes mellitus. The AleCardio trial aimed to characterize the efficacy and safety of PPAR $\alpha\gamma$ agonist aleglitazar in patients with type 2 diabetes mellitus and acute coronary syndrome. The trial terminated early due to futility and safety signals. It is unknown whether increased exposure to aleglitazar contributed to the safety findings in the AleCardio trial. The aim of the current study was therefore to characterize the interindividual variation in exposure to aleglitazar, to determine the factors associated with aleglitazar exposure, and to assess the association between aleglitazar exposure and safety and efficacy measures.

Methods: A population pharmacokinetic analysis was conducted to identify covariates that explained interindividual variability in exposure to aleglitazar. Subsequently, the effect of these covariates on surrogate and clinical outcome was assessed using ANCOVA and Cox proportional hazard models.

Results: Concomitant use of clopidogrel was identified in the population pharmacokinetic model as a covariate that could explain interindividual variability in exposure to aleglitazar. In the pharmacodynamic analysis, the effect of aleglitazar compared to placebo on HbA1c, haemoglobin, serum creatinine and adiponectin was modified by concomitant clopidogrel use (p for interaction 0.007, 0.002, <0.001 and <0.001 respectively, Table 3). The effect of aleglitazar compared to placebo on body weight and triglycerides was not modified by concomitant clopidogrel use (p for interaction 0.434 and 0.318 respectively). The effect of aleglitazar compared to placebo on the risks of hospitalization for heart failure was modified by clopidogrel use (p for interaction 0.01).

Conclusion: Concomitant administration of clopidogrel resulted in an increased exposure of aleglitazar, an additional decrease in HbA1c at the expense however of an additional decrease in haemoglobin and increase in the risk for hospitalisation for heart failure. Clopidogrel is a moderate inhibitor of the CYP2C8 enzyme, since aleglitazar is partially metabolized by the CYP2C8 enzyme, a pharmacokinetic interaction could explain the observed differences between patients with and without clopidogrel.

Effectiveness and tolerability of urea as second-line treatment for hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion

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Introduction: Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) can pose a therapeutic challenge. After fluid restriction, urea is recommended as second-line treatment by the Dutch Practice Guideline ‘Het Acute Boekje’ (Nederlandse Internisten Vereniging, 2017). Data on this practice are still scarce. We introduced urea for the treatment of SIADH in our hospital in December 2017 and designed a protocol to prospectively examine its effectiveness and tolerability.

Methods: We describe a case series of in-hospital patients with moderate to severe hyponatremia (serum sodium ≤ 129 mmol/L) due to SIADH, who were treated with urea in a dose of 0,25g-0,50g/kg/day when a prescribed fluid restriction had no effect or could not be applied. Patients were treated in accordance with our protocol between December 2017 and January 2019. Measurement of serum sodium was performed at baseline, after the first (at 12-24 hours) and second (at 36-48 hours) dose of urea and at the end of in-hospital treatment. Values of serum sodium at 24- and 48 hours before baseline were also collected. Statistical analysis included the Wilcoxon signed-rank test.

Results: Thirteen patients were treated with urea over a median of 5 days (range 2-10). Median serum sodium at baseline was 124 mmol/L (interquartile range 122-128), similar to median serum sodium at 48 hours before baseline, and increased to 128 mmol/L (IQR 123-130) ($P = 0,003$) after the first; and to 130 mmol/L (IQR 127-133 mmol/L) ($P = 0,002$) after the second dose of urea. At the end of in-hospital treatment normalization of serum sodium (≥ 135 mmol/L) was seen in 8 (62%) patients. Seven (54%) patients reported moderate intake difficulties due to the taste of urea. Six of them completed in-hospital treatment. In one patient urea was discontinued because of co-reported nausea.

Conclusion: Our data show that urea is an effective treatment strategy in hospitalized patients with hyponatremia due to SIADH, when fluid restriction is not effective or can not be applied. A majority of our patients experienced moderate intake difficulties due to the taste of urea. In most cases this did not lead to discontinuation of treatment.

PREDICTING OVERSEDATION IN CHILDREN IN THE INTENSIVE CARE USING A LOGISTIC PK/PD MODEL FOR MIDAZOLAM AND MORPHINE

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Introduction: Analgosedation in children after cardiac surgery is predominantly achieved with a combination of midazolam and morphine.¹ However, it is currently unknown at which concentrations of these sedative agents oversedation occurs. In this study, we therefore developed a model that predicts the probability of oversedation based on midazolam and morphine concentrations. Eventually, this can help us to establish a maximum recommended therapeutic dose for these drugs in order to prevent oversedation in children.

Methods: The patient data that was used in this project was collected as part of a study performed by *Valkenburg et al., 2016*² and *Peeters et al.*³. We included data from 35 patients, aged 3-36 months, that underwent cardiac surgery. Oversedation was defined as having a COMFORT-B score below 11. A population PK/PD model with logistic regression was developed using NONMEM to characterize the influence of midazolam and morphine plasma concentrations on oversedation.

Results: Oversedation was observed during 74 (13.1%) COMFORT-B assessments. The probability of oversedation was best modelled by a baseline probability of 6.5%, an anaesthetic washout period and functions related to midazolam and morphine concentrations. The anaesthetic washout, with an estimated half-life of 60 minutes, was included reflecting an increased probability of oversedation which was observed in the first hours after surgery. Midazolam concentrations were found to have a linear relationship with the log odds of oversedation, while the effect of morphine was modelled with a step function. A midazolam concentration of 2.0 micromol/L was found to correspond with an 11.3% probability of oversedation. For morphine, it was found that concentrations above 47.2 ng/ml increased the probability of oversedation to 16.0%; these concentration levels were present in almost 20% of the observations.

Conclusion: In this study, we developed a model to predict oversedation in children, in which the influence of midazolam and morphine concentration was quantified. While for midazolam a linear relationship was identified, for morphine it was found that morphine concentrations exceeding 50 ng/ml significantly increased the probability of oversedation. This suggests that morphine's side effects might outweigh any additional analgesic effects above these levels.

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ONTOGENY OF HUMAN KIDNEY OCT2 EXPRESSION ACROSS THE PAEDIATRIC AGE RANGE.

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Background: In adults, the organic cation transporter 2 (protein name OCT2, gene name *SLC22A2*) is localised in the kidney proximal tubules where it mediates organic cation secretion. Hence, the transporter plays a role in the disposition and excretion of several drugs and drug-drug interactions. To better understand the disposition of OCT2 substrate drugs in children, we studied OCT2 localisation and expression in paediatric kidney tissue.

Methods: The expression of OCT2 was visualised in tissue using immunohistochemical staining. Tissues were derived post-mortem from children aged 0 -14 years. Gestational age varied between 24 and 40 weeks. Intensity of the staining at the basolateral membrane was scored by two individual observers using three categories; negative, detectible and high. Agreement between two observers was determined using Cohen's kappa.

Results: 44 kidney samples (n=17 neonates, n=17 infants, n=7 children, n=3 adolescent) were analysed and scored. There was substantial agreement between two judgements with a kappa of 0.773 (p<0.005). No age related pattern was observed in the expression of OCT2. Even in the youngest age group, the expression of OCT2 was clearly visible.

Conclusion: The kidney expression of OCT2 did not show an age-related pattern. In all age groups, expression levels were similar and OCT2 was properly localised at the basolateral membrane. These findings suggest that, with increasing age, OCT2 will not influence the renal excretion of its substrates.

PHARMACOKINETICS AND METABOLISM OF AN ORAL [¹⁴C]MIDAZOLAM MICRODOSE IN 46 CRITICALLY ILL CHILDREN

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Background

Microdose studies present an interesting innovation to study age-related changes in drug metabolism in young children. Midazolam (MDZ) is metabolized by CYP3A into OH-MDZ, which is next glucuronidated into OH-MDZ-glucuronide. We aimed to study pharmacokinetics (PK) and metabolism of an oral [¹⁴C]MDZ microdose in children, to ultimately delineate maturation of involved drug metabolism pathways.

Methods

Children (0-6 yrs) admitted to the pediatric intensive care were eligible when they received IV midazolam for therapeutic reasons and had arterial line in place for bloodsampling. After administration of a single oral [¹⁴C]MDZ microdose, blood samples were taken up to 24 hrs. Plasma concentrations of [¹⁴C]MDZ and the [¹⁴C]metabolites were determined by AMS. PK parameters were estimated with PK solver software.

Results

Of 454 eligible patients, 358 were excluded, and informed consent was obtained from parents of 46 children [median age 2.1 months (range 2 days – 5.3 years)] who received a [¹⁴C]MDZ microdose (20.3 [14.1-23.6] ng/kg; 58 [40-67] Bq/kg). There was a wide range in all PK parameters and difference with literature data in preterm infants and healthy children:

	Our study			Preterm infants - NICU*		Healthy children (6mth-2yr)**	
	MDZ	I-OH-MDZ	OH-MDZ-GLUC	MDZ	I-OH-MDZ	MDZ	I-OH-MDZ
CL (L/h/kg)	0.32 (0.04-6.03)	-	-	0.16 (0.04-0.93)	-	3.0 ± 1.4	-
DN AUC ₀₋₄ (ng/ml*h)	279.45 (16.25-1497.25)	20.88 (1.85-125.18)	645.35 (162.88-2134.06)	613 (90-2286)	68.9 (<0.01-272.6)	-	-
DN AUC _{0-inf} (ng/ml*h)	811.82 (16.60-2802.94)	29.07 (4.51-132.74)	870.10 (179.52-4984.74)	642 (108-2465)	71.8 (1.6-305.0)	68.4 ± 58.1	39.3 ± 22.0
T _{0.5} (h)	4.63 (0.88-27.02)	-	-	7.6 (1.2-15.1)	-	3.1 ± 1.5	1.7 ± 0.8 2.0 0.8
Vd/F (L/kg)	2.21 (0.83-11.08)	-	-	1.4 (0.3-12.1)	-	14.7 ± 10.6	-

DN=Dose Normalized to 0.1 mg/kg MDZ. *Wildt et al. BJCP,2002 **Reed et al. J Clin Pharm, 2001

Discussion/conclusion

In conclusion, we successfully used an oral [¹⁴C]MDZ microdose to study the PK and metabolism of MDZ in children. The wide range in PK parameters and discrepancy with literature data potentially results from the influence of age or disease. We further aim to use a population PK approach, to elucidate the absolute bioavailability of MDZ and the influence of age and disease on intestinal and hepatic CYP3A by including the unlabeled midazolam data from the IV therapeutic dose.

Conversion of STOPP/START version 2 into coded algorithms for software implementation: a multidisciplinary consensus procedure

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Background: The rapid digitalization of medical practice has attracted growing interest in developing software applications for clinical guidelines and explicit screening tools to detect potentially inappropriate prescribing, such as STOPP/START criteria. The aim of the current study was to develop and provide logically unambiguous algorithms of STOPP/START criteria version 2, encoded with international disease and medication classification codes, to facilitate the development of software applications for multiple purposes.

METHODS: A four round multidisciplinary consensus and validation procedure was conducted to develop implementable coded algorithms for software applications of STOPP/START criteria version 2, based on ICD, ICPC, LOINC and ATC classification databases.

RESULTS: Consensus was reached for all 34 START criteria and 76 out of 80 STOPP criteria. The resulting 110 algorithms, modeled as inference rules in decision tables, are provided as supplementary data.

CONCLUSION: This is the first study providing implementable algorithms for software applications based on STOPP/START version 2, validated in a computer decision support system. These algorithms could serve as a template for applying STOPP/START criteria version 2 to any software application, allowing for adaptations of the included ICD, ICPC and ATC codes and changing the cut-off levels for laboratory measurements to match local guidelines or clinical expertise.

IMPLEMENTATION OF A GERIATRIC STEWARDSHIP REDUCED POST-DISCHARGE PATIENT-REPORTED ADVERSE DRUG EVENTS BY HALF

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Background

A main obstacle of inpatient medication review is the lack of insight into patient needs and the outpatient medical history.

Aim

To establish whether post-discharge drug-related problems (DRPs) can be reduced via Geriatric Stewardship, which entails inpatient medication reviews based on patient interviews and consultations with primary care providers.

Methods

This implementation study with a pre-post design included hospitalized elderly with polypharmacy and a risk factor for frailty who were admitted to orthopedic or surgical wards. The pre-cohort received usual care; the after-cohort received an extended medication review based on 1) a review of the clinical records, 2) a consultation with the general practitioner and community pharmacist, 3) a patient interview, and 4) a multidisciplinary evaluation of all the recommendations of step 1 to 3. Two weeks after discharge, patient-reported DRPs were assessed by telephone using a validated questionnaire. DRPs were classified into 1) patient-reported adverse drug events (pADEs) (e.g. coughing), 2) practical problems (e.g. dysphagia), and 3) questions about medication (e.g. duration of treatment).

The primary outcome was the number of DRPs per patient in each group. A Poisson regression was performed to compare the groups, adjusted for potential confounders. Secondary, we assessed the number of recommendations that were altered after patient interviews and consultations with primary care providers in the intervention group.

Results

Of 127 included patients (control: 74, intervention: 53), intervention patients reported fewer DRPs after discharge than patients that received usual care, 2.8 vs. 3.3 per patient (RR_{adjusted} 0.83, 95%CI 0.66-1.05). The difference was mainly due to a 50% reduction in pADEs. In the intervention group, nearly 30% of the medication review recommendations based on the clinical records were altered after consulting with the patient and primary care providers.

Conclusion

The implementation of a Geriatric Stewardship reduced DRPs after discharge in this cohort. Significance was not reached but further research with larger patient numbers may confirm this effect and determine the effect on clinical outcomes. The importance of patient interviews is consistent with the findings of Viktil (2006) on the value of patient interviews in an inpatient setting. No previous study considered consultations of primary care providers.

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A CLINICAL VALIDATION STUDY OF A DRIED BLOOD SPOT ASSAY FOR EIGHT ANTIHYPERTENSIVE DRUGS

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Background: In patients with resistant hypertension there is a need to optimize pharmacotherapy by identifying non-adherence. Dried blood spot (DBS) sampling is a minimal invasive method designed to objectify non-adherence, which enables sampling at a random time point at any location. We therefore developed and clinically validated a DBS method for qualifying eight antihypertensive drugs (AHDs) and four active metabolites using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). We also studied if DBS could be used as a quantifying method for AHDs.

Methods: Validation of the DBS assay was carried out in accordance to the FDA requirements. For clinical validation, paired peak and trough levels of DBS and venous plasma samples were analyzed with Deming regression and Bland-Altman analyses were performed to validate DBS as quantifying method for AHDs.

Results: The UPLC-MS/MS method was successfully validated to simultaneously measure eight AHDs and their metabolites in DBS. Deming regression was used to predict bias when comparing plasma and DBS. No bias was observed in N=2; constant bias was seen in N=1 and proportional bias in N=9 of the AHDs and metabolites. After correction for bias we found an agreement between plasma and DBS for all antihypertensive drugs except for hydrochlorothiazide. Using the Bland-Altman analysis, only valsartan met the strict acceptance criteria for quantification.

Conclusion: This study showed that DBS is a reliable and convenient method to assess AHD adherence. Furthermore, DBS is a valid method to quantify valsartan concentrations.

MAJOR BLEEDING RATES ARE SIMILAR IN PATIENTS WHO USE DOACS WITH INTERACTING ANTIARRHYTHMICS AS COMPARED WITH DOAC MONOTHERAPY

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Background: Patients with atrial fibrillation (AF) frequently require oral anticoagulant therapy, combined with antiarrhythmics such as amiodarone and verapamil. These antiarrhythmics are P-glycoprotein inhibitors and interact with direct oral anticoagulants (DOACs) which may result in major bleeding. However, data are lacking on major bleeding rates stratified by DOAC and antiarrhythmic use.

Aims: To determine incidence rates and relative risks of major bleeding in AF patients who use a DOAC and an interacting antiarrhythmic compared with DOAC monotherapy users.

Methods: This nationwide cohort study included Danish patients aged 50 years or older diagnosed with incident AF who started DOAC treatment from 2011-2015. Six exposure categories (based on prescription data) were considered: dabigatran, Xa-inhibitor, dabigatran with verapamil, dabigatran with amiodarone, Xa-inhibitor with verapamil, Xa-inhibitor with amiodaron. Incidence rates (IRs) of major bleeds were calculated per 100 patient-years, and hazard ratios

and 95% confidence intervals (CIs) were estimated by time-dependent Cox regression.

Results: Of 48,052 AF patients using DOACs at baseline, 43,513 (91%) used DOAC monotherapy, 2233 (5%) used a combination with amiodarone, and 2306 (5%) used a combination with verapamil. 1620 major bleeds occurred during a follow-up of 63,377 patient-years. The IR for bleeds during dabigatran monotherapy was 2.09 (95% CI 1.95-2.24) and similar for patients who also used amiodarone (2.23, 95% CI 1.62-3.01) or verapamil (2.10, 95% CI 1.56-2.78). The hazard ratios were 1.03 (95% CI 0.75-1.42) and 1.02 (95% CI 0.76-1.38), respectively. The IR for bleeds during Xa-inhibitor monotherapy was 3.35 (95% CI 3.11-3.60) and similar for patients who also used amiodarone (3.34, 95% CI 2.40-4.53) or verapamil (3.35, 95% CI 2.39-4.60). The hazard ratios were 0.99 (95% CI 0.71-1.37), and 1.02 (95% CI 0.73-1.43), respectively.

Conclusion: Major bleeding rates and risk estimates were similar in AF patients using amiodarone or verapamil with a DOAC as compared with DOAC monotherapy. Different types of DOACs had similar risk estimates.

mTOR inhibition by metformin impacts monosodium urate crystal induced inflammation and cell death in gout: a prelude to a new add-on therapy?

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Introduction and aim: Gout is the most common inflammatory arthritis worldwide, patients experience a heavy burden of cardiovascular and metabolic diseases. The inflammation is caused by the deposition of monosodium urate (MSU) crystals in tissues, especially in the joints, triggering immune cells to mount an inflammatory reaction. Recently it was shown that MSU crystals can induce mechanistic target of rapamycin (mTOR) signaling in monocytes encountering these crystals in vitro. The mTOR pathway is strongly implicated in cardiovascular and metabolic disease. We hypothesized that inhibiting this pathway in gout might be a novel avenue of treatment in these patients, targeting both inflammation and comorbidities.

Results: We show that ex vivo immune cells from gout patients exhibit higher expression of the mTOR pathway ($P < 0.0001$), which we can mimic in vitro by stimulating healthy immune cells (B lymphocytes, monocytes, T lymphocytes) with MSU crystals. Monocytes are the most prominent mTOR expressers compared to the other immune cell subsets. By using live cell imaging, we demonstrate that monocytes, upon encountering MSU crystals, initiate cell death and release a wide array of pro-inflammatory cytokines. By inhibiting mTOR signaling with metformin or rapamycin a significant reduction of cell death and release of inflammatory mediators was observed. Consistent with this, we show that patients with gout that are treated with the mTOR inhibitor metformin have a lower frequency of gout attacks. 2.04 (95% CI 1.29-2.38) flares per year in the allopurinol with metformin group versus 4.00 (95% CI 2.57-5.43) in the group with allopurinol with standard treatment.

Conclusions: We propose mTOR inhibition as a novel therapeutic target of interest in gout treatment.

WOMEN ARE STARTED ON A LOWER DAILY DOSE OF METOPROLOL THAN MEN IRRESPECTIVE OF DOSE RECOMMENDATIONS

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Introduction: An experimental study compared levels of metoprolol in healthy men and women after administration of 100 mg of metoprolol two times daily. Women had a twice higher C_{max} and a significantly higher AUC than men (1). Guidelines recommend a dose of 100 – 200 mg metoprolol daily in both men and women for all indications. In chronic heart failure, recommended starting doses are lower, however, over the course of a few weeks the daily dose should be titrated to a maintenance dose of 100 – 200 mg metoprolol. To evaluate whether physicians prescribe the same starting dose of metoprolol for men and women this study was conducted. To see if differences occurred after the start of metoprolol, the dosing regime was followed up to 10 prescriptions.

Method: The study had a cohort design and was performed in the Rotterdam Study (RS) and replicated in the Integrated Primary Care Information (IPCI) database. The study population comprised all incident patients aged 18 years and older who had at least one metoprolol prescription. The primary outcome was the mean daily dose in mg of the first prescription of metoprolol. The secondary outcome was the dose regimen, expressed in mean daily dose in mg during the first 10 prescriptions. Data were analysed using an independent t-test to compare the mean daily dose of metoprolol for men and women over the first 10 prescriptions

and a linear regression was used to adjust for age and the indications heart failure, atrial fibrillations, myocardial infarction, hypertension, and coronary heart disease.

Results: In total, 1,813 women and 1,393 men were included from the RS. The mean daily dose of the first prescription was significantly lower in women than in men; 69.8 mg and 75.4 mg, respectively. The dose of the 1st prescription was 5.6 mg (95%CI -8.4, -2.8) lower in women. The dosages increased over the first 10 prescriptions. The difference in dose between women and men remained significant for the first five prescriptions. In total 23,074 women and 19,562 men were included from the IPCI database. The mean daily starting dose of metoprolol was significantly lower in women compared to men; 57.3 mg and 62.0 mg, respectively. The dose of the first prescription was 4.6 mg (95% CI -5.3, -4.0) lower in women. Dosages for both women and men increased slightly from the 1st to the 10th prescription up to 68.1 mg and 71.7 mg at prescription 10, respectively. In either database both men and women received lower doses than recommended by guidelines.

Conclusion: Women received a significantly lower dose of metoprolol than men. Both men and women received lower doses than recommended by guidelines.

Reference: 1. Luzier AB, et al. Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. Clin Pharmacol Ther 1999;66:594-601.

Exposure-Response relationships of dapagliflozin on cardiovascular risk markers and adverse events

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Introduction: Dapagliflozin is a sodium glucose co-transporter 2 inhibitor which has been developed as oral glucose lowering drug. Dapagliflozin has also been shown to decrease other cardiovascular risk markers including body weight, systolic blood pressure, and albuminuria. A large outcome trial with dapagliflozin 10 mg daily reported reductions in the risks of hospitalization for heart failure and renal outcomes. These benefits appear to be largely independent of glycaemic control. Since the original dose finding studies focused on glycaemic effects, this analysis aimed to characterize the exposure-response relationship between dapagliflozin and non-glycaemic risk markers as well as adverse events, in order to evaluate whether the currently registered 10 mg dose is optimal for cardiovascular protection.

Methods: For each individual patient, the exposure was estimated using a previously developed population pharmacokinetic model. The exposure-response relationship was then quantified using population pharmacodynamic- and repeated time-to-event models for each response parameter of interest. Data was obtained from a pooled database of thirteen 24-week randomized controlled clinical trials of the clinical development program of dapagliflozin.

Results: A dose of 10 mg dapagliflozin resulted in an average individual exposure of 638 ng.h/mL (95% Prediction Interval (PI): 354 to 1061 ng.h/mL), which translated in 71.2% (95% PI: 57.9 to 80.5%), 61.1 % (95% PI: 58.0 to 64.8%) and 91.3 % (95% PI: 85.4 to 94.6%) of its estimated maximum effect for fasting plasma glucose, haematocrit and serum creatinine, respectively. For urinary albumin-creatinine ratio, 10 mg dapagliflozin achieved 25.7% (95% PI: 23.5 to 28.3%) of the maximum effect and, for both systolic blood pressure and uric acid, 10 mg dapagliflozin induced less than 10% of the estimated maximum effect.

Conclusion: The analysis demonstrated that a dose higher than 10 mg could provide additional beneficial effects in haematocrit, systolic blood pressure, urinary albumin-creatinine ratio and uric acid. Furthermore, the exposure-response analysis for genital tract infections suggested that higher doses than 10 mg/day did not lead to a higher incidence. The exposure-response relationship for the evaluated non-glycaemic effect parameters raise the question whether clinical outcome trials specifically assessing the benefits of higher than currently registered doses of dapagliflozin are merited.

ASSOCIATION BETWEEN INDIVIDUAL CHOLESTEROL AND ALBUMINURIA RESPONSE AND EXPOSURE TO ATORVASTATIN OR ROSUVASTATIN

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Objective: The PLANET trials showed that atorvastatin 80 mg (ATOR) but not rosuvastatin at either 10 or 40 mg (ROSU) reduced urinary albumin:creatinine ratio (UACR) while effects on LDL cholesterol were similar. However, individual changes in both UACR and LDL cholesterol to these statins varied widely between patients. This interindividual variability could not be explained by patients physical or biochemical characteristics. We assessed whether the plasma concentration of the statins were associated with LDL cholesterol and albuminuria response.

Design, setting and patients: the PLANET trials randomized patients with an urine protein:creatinine ratio of 500 – 5000 mg/g, fasting LDL cholesterol >2.3 mmol/L and stable treatment with ACE or ARB to a 52 week treatment period with ATOR 80 mg, ROSU 10 mg or 40 mg. For the current analysis available samples on week 52 from therapy adherent patients (>80% compliance by pill count) were included (N=295). Plasma concentrations of ATOR and ROSU and of active metabolites were measured by Liquid Chromatography Mass Spectrometry.

Main Outcome Measurement: Percentage change in UACR and absolute change in LDL cholesterol (delta LDL), comparing baseline to week 52.

Results: Median (interquartile range) plasma concentrations at week 52 for ATOR 80 mg was 2.8 ng/mL (1.7 – 8.5) in the Atorvastatin group; for ROSU 10 mg 0.7 ng/mL (0.6 – 1.8) and ROSU 40 mg 2.5 ng/mL (1.9– 6.6) in the Rosuvastatin group. The variation in plasma concentration of the statin was (weakly) associated with the LDL changes and not with UACR changes for both statins (table). Serum albumin ($\beta = 0.63$, $p = 0.05$) and eGFR per 10 ml/min ($\beta = -0.09$; $p = 0.04$) were independently associated with ROSU plasma conc. Active metabolites concentration of either ROSU or ATOR did not correlate with LDL and UACR changes.

Conclusions: Individual variation in plasma concentrations of both atorvastatin and rosuvastatin explained partly the LDL changes of the patients. The individual variation in albuminuria effects of ROSU and ATOR were not explained by the level of plasma concentration of statin or its metabolites.

Table: Pearson correlations between plasma concentration ATOR and ROSU and change in LDL cholesterol and UACR

	Delta LDL		Delta UACR	
	Pearson Correlation	P-value	Pearson Correlation	P-value
Atorvastatin (n=92)	-0.20	0.06	0.14	0.20
Rosuvastatin (n=203)	-0.25	0.0006	-0.06	0.45

THE REASONS FOR DISCONTINUATION OF NOAC THERAPY IN ATRIAL FIBRILLATION PATIENTS TREATED IN NOAC CLINIC

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Introduction: Because of the growing numbers of NOAC (novel oral anticoagulants) users there is also a growing interest in patient experience in real life with these new type of drugs. At this moment we know that about 20% of NOAC patients discontinue the therapy. Less is known about reasons for discontinuation and what effect it has on patient (preference) in real life. These data could help to understand how patients deal with NOAC use when intensive monitoring under Thrombosis Service is unnecessary. The aim of this study is to investigate the reasons for discontinuation of NOAC therapy. In addition, risk indicators for discontinuation and discontinuation rates between NOAC's will be evaluated.

Methods: This is a retrospective observational cohort study of 875 Atrial Fibrillation patients which use apixaban, dabigatran or rivaroxaban, referred to a regional NOAC outpatient clinic between February 2013 to October 2017. The clinical data were

prospectively collected using electronic patients medical records as part of the usual care provided by the NOAC clinic.

Results: There were no association between patient characteristics and discontinuation variables in univariate model. Only significant predictor for discontinuation was type of NOAC therapy with dabigatran HR 95% CI 2,14 (1,37-3,33) p value 0,0008 and rivaroxaban HR 95%, CI 1,63 (1,04-2,55) p value 0,00347 versus apixaban. In multivariate analyses, apixaban was better tolerated than dabigatran and rivaroxaban. Apixaban has the lowest discontinuation rates and significantly lowest total amount of reported side effects. Discontinuation of NOAC therapy was mainly caused by side effects (65% of all discontinuations) followed up by patient decision (14%) and bleeding event (12%)

Conclusion: In our NOAC outpatient clinic the discontinuation rates varied significantly among different NOAC's, related mainly to drug-specific side effects. We found no association between patient characteristics and discontinuation variables.

METABOLOMICS IN CHILDREN WITH HEART FAILURE USING ACE-INHIBITORS, AN EXCITING OPPORTUNITY?

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Introduction: ACE inhibitors (ACEi) have a prominent place in the treatment of heart failure in children. However, there is a significant interpatient variability in efficacy and safety in those children that is not completely understood.

Metabolomics provides an interesting innovative approach to better understand underlying mechanisms for variation in disease and response to therapy. With this review, we aim to provide an overview of metabolomics in the field of heart failure therapy with or without ACEi in both adults and children and try to identify gaps in this field.

Methods: The PubMed database was systematically searched using several search strategies. Articles were labelled as relevant when they included information on either metabolomics of adult patients with heart failure and/or ACEi-therapy or in children. This yielded 42 relevant articles

Results: 24 articles were found describing metabolomics in adults with heart failure, either with or without ACEi-therapy. In addition, several metabolites were identified in adults correlating with either ACEi-efficacy or safety. No metabolomics articles were found in children with heart failure or in children on ACEi-therapy. Several papers (18) were found on metabolomics in children for other diseases and/or treatments.

Conclusion: Metabolomics in adult heart failure patients has helped to unravel part of observed disease and therapy variability, and appears helpful in identifying patients at risk for therapy failure as well as detecting novel targets for heart failure therapy. In children, a significant information gap exists. This provides exciting opportunities for personalized treatment of heart failure.

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REDUCED MOXIFLOXACIN EXPOSURE IN PATIENTS WITH TUBERCULOSIS AND DIABETES

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Introduction: Prevalence of diabetes mellitus (DM) in patients with tuberculosis (TB) is increasing and may negatively impact outcome. Gastrointestinal problems may affect drug absorption in patients with DM resulting in suboptimal drug exposure and poor outcome. Reduced plasma concentrations were observed for first-line antibiotics in patients with TB and DM compared to patients with TB only in some, but not all studies. Moxifloxacin (MFx) is a potent bactericidal drug against *Mycobacterium tuberculosis* and is key for the treatment of multidrug-resistant TB (MDR-TB). Moreover, MFx can be recommended for TB treatment in patients with monoresistance or intolerance to first-line drugs. Whether MFx exposure is also reduced in patients with TB and DM is currently unknown.

Methods: We retrospectively identified all patients, aged ≥ 16 years treated orally with MFx 400 mg once daily and who underwent routine TDM using at least 3 time points for MFx as part of their TB treatment in the period of 2006-2018. Controls were TB patients without DM, matched on age, sex

and rifampicin use. PK parameters were calculated using two models for MFx (in the absence and presence of rifampicin).

Results: 126 TB patients were eligible for evaluation. 16 patients with DM were identified (type 1: 1 patient, type 2: 12 patients, steroid-induced 3 patients) of which 9 patients used rifampicin. In the control group, 7 patients used rifampicin. No differences were observed for demographics between patients with DM and control patients.

Exposure to MFx (AUC_{0-24}) was significantly lower in patients with DM compared to control patients. In line, the maximum concentration (C_{max}) and trough concentration (C_{min}) were also lower in patients with DM. No significant differences were observed for time to C_{max} . Clearance (CL/F) of MFx was increased in DM patients compared to controls. No differences were observed between both groups for lag time (T_{lag}), volume of distribution (V_D) or absorption rate constant (k_a).

To establish clinical relevance, AUC_{0-24h}/MIC ratios were calculated. MICs were available for 12 control patients and 7 patients with DM resulting in adequate AUC/MIC ratios for 10 control patients and 3 patients with DM. When assuming a MIC of 0.25 mg/l for all patients, AUC ratios were adequate for 7 control patients, whereas no adequate exposure was observed in patients with DM ($P=0.007$ Fisher's exact test).

Conclusion: Exposure to MFx is reduced in patients with TB and DM. This reduction is clinically relevant, suggesting that higher doses of 600-800 mg may be necessary to improve treatment outcomes. Whether these doses result in adequate exposure and are safe should be addressed in future studies.

THE IMPACT AND EXTENT OF RENAL FUNCTION ON THE CLEARANCE OF CIPROFLOXACIN IN ICU PATIENTS USING DIFFERENT MAKERS FOR RENAL FUNCTION

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Introduction Currently ciprofloxacin dosing is adjusted based on renal function. Yet, the impact of renal function on the clearance of ciprofloxacin is largely unknown including which estimation of glomerular filtration rate best predicts ciprofloxacin clearance. We set out to explore how renal function correlates with ciprofloxacin clearance and we hypothesized that eGFR estimated using both serum creatinine (sCr) and serum cystatin C (sCysC) provides better prediction of ciprofloxacin pharmacokinetics in critically ill (ICU) patients than eGRF estimation on sCR alone.

Materials/methods: In this observational multi-center study, adult ICU patients receiving ciprofloxacin were eligible for inclusion. Patients on renal replacement therapy were excluded. Dose and duration of therapy were determined by the patient's physician. Within 24 hours of initiation of ciprofloxacin, a pharmacokinetic (PK) curve was drawn at 8

different timepoints and sCR, sCysC and urinary creatinine were collected. Linear regression was performed to determine relations between log-transformed pharmacokinetic parameters AUC₀₋₂₄ and clearance (CL) and MDRD, CKD-EPI_{creat}, CKD-EPI_{cys}, CKD-EPI_{creat-cys} and 24-hour urine creatinine clearance.

Results: Thirty-seven patients (17 female) were evaluable, median (range) age 68 (30-87) years, sCr 88 (43-257) μ mol/L and sCysC 1.42 (0.66-3.58) mg/L. PK sampling resulted in a median dose corrected AUC₀₋₂₄ of 30.35 mg·h/L (range 14.46–103.48 mg·h/L), median trough concentration of 0.56 mg/L (range 0.13–3.26 mg/L), median maximum concentration of 3.15 mg/L (range 1.15–7.35 mg/L) and a median CL of 26.35 L/h (range 7.73–55.32 L/h).

Measured urinary creatinine clearance and different equations of eGFR are significantly (P<0.5) correlated with AUC with Rsquare of: MDRD 0.4933, CKD-EPI_{creat} 0.4815, CKD-EPI_{cys} 0.3744, CKD-EPI_{creat-cys} 0.4495 and 24-hour urine creatinine clearance 0.4584. CKD-EPI_{cr-cys} based on sCr and sCysC did not prove to correlate better to ciprofloxacin AUC₀₋₂₄ than estimations of eGFR using sCR alone.

Conclusions: Renal function markers are a poor predictors of ciprofloxacin clearance. In addition, estimating eGFR using combined filtration markers, sCysC and sCr, did not provide better prediction of ciprofloxacin pharmacokinetics than eGRF estimation on sCR alone. None of the ICU patients attained sufficient exposure to treat pathogens with an MIC of 1 mg/L and above (AUC₀₋₂₄/MIC > 125 mg·h/L)

Unregistered use of fosfomycin-trometamol in the Dutch health care setting.

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Background: Fosfomycin-trometamol is solely registered as a single dose use for uncomplicated cystitis in women. Interest exists in widening its spectrum, since its use in variable doses and dosing regimen and for indications increased to a fivefold between 2013 and 2017. It is important to map the size of this unregistered use as it indicates the need of, and should guide future research. Our objective is to report the unregistered use of oral fosfomycin in Dutch primary and secondary healthcare.

Materials/methods: Prescription records of fosfomycin-trometamol were collected of 65 general practices (GP) from the Julius GP database and from two academic Dutch hospitals between 2013 and 2017 (the University Medical Center Utrecht-UMCU and the Erasmus Medical Center-EMC). The amount of use, dose, interval, and patient's age and sex were evaluated. Additionally, the indication and regimen was evaluated of the first 150 prescriptions in 2013 and the last 300 prescriptions in 2017 for GP patients and of first 50 and last 100 UMCU and EMC prescriptions, respectively.

Results: In primary healthcare, fosfomycin was prescribed 1494 times in 2013 and 3799 times in 2017, of which 1.9%

and 3.6% in men and 5.3% and 8.5% as multiple dose, respectively. In secondary healthcare, fosfomycin use has increased from 2013 to 2017 with large differences of use in men and multiple dose prescriptions between the hospitals (table). In both primary and secondary care, the 3g dose was prescribed a range of every 1 to 4 days for therapeutic use and every 3 to 10 days for cystitis prophylaxis, whereas formulations other than 3 gram were rarely prescribed. The most common unregistered indications in primary and secondary healthcare were cystitis in patients with diabetes mellitus and prophylaxis for cystitis, respectively.

	65 GPs	UMC Utrecht	Erasmus MC
Number of FT prescriptions			
2013	1494	60	7
2017	3199	476	271
In men (%)			
2013	29 (1.9)	22 (37)	2 (28.6)
2017	116 (3.6)	128 (27)	37 (13.7)
As multiple dose (%)			
2013	79 (5.3)	7 (12)	0
2017	259 (8.5)	112 (24)	21 (7.8)
Most common indication of unregistered FT in 2017	Cystitis diabetes mellitus pt. (67/250, 27%)	Cystitis prophylaxis (18/100, 18%)	Cystitis in immunocomp. pt. (11/100, 11%)

Conclusions: Unregistered use of fosfomycin-trometamol has increased from 2013-2017 in primary and secondary healthcare for divergent indications. It was used in varying treatment intervals. Research should be guided on estimating efficacy and finding the optimal treatment regimen for these indications.

THE EFFECT OF PHARMACOLOGICAL ANTIPYRESIS ON MORTALITY IN PATIENTS WITH SEPSIS

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Introduction: There is no accepted international guidance on the use of paracetamol for fever control in sepsis. Fever is important for immune function and it therefore seems counterintuitive to administer antipyretic drugs in sepsis. The aim of this study is to determine whether antipyretic medication influences mortality in patients with sepsis.

Methods: We performed a sub-analysis of the Prehospital Antibiotics Against Sepsis (PHANTASi) trial (Alam et al., 2018)¹ to compare patients with sepsis who received 1,000 mg paracetamol in the ambulance and patients who did not. The primary outcome was 28-day mortality. In addition we compared the 28-day mortality for hypothermic, normothermic and hyperthermic patients, to provide better insights into the effects of body temperature on mortality in

Sepsis.

Results: 2528 patients were included in the primary outcome analysis: 254 patients received paracetamol in the ambulance and 2274 did not. There was no significant difference in 28-day mortality between the paracetamol and non-paracetamol groups (OR: 0.63 [95% CI 0.35 to 1.13]; p=0.12). Furthermore, hyperthermic patients had lower mortality rates when compared to hypothermic and normothermic patients (OR: 0.64 [95% CI: 0.47-0.87]; p=0.004).

Conclusion: Administration of paracetamol to patients with lower body temperature does not seem to influence mortality rates in patients with sepsis. Our results suggest that fever might not have a protective role in sepsis, but the negative effects of hypothermia may create the false appearance of a protective effect of fever.

References: 1) Alam, N., et al., *Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial*. Lancet Respir Med, 2018. 6(1): p. 40-50.

THERAPEUTIC DRUG MONITORING OF POSACONAZOLE IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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Introduction: It is recommended to use posaconazole as primary prophylaxis against invasive fungal infections in the setting of prolonged neutropenia secondary to chemotherapy in hematologic malignancy patients (ALL, AML, MDS). In contrast to posaconazole suspension, delayed-release tablets have shown better oral availability and increased exposure. In addition, posaconazole exposure does not appear to be significantly affected by food and co-medication. A trough concentration of > 0.7 mg/L has been suggested as target level for prophylaxis. However, therapeutic drug monitoring of posaconazole in the setting of prophylaxis is currently not standard of care, because initial studies have shown that 90% of patients treated with the tablets had a trough concentration of > 0.7 mg/L. In the Haga Hospital, posaconazole trough concentrations are measured in the prophylactic setting. It appears that even with the use of delayed-release tablets posaconazole trough concentrations are highly variable. Additionally, a trough concentration below 0.7 mg/L was observed in one quarter of patients. Here, we report two patients with low posaconazole concentrations.

Cases: Two acute myeloid leukaemia patients received posaconazole 300 mg once daily after a loading dose of 300 mg twice daily (prophylactic treatment). In both patients, a trough concentration of 0.3 mg/L was observed after 4 days of treatment. Patient 1 appeared to use other co-medication,

including omeprazole, ranitidine (gastric acid inhibiting drugs) and carbamazepine (strong inducer). The posaconazole dose was doubled and carbamazepine stopped. However, the posaconazole concentration remained low (0.4-0.7 mg/L). Although it is assumed that co-medication is of little influence on the absorption/kinetics of posaconazole tablets, the use of these drugs together with posaconazole seems to be the most plausible explanation for the low concentrations. An initial trough concentration of 0.3 mg/L was also observed in a second patient. This patient did not receive gastric acid inhibiting drugs or other (known) interacting drugs. The patient received a higher posaconazole dose and it was recommended to take posaconazole tablets with cola. The posaconazole concentration increased to 2.0 mg/L. After dose reduction, the posaconazole concentration remained adequate (1.5 mg/L). Administration of posaconazole tablets with cola resulted in an adequate serum concentration in another patient.

Discussion: Recent studies have shown that posaconazole exposure is highly variable, even with delayed-release tablets. Posaconazole concentrations measured at our hospital were also variable. In addition to the use of interacting co-medication (gastric acid inhibiting drugs, steroids, enzyme inducers), mucositis and diarrhea, other (unknown) factors may contribute to low posaconazole concentrations. Therapeutic drug monitoring of posaconazole should therefore be standard of care in the setting of prophylaxis. Dose increase, stopping interacting co-medication and the administration of posaconazole with cola can result in adequate posaconazole exposure.

PHARMACOKINETICS AND TARGET ATTAINMENT OF ANTIBIOTICS IN CRITICALLY ILL CHILDREN – A SYSTEMATIC REVIEW OF CURRENT LITERATURE

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BACKGROUND: Pharmacokinetics (PK) are severely altered in critically ill patients due to changes in volume of distribution (Vd) and/or drug clearance (Cl). To what extent this affects the PK of antibiotics in critically children is largely unknown. We aimed to identify gaps in current knowledge and to compare PK parameters of antibiotics in critically ill children to healthy children and critically ill adults

METHODS: Systematic literature search in PubMed, EMBASE and Web of Science. Articles were labelled as relevant when they included information on PK of antibiotics in critically ill, non-neonatal, pediatric patients. Extracted PK-parameters included Vd, Cl, trough concentrations, AUC, probability of target attainment, and half-life

RESULTS: A total of 44 articles were included from the search. Studies focussing on vancomycin were most prevalent (15/44). Other studies included data on penicillins, cephalosporins, carbapenems and aminoglycosides. Frequently used antibiotic agents such as ceftriaxone, ceftazidime, penicillin and metronidazole completely lack PK data in this patient population. Critically ill children generally show a higher Vd and Cl than healthy children and critically ill adults. 31/44 articles included information on both Vd and Cl, but a dosing advice was given in only 18 articles

CONCLUSION: The majority of studies focus on agents where TDM is applied, while other antibiotics lack data altogether. A higher Vd and Cl might warrant higher dosing of antibiotics in critically ill children. Studies frequently fail to provide a dosing advice for this patient population, even if the necessary information is available. Our study shows gaps in current knowledge and encourages future researchers to provide dosing advice for special populations when possible

IMPACT OF CURCUMIN WITH OR WITHOUT PIPERINE ON THE PHARMACOKINETICS OF TAMOXIFEN

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Introduction:

Tamoxifen is a prodrug that is primarily metabolized by CYP3A4 and CYP2D6, particular into the pharmacologically active metabolite endoxifen and eventually into inactive metabolites through phase II metabolism. The herb curcumin is widely used among cancer patients and may increase endoxifen exposure by affecting phase II metabolism. Therefore we performed a randomized cross-over study to compare endoxifen and tamoxifen exposure in breast cancer patients with or without curcumin, and with addition of the bio-enhancer piperine.

Methods:

Pharmacokinetic sampling was performed in 16 patients on

day 28, 56 and 84 of the study. Prior to pharmacokinetic sampling tamoxifen (20-30mg q.d.) was either given alone, or combined with curcumin (1,200mg t.i.d.) +/- piperine (10mg t.i.d.). Genotyping was performed to determine CYP2D6 and CYP3A4 phenotypes. The primary endpoint of this study was difference in geometric means for the area under the curve (AUC) of endoxifen.

Results:

The endoxifen AUC_{0-24h} decreased with 7.7% (95%CI: -15.4 to 0.7%; P=0.07) with curcumin and 12.4% (95%CI: -21.9 to -1.9%; P=0.02) with curcumin and piperine, compared to tamoxifen alone. Endoxifen C_{trough} also decreased with 5.6 % with curcumin (95%CI: -15.6 to +5.5, P=0.43) and 12.4% with curcumin and piperine respectively (95%CI: -20.9% to -3.0%, P=0.01) Tamoxifen AUC_{0-24h} showed similar results. For patients with an extensive CYP2D6 metabolism phenotype (EM), effects of curcumin with piperine on endoxifen and tamoxifen exposure were more pronounced than for intermediate CYP2D6 metabolizers (IM). No severe toxicity resulting from co-treatment was observed.

Conclusions:

The exposure to tamoxifen and endoxifen was significantly decreased by concomitant use of curcumin (+/-piperine). Although limited effects were observed in most patients, co-treatment with curcumin could lower endoxifen concentrations below the threshold for efficacy (potentially 20-40% of the patients), especially in EM patients.

BOOSTING PAZOPANIB EXPOSURE BY SPLITTING INTAKE MOMENTS – A PROSPECTIVE PHARMACOKINETIC STUDY IN CANCER PATIENTS

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Background. Pazopanib is approved for the treatment of renal cell carcinoma (RCC) and soft tissue sarcoma (STS). Due to high (40-70%) interpatient variability in pharmacokinetic (PK) exposure, 16-20% of patients do not reach the 20 mg/L exposure threshold related to prolonged progression free survival (20 weeks versus 52 weeks, respectively) with the currently used fixed dose of 800 mg QD (Suttle, 2014; Verheijen, 2017). PK simulations showed that, due to non-linear absorption of pazopanib, splitting the intake (400 mg BID) leads to an increase in C_{\min} and AUC_{0-24h} of 75% and 59%, respectively (Yu, 2017). This study aimed to show whether switching patients from an 800 mg QD to a 400 mg BID dose schedule will lead to a significant increase in PK exposure.

Methods. We performed a prospective PK trial (NL6137) in which PK sampling at the 800 mg QD dose schedule occurred

at day 1, after which the intake moments were split into 400 mg BID during one week, followed by PK sampling at day 8. Paired samples t-tests were used to assess differences in C_{\min} , C_{\max} and AUC_{0-24h} between these two dose schedules. To detect an increase in PK exposure of 50% (2-sided $\alpha = 0.05$ and $\beta = 0.20$), 10 evaluable patients were needed.

Results. Eleven patients (6 RCC and 5 STS) have been included, of whom ten were evaluable for PK analyses. Using the 800 mg QD dose schedule mean C_{\min} , C_{\max} and AUC_{0-24h} were 26.7 mg/L (coefficient of variation (CV%) 44.7), 46.1 mg/L (CV% 37.1) and 809 mg h/L (CV% 42.1), respectively. Switching to 400 mg BID resulted in an increase of both C_{\min} and AUC_{0-24h} to 40.7 mg/L (CV% 37.0, $p=0.013$) and 1059 mg h/L (CV% 33.1, $p=0.068$), respectively, while C_{\max} did not significantly change (56.5 mg/L, CV% 33.2, $p=0.185$). One patient (9%) experienced grade 3 diarrhea after splitting intake moments, leading to treatment interruption. This strategy could potentially save up to 2000 USD/patient/month compared to conventional dose increments.

Conclusion. This study demonstrates that boosting pazopanib exposure by splitting intake moments leads to a significant increase in C_{\min} of 52%, with acceptable tolerability. Therefore, this new dose schedule offers a safe and cost-neutral opportunity to optimize treatment for patients with low PK exposure.

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TRough vs. AUC Monitoring of ciclosporine: A randomized comparison of adverse drug reactions in allogeneic stem cell recipients (TRAM study)

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Introduction

In this study Therapeutic Drug Monitoring (TDM) of ciclosporine is investigated in allogeneic stem cell recipients. Current accepted practice is TDM of ciclosporine using 'trough' concentration (C₀). However, other therapeutic goals could yield better predictions of treatment outcome. The objective of this study is to investigate the number and severity of adverse drug reactions (renal function, nausea, tremor, headache, hypomagnesaemia, hyperkalemia and hypertension) of ciclosporine using AUC targeted TDM compared to C₀ targeted TDM.

Methods

This was a single-blind, monocentre, randomized, intervention study. After informed consent, subjects were 1:1 randomized in an AUC targeted TDM group and a C₀ targeted group. Subjects performed Dried Blood Spot (DBS) sampling 3 times after start with ciclosporine (once a week). Adverse drug reactions were collected two and four weeks after start of ciclosporine. Incidence of no toxicity versus any toxicity and no toxicity or grade 1 toxicity versus grade 2/3 toxicity between both groups was evaluated using Fisher's exact test.

Results

Between 2014 and 2016 40 patients were included, of whom 28 patients finished the necessary sampling for at least 2 measurement days, resulted in 15 subjects in the AUC targeted TDM group and 13 subjects in the trough levels targeted TDM group. Subjects received different conditioning regimens prior to transplantation. Any adverse drug reaction of ciclosporine was seen in all subjects, grade 2/3 toxicity was seen in 46% of subjects in trough levels TDM group versus 60% in the AUC targeted TDM group (p=0.463). Nausea, renal dysfunction and hypomagnesaemia were recorded most often. There was no significant difference between the two groups in incidence and severity 2 weeks and 4 weeks after start of ciclosporine of nausea (p=0.142 resp. p=0.122) renal dysfunction (p=0.464 resp. p=1.000) and hypomagnesaemia (p=1.000 resp. p=0.411). In the AUC targeted group versus trough levels targeted group subjects reached the target earlier (72,7% versus 43,0% at third sampling point, p=0.332) and more patients were within the target range at any time.

Conclusion

This is the first prospective randomized study to investigate 2 strategies of TDM of ciclosporine in allogeneic stem cell recipients. Toxicity of ciclosporine occurs frequently. This study showed no reduction in incidence and severity of ciclosporine induced adverse drug reactions with AUC targeted TDM versus trough levels. Although modelled dosing based on AUC led to higher optimal target attainment compared to trough level-based dosing, this did not result in less toxicity in the early days after transplantation. This is possible due to the high target levels: AUC[0-24] 6400 ug.h/L and C₀ 250 ug/L.

INFLUENCE OF THE PROTON PUMP INHIBITOR ESOMEPRAZOLE ON THE BIOAVAILABILITY OF REGORAFENIB:
A RANDOMIZED CROSS-OVER PHARMACOKINETIC STUDY

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Introduction:

The multikinase inhibitor regorafenib is widely used in the treatment of gastro-intestinal stromal tumor, hepatocellular carcinoma and metastatic colorectal cancer. Regorafenib exposure could potentially be influenced with acid reducing drugs such as esomeprazole.

Methods:

This prospective cross-over trial was approved by the medical ethics committee of the Erasmus MC. Patients were randomized into 2 sequence groups consisting of 3 phases: regorafenib intake alone, regorafenib with concomitant esomeprazole, and regorafenib 3 hours preceded by esomeprazole. Patients were treated with regorafenib 120 or 160 mg daily, and no dose reductions were allowed after the first 14 days. Pharmacokinetic blood sampling was performed at the 21th, 49th and 77th day. Primary endpoint was the relative difference (RD) in geometric means for regorafenib exposure (AUC_{0-24h}), and was analyzed by a linear mixed model.

Results:

A total of 14 patients were evaluable for the primary endpoint. All patients used regorafenib 120 mg at steady state. AUC_{0-24h} for regorafenib alone was 55.9 µg*h/mL (CV: 40%), and for regorafenib with concomitant esomeprazole or with esomeprazole 3 hours prior AUC_{0-24h} was 53.7 µg*h/mL (CV: 34%) and 53.6 µg*h/mL (CV: 43%), respectively. No significant differences were identified when regorafenib alone was compared to regorafenib with concomitant esomeprazole (RD: -3.9%, 95% CI: -20.5-16.1%, p=1.0) or regorafenib with esomeprazole 3 hours prior (RD: -4.1%, 95% CI: -22.8-19.2%, p=1.0). Furthermore, no significant differences were observed in other PK-parameters of regorafenib and its metabolites M-2 and M-5 (i.e. C_{max}, T_{max}).

Conclusion:

The use of esomeprazole concomitantly or 3 hours prior to regorafenib intake did not alter regorafenib pharmacokinetics and therefore can be combined with regorafenib without the appearance of a significant pharmacokinetic interaction.

Note: manuscript is accepted for publication in Clinical Pharmacology & Therapeutics

PROOF OF CONCEPT STUDY WITH THE HISTONE DEACETYLASE INHIBITOR (HDACi) VORINOSTAT IN PATIENTS WITH RESISTANT BRAF^{V600E} MUTATED ADVANCED MELANOMA

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Introduction: The clinical benefit of combined treatment with BRAF- and MEK-inhibitors (BRAFi; MEKi) in BRAF^{V600E} mutant (BRAFm) melanoma is limited due to development of drug resistance after 6-14 months of treatment, which is most often associated with emerging secondary mutations. (1, 2) Withholding of treatment with BRAFi and/or MEKi leads to a reversible hyperactivation of the MAPK pathway, causing a transient growth arrest and increase in Reactive Oxygen Species (ROS). Treatment of BRAFi and/or MEKi resistant melanoma with vorinostat, a histone deacetylase inhibitor (HDACi), leads to a further increase in ROS levels, effectively killing the BRAFi resistant cells. *In vivo*, switch from a BRAFi to vorinostat in BRAFi resistant BRAFm melanoma resulted in a decline in tumor volume. (3)

Aims: The primary aim of this proof of concept study is to demonstrate significant anti-tumor activity of progressive lesions with intermittent treatment with vorinostat in advanced resistant BRAFm melanoma. Secondary aims are to detect emerging resistant clones with a secondary mutation in the MAPK pathway by ctDNA analysis, to assess whether such clones can be purged by temporary treatment with vorinostat and to explore the safety, pharmacokinetics (PK), pharmacodynamics (PD) and pharmacogenetics (PG) of this strategy.

Methods: A total of 28 evaluable patients with resistant BRAFm melanoma will be treated with vorinostat 360 mg continuously in this proof of concept study. Blood and tumor biopsies will be taken to explore PK, PD and PG.

Results/conclusions: The first six treated patients in this study revealed regression of mutant clones and progression of BRAFi sensitive clones during vorinostat treatment. Importantly, biopsies showed newly developed secondary MAPK pathway mutations, e.g. NRAS^{Q61H} and KRAS^{G12C} amplifications at start and a complete absence of these resistant mutations after two weeks of vorinostat treatment. Based on these clinical results we postulate that BRAFi-resistant BRAFm melanoma cells can be eliminated by a short treatment with vorinostat due to killing of tumor cells harboring a secondary mutation in the MAPK-pathway. This confirms previous *in vitro* experiments in human cell lines. The PK of vorinostat and metabolites are similar to literature data. No safety concerns were seen.(4) Patient enrolment is ongoing to investigate new treatment regimens with switching back and forth BRAFi and/or MEKi to vorinostat guided by detection of resistant clones. Besides, we will closely monitor mutations in patients by analysing ctDNA during treatment.

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COMPARISON OF TOXICITY AND EFFECTIVENESS BETWEEN FIXED-DOSED AND BODY-SURFACE AREA (BSA)-DOSED CAPECITABINE

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Introduction:

Capecitabine is generally dosed based on body-surface area (BSA). This dosing strategy has several limitations, however evidence for alternative strategies is lacking. Therefore, we analyzed the toxicity and effectiveness of fixed-dosed capecitabine and compared this strategy with BSA-dosed capecitabine in a large set of patients.

Methods:

Patients treated with fixed-dosed capecitabine between 2003 and 2015 were studied. A comparable group of patients, dosed on BSA, was chosen as a control cohort. Two combined scores were used: capecitabine-specific toxicity (diarrhea NCI-CTC grade ≥ 3 , hand-foot syndrome ≥ 2 , or neutropenia ≥ 2), and clinically relevant events due to toxicity, i.e. hospital admission, dose reduction, or discontinuation.

Per treatment regimen, patients were divided into 3 BSA-groups based on BSA-quartiles corrected for gender. Toxicity scores were compared by X^2 -test between cohorts, and within cohorts using BSA-groups. Progression-free survival (PFS) was estimated by the Kaplan-Meier method.

Results:

A total of 2,319 patients was included (fixed-dosed $n=1,126$ and BSA-dosed $n=1,193$). Four regimens were evaluated: capecitabine-radiotherapy ($n=1,178$), capecitabine-oxaliplatin ($n=519$), capecitabine-triplet ($n=181$) and capecitabine monotherapy ($n=441$). The incidence of capecitabine-specific toxicity and clinically relevant events was comparable between fixed-dosed and BSA-dosed patients, while a small difference (7.1%) in absolute dose was found. Both cohorts showed only a higher incidence of both toxicity scores in the lowest BSA-group of the capecitabine-radiotherapy group ($P<0.05$). Subgroups of the fixed-dosed cohort analyzed for PFS, showed no differences between BSA-groups.

Conclusion:

Fixed-dosed capecitabine is comparably safe and effective as BSA-based dosing and could be considered as a reasonable and practical alternative for BSA-based dosing. Therefore, we would recommend implementing fixed dosing in future clinical studies and we found no arguments why it could not be used in daily clinical care.

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TNF α INHIBITOR TREATMENT PATTERNS IN PATIENTS WITH RHEUMATIC DISEASES AND THOSE WITH INFLAMMATORY BOWEL DISEASE

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Background

TNF α inhibitors are the first line biological treatment for patients suffering from rheumatic diseases (RD) and inflammatory bowel disease (IBD). Limited information is available about long-term treatment patterns of patients starting a TNF α inhibitor and whether these differ between patients suffering from RD and IBD.

Objectives

To compare treatment patterns of patients with RD and IBD starting a TNF α inhibitor.

Method

Included were all patients starting (i.e. no prior use of a biological) with a TNF α inhibitor (ATC code: L04AB) between 1 July 2012 and 1 July 2017 at a Dutch general teaching hospital (the Spaarne Gasthuis, Haarlem/Hoofddorp) and with a RD or IBD diagnosis. All patients were followed for at least one year. Outcomes at one year of follow-up were: continuous use of the first TNF α inhibitor, switch to a

different TNF α inhibitor or to a biological with another mode of action, or discontinuation. In addition, median duration of first TNF α inhibitor treatment were compared for patients with RD and IBD using the Kaplan Meier method. Data were analyzed by Pearson's chi square and Kruskal Wallis test.

Results

646 patients were included (median age 46 years, 84% female), of which 63.9% (n=413) received a TNF α inhibitor for RD and 36.1% (n=233) for IBD. After 1 year, 60.1% of patients continuously used their first TNF α inhibitor, 13.4% switched to another biological and 26.5% discontinued treatment. Significantly less RD patients continued their TNF α inhibitor compared to IBD patients (54.4% versus 70.0%, RR 0.78, 95% CI 0.69-0.88) and RD patients discontinued treatment more frequently than IBD patients (33.0% versus 15.0%, RR 2.19, 95% CI 1.57-3.06). 12.6% of RD patients and 15.0% of IBD patients had switched, most patients (71.1% of RD switchers and 91.4% of IBD switchers) to a second TNF α inhibitor. The median treatment duration of the first TNF α inhibitor was significantly (p<0.01) lower for RD patients (437 days, IQR 686 days) when compared with IBD patients (728 days, IQR 988 days).

Conclusions

RD patients discontinue their first TNF α inhibitor significantly more often than IBD patients and have a shorter duration of treatment, patterns of switching are equal in both indications. These findings show the importance of underlying disease in the use of TNF α inhibitors. Future research should focus on the reasons for this difference and cross-indication learning.

HIGH THERAPEUTIC BUPRENORPHINE LEVELS REDUCE IV FENTANYL RESPIRATORY DEPRESSION

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Introduction: The number of U.S. drug overdose deaths exceeded 70,000 in 2017, partially driven by an increase in deaths involving potent synthetic opioids such as fentanyl. Fentanyl overdose can cause respiratory depression, followed by decreased mental status, brain damage, and death. Patients who enter medication-assisted treatment programs for opioid use disorder (OUD) have reduced risk of overdose and death but are still often exposed to fentanyl via illicit drug use. This study examined the effects of sustained buprenorphine concentrations on respiratory depression induced by intravenous (IV) fentanyl injection.

Methods: Eight opioid-tolerant patients using >90 mg daily oral morphine equivalents completed this open-label, 2-period study. Patients received placebo (PLC)/fentanyl on Day 1 and buprenorphine (BUP) /fentanyl on Day 3. Minute ventilation (MV) was measured at isohypercapnia (baseline MV~20 L/min) through a facemask connected to a pneumotachograph. Once ventilation was stable, pulsed-continuous infusions of placebo or buprenorphine were initiated. Buprenorphine infusion targeted plasma concentrations of 1 (n=2), 2 (n=3) or 5 ng/mL (n=3) for 6 h, consistent with concentrations achieved with RBP-6000, a buprenorphine extended-release subcutaneous injection. Prior studies indicate that plasma concentrations of buprenorphine >2 ng/mL achieve 70% brain

mu-opioid receptor occupancy and block the subjective drug-liking effect full opioid agonists, such as hydromorphone. Following initiation of BUP or PLC infusion, IV fentanyl boluses of 250, 350, 500 and 700 mcg/70 kg were administered at 2, 3, 4, and 5 h, respectively. For these preliminary analyses, drug effects were measured as a decrease in MV, number/duration of apneic events (lasting >20 seconds), need for ventilatory stimulation and changes in oxygen saturation.

Results: During the PLC period, abrupt declines in MV were generally evident following each fentanyl bolus and 6 of 8 patients (75%) experienced 1 or more apneic events requiring verbal ventilatory stimulation to maintain adequate MV. IV fentanyl dose escalation was stopped early after the 2nd (n=2) or 3rd bolus (n=2) in 4 subjects because of prolonged apnea or changes in oxygen saturation (5 subjects had oxygen saturation values <90%). During the BUP period, each patient completed 4 fentanyl boluses and only 1 patient experienced apneic episodes after the 3rd and 4th boluses. With BUP, none of the patients required verbal ventilatory stimulation and oxygen saturation did not drop below 90%. For the low-dose BUP infusion targeting 1 ng/mL, declines in MV were evident after fentanyl boluses and the 1 patient with apneic events during BUP infusion was in this group. For the high-dose BUP infusion targeting 5 ng/mL, marked changes in MV did not occur after the fentanyl infusions and repeated apneic events did not occur.

Conclusions: These data suggest buprenorphine acts as a competitive inhibitor of fentanyl boluses at doses up to 700 mcg/70 kg and reduces fentanyl-induced respiratory depression.

BE AWARE OF A BARBITURATE INTOXICATION

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Introduction: The last several years the number of suicide is increasing [CBS, 2017]. The majority of suicide attempts involve the use of medication. Pentobarbital is one of the recommended drugs to perform self- euthanasia by diverse websites [DeEinder, Levenseindecounseling, NNVE]. Due to online access, pentobarbital can easily be obtained [Met waardigheid, Vredes] or ordered with the help of an organization [DeEinder, Levenseindecounseling]. Pentobarbital is labelled as a different substance to mislead custom control. In this abstract 4 cases on pentobarbital intoxications are presented, in which 3 resulted in death.

Methods: Patients (n=4, 2 male, 2 female) were admitted to the emergency room or found death in their home. Toxicology analysis was performed with a validated HPLC-UV method in the ISO15189 pharmacy laboratory of Erasmus MC.

Results: The first case concerns a successful tentamen suicidii (TS) where the laboratory pharmacist received two bottles of 100 mL of 'natural skin cleanser'. After analysis these bottles contained pentobarbital in a concentration of 70 g/L. Two other postmortem investigations represented two cases with measured serum pentobarbital concentrations of 45 mg/L and 18 mg/L (therapeutic range 20-40 mg/L for coma). Antiemetics were also identified, i.e. domperidon and metoclopramide. These are recommended to be ingested during 24 hours prior to the pentobarbital liquid. Lastly, at the

Emergency Unit a patient was admitted in a critical sedated condition after an attempted suicide without indication which substance was taken. Surprisingly the urine screening turned positive for barbiturates, consequently the serum pentobarbital concentration was 9 mg/L. After a time period on the ICU, the patient survived.

Conclusion: Four pentobarbital cases were seen in Erasmus MC over the last half year of 2018. The cases represented not only postmortem cases, but also one patient who survived the TS with pentobarbital. The pentobarbital was labelled as a natural cosmetic skin cleanser. Health care providers should be aware of an increased risk of pentobarbital intoxications, since it can easily be accessed online and it is a recommended drug on diverse suicide websites.

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THE PHARMACOTHERAPY TEAM: A NOVEL MULTIDISCIPLINARY STRATEGY USING PARTICIPATORY ACTION RESEARCH TO REDUCE IN-HOSPITAL PRESCRIBING ERRORS

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Introduction: Inappropriate prescribing leads to increases in medication-related patient harm, preventable hospital admissions and healthcare costs. Several interventions to improve appropriate prescribing have been introduced in Dutch primary care (1). However, a thorough and structural approach in secondary care is still lacking. Due to the complexity of the prescribing process, interventions to improve prescribing are more likely to be effective if they include a multidisciplinary, multifaceted and tailor-made aspect. For this purpose, Participatory Action Research (PAR) (2), a research approach that involves relevant stakeholders to improve complex problems by tailor-made interventions, could be useful. The aim of this study is to investigate whether a multidisciplinary team using PAR is effective in reducing in-hospital prescribing errors (PEs).

Methods: A prospective non-randomized, pre- and post-intervention study was performed between June 2015 and April 2018 involving 11 clinical wards of Amsterdam UMC – location VUmc. A multidisciplinary ‘pharmacotherapy’ team was compiled, consisting of two physicians/clinical pharmacologists, a hospital pharmacist, an internist, a quality consultant and two medical students. The team identified relevant stakeholders (junior doctors, consultants and nurses) of each ward and coordinated a 10-month tailor-made intervention. Interventions focused on organizational (e.g.

redesigning working process), disciplinal (e.g. improving guideline accessibility) and individual aspects (e.g. education). Medication orders (MOs) of patients admitted to these wards were screened for PEs using a structured medication review. Identified PEs were categorized by the team according to the NCCMERP classification.

Results: A total of 273 patients with 2,683 MOs were included during the pre- and 178 patients with 2,233 MOs during the post-intervention period. The total of MOs containing at least one PE decreased from 13.6% (SD 17.6) during pre-intervention period to 12.5% (SD 14.8) during the post-intervention period, although this difference was not statistically significant ($p = 0.69$). There were differences in reduction between medical and surgical wards ranging from 1.0% to 6.0%. During the pre- and post-intervention period, incorrect dosage (respectively 38.3% and 53.8% of all PEs) and a lack of indication (respectively 32.9% and 31.7% of all PEs) were the most commonly encountered errors.

Conclusion: A novel multidisciplinary team using PAR was not effective in overall reduction of in-hospital PEs, although there were differences in reduction between clinical wards. Critical success factors were dedicated on-ward stakeholders and awareness about PEs within this group. Specific focus on high risk patients or high risk medications in future studies will possibly have more impact.

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CLINICAL RULE GUIDED PHARMACISTS' INTERVENTION IN HOSPITALIZED PATIENTS WITH HYPOKALEMIA:
A TIME SERIES ANALYSIS

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Introduction: Hypokalemia is one of the most frequent electrolyte disturbances in hospitalized patients. Severe hypokalemia requires immediate treatment because of the increased risk of cardiac arrhythmia and sudden death. Previous studies have shown suboptimal physician response with respect to frequency of patients treated and speed of initiating supplementation. It has been suggested that clinical rule based pharmacists' interventions could improve response. The aim of this study was to evaluate outcomes in patients who developed hypokalemia (<2.9 mmol/L) during hospitalization, after clinical rule based pharmacist's intervention compared to showing only passive alerts in the electronic health records. **Methods:** A before- (2007-2009) after (2010-2017) study with time series design was performed. Unique patients, >18 years were included, with a serum potassium level (SPL) <2.9 mmol/L measured at least 24 hours after

hospitalization and in whom no potassium supplementation was initiated within 4 hours after measurement nor normalization of SPL within 4 hours. Hemodialysis patients were excluded. Five endpoints were compared: 1. percentage of patients with a subsequent prescription for potassium; 2. time to prescription; 3. percentage of patients to achieve normokalemia; 4. time to achieve normokalemia; 5. total duration of hospitalization. **Results:** 693 patients were included whereof 278 in the intervention phase. Percentage of patients prescribed potassium supplementation as well as time to prescription improved from 76.0% in 31.1 hours to 92.0% in 11.3 hours (p<0.01). No changes were observed in patients reaching normokalemia (p=0.69) nor in time to reach normokalemia (p=0.71), 87.5% in 65.2 hours pre-intervention compared to 90.2% in 64.0 hours. A non-significant decrease of 8.2 days was observed in duration of hospitalization, 25.4 compared to 17.2 days (p=0.29). **Conclusion:** Implementation of clinical rule guided pharmacists' intervention showed improvement in response rate and time to supplementation, however showed no significant effect on percentage and time to normokalemia and hospitalization.

THE ASSOCIATION BETWEEN THE USE OF SSRIS AND THE OCCURRENCE OF INR ≥ 5 AND MAJOR BLEEDINGS DURING TREATMENT WITH VKAS – WHAT IS THE UNDERLYING MECHANISM?

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Background: Two theories exist on mechanisms by which selective serotonin reuptake inhibitors (SSRIs) increase the risk of major bleeding during vitamin K antagonist (VKA) use. The first theory states that SSRIs inhibit serotonin reuptake in platelets, which results in a decreased platelet aggregation and an increased risk of major bleeding. The second theory states that fluvoxamine and fluoxetine inhibit cytochrome P450 2C9 (CYP2C9), which decreases the VKA metabolism. This could result in a high INR and increased bleeding risk. However, results concerning CYP2C9 inhibitors are conflicting and it remains unclear to what extent and how SSRIs increase the risk of major bleeding. Our aim was therefore to determine to what extent and how SSRIs cause major bleeding during VKA treatment.

Methods: All patients who started VKA treatment at the Anticoagulation Clinic Leiden between 2006 and 2018 were selected. Information on medication and bleeding complications was obtained from patient records. Patients were considered exposed when using a SSRI. In addition, tricyclic antidepressant (TCA) users were the second exposure category to account for confounding by indication by means of an active comparator study design. We estimated hazard ratios

(HRs) and 95% confidence intervals (CIs) by time-dependent Cox regression and adjusted for confounding (i.e. sex, age and co-medication) to study the effect of SSRIs on major bleeding with non-users as a reference group. In the second analysis, we estimated odds ratios (ORs) by conditional logistic regression to study the effect of SSRI initiation on a high international normalized ratio (INR, i.e. ≥ 5) within two months as compared with matched patients who did not initiate a SSRI.

Results: 18,662 Patients on VKA were included (mean age 69 years, 53% male), of whom 704 were SSRI users and 167 were TCA users. 945 major bleeds occurred during a follow-up of 34,932 person-years. SSRI use yielded adjusted risk estimates around unity (HR 1.2, 95%CI 0.9-1.5). After stratification for CYP2C9 inhibiting SSRIs, risk estimates remained similar (CYP2C9 inhibitor HR 0.9, 95%CI 0.3-2.8 versus other SSRIs HR 1.2, 95%CI 0.9-1.6). TCA use was associated with similar bleeding risks as SSRI use (HR 1.0, 95%CI 0.6-1.7).

SSRI initiation was associated with a 2.2-fold (95%CI 1.6-3.0) increased risk for a high INR. After stratification for CYP2C9 inhibiting SSRIs, a 6-fold increased risk for a high INR was observed among CYP2C9 inhibitors (OR 6.2, 95%CI 1.4-27.1), while risk estimates remained similar among other SSRI initiators (OR 2.1, 95%CI 1.5-2.8). TCA initiation yielded a risk estimate around unity (OR 1.3, 95%CI 0.7-2.3).

Conclusion: SSRI use was not associated with an increased risk of major bleeding, indicating that platelet inhibition may not result in an increased risk for major bleeding. SSRI use was associated with a 2-fold increased risk of a high INR and CYP2C9 inhibitors were associated with a 6-fold increased risk, which supports the theory of a pharmacokinetic interaction.

Calcium channel blocker withdrawal-induced cardiac arrest in a patient with vasospastic angina

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Background: Vasospastic angina (VA) is a less common form of angina which is most frequently treated with calcium channel blockers (CCBs) and nitrates in high dose. Here we present a patient with refractory VA undergoing renal denervation (RDN) complicated by cardiac arrest due to changes in the medication regimen. It is our aim to create awareness for the potential lethal consequences of inadvertent changes in chronic medical treatment in vulnerable patients.

Case description: A 46-years old woman with refractory VA was referred to undergo RDN. She used high dose verapamil with controlled release (CR) (total daily dose (TDD) 480 mg), isosorbide mononitrate CR (TDD 120 mg) and perindopril (TDD 2 mg). At arrival, perindopril was stopped, isosorbide mononitrate was switched to nitroglycerine intravenously (1.5 mg/hour) and verapamil was switched from CR to normal release tablets (120 mg 4 times/day) because verapamil CR tablets were not available.

Approximately five hours after the procedure she developed a cardiac arrest with pulseless electrical activity and although resuscitation after two recurrences was successful, extracorporeal membrane oxygenation was needed. Coronary angiography confirmed extensive coronary vasospasm. Critically reviewing the medication charts, it appeared that due to the substitution and the procedure, she only received one dose of 120 mg verapamil with normal release, and subsequently developed the so called CCB withdrawal phenomenon.

Conclusion: Careful monitoring the process of drug substitution with respect to equal therapeutic dosages and whether drug intake is possible when away for a procedure is therefore a necessity, especially in vulnerable patients.

TMS-EMG AND TMS-EEG AS A BIOMARKER FOR PHARMACOLOGICAL EFFECTS ON CORTICAL EXCITABILITY

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Introduction: Transcranial magnetic stimulation (TMS) combined with electromyography (EMG) or electroencephalography (EEG), offers a non-invasive opportunity to study cortical excitability. This potentially makes TMS a valuable biomarker to study effects of drugs that are expected to affect nerve or cortical excitability in clinical trials.

Aim: To evaluate effects of oral valproic acid, levetiracetam and lorazepam on cortical excitability measurements in healthy volunteers as measured by single pulse TMS-EMG and TMS-EEG and validate the method as a biomarker.

Methods: In this double-blind, placebo-controlled, single-dose, four-way cross-over study, subjects received the following treatments in a randomized order: valproic acid oral solution 1000 mg and placebo capsules; levetiracetam oral solution 2000 mg and placebo capsules; lorazepam capsules 2 mg and placebo solution; placebo capsules and solution. TMS-EMG and TMS-EEG were performed at baseline, and 1.5h and 7h post dose. The peak-to-peak amplitude of the motor evoked potential (MEP) was measured as TMS-EMG outcome. The TMS-EEG outcomes are the amplitudes of TMS evoked potential (TEP) components (N15, P30, N45, P55, N100 and P180). Analysis was performed using a mixed model analysis of covariance with baseline as covariate.

TMS-EEG analysis was performed using two approaches: analysis of EEG components at a single lead (Cz) and cluster-based permutation analysis (CBPA) incorporating all leads.

Results: A total of 16 healthy male subjects completed the study. All three treatments significantly decreased the MEP amplitude in the single pulse TMS-EMG response when compared to placebo, with an estimated difference of 378.4 μ V (95% CI: 112.5, 644.3), 268.8 μ V (95% CI: 4.6, 532.9) and 330.7 μ V (95% CI: 65.8, 595.6) for levetiracetam, valproic acid and lorazepam respectively.

For single pulse TMS-EEG, the following effects on TEP components were observed:

Levetiracetam vs. placebo:

- Cz lead: estimated difference in amplitude of N100 TEP component -1.60 μ V (95% CI: -3.12, -0.08)
- CBPA: significant clusters with decreased amplitude of N45 TEP component ($p=0.004$) and increased amplitude of N100 TEP component ($p=0.007$)

Valproic acid vs. placebo:

- Cz lead: estimated difference in amplitude of N15 TEP component 3.96 μ V (95% CI: 0.09, 7.82)
- CBPA: No significant effects

Lorazepam vs. placebo:

- Cz lead: estimated difference in amplitude of N100 TEP component -1.55 μ V (95% CI: -3.07, -0.02)
- CBPA: No significant effects

Conclusions: Levetiracetam, valproic acid and lorazepam show significant effects on cortical excitability in healthy subjects, measured by single pulse TMS-EMG and TMS-EEG.

A COMPREHENSIVE CNS PBPK MODEL: EXTENSION WITH PH EFFECT AND BRAIN BINDING

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Introduction: CNS (central nervous system) pharmacokinetic and pharmacodynamic profiling is key in CNS drug development. Traditional methods of pharmacokinetic assessment often fail for CNS mainly due to ethical limitations of CNS sampling in humans, the inaccuracy of “lumbar” cerebrospinal fluid (CSF) as an estimate of brain concentrations, and the complexity of CNS physiology. A recently published CNS physiology-based pharmacokinetic (PBPK) model can predict pharmacokinetic profiles of a spectrum of small drugs in multiple CNS tissues (Yamamoto et al., 2017). This model does not consider essential physiological processes (e.g. metabolism, active transport, pH, tissue binding), which limits its application in drug development. Here, we extended this model with explicit description of brain tissue binding and pH effects on pharmacokinetic profiles.

Methods: We started with a published and validated CNS PBPK model, which predicts CNS PK profiles in multiple CNS regions (extracellular and intracellular concentrations, subcellular organelles, and CSF ventricles) using the drug’s physicochemical properties and CNS physiology. We extended the model with drug lipophilicity to describe brain tissue binding and Henderson-Hasselbach method to describe pH effect on the drug ionization. To evaluate the model, we

calculated prediction errors and symmetric mean absolute percentage error (SMAPE). In addition, the median and 90% prediction intervals of 200 simulations (including interindividual variability of the plasma PK model) were compared to previously published observed paracetamol and atenolol CNS unbound concentrations in rat (Yamamoto et al., 2017). Model-based simulations were performed using RxODE (an R-based package); plasma pharmacokinetics was modeled in NONMEM V7.3.

Results: Model-based simulations and the resulting median and 90% prediction intervals described the observed paracetamol and atenolol rat data from the different CNS compartments. Mean prediction errors (standard deviation) for paracetamol were 0.47 (0.75), 0.03 (0.64), and -0.19 (0.69) for extracellular fluid, lateral ventricles, and cisterna magna and for atenolol was 0.07 (0.56) for extracellular fluid. The overall SMAPE of the model was 68%, 50%, and 60.2 % for the ECF, lateral ventricles, and cisterna magna. These results indicate that the model can predict the pharmacokinetic profiles in these compartments with less than two-fold error.

Conclusion: A CNS PBPK model has been successfully extended with brain tissue binding and pH effect. With the addition of other relevant physiological processes (e.g. metabolism, active transport), this model can incorporate pathophysiological changes due to CNS diseases and thus translate to predict PK profiles in diseased populations.

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UNEMPLOYMENT IS ASSOCIATED WITH AMISULPRIDE-INDUCED WEIGHT GAIN

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Introduction: Antipsychotic-induced weight gain (AIWG) is a debilitating adverse effect of most antipsychotics. First-episode psychosis patients are especially vulnerable to AIWG and its detrimental effects, e.g. social isolation and noncompliance. To date, the majority of studies investigating determinants of AIWG have targeted a heterogeneous group of antipsychotics in schizophrenia patients with relatively long duration of illness. Out of all antipsychotics, particularly amisulpride is known for its efficacy and relatively mild adverse effects profile. Here, we aimed to comprehensively dissect the phenotypic variables associated with amisulpride-induced weight gain to enhance insight into the patient characteristics associated with this harmful side-effect.

Methods: Data of the OPTiMiSE (Optimization of Treatment and Management of Schizophrenia in Europe) trial were used and two multivariable regression models with various sociodemographic and other phenotypic variables in first-episode users of amisulpride were performed (N=320).

The outcome variables were bodyweight gain as a continuous variable and clinically relevant bodyweight gain (defined as $\geq 7\%$ weight gain compared to baseline).

Results: Four weeks of amisulpride therapy led to a significant increase in absolute body weight from 69.7 ± 14.2 at baseline to 72.39 ± 14.13 at end of phase I (t-test, $p < 0.01$). In the linear regression model unemployment ($p = 0.016$), lower age ($p = 0.031$) and absence of comorbid major depression disorder ($p = 0.034$) were positively associated with amisulpride-induced weight gain. Clinically relevant bodyweight change was observed in 70 (21.9%) patients. In the logistic regression model unemployment ($p = 0.001$), diagnosis of schizophreniform disorder ($p = 0.025$) and low baseline bodyweight ($p = 0.032$) increased the likelihood of clinically relevant bodyweight gain. Variables previously associated with AIWG in response to other antipsychotics (such as antipsychotic naïve status, sex and race) were not associated with amisulpride-induced weight gain. Similarly, no differences in weight gain were observed between inpatient and outpatient settings.

Conclusions: We provide comprehensive evidence showing that weight increasing variables associated with amisulpride-induced weight gain differ from those previously reported in the literature for other antipsychotics. Notably, unemployment status is associated with vulnerability to amisulpride-induced weight gain. Clinicians prescribing this compound may choose to closely monitor and possibly treat weight gain more aggressively in unemployed first-episode patients.

OPTIMIZING DOSING REGIMENS OF CLONIDINE IN INTENSIVE CARE UNIT PATIENTS WITH POPULATION PHARMACOKINETICS

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Introduction: Clonidine is often used in the Netherlands as an off-label drug for sedation in the intensive care unit (ICU). However, no standardized dosing regimens are available for this indication. Although the α_2 -agonist clonidine has been approved for the treatment of hypertension, its analgesic and sedative effects have been established as well. Davies *et al.* (1977) demonstrated that adequate sedation is achieved when clonidine plasma concentrations are above 1.5 $\mu\text{g/L}$. In this present study, a population pharmacokinetic (PK) model was developed to optimize dosing regimens for clonidine as sedative.

Methods: A population nonlinear mixed effects model was constructed, based on data from 24 patients: median age 67 yr (interquartile range (IQR) 60 – 74 yr) and bodyweight (BW) 84 kg (74 – 90 kg). Patients received a continuous IV infusion of 600, 1200 or 1800 $\mu\text{g/day}$, with or without a loading dose of 300, 600 or 900 μg infused over 4h. One, two and three compartment models were tested. The following covariates were tested on the PK parameters: BW, BSA, BMI, age, gender, creatinine clearance, albumin, bilirubin and time after start infusion. After univariate covariate selection, using linear functions, and power functions,

covariates were liberally introduced into the multivariate model and then stepwise eliminated using more rigid criteria. The stability of the model was tested by goodness-of-fit plots, bootstrapping and a visual predictive check. After modelling, Monte Carlo simulations were performed to find optimal dosing regimens.

Results: A two compartment model fitted the concentration-time data best. Time had significant influence on the clearance (CL), which increased with 0.21% per hour. Additionally, allometric scaling of the central volume of distribution (V1) by BW further improved the model. Population PK parameters values [relative standard errors] for CL, V1, Q (inter-compartmental CL) and V2 (peripheral volume of distribution) were respectively: 17.1 [10%] (L/h), 123 [33%] (L/70kg), 84.4 [31%] (L/h) and 179 [18%] (L). Simulations with the final model showed that a loading dose of 500 μg in 4h, resulted in 65% of the population reached $>1.5 \mu\text{g/L}$. Thereafter, a maintenance dose of 1200 $\mu\text{g/day}$ resulted in 93% of the population reached $>1.5 \mu\text{g/L}$ at steady state.

Conclusions: The developed population PK model allowed the optimization of dosing regimens for clonidine as a sedative agent in ICU patients.

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PHARMACOKINETICS OF LIDOCAINE AS ANTI-EPILEPTIC DRUG IN TERM AND PRETERM NEONATES

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Background: Lidocaine is used as an add-on anti-epileptic drug in neonates when seizures persist despite treatment with first line anticonvulsants. Although lidocaine has shown to be an effective anticonvulsant, cardiac toxicity associated with plasma concentrations >9 mg/L have limited its wide scale use. Previous studies from our group have described lidocaine pharmacokinetics (PK) in preterm and term neonates with and without therapeutic hypothermia (TH) and have proposed a dosing regimen for safe and effective lidocaine use with plasma concentrations not exceeding 9 mg/L.

Aim: To describe lidocaine PK in term and preterm neonates including the effect of TH on clearance and to evaluate the previously developed dosing regimen.

Methods: Data collected in three prospective cohort studies were combined with data collected during routine clinical care between 2004 and 2018. Neonates refractory to at least one anti-epileptic drug received lidocaine according to the local clinical protocol. Plasma concentrations of lidocaine and its metabolite MEGX were measured in samples either taken as

per study protocol or for routine clinical care. PK analyses were performed using NONMEM (version 7.3).

Results: Lidocaine data were available for 159 patients (mean gestational age 36+6 weeks [range 24+6 – 42+5], mean weight 2.89 kg [range 0.675 – 4.89 kg], male 54.1%). Of these, 49 neonates (30.8%) were treated with therapeutic hypothermia. In all patients, lidocaine was administered as continuous infusion with varying dosing regimens in line with the updated treatment protocols over time. Lidocaine and/or MEGX plasma concentrations were analysed in 444 samples. PK parameters were best described with a one-compartment model for lidocaine and a subsequent one-compartment model for MEGX using birth weight (BW) based allometric scaling for body size and postmenstrual age (PMA) for maturation. Average lidocaine clearance for a neonate with BW 3.5 kg and PMA 40 weeks was 1.77 L/h (relative standard error (RSE) 7%). TH reduced lidocaine clearance by 21.7% (RSE 45%). Simulations using the final PK parameters showed that the proposed lidocaine dosing regimen starting with a 2 mg/kg loading dose followed by a weight-differentiated three stage maintenance phase tapered over 28 hours resulted in average lidocaine plasma concentrations below 9 mg/L during the entire interval in both preterm as well as term neonates with and without TH. Furthermore, highest lidocaine plasma concentrations in neonates treated with this dosing regimen (n=23) was 9.15 mg/L. No cardiac toxicity occurred.

Conclusion: Lidocaine PK in this large, combined dataset are in line with previous reports including the effect of TH and confirms that the proposed dosing regimen does not lead to potentially toxic lidocaine plasma concentrations in neonates.

PHARMACOKINETICS AND CLINICAL EFFECT OF PIPAMPERONE IN CHILDREN AND ADOLESCENTS

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Introduction: Although pipamperone is one of the mostly used antipsychotics in children and adolescents in the Netherlands¹, no pharmacokinetic data is known and information about efficacy is lacking in this population. The aim of this study was to describe the population pharmacokinetics of pipamperone and its correlates with clinical improvement in children and adolescents.

Methods: We performed a population pharmacokinetic analysis based on 70 pipamperone concentrations in 30 children and adolescents (median age 13.0 years, range [5.58-17.73], and bodyweight 50.4 kg [24.8-100.4]), using NONMEM 7.4. The sample consisted of Dutch patients from a prospective naturalistic trial (n=8), and German patients from a TDM service (n=22). Additionally, a random sample of 21 German patients with 33 pipamperone concentrations from the same TDM service was used for external validation (median age 14.9 years [7.2-20.6], bodyweight 47.4 kg [24.0-118]). Pipamperone samples were collected by venepuncture and Dried Blood Spot (DBS) and analysed by previously validated LCMS and HPLC methods. Correlates of pharmacokinetic parameters and clinical improvement, based

on Clinical Global Impression Improvement scores, in patients without psychotropic comedication and with Autism Spectrum Disorder (ASD) (n=8) were analysed by Pearson correlation coefficients.

Results: Pharmacokinetics of pipamperone in children and adolescents were described using a 1-compartment model with a fixed value for absorption rate ($k_a=2.0h^{-1}$). No significant covariates were identified and the error model included corrections for differences in matrix and analytical method. The pharmacokinetic model was successfully externally validated. The mean volume of distribution was 720 L and the apparent clearance 25.1 L/h (interpatient variability 36.1%). The improvement in CGI since start of therapy did not correlate with trough levels (n=13, $p=0.64$) or AUC (n=12, $p=0.84$).

Conclusions: This is the first study that describes pharmacokinetic parameters of pipamperone in children and adolescents, which correspond to adult values found in the literature.² Although no correlation with clinical improvement was found in the limited sample of 8 children with ASD and pipamperone monotherapy, our findings can guide therapeutic drug monitoring in this population.

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NEED FOR ADDITIONAL SEDATION AFTER CARDIAC SURGERY IN CHILDREN WITH AND WITHOUT DOWN SYNDROME: A PHARMACODYNAMIC AND PHARMACOKINETIC ANALYSIS OF MIDAZOLAM

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Introduction: Children with Down syndrome are reported to require more sedatives after cardiac surgery. The aim was to evaluate the pharmacodynamics and pharmacokinetics of midazolam after cardiac surgery in children with and without Down syndrome.

Methods: Twenty-one children with Down syndrome and 17 without (3 to 36 months old) scheduled for cardiac surgery, were included in this prospective observational study. Analysis of the pharmacokinetics and pharmacokinetics of morphine in this cohort has been published before (Valkenburg *et al.*, 2016). During intensive care admission, nurses regularly assessed pain and discomfort with validated instruments (COMFORT-B scale; Numeric Rating Scale-for pain). These scores guided analgesic and sedative treatment. Morphine was the first-line analgesic agent. Undersedation was defined as COMFORT-B score >16 and NRS<4 (indication to start midazolam). NONMEM was applied for population pharmacokinetic and pharmacodynamic modelling.

Results: Twenty-six of the subjects (68%) required midazolam postoperatively. There were no statistically significant differences between children with and without Down syndrome in terms of cumulative midazolam dose (p=0.61) or time before additional sedation was initiated (p=0.71). Population pharmacokinetic and pharmacodynamics analysis revealed no statistically significant differences between the children with and without Down syndrome. Bodyweight was found to be a significant covariate for the clearance of 1-OHmidazolam to 1-OHglucuronide.

Conclusion: The majority of children require sedation besides the standard morphine infusion after elective cardiac surgery, irrespective of Down syndrome. Midazolam pharmacokinetics and pharmacodynamics do not seem to be altered between children with and without Down syndrome after cardiac surgery.

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DEVELOPMENT OF PRESCRIBING KNOWLEDGE AND SKILLS OF JUNIOR DOCTORS IN THE FIRST YEAR AFTER GRADUATION

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Background: Poor prescribing may have negative effects on patient safety and healthcare costs. Studies have shown that medical students in Europe lack prescribing knowledge and skills at graduation (Brinkman et al., 2017, Brinkman et al., 2018), probably due to inadequate clinical pharmacology and therapeutics (CPT) education during the undergraduate medical curriculum (Brinkman et al., 2017). However, little is known about the development of prescribing knowledge and skills of junior doctors after graduation. This is important to develop educational interventions after graduation.

Objectives: The aim of this study is to investigate how the prescribing knowledge and skills of junior doctors in the Netherlands and Flanders develop in the first year after graduation.

Methods: This is a prospective cohort study among medical graduates from 11 medical schools in the Netherlands and Flanders. In total, 1.506 medical students graduating between July 2017 and March 2018 were invited to participate. They were asked to complete an online assessment at three different time points: T0= around graduation, T1= six months after graduation, T2= one year after graduation. Each assessment contained 35 multiple choice questions extracted from the Dutch Pharmacotherapy Assessment, divided into seven subjects (Kramers et al, 2017).

Results: In total, 556 (36.9%.) medical students agreed to participate of which 326 (58.6%) completed all three rounds. Overall, prescribing knowledge increased significantly from 69.4% (SD 13.0) to 77.1% (SD 11,4) during the first six months but then decreased from 77.1% (SD 11,4) to 69.3% (SD 13,6) at the end of the year ($p<0.001$). For 5/7 subjects (anticoagulants, cardiovascular drugs, antidiabetics, pschycotropics and basic pharmacokinetics and drugs calculation) there was a significantly increase in prescribing knowledge during the first six months ($p<0.001$). However, this knowledge decreased during the second six months ($p<0.001$). For antibiotics, the prescribing knowledge increased significantly after one year, for analgesics it decreased significantly after one year (both $p<0.001$).

Conclusion: There is an increase in prescribing knowledge of junior doctors in the first six months after graduation but then decreased after one year to the level at graduation. This study indicates that CPT education interventions six months after graduation are needed to maintain or improve prescribing knowledge.

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IMPLEMENTATION OF THE NATIONAL MEDICATION SAFETY TEST AT ERASMUS MC. IS A 'LICENCE TO PRESCRIBE' EASILY OBTAINED OR NOT?

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Introduction: In October 2018, the national pharmacotherapy test focusing on medication safety was implemented in the medical master curriculum at Erasmus MC. During implementation, two master curricula were running simultaneously. The “old”, quite traditional master program, in which the last students enrolled in September 2016, and the “new” master curriculum, which started in September 2017, where the ‘flipped classroom model’ and ‘just-in-time learning’ were implemented. In both curricula, the test is taken halfway the master curriculum, just before the start of the psychiatry internship. The test is taken in Tesvision software. This allowed for analysis of how well students performed in general and on specific subject classes, and whether there are differences in performance between students in the old and the new curriculum.

Methods: We obtained both qualitative and quantitative data at the start of this national test in Rotterdam. We compared test results of students in both curricula, and we analyzed the performance on the different subject classes that are covered within the test (e.g. ‘antidepressants’, ‘drug allergy’, etc.) Furthermore, we analyzed written evaluations and we attended face-to face evaluation sessions. Outcomes are presented as descriptive data, without statistical analysis, aiming to

have a ‘glance’ of the performance of students following implementation start of the test in our medical school.

Results: In February 2019, 84 students in the new curriculum and 78 in the old curriculum have taken the test. The percentage of students that pass when they do the test for the first time is higher in the new master curriculum (60% passed, with an average score of 84%) compared to the students in the old master curriculum (41%, with an average score of 81%). In general, questions on anticoagulants seemed a hard nut to crack for all students, irrespective of the curriculum they were in. This seems also the case for questions on basic pharmacokinetics. Questions on pain medication seemed the ‘easiest’ category for our students. In general, students conveyed that they underestimated the test and acknowledge that to pass the test they need to study hard, indicating that most of them had skipped or forgotten considerable parts of the pharmacotherapy education from the Bachelor program.

Conclusion: We can only speculate about the difference between results between two curricula. One speculation is that students in the new curriculum are generally hard working, ‘nominal’ students while the “tail” of the old curriculum consists of a complete different student population. The unfavorable results of anticoagulants questions deserve further investigation. Should anticoagulants get more attention during our bachelors curriculum? Is the relatively low score due to local differences in policies and guidelines regarding anticoagulants? It would be interesting to compare our results with those obtained in other centers. By 12th of april 2019 we will be able to present statistically tested results and show more detailed figures of performance on subject classes.

SUCCESS RATE OF TEST QUESTIONS CONCERNING PHARMACOKINETICS IS LOWER COMPARED TO PHARMACODYNAMICS IN CLINICAL PHARMACOLOGY TEACHING IN A HEALTH AND LIFE SCIENCES CURRICULUM

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Introduction

Pharmacokinetics (PK) and pharmacodynamics (PD) form the backbone topics in a course on clinical pharmacology for second year Health and Life Sciences students at the Vrije Universiteit Amsterdam (VU). Although both topics address different aspects of basic pharmacology principles, both PK and PD require sufficient insight to (fully) grasp their content and be able to use the obtained knowledge within a different context. In our clinical pharmacology course, knowledge is transferred via lectures, whereas problem-based learning (flipped classroom setting) and practicals are used to provide students with tools for deep learning. Student evaluations and personal teacher experience indicate that students experience PK and PD as most difficult, and especially seem to struggle with components that require insight into the often abstract basic content of pharmacology. Interestingly, between PK and PD topics, students indicate PK as most challenging. However, until now, objective analysis of the above-mentioned experiences is lacking to motivate (additional) improvement of course content with respect to PK and PD.

Objectives

To determine success rate of PK and PD test questions, subdivided in ‘knows’ and ‘knows how’ questions, of 3 sequential yearly cohorts of enrolled students of the second year Health and Life Sciences curriculum at the VU.

Methods

Success rate analysis of PK/PD multiple-choice (mc)-questions, subdivided into ‘knows’ and ‘knows how’, was performed in tests of the ‘pharmacology’ course at bachelor level from 3 cohorts (total n = 377) of second year Health and Life Sciences students of the VU. Tests consist of a total of 60 mc-questions, n = 20 on PK and n = 17.3±1.5 on PD. Difficulty and distinctiveness index was performed. Normal distribution of success rate of all question groups, between cohorts was determined. Success rate was analyzed on question and student level.

Results

Success rate of PK/PD questions, as well as the ‘knows’ and ‘knows how’ questions, was equally distributed between cohorts. Difficulty index demonstrated a ‘medium’ difficulty level and no significant difference in p-values between cohorts. Distinctiveness index of the questions was scored as ‘sufficient’. We found an overall reduction (p < 0.001) in success rate in PK mc-questions compared to PD. In addition, a reduction (p < 0.001) in success rate of mc-questions was found between overall ‘knows’ and ‘knows how’ PK/PD-questions.

Conclusion

Success rate of PK test questions is lower compared to PD and ‘knows how’ test questions on PK/PD are most challenging, confirming student and teacher experience. These data will be used to guide improvements in our course, i.e. reinforcing time and effort on PK, and increasing deep learning in PK/PD by strengthening the role of active learning tools in our course.

EXPLORING THE IMPACT OF LONG-READ SEQUENCING COMBINED WITH A NEURAL NETWORK PREDICTIVE MODEL TO IMPROVE THE PREDICTION OF CYP2D6 ENZYME ACTIVITY

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Introduction

Conventional genotyping assays used in clinical practice only partially explain the variability in CYP2D6 enzyme activity. These assays rely on interrogating a limited number of variants to group individuals into phenotypic categories rather than assessing all the genetic variability. Sequencing of *CYP2D6* presents an attractive alternative. However, the complexity of the *CYP2D6* gene limits the value of short read-sequencing. Long-read sequencing can cover the entire *CYP2D6* locus in one read which allows for haplotype phasing, identification of hybrid structures and accurate variant calling of the entire locus. In this study, we used long read sequencing combined with a deep neural network predictive model to fully resolve *CYP2D6* diplotypes and to elucidate the role of all observed *CYP2D6* variants on enzyme activity.

Methods

DNA and steady state trough levels of tamoxifen and its metabolites from 572 subjects of the CYPTAM study (Sanchez-Spitman et al., 2019) were available. The metabolic ratio (MR) of desmethyltamoxifen to endoxifen was used as proxy for CYP2D6 activity. A two-step long-range PCR followed by PacBio sequencing was used to resolve fully phased allelic sequences. (Buermans et al., 2017)

We built a deep neural network to predict the MR based on allele-specific variants observed in each individual. Results of the neural network were compared to conventional phenotype calling based on haplotype translation tables(www.pharmgkb.org). The contribution of individual alleles was compared to the conventional gene activity scores. Finally, the neural network was validated with 20 independent samples.

Results

Conventional phenotyping and the sequencing based neural network explained 53% and 78% of the observed variability in CYP2D6 activity, respectively. The CYP2D6 activity of the validation samples was accurately predicted ($R^2 = 0.89$). These results indicate that the use of a continuous phenotype increases the explained CYP2D6 variability substantially. Allele contributions did differ between the neural network predicted contributions and conventional assignments. For example, *CYP2D6**2 predicted activity ranged from 0.53-0.83 as opposed to the conventional 1.0 allele activity.

Conclusion

Condensing genetic test results into phenotype categories leads to loss of information, a generalization that contradicts with personalized medicine. This study highlights a novel approach for assessing CYP2D6 activity in the context of tamoxifen metabolism. Currently, replication studies are ongoing with the aim of validating and further developing the neural network.

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CRITICAL ASSESSMENT OF YIELD AND VARIABILITY IN ISOLATION AND CHARACTERIZATION OF EXTRACELLULAR VESICLES FROM HUMAN PLASMA USING DIFFERENT METHODOLOGIES

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Introduction: Extracellular vesicles (EVs) are functional nano-sized particles secreted by different cells of body, which contain specific molecular information of their parent cells. EV based biomarkers holds great potential in disease diagnosis, however, the isolation methods and detection protocols for EVs are highly variable from different research groups especially for plasma samples. Different EV isolation methodology may have great impact on the biomarker profile discovered in downstream analysis. In this study we aim to investigate different EV isolations from pooled human plasma sample with different characterization technologies to display the feature of yields and the variability as well as reproducibility of these isolation methods.

Methods: Three different commercially available EV isolation kits (Exoquick® System Biosciences, Exo-spin® Cell Guidance Systems and qEV® iZON science) have been applied to isolate EVs from pooled plasma sample of the healthy volunteers. Nanoparticle tracking analysis (NTA) was used to measure the particle concentration and size distribution of the isolates. Western blotting and Wes (ProteinSimple) was used to characterize specific protein markers in the isolates. EVQuant (Erasmus MC) was used to measure the quantity of general vesicles and immune-labeled EVs.

Transmission electron microscopy (TEM) was used to characterize the morphology of EVs in isolates from different isolations.

Results: Double peak pattern for the particle size distribution of EV isolates was found from each method in NTA, where the second peak (175nm – 250nm) matches the size of EVs. In protein characterizations: CD9 bands (20-25 kDa) were found in qEV fraction 2 and 3, in Exoquick and Exo-spin samples but not recognizable with parallel isolates. A CD9 antibody specific band at 45-50 kDa were repeatedly found in Exoquick and Exo-spin samples and is not previously reported. Flotillin-1 band (49 kDa) were observed except for qEV fraction 3. CD63 bands (50-55 kDa) were found specific to Exo-spin samples and qEV fraction 3. TSG101 bands (45-48 kDa) were found in Exoquick and Exo-spin samples but not in qEV fractions. TEM also showed different patterns of morphology between EVs from different isolation methods.

Conclusion: Different isolation method tends to enrich certain subpopulation of EVs where no isolation method includes all the tested EV protein markers. This could impact the downstream EV based biomarker analysis. Thus, in EV based biomarker studies, cautions need to be paid for the isolation method used, and the characterization evidence need to be provided to display the feature of EV samples undergoing analysis.

MAJOR BLEEDING RATES ARE HIGH IN PATIENTS WITH A HIGH INR COMBINED WITH A G1639A SNP IN THE VKORC1 GENE

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Background: The A variant of SNP rs9923231 (G1639A) is associated with decreased expression of VKORC1 and increases sensitivity to vitamin K antagonists (VKAs). Whether this results in a higher major bleeding risk is not well-established. It is also unknown whether the increased VKA-sensitivity combined with other risk factors affects major bleeding risk.

Aims: Determine the association of VKORC1 G1639A with(out) additional risk factors with major bleeding during VKA treatment.

Methods: DNA was collected from the BLEEDS cohort of 16,570 patients starting VKA treatment between January 2012 and July 2014. Patients were followed until major bleeding, end of VKA therapy, death, or December 31st 2014, whichever came first. From the cohort, a case-cohort study was assembled that included all cases with a major bleeding (326) and a random sample of 978 patients at baseline

(subcohort). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by weighted Cox regression, stratified by treatment period, and high international normalized ratio (INR_≥4).

Results: Results were available from 239 cases and 791 subcohort members. The AA genotype was associated with a 1.5-fold (95%CI 1.0-2.3) increased risk for major bleeding compared with GG carriers. While the major bleeding risk was higher during the first six months of treatment (HR 2.1, 95%CI 0.9-4.9), the incidence rate decreased over time. GG carriers with high INRs had similar incidence rates of major bleeding per 100 patient years (IRs) compared to those with low INRs (IR 1.6 (95%CI 0.27 – 5.29) - 3.1 (95%CI 0.16 – 15.4) versus 1.9 (95%CI 1.33 – 2.51) - 3.4 (95%CI 1.83 – 5.73) respectively). In sharp contrast, high INR GA carriers had high IRs (8.0 (95% CI 4.64 – 12.9) - 10.2 (95% CI 3.74 – 22.6)), and high INR AA carriers had very high IRs (18.8 (95%CI 7.60 – 39.0) - 20.2 (12.5 – 31.0)).

Conclusion: The AA genotype of VKORC1 G1639A is associated with an increased risk for major bleeding. Very high major bleeding rates among AA carriers with a high INR warrant monitoring and consideration of VKA therapy in these patients.

PHARMACOKINETICS OF PYRAZINAMIDE DURING THE INITIAL PHASE OF TUBERCULOUS MENINGITIS TREATMENT

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Introduction. Tuberculosis (TB) is the leading infectious disease killer worldwide. TB meningitis (TBM) is the most severe manifestation of TB, leading to death or permanent disability in more than 30% of those affected.

Pyrazinamide (PZA) is a pivotal anti-TB drug, but its dose has not been optimized for TBM. Available data suggest that a higher than standard dose of PZA could be more efficacious in pulmonary TB. This strategy could be used for optimizing TBM treatment as well.

Methods. Plasma PZA pharmacokinetic data were assessed on days 2 and 10 of standard TBM treatment in 52 adult Indonesian TBM patients. A CSF-to-plasma concentration ratio was determined at day 2. Predictors of plasma PZA exposure were assessed, plasma and CSF exposures were correlated, and the performance of PZA doses (in mg/kg)

and plasma AUC_{0-24h} to predict CSF concentrations was evaluated.

Results. All patients received a fixed dose of 1500 mg PZA daily, resulting in a median daily dose of 33.3 mg/kg (range 19.2-44.5 mg/kg). The geometric mean plasma PZA exposure (AUC_{0-24h}) and peak concentration (C_{max}) at day 2 were 709 h*mg/L and 59 mg/L, respectively. The plasma AUC_{0-24h} on day 10 (520 h*mg/L) was lower than the AUC_{0-24h} on day 2 (p<0.001).

Only PZA dose in mg/kg and BMI were correlated with plasma AUC_{0-24h} and C_{max} values.

The geometric mean CSF concentration at 3-6 h post dose was 42 mg/L and the mean CSF-to-plasma ratio was 90% (range 55-115%).

Plasma AUC_{0-24h}, C_{max} and CSF concentrations were all highly correlated to each other (r_s at least 0.80, p<0.001). CSF concentrations could be predicted based on PZA dose and plasma AUC_{0-24h} with -4.4% and 1.5% bias and with 20.6% and 12% imprecision, respectively.

Conclusion. Exposure to PZA during the first days of TBM treatment was high and had decreased on day 10. This is possibly due to an evolving inductive effect of rifampicin, pointing to a previously unknown interaction between PZA and rifampicin. PZA showed good penetration in CSF. The association between PZA doses, exposures in plasma and CSF provides a rationale for research into the merits of higher doses of PZA for TBM.

POPULATION PHARMACOKINETIC MODELING OF PAROMOMYCIN IN EAST AFRICAN VISCERAL LEISHMANIASIS PATIENTS

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Introduction: There is a high need for new therapies for the neglected tropical parasitic disease visceral leishmaniasis (VL), as effective, safe and affordable treatments are still lacking. Paromomycin sulphate (PM) has been shown to be effective in Indian VL patients (Sundar *et al.*, 2007) and is favourable over other therapies because of its affordability and its reasonable safety profile. However, a similar PM dosing regimen of 15 mg/kg/day for 21 days resulted in a lower efficacy in East Africa (Hailu *et al.*, 2010) and a dose increase or a combination therapy was required to achieve adequate efficacy (Musa *et al.*, 2012). In order to obtain a better understanding of the differences between populations, a population PK model of PM in different African patient populations will be developed.

Methods: A multi-centre randomized controlled trial (RCT) was performed in VL patients from Kenya, Sudan, and Ethiopia (Musa *et al.*, 2012). Intramuscular PM monotherapy (20 mg/kg/day for 21 days) and PM plus intravenous sodium stibogluconate (SSG) combination therapy (PM 15 mg/kg/day and SSG 20 mg/kg/day for 17 days) were compared to SSG monotherapy (20 mg/kg/day for 30 days). Of 500 plasma samples from 74 patients, paromomycin concentrations were obtained using HPLC-UV. A PK model of PM was developed using NONMEM (v 7.3). Tested covariates included study site, country, treatment group (monotherapy or combination

therapy with SSG), creatinine plasma levels, glomerular filtration rate (GFR), and albumin plasma levels. To evaluate the model fit, goodness-of-fit plots were inspected and a visual predictive check (VPC) was performed.

Results: A one-compartment model with first-order absorption was found to best describe PM in plasma. Typical parameter estimates (% CV) were a clearance of 3.91 L/h (9%), central volume of distribution (V_c) of 14 L (13%), and an absorption rate constant (k_a) of 1.43 h⁻¹ (20%). Body weight was included on clearance and V_c , with a fixed power of 0.75 and 1.00, respectively. Ethiopian patients had a significantly different bioavailability (4.27 times higher) and a slower k_a (0.10 h⁻¹). Additionally, for all patients, a decrease in clearance over time was found of 33.2% from start to end of treatment (day 21), which could not be explained by either GFR, creatinin or albumin. $AUC_{0-\tau,SS}$ (median [SD]) was significantly higher in Ethiopia (530.9 $\mu\text{g}\cdot\text{h}/\text{mL}$ [1882.2]) compared to Kenya and Sudan (160.8 $\mu\text{g}\cdot\text{h}/\text{mL}$ [154.6]).

Conclusion: The developed PK model of PM in East African VL patients showed a higher PM exposure in Ethiopia, compared to Kenya and Sudan. The difference in PK between countries might explain the observed differences in clinical efficacy with Indian patients. To further understand this diversity, it is planned to compare the PK of PM in East African countries with the PK in the Indian population.

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EXPOSURE-RESPONSE ANALYSIS OF ALK-INHIBITOR CRIZOTINIB IN NON-SMALL CELL LUNG CANCER PATIENTS

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Introduction: Crizotinib is an ALK-inhibitor approved for the treatment of ALK- or ROS1-positive advanced non-small cell lung cancer (NSCLC). Crizotinib shows a large interpatient variability in pharmacokinetic exposure. [1] Clinical trials indicated that pharmacokinetic exposure to crizotinib might be related to efficacy. [1] The aim of this study was to explore whether crizotinib exposure is related to efficacy in a real-world patient cohort.

Methods: A retrospective observational study was performed. NSCLC patients who were treated with crizotinib and of whom plasma concentrations were drawn as part of routine care were included. Calculated minimum plasma concentrations (C_{\min}) were taken as a measure of exposure. Efficacy endpoints were progression-free survival and overall survival. Univariate and multivariate exposure-response analyses were performed using a previously defined pharmacokinetic threshold of > 235 ng/ml. [1]

Results: 79 patients were included in this study. A total of 322 plasma samples were eligible for analysis. Median number of samples per patient was 3 (range 1–15) and median C_{\min} per patient was 253 ng/ml (interquartile range: 173.5–354 ng/ml).

Median progression-free survival was 10.8 and 5.3 months for patients with median crizotinib $C_{\min} >235$ ng/ml and <235 ng/ml, respectively (log-rank test, $p = 0.02$, see Fig. 1). In multivariate analysis $C_{\min} <235$ ng/ml resulted in a hazard ratio of 2.14 (95% CI 1.20–3.81, $p = 0.01$).

Conclusion: This study shows that crizotinib exposure is related to efficacy in a real-world patient cohort. Therefore, therapeutic drug monitoring for individualized treatment may be appropriate.

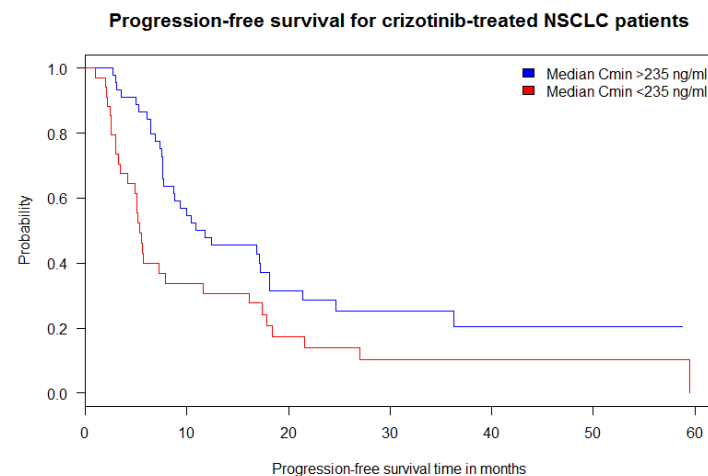


Fig. 1 Kaplan-Meier plot of progression-free survival in NSCLC patients.

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Pilot study to predict the pharmacokinetics of a clinically relevant gemcitabine dose from a microdose

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Introduction: Microdosing studies are exploratory investigational new drug trials to early determine drug pharmacokinetics in human. The role of microdose trials in oncology has not been established as the question arises whether pharmacokinetic data from microdose studies can be directly extrapolated to a therapeutically relevant dose. In this trial, we examined whether the pharmacokinetics of gemcitabine in a therapeutic dose could be predicted from the pharmacokinetics of a microdose.

Methods: This was a prospective, open-label microdosing study in which a gemcitabine microdose (100 µg) was given to participants on day 1, followed by a therapeutic dose (1250 mg/m²) on day 2. Both dosages were administered via a 30-minute infusion. Gemcitabine and its metabolite were quantified in plasma samples using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method. Non-compartmental analysis was performed.

Results: Ten patients participated in this study. No toxicities were observed after administration of the microdose. The median area under the curve to infinity (AUC_{0-inf}) after microdosing was 12 h·mg/L (linearly extrapolated to 1250 mg/m²) and the median AUC_{0-inf} after therapeutic dosing was 15 h·mg/L. The exposure after the therapeutic dose was within two-fold of the exposure following a microdose in all individuals. However, the shape of the concentration-time curve was different (Fig. 1). This was reflected by poor scalability in volume of distribution of the microdose (929 L) compared to the therapeutic dose (242 L).

Conclusion: The exposure of gemcitabine at therapeutic dose was accurately predicted by the pharmacokinetics of a gemcitabine microdose, showing the feasibility of these type of trials in oncology.

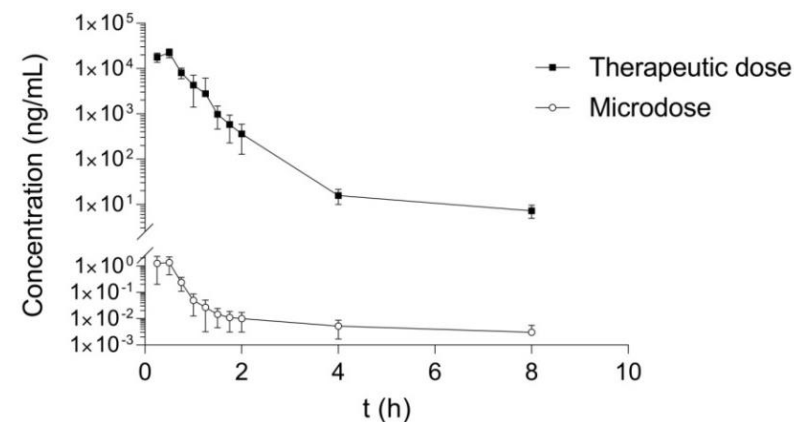


Fig. 1: Concentration-time curves of gemcitabine at therapeutic dose and microdose.

**DASHBOARD DRIVEN VERSUS CONVENTIONAL DOSING OF INFLIXIMAB IN INFLAMMATORY BOWEL DISEASE:
THE PRECISION TRIAL.**

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Introduction

Loss of response to infliximab (IFX) complicates the management of inflammatory bowel disease (IBD). Up to date, no prospective study has demonstrated the benefit of proactive dose adjustment based on serum IFX levels. However, more personalized dosing strategies using a dashboard to achieve and maintain well-defined IFX target trough levels (TLs) may prevent loss of response. The aim of the PRECISION trial was to investigate the efficacy of dashboard driven IFX dosing in IBD patients during one year.

Methods

In this multicenter 1:1 randomized prospective trial, patients in clinical remission (Harvey Bradshaw Index (HBI) ≤ 4 for Crohn's disease (CD) or partial mayo score (PM) ≤ 2 for ulcerative colitis (UC)) receiving IFX maintenance treatment were included.

Patients in the precision dosing group (PG) received IFX dosing guided by a Bayesian pharmacokinetic model, aiming to achieve and maintain an IFX TL of 3 $\mu\text{g/ml}$ by treatment (de-)escalation as indicated by the dashboard¹. Patients in the control group (CG) continued IFX treatment regimen given prior to randomization without dose adaptation. Biochemical remission was defined as a fecal calprotectin $<250 \mu\text{g/g}$ and CRP $<0.5 \text{ mg/L}$. Clinical loss of response was defined as a HBI >4 or PM score >2 at two consecutive visits.

Results

In total, 80 patients were included (66 CD and 14 UC) with a median age ([interquartile range; IQR]) of 37 years [27-51]. Median IFX treatment duration was 3.5 years [2-7.8] in the PG and 4.0 years [1.3-5.8] in the CG. Median TLs were 3.7 $\mu\text{g/ml}$ [1.6-6.4] and 3.0 $\mu\text{g/ml}$ [1.9-5.2] in the PG and CG respectively. Fifteen out of 80 patients (37.5%) in the PG and 17 out of 40 patients (42.5%) in the CG were treated in combination with an immunomodulator. Clinical loss of response was observed in 14/39 (36%) patients in the CG compared to 4/32 (13%) patients in the PG ($p=0.03$). Three patients (7.5%) in the PG were considered failures because of re-opening of their perianal fistula after dose de-escalation to achieve a TL of 3 $\mu\text{g/ml}$.

Conclusion

Dashboard guided dosing resulted in a significant higher proportion of patients who maintained clinical remission during 1 year of treatment compared to patients that continued treatment without proactive adjustments.

