Scientific Spring Meeting
Friday April 7, 2017

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

Nederlandse Vereniging voor
KLINISCHE FARMACOLOGIE
en Biofarmacie

PROGRAMME of the SCIENTIFIC MEETING
Friday April 7, 2017
Auditorium Radboud university medical center Nijmegen

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

09.00 h **Welcome & coffee**

ORAL PRESENTATIONS

09.30 h *A. Abdulla, N.G.M. Hunfeld, A. Dijkstra, S. Duran, J.W. Mouton, D.A.M.P.J. Gommers, T. van Gelder, B.C.P. Koch* (Rotterdam): Beta-lactam and fluoroquinolone pharmacokinetic/pharmacodynamic target attainment in critically ill patients (EXPAT)

09.45 h *P.C.D. Bank, J.J. Swen, R.D. Schaap, D.B. Klootwijk, R.F. Baak – Pablo, H.J. Guchelaar* (Leiden): Implemention of pharmaco-genomics into primary care

10.00 h *E. Beers, A.M. Caro, A.S. Vos, H.C.P.M. van Weert* (Amsterdam): Deprescribing in cancer patients with a limited life expectancy in primary care: a retrospective longitudinal study

10.15 h *P.A.J.G. De Cock, H. Mulla, S. Desmet, F. De Somer, B.C. McWhinney, J.P.J. Ungerer, A. Moerman, S. Commeyne, J. Vande Walle, K. Francois, J.G.C. van Hasselt, P. De Paepe* (Gent): Optimizing cefazolin dosing in children undergoing cardiac surgery with cardiopulmonary bypass using a model-based dosing regimen

10.30 h *L.G. Franken, A.D. Masman, M. van Dijk, F.P.M. Baar, D. Tibboel, B.C.P. Koch, T. van Gelder, R.A.A. Mathot, B.C.M de Winter* (Rotterdam): A pharmacodynamic model of midazol-induced sedation in terminally ill patients

10.45 h *H. Maagdenberg, M.B. Bierings, A. de Boer, A.H. Maitland-van der Zee on behalf of the CAPS collaborators* (Utrecht): The children anticoagulation and pharmacogenetics study (CAPS): developing a dosing algorithm for acenocoumarol for paediatric patients

11.00 h **Coffee and Tea Break**

11.15 h *S. Schalkwijk, A.O. Buaben, J. Freriksen, A.P. Colbers, D.M. Burger, R. Greupink, F.G.M. Russel* (Nijmegen): Dosing for two: placental transfer and fetal darunavir exposure

11.30 h *R.B. Verheijen, T.T. van Duijl, M.M. van den Heuvel, J.H. Beijnen, J.H.M. Schellens, D. van den Broek, N. Steeghs, A.D.R. Huitema* (Amsterdam): Monitoring of circulating tumor DNA in non-small cell lung cancer patients treated with EGFR-inhibitors

11.45 h **GENERAL MEETING of the 'NVKFB'**

12.30 h **LUNCH and POSTER SESSION**

1. *R.A. Wijma, B.C.P. Koch, T. van Gelder, J.W. Mouton* (Rotterdam): An evaluation of the effectivity of the current treatment of uncomplicated urinary tract infections with fosfomycin based on urinary concentrations in healthy volunteers

2. *C. van der Heijden, M. Duizer, B. Veldman, T. Sprong, H. Fleuren, A. Dofferhoff, C. Kramers* (Nijmegen): Intravenous flucloxacillin treatment is associated with hypokalemia in hospitalized patients

3. *L. Dossche, R. Michelet, P. De Bruyne, J. Van Bocxlaer, A. Vermeulen, J. Vande Walle* (Gent): Bioequivalence in adults does not mean bioequivalence in children

4. *Z.Z.R.M. Weerts, D. Keszthelyi, H.W. Frijlink, J.R.B.J. Brouwers, L. Vork, D.M.A.E. Jonkers, A.A.M. Mascle* (Maastricht): A randomized, double-blind, crossover study on pharmacokinetics of peppermint oil in healthy volunteers: enteric-coating versus colon-targeted-delivery

5. *R. Admiraal, S. Nierkens, M.A. de Witte, E.J. Petersen, G. Fleurke, L. Verrest, S.V. Belitser, R.G.M. Bredius, R.A.P. Raymakers, C.A.J. Knibbe, M.C. Minnema, C. van Kesteren, J. Kuball, J.J. Boelens* (Utrecht): Optimising anti-thymocyte globulin exposure in hematopoietic cell transplantation: a retrospective pharmacokinetic-pharmacodynamic analysis

6. *S.T. de Vries, M.J.M. van der Sar, P. Denig, P.G.M. Mol on behalf of SCOPE work package* (Groningen): Communication on safety of medicines in Europe: current practices and general practitioners' awareness and preferences

7. *A.E. Kip, S. Blesson, F. Alves, R. Kimutai, P. Menza, B. Mengesha, J.H.M. Schellens, J.H. Beijnen, A. Hailu, E. Diro, T.P.C. Dorlo* (Amsterdam): Pharmacokinetics of simultaneously administered antileishmanial and antiretroviral drugs in visceral leishmaniasis patients co-infected with HIV in Ethiopia

8. *J.A. Dijkstra, T. van der Laan, O.W. Akkerman, M.S. Bolhuis, W.C.M. de Lange, J.G.W. Kosterink, T.S. van der Werf, J.W.C. Alffenaar, D. van Soolingen* (Groningen): Comparison of the in vitro activity of amikacin and kanamycin against Mycobacterium tuberculosis and target attainment

9. *A.H. Neerincx, S.J.H. Vijverberg, P. Brinkman, A.D. Kraneveld, U. Potocnik, M. Pino-Yanes, O. Sardon Prado, M. Kabesch. A.H. Maitland-van der* Zee (Amsterdam): A systems pharmacology approach to difficult-to-treat pediatric asthma: design of the SysPharmPediA study

10. *M.T.J. van Bussel, D. Pluim, B. Milojkovic-Kerklaan, D. van den Broek, J.H. Beijnen, W. Boogerd, J.H.M. Schellens, E. Le Rhun, D. Brandsma* (Amsterdam): Circulating tumor cells and circulating tumor DNA analysis in cerebrospinal fluid in melanoma patients with suspected leptomeningeal metastasis

11. *S.E. Berends, G. D'Haens, J.C.J. van Selm, A.S. Strik, M. Löwenberg, C.Y. Ponsioen, R.A.A. Mathôt* (Amsterdam): Factors influencing clearance of adalimumab in patients with Crohn's disease: a population pharmacokinetic study

12. *A. Colbers, S. Schalkwijk, D. Konopnicki, A. Gingelmaier, J. Lambert, M. van der Ende, J. Moltó, D. Burger on behalf of the PANNA network* (Nijmegen): Substantially lower rilpivirine plasma concentrations during prgnancy

13. *D.J. Brinkman, J. Tichelaar, M. Okorie, L. Bissell, T. Christiaens, R. Likic, R. Maciulaitis, J. Costa, E. Sanz, B.I. Tamba, S.R. Maxwell, M.C. Richir, M.A. van Agtmael* (Amsterdam): Pharmacology and therapeutics education in EU needs harmonisation and modernisation: a cross-sectional survey among 185 medical schools in 27 countries

14. *M.B.S. Crombag, J.G.C. van Doremalen, A.H.M. de Vries Schultink, J.H.M. Schellens, J.H. Beijnen, A.D.R. Huitema* (Amsterdam): Hematological toxicity in older patients treated with docetaxel or docetaxel-containing regimens

15. *M.B.S. Crombag, J.G.C. van Doremalen, J.H.M. Schellens, J.H. Beijnen, N. Steeghs, A.D.R. Huitema* (Amsterdam): Therapeutic drug monitoring of tyrosine kinase inhibitors in older patients

16. *S. Völler, R.B. Flint, L.M. Stolk, P.L.J.M. Degraeuwe, S.H.P. Simons, D.M. Burger, C.A.J. Knibbe* (Leiden): A population pharmaco-kinetic model for phenobarbital in term and preterm neonates

17. *P.A.J.G. De Cock, M. Wollaert, S. Desmet, B. McWhinney, A. de Jaeger, J. Vande Walle, P. De Paepe* (Gent): Observational study on target attainment and protein binding of teicoplanin in critically ill children

18. *P. De Bruyne, J. Vande Walle, on behalf of the SAFE-PEDRUG consortium (IWT SBO-130033)* (Gent): The safe-pedrug initiative: a new approach for efficient and ethical paediatric drug research

19. *N. Farzan, S.J. Vijverberg, J.A. Raaijmakers, A.H. Maitland-van der Zee on behalf of the PiCA consortium* (Utrecht): 17q21 gene variation increases the risk of exacerbations in asthmatic children treated with inhaled corticosteroids: a meta-analysis in the multi-ethnic PiCA consortium

20. *B.C. Witjes, A.S. Zandvliet, J.A. Dijkstra, W.A. Kors, F.C. Abbink, S.E. Smetsers, E.L. Swart, F. Sombogaard, A.J. Wilhelm* (Amsterdam): Voriconazole dosing strategies in young children: challenges and recommendations

21. *O. van Katwijk, S. Croes, A. Verbon, D. Posthouwer, M.B. Haeseker, L.M.L. Stolk* (Maastricht): Augmented vancomycin clearance in neutropenic patients: assessing predictors and adequate treatment

22. *B.D. van Groen, E. van de Steeg, M.M.H. van Lipzig, M.G. Mooij, H.M. Wortelboer, D. Tibboel, W.H. Vaes, S.N. de Wildt* (Rotterdam): Maturation of human hepatic membrane transporter proteins in the first four months of life

23. *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): Pediatric microdose study of [^{14}C]midazolam to study the ontogeny of CYP3A mediated drug metabolism

24. *Y.A. Bijleveld, T.R. de Haan, R.A.A. Mathôt* (Amsterdam): Population pharmacokinetics of amoxicillin and gentamicin in term neonates undergoing moderate hypothermia

25. *I. Önsesveren, R. van Westrhenen, A.I. Wierdsma, L. de Haan, C.L. Mulder* (Rotterdam): Penfluridol (oral long acting antipsychotic agent) as compared to second-generation antipsychotics: an ongoing randomized controlled trial on effectiveness

26. *T. Preijers, H.C.A.M. Hazendonk, R. Liesner, P. Chowdary, M.H.E. Driessens, D. Hart, D. Keeling, B.A.P. Laros-van Gorkom, F.J.M. van der Meer, K. Meijer, K. Fijnvandraat, F.W.G. Leebeek, P.W. Collins, M.H. Cnossen, R.A.A. Mathôt for the "OPTI-CLOT" study group* (Amsterdam): Population pharmacokinetic analysis of perioperative factor IX dosing in hemophilia B

27. *A.N. Bindraban, J. Rolvink, F.A. Berger, P.M.L.A. van den Bemt, R.T.M. van der Hoeven, A.K. Mantel-Teeuwisse, M.L. Becker* (Haarlem): Development of a model to predict QTc prolongation in patients who use one or more QT-prolonging drugs

28. *J.J.M. Rood, A. Jamalpoor, M.J. van Haren, M.J. Janssen, J.H.M. Schellens, J.H. Beijnen, R.W. Sparidans* (Utrecht): Extrahepatic metabolism of the targeted covalent inhibitor ibrutinib through the glutathione cycle

29. *A. Raaijmakers, Z.Y. Zhang, E. Levtchenko, S. Simons, B. van den Heuvel, L. Jacobs, J.A. Staessen, K. Allegaert* (Leuven): Perinatal drug exposure in extreme low birth weight infants and subsequent renal outcome in childhood: a safety study is feasible

30. *E.M.J. van Brummelen, A. de Boer, J.H. Beijnen, J.H.M. Schellens* (Amsterdam): *BRAF* mutations as predictive biomarker for response to anti-EGFR monoclonal antibodies: proposal for an update of the drug label of panitumumab and cetuximab

31. *F. Besemer, C. Kramers, K. Brinkman, A.R.M.M. Hermus, A.E. van Herwaarden, D.M. Burger* (Nijmegen): Prevalence of hypothalamic-pituitary-adrenal axis suppression by inhalation or nasal corticosteroids in HIV-infected patients

32. *K. Meesters, R. Mauel, J. Vande Walle, P. De Bruyne* (Brussel): Systemic fluoroquinolone use in hospitalized children in Belgium, results of a multicenter retrospective drug utilization study

33. *L.C. Martial, R.E. Aarnoutse, M.F. Schreuder, S.S. Henriet, R.J.M. Brüggemann, M.A. Joore* (Nijmegen): Cost evaluation of dried blood spot home sampling as compared to conventional sampling for therapeutic drug monitoring in children

34. *L.M. Henricks, E. Kienhuis, F.M. de Man, A.A.M. van der Veldt, P. Hamberg, A.B.P. van Kuilenburg, C.A.T.C. Lunenburg, H-J. Guchelaar, J.H.M. Schellens, R.H.J. Mathijssen* (Amsterdam): Safe treatment of homozygous or compound heterozygous *DPYD* variant allele carriers with low dose fluoropyrimidines is feasible

35. *L. van Andel, Z. Zhang, S. Lu, V. Kansra, S. Agarwal, L. Hughes, M.M. Tibben, A. Gebretensae, L. Lucas, M.J.X. Hillebrand, H. Rosing, J.H.M. Schellens, J. H. Beijnen* (Amsterdam): Human mass balance and metabolite profiling of ^{14}C-niraparib in patients with cancer

36. *R.A. Wijma, S. Bahmany, E.B. Wilms, T. van Gelder, J.W. Mouton, B.C.P. Koch* (Rotterdam): A simple and fast LC-MS/MS method for the quantification of fosfomycin in urine and plasma using one sample preparation method and HILIC chromatography

37. *J.M. Bos, S. Natsch, P.M.L.A. van den Bemt, J.L.W. Pot, J.E. Nagtegaal, A. Wieringa, G.J. van der Wilt, P.A.G.M. De Smet, C. Kramers* (Nijmegen): A multifaceted intervention to improve guideline adherence among prescribing physicians at surgical wards

38. *S.C. Bergheanu, K.M.S. Kanhai, Y.L. Wagenaar, J.A. Nij Bijvank, E.S. Klaassen, K.S. Lim, A. Petzold, A. Verma, R. van Rijn, G.J. Groeneveld* (Leiden): Effects of a single-dose fampridine on internuclear ophthalmoplegia (INO) severity in patients with multiple sclerosis (MS)

39. *C. Bastida, D. Soy, A.H.M. de Vries Schultink, V. Ruíz, R. Sanmartí, M. Pascal, J. Yagüe, A.D.R. Huitema* (Amsterdam): Population pharmacokinetic analysis of intravenous tocilizumab in rheumatoid arthritis patients

40. *M.S. Bolhuis, E. Van Kampenhout, J.W.C. Alffenaar, J.G.W. Kosterink, T.S. van der Werf, O.W. Akkerman* (Groningen): Pharmacokinetics of moxifloxacin and linezolid during and after pregnancy in a MDR-TB patient

41. *P. Mian, A.J. Valkenburg, K.M. Allegaert, B.C.P. Koch, C.V. Breatnach, C.A.J. Knibbe, D. Tibboel, E.H.J. Krekels* (Rotterdam): Population pharmacokinetic modelling of paracetamol after cardiac surgery in children with and without Down syndrome

42. *J.M. Janssen, C.M. Zwaan, J.H.M. Schellens, J.H. Beijnen, A.D.R. Huitema* (Amsterdam): Clinical trial simulations in paediatric oncology: a feasibility study with bosutinib in paediatric CML

43. *M. Herbrink, N. de Vries, H. Rosing, A.D.R. Huitema, B. Nuijen, J.H.M. Schellens, J.H. Beijnen* (Amsterdam): Development and validation of a liquid chromatography-tandem mass spectrometry assay for the therapeutic drug monitoring of 8 novel anticancer drugs

44. *T. De Backer, C. Detremerie, M. Petrovic* (Gent): Treatment of hypertension in the frail elderly

45. *J.J. Geenen, G.M. Dackus, P.C. Schouten, S. Marchetti, H. van Tinteren, J.H. Beijnen, G.S. Sonke, S.C. Linn, J.H. Schellens* (Amsterdam): The REVIVAL study: olaparib and carboplatin as first line treatment in advanced BRCA mutated breast cancer

46. *L.M. Andrews, B.C.P. Koch, D.A. Hesselink, E.A. Cornelissen, S.N. de Wildt, T. van Gelder, K. Cransberg, B.C.M. de Winter* (Rotterdam): New population pharmacokinetic model that predicts the starting dose of tacrolimus following pediatric renal transplantation

47. *S.C. Goulooze, E.H.J. Krekels, S.J.G.M. Ahlers, M.A. Saleh, P.A.J. Välitalo, D. Tibboel, C.A.J. Knibbe* (Leiden): Repeated time-to-event modeling of rescue morphine during recovery from cardiac surgery

48. *M.L. Toren-Wielema, R.B. Veenhuizen, J.W. Kappelle, N.J.G.M. Veeger, E.N. van Roon* (Leeuwarden): Efficacy of a standardized oral vitamin D dosing regimen in somatic and psychogeriatric nursing home residents

49. *S. Cristea, A. Smits, A. Kulo, C.A.J. Knibbe, M. van Weissenbruch, E.H.J. Krekels, K. Allegaert* (Leiden): Amikacin pharmaco-kinetics to optimize dosing recommendations in neonates with perinatal asphyxia treated with hypothermia

50. *S.M. Kloosterboer, B.C.M. de Winter, T. van Gelder, B. Dierckx, B.C.P. Koch* (Rotterdam): Clinical validation of a Dried Blood Spot method for determination of risperidone, aripiprazole, pipamperone and their major metabolites

51. *S. Wassenaar, H.H. Bijma, B.J. Sibbles, A.J. Schneider, A.A. Aaldriks, B.C.N. van der Nagel, E.A.P. Steegers, B.C.P. Koch* (Rotterdam): Prevalence estimation of alcohol consumption by pregnant women using the new biomarker phosphatidylethanol (PEth)

52. *M. Roskam-Kwint, P. Bollen, A. Colbers, M. Duisenberg-van Essenberg, V. Harbers, D. Burger* (Nijmegen): Crushing of dolutegravir combination tablets increases dolutegravir exposure

53. *P.J. Glerum, Y. Yu, W. Yamada, M. Neely, M. Maliepaard, D. Burger, C. Neef* (Utrecht): Robustness of the conclusion of bioequivalence; a non-parametric comparison

54. *N. Boone, L. Lui, M. Romberg, L. Duijsens, H. van der Kuy, R. Janknegt, A. van Bodegraven* (Sittard): Transition study of biosimilar infliximab in patients with inflammatory bowel disease

55. *C. Mestres Gonzalvo, H.A.J.M. de Wit, B.P.C. van Oijen, D. Deben, K.P.G.M. Hurkens, W.J. Mulder, R. Janknegt, J.M.G.A. Schols, F.R. Verhey, B. Winkens, P.H.M. van der Kuy* (Sittard-Geleen): Prospective validation of an automated delirium prediction model

13.30 h *Prof. dr. A. de Boer:* **DOACS: what have we learned from post-marketing studies?**

13.50 h Lecture of the winner of the **'NVKFB'-Thesis Award 2016**

14.10 h Lecture of the winner of the **'NVKFB'-TOP Publication Award 2016**

14.25 h Lecture of the winner of the **`NVKFB´-Education Award 2016**

ORAL PRESENTATIONS

14.45 h *R.E. Wasmann, R. ter Heine, D.M. Burger, C.A. Knibbe, R.J. Brüggemann* (Nijmegen): One size does not fit all: How to adjust the dose of anidulafungin in obesity

15.00 h *T.M. van der Zanden, M. de Hoog, J.D. Windster, S.N. de Wildt, I.H. van der Sijs* (Rotterdam): Reduction of calculation errors with the Dutch pediatric formulary's web-based paediatric dosing calculator

15.15 h *V.A. de Weger, A.D.R. Huitema, B. Nuijen, J.H. Beijnen, S. Pulleman, M. Mergui, J.H.M. Schellens, S. Marchetti* (Amsterdam): Phase I dose-finding studies with the oral docetaxel formulation ModraDoc006 co-administered with ritonavir (ModraDoc006/r)

15.30 h *A. Smits, P. Steven, M. Oyaert, N. Peersman, I. Spriet, V. Saegeman, K. Allegaert* (Leuven): Vancomycin protein binding in neonates and young infants

15.45 h Closure

16.30 h Inaugural lecture prof. dr. S.N. de Wildt (Aula Radboud University, Comeniuslaan 2, Nijmegen)

BETA-LACTAM AND FLUOROQUINOLONE PHARMACOKINETIC/PHARMACODYNAMIC TARGET ATTAINMENT IN CRITICALLY ILL PATIENTS (EXPAT)

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Introduction: The extreme pharmacokinetic (PK) behaviour of drugs sometimes observed in critically ill patients poses a significant threat to the achievement of optimal antibiotic treatment outcomes. Therapeutic drug monitoring (TDM) is a commonly used dosing strategy to optimize exposure and thereby minimize toxicity and maximize the efficacy. However, expansion of this practice to β-lactams and quinolones is not widely used as a routine intervention and data are still sparse as to whether individual patient variability would merit TDM for these two classes. The main objectives of this study are to (1) assess exposures of β-lactams and quinolones commonly use in critically ill patients in a routine ICU setting, and (2) whether the turnaround time of assays would justify TDM of these classes.
Methods: The EXPAT is an ongoing prospective, observational PK/PD study in 2 ICUs (teaching and academic hospital) in the Netherlands. We enrolled patients ≥18 years old administered frequently used β-lactams and quinolones, over a 6-month period. Based on optimal sampling, five separate 5-mL samples were taken at various time points. Plasma concentrations were determined by a validated multi-analyte UPLC-MS/MS assay, with a simple and rapid preparation procedure and a total run-time of 5.20 minutes. The percentage *f*T>MIC were determined by calculating the intercept of the MIC values (0.5 to 8.0 mg/L) with the concentration-time curve. For the β-lactam antibiotics (cefotaxime, ceftriaxone), the primary PK/PD endpoints were the free concentrations above the minimum inhibitory concentration (MIC) at 100% (ICU target) of the dosing interval (100% *f*T>MIC and 100% *f*T>4xMIC). For the quinolones (ciprofloxacin), we determined the area under the free concentration time curve-to-MIC ratio (*f*AUC/MIC>100) and the maximum concentration of drug in serum-to-MIC ratio (*f*Cmax/MIC>10). In the absence of cultures, the MIC values were derived from the EUCAST epidemiological cut-off (ECOFF) breakpoints.
Results: A total of 80 patients were included in this first interim analysis. The median age was 62 years, 60% of the patients were male, median APACHE II score was 23 and median creatinine clearance rate was 66 mL/min. All samples were assayed during routine lab procedures. The 100% *f*T>MIC and 100% *f*T>4xMIC targets for MIC 4 mg/L (*Staphylococcus aureus* ECOFF) in the β-lactam patients were attained in 65% and 26%, respectively. The *f*AUC/MIC>100 and *f*Cmax/MIC>10 targets for MIC 0.5 mg/L (*Pseudomonas aeruginosa* ECOFF) in the quinolone patients was attained in 38% and 19%, respectively.
Conclusions: The interim analysis at 6-months demonstrated that TDM of β-lactams and quinolones is feasible in a routine clinical setting. Empiric approaches to β-lactam and quinolones dosing in critically ill patients results in poor target attainment and would merit TDM for these agents.

IMPLEMENTION OF PHARMACOGENOMICS INTO PRIMARY CARE

P.C.D. Bank, J.J. Swen, R.D. Schaap, D.B. Klootwijk, R.F. Baak - Pablo & H.J. Guchelaar
Department of Clinical Pharmacy & Toxicology, Leiden University Medical Centre, Leiden, The Netherlands

Despite the availability of the guidelines of the Dutch Pharmacogenetics Working Group (DPWG) encompassing therapeutic recommendations for 84 gene-drug combinations and the integration of these guidelines in nationwide electronic clinical decision support (CDS) systems, the application of Pharmacogenomics (PGx) in primary care in the Netherlands remains limited [1,2]. Research shows that healthcare professionals are enthusiastic about PGx and believe in the concept, but the majority feels unqualified to interpret and handle upon PGx data. It appears that the integration of guidelines providing therapeutic recommendations for relevant drug-gene-interactions into the workflow does not lead to a higher adoption of PGx in (primary) care [3]. In this study we set out to investigate whether genotype guided pharmacotherapy in primary care as part of the workflow of clinicians is feasible.

Patients with an incident prescription for amitriptyline, atomoxetine, atorvastatin, (es)citalopram, clomipramine, doxepin, nortriptyline, simvastatin or venlafaxine and historical use of one other of the nine selected drugs were recruited through community pharmacies. DNA was extracted from a saliva sample and genotyped for 40 variants in *CYP2C9, -2C19, -2D6, -3A5, DPYD, SLCO-1B1, TPMT* and *VKORC1* using the Affymetrix DMET-plus supplemented with a *CYP2D6* copy-number assay. A report containing the genotypes, predicted phenotypes and a therapeutic recommendation for the incident prescription based on the DPWG guidelines were communicated to the pharmacist and general practitioner for genotype guided dosing using CDS. In the period from November 2014 up till July 2016 200 patients were included into the study by 31 participating pharmacies in the vicinity of Leiden, The Netherlands. Of the included patients the majority received an incident prescription for a statin with 57.0% and 14.5% receiving atorvastatin and simvastatin respectively. The remainder of 28.5% of the included patients received a TCA (16.5%), SSRI (4.5%) or SNRI (7.5%). Genotyping revealed that 89.5% of the patients carried at least one actionable genotype in the selected PGx panel. In all of the eight tested genes the frequency of patients with an aberrant phenotype was higher than 5% (ranging from 7.0% for *DPYD* up to 47.0% for *CYP2D6*). In 31.0% of the incident prescriptions a drug-gene interaction was present and a therapeutic recommendation was provided which required additional action by treating pharmacists.
Based on these results we conclude that implementation of PGx in primary care is feasible and the frequency of actionable DGI's for the selected drugs among the included patients is high.

References:

1) Swen et al. Clin Pharmacol Ther. 2008 May;83(5):781-7
2) Swen et al. Clin Pharmacol Ther. 2011 May;89(5):662-73
3) Bank et al. Pharmacogenomics. 2017 Feb;18(3):215-225

DEPRESCRIBING IN CANCER PATIENTS WITH A LIMITED LIFE EXPECTANCY IN PRIMARY CARE: A RETROSPECTIVE LONGITUDINAL STUDY

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Introduction
For patients with advanced cancer and a limited life expectancy, treatment goals shift from disease-oriented to symptom-oriented. This means that medication with a longer time until benefit than life expectancy become potentially inappropriate (PIM) and can be deprescribed, i.e. stopped or tapered. In the Netherlands, the general practitioner (GP) is the gatekeeper and coordinator during the patient's last stage of life. No longitudinal studies have been performed on the deprescribing of preventive medication in patients with advanced cancer and limited life expectancy.

Aims
To assess the prevalence of PIMs and the frequency and time frames of deprescription of PIMs among patients with advanced cancer and limited life expectancy in primary care.

Methods
This was a retrospective longitudinal cohort study with routinely collected primary care data of 49 GPs in southeast-Amsterdam. Patients with a malignancy of the pancreas, stomach, oesophagus or lungs were included. All medication at time of diagnosis was evaluated for its appropriateness according to the validated OncPal deprescribing guideline (Lindsay *et al.*, 2015). Patients with at least one prescription for PIM were followed through time, to establish whether and when PIMs were deprescribed. Outcome measures were the prevalence of PIMs at diagnose, the frequency of deprescription and the time frames between diagnose, deprescription and death. Descriptive statistics were used. Since the data used in this study were part of an anonymized database, approval of an Ethics Review Board was not necessary.

Results
The mean age of the 154 participants was 67.0 years (standard deviation 10.8). Overall, the median number of medications at diagnosis was 3 (range 0-19). PIMs were present in 99 patients (64.3%). The median number of PIMs was 3 (range 1-8). In 65.7% of patients (65/99), at least one PIM was deprescribed. In 41.4% (41/99) of patients, all PIMs were deprescribed before death. The median time between diagnosis and deprescription of the first PIM was 61 days (IQR 20-135); between deprescription of the last PIM and death were 66 days (IQR 21-195).

Conclusion
The prevalence of PIMs in this primary care study was considerable. Although deprescription of PIMs after cancer diagnosis was initiated, a third of patients received prescriptions for PIMs until death. From the perspective of *primum non nocere* complete deprescription of PIMs in the last stage of life can be improved.

References
Lindsay J, *et al*. Support Care Cancer, 2015. 23(1): p. 71-8.

OPTIMIZING CEFAZOLIN DOSING IN CHILDREN UNDERGOING CARDIAC SURGERY WITH CARDIOPULMONARY BYPASS USING A MODEL-BASED DOSING REGIMEN

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Aims: Cardiopulmonary bypass (CPB) is known to have a major impact on drug disposition. The objective of this study was to characterize cefazolin plasma pharmacokinetics in children before, during and after cardiopulmonary bypass, in order to develop an evidence-based dosing regimen.

Methods: This study included children who received cefazolin before surgical incision, before cessation of CPB, and after surgery. Blood samples of total and unbound cefazolin concentrations were collected before, during and after CPB. The cefazolin concentration-time profiles were analyzed using population pharmacokinetic modelling, and predictors for inter-individual variability in pharmacokinetic parameters were investigated. Subsequently, optimized dosing regimens were developed using stochastic simulations. The target efficacy exposure was defined as 100% $fT_{>MIC}$ during surgery and 50 % $fT_{>MIC}$ after surgery. To evaluate proposed dosing regimens, an infection with staphylococci and worst-case MIC breakpoint of 8 was used.

Results: A total of 56 children (age 6 days-15 years) and 494 total and unbound cefazolin concentrations were included. A three-compartment model with first-order elimination best described the data. The effect of CPB was modelled using a separate compartment; inter-compartmental clearance from this compartment was fixed to the pump flow rate and volume of distribution to the CPB priming volume. Clearance (1.56 L/h), intercompartmental clearance (5.44 L/h), central volume (1.93 L), and peripheral volume (2.39 L), were allometrically scaled by body weight. Estimated Glomerular filtration rate (eGFR) was identified as additional covariate on clearance. Finally, albumin was implemented as covariate to describe saturable protein binding. Our simulations showed that an additional bolus dose at start of CPB improves the probability of target attainment (PTA) in typical patients from 59% to >94%. Prolonged surgery and preserved renal function were found to have a negative impact on the PTA.

Conclusions: This is the first population pharmacokinetic analysis for cefazolin in children undergoing cardiac surgery. An optimized model-based dosing regimen was developed to avoid treatment failure due to inadequate antibiotic prophylaxis.

A PHARMACODYNAMIC MODEL OF MIDAZOL-INDUCED SEDATION IN TERMINALLY ILL PATIENTS

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Introduction Midazolam is the drug of choice for palliative sedation and is titrated to achieve the desired level of sedation. Because of large inter-individual variability (IIV) the time it takes to achieve adequate sedation varies widely. This IIV can partly be explained by differences in pharmacokinetics (PK) which have been linked to renal function and inflammatory status. Therefore a more individualised dosing strategy taking these aspects into account may result in improved sedation. This will however also be affected by pharmacodynamic (PD) variability. The objective of this study was therefore to evaluate the effect of midazolam on the level of sedation in terminally ill patients, to assess the extent of IIV and to find clinically relevant covariates.

Method A population pharmacodynamic analysis using nonlinear mixed effect models was performed with data from 43 terminally ill patients. PK profiles were predicted by a previously described population pharmacokinetic model and depth of sedation was measured using the Ramsay sedation score. The laplacian likelihood method was applied to estimate the probability of a specific Ramsay score given a certain midazolam concentration. The effect of the midazolam metabolites was evaluated with an additive interaction model. Patient and disease characteristics, concomitant medication and the time of day were evaluated as possible covariates using a forward inclusion, backward elimination method with P-values of 0.5 and 0.001.The final model was evaluated using a visual predictive check (VPC).

Results The effect of midazolam on the sedation level was best described with an Emax equation and a differential odds model. The EC50 value was 70.3 ug/L for a Ramsay score of 3 (drowsy or asleep responding only to commands) and 118.3 ug/L for a Ramsay score of 6 (asleep without any response). Neither of the midazolam metabolites showed an additive effect on the sedation level. IIV was incorporated in the model on overall effect and was estimated at 0.946. Co-medication with haloperidol was the only significant covariate found. The VPC of the final model showed good model predictability.

Conclusion We were able to accurately describe the pharmacodynamic effect of midazolam in terminally ill patients using a differential odds model with categorical data (the Ramsay sedation scale). As expected there was large variability in the overall response to midazolam. IIV was incorporated on overall effect as it could affect both the baseline estimates and the response to midazolam. In our model we did not find any additional effect of the midazolam metabolites. For 1-hydroxy-midazolam this is probably due to the fact that it is formation rate limited. The glucuronide metabolite on the other hand can accumulate however in this population midazolam treatment was not discontinued and therefore high concentrations of the metabolite occur together with high midazolam concentrations making it impossible to differentiate between the effect of midazolam and the metabolite. Finally the use of haloperidol was associated with a lower probability of sedation. This might be due to a paradoxical effect, or it can be a result of confounding by indication as haloperidol is used to treat delirium and agitation.

DOSING FOR TWO: PLACENTAL TRANSFER AND FETAL DARUNAVIR EXPOSURE

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Introduction: Fetal drug exposure during pregnancy can be a determinant of fetal drug toxicity or efficacy. Fetal exposure is usually derived from the cord-to-maternal (ctm) concentration ratio. This static parameter does not provide information on the pharmacokinetics *in utero*, limiting the assessment of a fetal exposure-effect relationship. Pregnancy physiologically-based pharmacokinetic (p-PBPK) modelling could provide a solution, although incorporation of placental transfer remains challenging. Here, we aimed to include placental transfer parameters derived from an *ex vivo* human cotyledon perfusion model into a p-PBPK model, to quantitatively simulate fetal exposure to the antiretroviral agent darunavir, co-administered with ritonavir, at term.

Methods: An existing and validated p-PBPK model of maternal darunavir/ritonavir exposure was coded in Berkeley Madonna syntax to allow expansion with a feto-placental unit. Bidirectional placental transport of darunavir at term was included. In order to parameterize the model, we determined maternal-to-fetal (mtf) and fetal-to-maternal (ftm) darunavir/ritonavir placental clearances with an *ex vivo* human cotyledon perfusion model. Simulated maternal PK profiles were compared with observed clinical data to verify the validity of the maternal model aspect. Next, population fetal PK profiles were simulated for different darunavir/ritonavir dosing regimens. These profiles were compared with available cord blood concentrations *in vivo.* Additionally, we explored the influence of different DRV/r dosing regimens on fetal exposure and antiviral effects.

Results: An average (±SD) mtf cotyledon clearance of 0.91±0.11 mL/min and ftm of 1.6±0.3 mL/min was determined (n=6 perfusions). Scaled placental transfer was included into a feto-placental unit and integrated in the p-PBPK model. For darunavir 600/100mg twice daily, the simulated fetal plasma C_{max}, C_{trough}, T_{max} and $T_{1/2}$ at steady state were; 1.1 mg/L, 0.57 mg/L, 3 hours, and 21 hours, respectively. This indicates that the fetal population C_{trough} is above the protein-adjusted EC_{90} for inhibiting the replication of wild type (0.20 mg/L) and around the EC_{90} for resistant virus (0.55 mg/L). The simulated ftm plasma concentration ratio (range) over a dosing interval was 0.30 (0.16 - 0.37), compared to a median (range) ratio for observed darunavir ctm plasma ratio of 0.18 (0 - 0.82; 0 reported if cord blood concentrations were below the lower limit of quantification [<0.09 mg/L] and hence no ratio could be determined).

Conclusion: A p-PBPK model for maternal darunavir exposure was extended with a feto-placental unit. The simulated fetal darunavir plasma concentrations were in the range of observed cord blood concentrations. This advanced model provides a valuable tool in assessing the implications of new dosing regimens, optimizing the safety of maternal pharmacotherapy and fetal antiretroviral treatment.

Intravenous Flucloxacillin Treatment is Associated with Hypokalemia in Hospitalized Patients

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Aim: Intravenous flucloxacillin is one of the most frequently used high-dose penicillin therapies in hospitalized patients, forming the cornerstone treatment of invasive *Staphylococcus aureus* infection. Being a non-reabsorbable anion, flucloxacillin has been suggested to cause hypokalemia, although the exact frequency and magnitude of this unwanted effect is unknown. We investigated the incidence and extent of hypokalemia after initiation of intravenous flucloxacillin compared to ceftriaxone therapy.

Methods: All adult patients admitted to our hospital from 2010-2015 receiving intravenous flucloxacillin or ceftriaxone (control) were retrospectively screened. Patients were included when they were normokalemic at start of antibiotic treatment, were treated for at least 48 hours and had a follow-up potassium level obtained at 48-120 hours after start of therapy. In addition, information on kidney function, diuretic use and in-hospital mortality was documented.

Results: In total, 77 patients receiving flucloxacillin (62% male, mean age 70,5 years (range 32-96 years)) and 84 patients receiving ceftriaxone (46% male, mean age 70,8 years (range 28-96 years)) were included; both groups had similar potassium levels at baseline (mean 3,9 mmol/l, range 3,3-4,7 mmol/l). Hypokalemia occurred significantly more often in patients receiving flucloxacillin than ceftriaxone (40% vs. 14%, respectively, $p<0,001$). Follow-up potassium levels were significantly lower during flucloxacillin therapy than during ceftriaxone therapy (3,4 mmol/l (range 2,3-4,7) vs. 3,6 mmol/l (range 2,6-5,4), $p=0,01$). This was not dependent on differences in mortality rate, diuretic use or kidney function.

Conclusion: Intravenous flucloxacillin use is associated with a striking incidence of hypokalemia after treatment onset. Therefore, standardized potassium measurements are necessary.

BIOEQUIVALENCE IN ADULTS DOES NOT MEAN BIOEQUIVALENCE IN CHILDREN

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Introduction

For a new formulation of an existing drug, as well as for generics, one has only to demonstrate pharmacokinetic (PK) bioequivalence with the original formulation to obtain registration. These PK tests are performed in healthy young volunteers, assuming that PK follows pharmacodynamics (PD). However, this methodology hardly takes into account potential gender, size, age, or maturation specific differences in bioequivalence. The FDA and EMA-regulations on pediatric drug research have tried to find a compromise between minimal exposure of children to a pediatric research program, and acquiring minimal PK/PD and safety-data in children to reassure safe prescription of the drug, and therefore do not request bioequivalence studies in the pediatric age.

Aim

The aim of the study was to investigate whether bioequivalence between different solutions is similar over all populations.

Methodology

Desmopressin (dDAVP), a synthetic vasopressin analogue, is a level 1, grade A treatment of monosymptomatic nocturnal enuresis (MNE). This oligopeptide has a low bioavailability with large variability, and existing PK/PD data from previous studies.

Results

Integrating the data of the different studies on different formulations, we observe

A higher PD effect for dDAVP lyophilisate (MELT) compared to tablet, when adjusted with nutrition *(Ref.1).*

A higher PK bioequivalent dose for lyophilisate (MELT) in children than in adults *(Ref.2).*

Compared with previous literature:

The relative bioavailability between the lyophilisate and tablet formulations is probably not the same in children as in adults.

Poor correlation between circulating PK and PD-effect (hysteresis-effect).

Conclusion

This overview demonstrates that for an oligopeptide with a narrow safety-profile, such as dDAVP, PK/PD bioequivalence of doses within the therapeutic range in children, cannot be extrapolated from adult data. This suggests that minor changes in formulation makes appropriate bioequivalence studies in children mandatory and collection of safety-data required.

Reference

1. De Guchtenaere A, Van Herzeele C, Raes A, Dehoorne J, Hoebeke P, Van Laecke E, Vande Walle. Oral lyophilisate formulation of desmopressin: superior pharmacodynamics compared to tablet due to low food interaction. Journal of Urology 2011;185:2308–13

2. Michelet R, Dossche L, De Bruyne P, et al. Effects of Food and Pharmaceutical Formulation on Desmopressin Pharmacokinetics in Children. Clin Pharmacokinet 2016;55:1159–70.

A RANDOMIZED, DOUBLE-BLIND, CROSSOVER STUDY ON PHARMACOKINETICS OF PEPPERMINT OIL IN HEALTHY VOLUNTEERS: ENTERIC-COATING VERSUS COLON-TARGETED-DELIVERY.

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Peppermint oil (PO) has been shown to reduce abdominal pain in patients with Irritable Bowel Syndrome (IBS). Menthol, the main constituent of PO, induces intestinal smooth muscle relaxation and desensitizes nociceptive nerve afferents. Enteric-coated (EC PO) capsules that release PO mainly in the small intestine are commercially available. In order to increase local, colonic anti-nociception, a colon-targeted-delivery peppermint oil (CTD PO) capsule has been developed. The aim of this study was to compare pharmacokinetic parameters of both formulations and to evaluate safety and tolerability.

In this randomized, double blind, placebo-controlled study, subjects received 182 mg of either EC PO or CTD PO in a crossover design with $\geq$14 days washout period in between. After baseline measurements and drug administration, blood samples to determine menthol-glucuronide (menthol is rapidly metabolized to menthol-glucuronide), blood pressure and heart rate measurements were collected at several time points. Side effects were evaluated using questionnaires.

The primary outcome was T_{max}: time to reach peak menthol-glucuronide concentration in plasma.

Eight healthy volunteers (50% female), aged between 20 and 65 years (median 22.2, IQR 20.8-28.8) were included. The T_{max} of CTD PO was significantly longer (in all volunteers) compared to EC PO with a median (IQR) of 360 (360-405) versus 180 (120-180) minutes, respectively, $p<0.05$. The Area Under the menthol-glucuronide plasma concentration time Curves were smaller with a median (IQR) of 2331µg*h/L (2006-2510) for CTD compared to 2623µg*h/L (2471-2920) for EC capsules, $p<0.05$. No significant differences were found in peak concentrations and elimination half-lives. No differences in vital signs or side effects were observed between both regimens. Remarkably, subjects noticed alterations in fecal odor after CTD PO but not after EC PO, again pointing to more distal delivery with CTD PO.

In conclusion, the CTD PO has a significantly delayed peak menthol-glucuronide concentration, and is thereby assumed to release peppermint oil in the more distal part of the intestine. This may enhance therapeutic efficacy of PO as the application of the CTD results in increased exposure to the colonic mucosal afferents. These results encourage our randomized controlled trial with CTD PO in IBS patients.

OPTIMISING ANTI-THYMOCYTE GLOBULIN EXPOSURE IN HEMATOPOIETIC CELL TRANSPLANTATION: A RETROSPECTIVE PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS

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Background:
Anti-thymocyte globulin (ATG) is used to prevent graft-versus-host-disease (GvHD) following allogeneic haematopoietic cell transplantation (HCT). However, ATG can also cause delayed immune reconstitution, negatively influencing survival. We studied the relation between exposure to ATG and clinical outcomes in adult patients with acute leukaemia and myelodysplastic syndrome.

Methods:
In a retrospective analysis, consecutive patients receiving a T-cell repleted allogeneic peripheral blood stem cell-HCT with ATG (Thymoglobulin) as part of non-myeloablative conditioning were included (March-2004 to June-2015). Active ATG levels were measured using a validated bioassay and pharmacokinetic exposure measures were calculated with a validated population PK-model. Main outcome of interest was overall survival (OS); other outcomes were relapse- and non-relapse mortality, acute- and chronic-GvHD and evaluation of current and optimal dosing. Cox proportional-hazard models and Fine-Gray competing risk models were used.

Results:
146 patients were included. ATG exposure after HCT was found the best predictor for 5-year OS. Optimal exposure after transplantation (60-95 AU*day/mL) yielded superior overall survival (69%, 95% confidence interval [CI] 55-86%) compared to below optimal (32% [95% CI 20-51%], hazard ratio [HR] 2.41, 95% CI 1.15-5.06, p=0.020) and above optimal exposure (48% (95% CI 37-62%), HR 2.11, 95% CI 1.04-4.27, p=0.038). Above-optimal exposure led to higher relapse-related mortality (HR 2.66, p=0.027). Below optimal exposure increased non-relapse mortality (HR 4.36, p=0.0040), grade 3-4 acute GvHD (HR 3.09, p=0.029) and a trend towards increased chronic GvHD (HR 2.38, p=0.070). Modelled dosing based on absolute lymphocyte counts led to higher optimal target attainment compared to weight-based dosing.

Conclusions:
Exposure to ATG impacts survival following HCT in adults, stressing the importance of optimal ATG dosing. Individualised dosing of ATG, based on lymphocyte counts rather than body weight, may improve survival chances after HCT.

COMPARISON OF THE IN VITRO ACTIVITY OF AMIKACIN AND KANAMYCIN AGAINST MYCOBACTERIUM TUBERCULOSIS AND TARGET ATTAINMENT

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Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* and responsible for 1.8 million deaths worldwide in 2015. *M. tuberculosis* frequently gains resistance to first-line treatment (MDR-TB), requiring the use of antibiotics such as aminoglycosides, disreputable for their harmful side effects. Amikacin and kanamycin, the only two aminoglycosides active against MDR-TB, are both used in a dosage of 15 mg/kg daily for 4-6 months.
The efficacy of aminoglycosides is quantified by the maximum serum concentration (C_{max}) divided by the minimum inhibitory concentration (MIC). However, a head-to-head, large scale comparison of amikacin and kanamycin MICs has not been performed yet.

In this study the MICs of amikacin and kanamycin were determined using the absolute concentration method (van Klingeren *et al*, 2007). Amikacin and kanamycin were both added to 7H10 medium in a concentration of 0.25, 0.50, 1.00, 2.00, 4.00, 8.00, 16.0, 32.0 and 64.0 mg/L. The media were inoculated with 10 μL of a *M. tuberculosis* suspension containing between $2x10^5$ and $10x10^5$ colony forming units per ml. The growth of the bacilli was visually checked after 14 days. Two control wells without antibiotics were inoculated with 10 μL suspension and a 1/100 dilution of the suspension, respectively, to determine the proportional inhibition.

In total, 57 clinical strains were tested. The kanamycin MIC was more than one dilution step higher than the amikacin MIC in 21% of all strains. The median MIC of amikacin and kanamycin was 2 and 4 mg/L, respectively. The amikacin MICs differed significantly from the kanamycin MICs (Wilcoxon Signed Rank Test, $p < 0.05$).

In conclusion, amikacin MICs are significantly lower than kanamycin MICs. The recommended amikacin dosage should therefore be reduced without impairing the efficacy. The C_{max}/MIC ratio of kanamycin is less favourable and its dosage should excess that of amikacine to achieve identical efficacy.

van Klingeren, B, Dessens-Kroon, M, van der Laan, T, Kremer, K, van Soolingen, D. 2007. Drug susceptibility testing of Mycobacterium tuberculosis complex by use of a high-throughput, reproducible, absolute concentration method. J. Clin. Microbiol. 45:2662-2668.

A systems pharmacology approach to difficult-to-treat pediatric asthma: design of the SysPharmPediA study

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Introduction: Childhood asthma is a complex multifactorial disease usually treated with inhaled corticosteroids (ICS) as controller medication. However, large variability in treatment response to, ICS is observed. A uniform, integrated systems pharmacology approach is needed to disentangle the complexity of the disease and identify phenotypes that are predictive of therapy response.

Aims: Identify genetic and non-genetic biomarkers to characterize phenotypes of non-response to standard asthma therapy with ICS and to construct computational algorithms that effectively predict phenotype of ICS response by using a set of system-wide biomarkers and their interactions with environmental and clinical factors.

Design: A systems pharmacology approach will be applied to a well-phenotyped set of 200 asthmatic children (6-18 years). In total 150 cases (asthmatic children with uncontrolled asthma symptoms or severe exacerbations under standard asthma therapy with ICS) and 50 controls (well controlled asthmatics under standard asthma therapy with ICS) will be included in 4 different countries (the Netherlands, Spain, Germany and Slovenia). Clinical data, saliva, faeces, peripheral blood & breath samples and throat/nose swabs will be collected and analysed within the consortium. Genomics, breathome, microbiome/metabolome and transcriptome/epigenome analyses will be performed and integrated to identify different pathways that classify distinct therapy responder asthma phenotypes. Data collection will start in the spring of 2017.

Conclusion: This is a unique approach to classify different phenotypes of asthmatic children that do not respond to standard therapy with ICS. In the future, the results of this study can lead to improved treatment strategies for pediatric asthma patients.

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CIRCULATING TUMOR CELLS AND CIRCULATING TUMOR DNA ANALYSIS IN CEREBROSPINAL FLUID IN MELANOMA PATIENTS WITH SUSPECTED LEPTOMENINGEAL METASTASIS

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Introduction: Two to five percent of patients with solid tumors develop leptomeningeal metastases (LM). Diagnosis of LM can be made on clinical symptoms and typical contrast enhancement of the leptomeninges on MRI of brain and/or spine. However, MRI has a low sensitivity (0.76) and specificity (0.77) for the diagnosis of LM. When MRI is normal or results are inconclusive, a lumbar puncture (LP) is performed to obtain cerebrospinal fluid (CSF). Sensitivity of CSF cytology is also low: 55% at first LP, increasing to 80% upon second sampling. To improve CSF diagnostics, enumeration of Circulating Tumor Cells (CTC) by immunoflow cytometry has been developed. To determine driver mutation status circulating tumor DNA (ctDNA) analysis can be performed in CSF.

Aim: To determine the sensitivity and specificity of a diagnostic immunoflow cytometry method in CSF in melanoma patients with suspected LM. To detect BRAF mutations in the primary tumor, CTC or cell free CSF.

Methods: We developed a melanoma-associated chondroitin sulfate proteoglycan (MCSP) and CD146 based CTC assay to detect melanoma cells in the CSF. We tested the performance of this assay versus CSF cytology in CSF in a prospective study in 24 patients with melanoma with a clinical suspicion of LM but a non-confirmatory MRI and in a subcohort of 5 patients with radiologically proven LM. BRAF mutation in the primary melanoma was determined as part of routine care BRAF-mutations in cell-free CSF and isolated CTCs were determined using digital droplet PCR.

Results: In patients with melanoma with a clinical suspicion of LM but a non-confirmatory MRI cytology had a sensitivity of 0.7 (0.35-0.92) (95% CI) and a specificity of 1 (0.70-1). At a cut-off value of >0.4CTC/mL the CTC assay had a sensitivity of 1 (0.66-1) and a specificity of 1 (0.70-1). We identified *BRAF* V600E mutations in ctDNA in CSF in 6 of the 7 *BRAF* V600E positive patients with LM. In addition, we could identify the *BRAF* V600E mutation by direct measurement in isolated CTCs. No *BRAF* V600E mutation was identified in the absence of LM or in the absence of a *BRAF* V600E mutation in the primary tumor.

Conclusion: The MCSP/CD146-based CTC assay can identify melanoma cells in CSF in patients with LM with a negative cytology. BRAF mutations can be detected in ctDNA in CSF of *BRAF* V600E positive patients with LM.

FACTORS INFLUENCING CLEARANCE OF ADALIMUMAB IN PATIENTS WITH CROHN'S DISEASE: A POPULATION PHARMACOKINETIC STUDY

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Introduction Adalimumab is a fully human subcutaneously delivered monoclonal antibody (mAb) directed against Tumor Necrosis Factor (TNF) approved for use in patients with Crohn's disease. Anti-TNF mAbs exhibit complex pharmacokinetics. The goal of this study was to evaluate the pharmacokinetics of adalimumab in patients with Crohn's disease and to identify factors influencing pharmacokinetics.

Methods In a retrospective cohort study, we reviewed the charts of 96 patients with Crohn's disease on adalimumab induction or maintenance treatment. Patients in the study had at least one measurement of their adalimumab serum concentration and anti-adalimumab antibody (AAA) serum concentration. Adalimumab and AAA serum concentrations were measured using an ELISA and an antigen-binding test, respectively, by Sanquin Laboratories. Additional data that were collected included age, gender, bodyweight, anti-TNF naive/exposed status, albumin serum levels, CRP serum levels, treatment duration and dosing regimen. Population pharmacokinetic analysis was performed using nonlinear mixed effects modelling (NONMEM).

Results From 96 patients with Crohn's disease, a total of 180 serum samples were available. AAAs were detected in 14% of the patients using a drug sensitive assay. Primary median parameters were: bodyweight 66 kg (interquartile range [IQR], 58-76), albumin 43 g/L [40-45] and CRP 3.4 mg/L [1.3-7.4]. Data were best described using a 1-compartment model with first-order absorption and elimination. The apparent clearance of adalimumab increased 1.7-fold in the presence of AAAs. Patients who received adalimumab every week had a 42% higher clearance compared to patients who were treated every other week. For a patient receiving adalimumab every other week estimates for apparent clearance and apparent volume of distribution were 0.31 L/day and 4.0 L, respectively. The between-subject variability for clearance was 43%. Bodyweight, albumin and CRP were not significantly associated with clearance. The number of data and the small distribution of these parameters could be of influence.

Conclusion This population pharmacokinetic analysis demonstrates that clearance of adalimumab in patients with Crohn's disease was highly influenced by the presence of AAAs. In clinical practice, the decision to intensify adalimumab treatment to weekly administrations is primarily based on disease activity. Patients who were treated every week exhibited higher clearance compared to patients who were treated every other week. Increased disease activity may be the result of higher clearance leading to lower drug concentrations. However, increased disease activity may also increase clearance due to increased target engagement (target mediated drug disposition). The causal relationship between these factors remains to be elucidated.

SUBSTANTIALLY LOWER RILPIVIRINE PLASMA CONCENTRATIONS DURING PRGNANCY

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INTRODUCTION: During pregnancy adequate antiretroviral exposure is important to prevent treatment failure, resistance and mother-to-child transmission (MTCT). However, pregnancy-related physiological changes may result in decreased antiretroviral exposure. Limited data is available on the pharmacokinetics (PK) of rilpivirine (RPV) during pregnancy. We aimed to study the PK of RPV during pregnancy, including placental transfer.

METHODOLOGY: An open-label, multi-centre phase IV study in HIV-1-infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with RPV 25mg once daily during pregnancy had intensive steady-state 24-hour PK profiles in the third trimester and postpartum. RPV was taken with food. When feasible, cord blood and matching maternal blood samples were taken at delivery to asses placental transfer. RPV plasma concentrations were determined with a validated LC-MS method. The proposed minimum effective concentration of RPV was 0.04 mg/L (based on ECHO/THRIVE PK data).

RESULTS: Fifteen patients (10 black, 2 white, 2 Asian and 1 other) with a median (range) age of 30 (19-36) years were included in the analysis. Median (range) gestational age at delivery was 40 weeks (38-42); birth weight was 3480 (2770-4470) gr. Approaching delivery all patients had a VL <50 cps/mL. No children were HIV-infected, no birth defects were reported.
15 PK curves during 3rd trimester and postpartum were available. Geometric Mean Ratios (90% confidence interval) of PK parameters third trimester/postpartum were: 0.53 (0.45-0.63) for AUC0-24; 0.63 (0.54-0.74) for Cmax; and 0.46 (0.37-0.56) for C0h. Two out of 15 patients had a sub-therapeutic C0h in the third trimester, no sub-therapeutic levels were observed postpartum.
The median (range, n=5) ratio of cord blood/maternal plasma RPV concentrations was 0.5 (0.35-0.81).

CONCLUSIONS: In this study exposure to RPV was about 50% lower in the third trimester of pregnancy, however, in this limited number of patients, this did not lead to detectable maternal VL or MTCT. It is important that RPV is taken with a meal during pregnancy and we would advice TDM in the third trimester to avoid sub-therapeutic exposure.

Pharmacology and therapeutics education in EU needs harmonisation and modernisation: a cross-sectional survey among 185 medical schools in 27 countries

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Introduction
Prescribing drugs safely and effectively is a fundamental skill that medical graduates must acquire. Inappropriate prescribing may lead to prescribing errors, resulting in exacerbation or prolongation of illness, patient harm, and high healthcare costs (Dean *et al.*, 2002a, Dean *et al.*, 2002b). Effective teaching in pharmacology and clinical pharmacology and therapeutics (CPT) is necessary to ensure that graduates become competent prescribers (Ross *et al.*, 2012). As there has been no recent analysis of the structure of CPT education in the European Union (EU), we investigated the current structure, delivery, and assessment of CPT education in EU medical schools.

Methods
We designed and validated an online questionnaire that was sent to the teachers with overall responsibility for CPT education in EU medical schools. Questions focused on undergraduate teaching and assessment of CPT and students' preparedness for their future prescribing task. The quality and alignment of the CPT learning objectives of each school were assessed, using a SMART scoring rubric (1= poor, 2= suboptimal, 3= adequate). Ethical approval was given by the Dutch Ethics Review Board of Medical Education.

Results
Between May and November 2016, 185 of 290 eligible medical schools (64%) from 27 EU countries responded. 166 (90%) schools offered a CPT course, of which 73 (44%) identified their course as vertically integrated. A large proportion of schools (n= 72; 39%) used merely traditional-learning methods, and 108 (58%) schools did not provide students with the opportunity to practise real-life prescribing. 113 (61%) schools integrated the CPT assessment in a broader course assessment and 86 (47%) did not have a final prescribing assessment before graduation. Overall, 127 (69%) of the respondents believed that their students were not well prepared for prescribing. Learning objectives were of poor quality (1.94 ±0.57), and often not properly aligned with the learning and assessment activities.

Conclusion
There is a marked variation in the quality and quantity of CPT education within and between EU countries. Furthermore, CPT teaching and assessment throughout EU is mainly based on traditional-learning methods. This has potential consequences for patient safety. To ensure that future graduates have a uniform level of prescribing competencies, a collaborative approach should be adopted to harmonise and modernise the undergraduate teaching and assessment of CPT across the EU.

References
Dean *et al.* Qual Saf Health Care 2002;11(4): 340-344.
Dean *et al.* Lancet 2002;359(9315): 1373-1378.
Ross *et al.* Br J Clin Pharmacol 2012;74(4): 644-661.

HEMATOLOGICAL TOXICITY IN OLDER PATIENTS TREATED WITH DOCETAXEL OR DOCETAXEL-CONTAINING REGIMENS

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Introduction: Older cancer patients may be more prone to chemotherapy-induced hematological toxicity, due to progressive reduction in organ functions and multiple co-morbidities. Tailored docetaxel dosing guidelines in elderly are lacking because of a paucity of real-life PK-PD data. This study aims to compare the incidence of hematological toxicity of docetaxel-containing regimens in older patients with their younger counterparts in routine clinical practice.

Methods: Patients receiving docetaxel at the MC Slotervaart or Netherlands Cancer Institute (NKI; Amsterdam, the Netherlands) between January 2006 and January 2016 were included, if docetaxel dosing information and subsequent laboratory values were available. Patient characteristics, laboratory values, underlying malignancies, and treatment and dosing regimen were retrospectively extracted from electronic patients' records. Relative dose intensity in older patients (≥70 years) and younger patients (<70 years) was compared using Wilcoxon rank sum test. Incidence of grade 3/4 hematological toxicity between both age groups was evaluated using Fisher's exact test. Logistic regression was performed to evaluate the influence of possible predictors of developing grade 3/4 hematological toxicity, including age.

Results: In total 913 patients receiving a docetaxel-containing regimen were enrolled, of which 96 patients were 70 years or older. Median age of our cohort was 56 years, ranging from 18 to 86 years. Baseline laboratory values were comparable between both age groups, except for significantly lower albumin, and estimated glomerular filtration rate in older patients. Significantly more males were enrolled in the older patient group. Starting dose and the incidence of treatment discontinuation were comparable between both age groups. Relative dose intensity over the median of 4 treatment cycles was significantly lower in older patients than in younger patients (p=0.03). After the first docetaxel-containing treatment cycle, 21% of older patients developed a grade 3/4 hematological toxicity, compared to 17% of younger patients (p=0.32). In multivariable logistic regression analyses adjusted for gender, baseline albumin, absolute administered dose, and treatment group (monotherapy vs. chemotherapy combinations), age did not significantly influence the risk of hematological toxicity, neither as a dichotomous nor as a continuous variable.

Conclusion: Treatment with docetaxel-containing regimens appeared feasible in older patients treated in routine clinical practice. Although docetaxel treatment was not discontinued more frequently in older patients, they underwent significantly larger and more frequent dose reductions than their younger peers. Overall, the incidence of hematological toxicity was not increased in older patients who were fit to receive docetaxel-containing chemotherapy. Emphasis on inclusion of older patients in clinical trials and prospective observational studies remains crucial to optimize docetaxel treatment in the heterogeneous older patient population.

A POPULATION PHARMACOKINETIC MODEL FOR PHENOBARBITAL IN TERM AND PRETERM NEONATES

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Background: In the past 50 years phenobarbital has been used as first-line therapy for neonatal seizures. Most of the pharmacokinetic studies in neonates date from the 1970s and 1980s. Since then, dosing regimens have been constantly adjusted and advanced statistical approaches have become available. In this study we analysed therapeutic monitoring data collected between 1997-2003 in the neonatal unit of the Maastricht University Medical Centre using population pharmacokinetic modeling.

Aim: To develop a population pharmacokinetic model for phenobarbital in preterm and term neonates.

Methods: Dosage histories, concentration and covariate data (including birth weight, actual weight, post-natal age (PNA), postmenstrual age, gestational age (GA), sex, liver and kidney function, APGAR-score) were collected from neonates who received phenobarbital for convulsions of different origins. Model development was carried out using NONMEM® version 7.3. The model fit was assessed by the objective function value, goodness-of-fit plots, npde and bootstrap analysis.

Results: 53 neonates (GA: 24 - 42 weeks (median: 37 weeks), actual body weight: 0.45 - 4.5 kg, PNA: 0-22 days) were included. Loading and maintenance doses, intravenous as well as oral, varied between 1.3 and 40.7 mg/kg, over 4 to 85 days. Modeling of 229 plasma concentrations, ranging from 3.2 to 75.2 mg/L, resulted in a one compartment model for phenobarbital (clearance (CL)=0.0091 L/h, RSE = 9%, volume of distribution (V_d)=2.38 L, RSE = 5%). The combination of birthweight and PNA proved the best predictor for CL maturation, with CL increasing by 36.7% per kg birthweight and 5.3% per postnatal day, respectively. The best predictor for the increasing V_d was actual body weight (0.31 L/kg). The absence of trends in diagnostic plots and the bootstrap during model evaluation suggests that the developed model is suitable to describe the data.

Conclusion: We successfully developed a population model for phenobarbital in term and preterm neonates derived from routine therapeutic drug monitoring data in which CL was found to mature in-utero as well as ex-utero. After external validation using an independent prospective dataset, this model can be used to guide dosing based on individual covariates in neonates.

OBSERVATIONAL STUDY ON TARGET ATTAINMENT AND PROTEIN BINDING OF TEICOPLANIN IN CRITICALLY ILL CHILDREN

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Aims: The objectives of this study were (i) to evaluate target attainment rates using commonly used PK/PD targets and (ii) to document plasma protein binding of teicoplanin in critically ill children.

Methods: Patients, admitted to the PICU in whom treatment with intravenous teicoplanin (10 mg/kg every 12 h for 3 loading doses, followed by 6-10 mg/kg once daily) was indicated, were enrolled. Blood samples were collected during first and/or assumed steady-state dose intervals. Evaluated pharmacokinetic/pharmacodynamic (PK/PD) targets included the area under the concentration-time curve divided by the minimal inhibitory concentration of the suspected pathogen (AUC/MIC ratio) ≥ 750 h, free AUC (*f*AUC)/MIC ratio ≥ 75 h and total trough plasma concentration (Cmin) ≥ 10 mg/L. *(f)*AUC was calculated using a non-compartmental analysis based on the log-linear trapezoidal rule with PKSolver (MsExcel). For first dose *(f)*AUC estimations, the extrapolated *(f)*AUC to infinity was taken into account. Correlation was assessed by means of a scatter plot and Spearman's Rank Correlation Coefficient.

Results: 130 plasma samples were collected from 27 patients (median age: 2.2 years; IQR: 0.8-4.8 years). The targets of AUC/MIC ratio (median: 823 h; IQR: 702-949 h) and *f*AUC/MIC ratio (n = 26; median: 72 h; IQR: 55-86 h) were achieved in 63% and 42% of patients respectively. The target Cmin (median: 16.0 mg/L; IQR: 10.3-17.9 mg/L) were reached in 78 % of patients. Cmin correlated well with the AUC/MIC ratio (Spearman's Rank Correlation Coefficient R = 0.84; $p < 0.01$); *f*AUC/MIC and AUC/MIC ratio did not (Spearman's Rank Correlation Coefficient R = 0.36; $p > 0.05$). The free teicoplanin fraction (n = 26; median: 8.6%; IQR: 7.0-11.7%) only varied slightly between patients.

Conclusions: Currently used teicoplanin dosing regimens frequently resulted in an AUC/MIC ratio and Cmin below widely accepted PK/PD targets. The *f*AUC/MIC ratio resulted in the lowest target attainment, despite plasma protein binding was similar to adults. Overall, target attainment rates varied widely depending upon the type of PK/PD target used. Future study is needed to define appropriate PK/PD indices in children.

THE SAFE-PEDRUG INITIATIVE: A NEW APPROACH FOR EFFICIENT AND ETHICAL PAEDIATRIC DRUG RESEARCH

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Background:
Drug evaluation in children is stimulated by initiatives of the government; in Europe by means of the Paediatric Regulation. As stated in this Regulation, Paediatric Investigational Plans must be submitted around the end of Phase I adult trials. However, the proposed paediatric trials tend to be amended frequently and postponed to the end of the drug evaluation process, as they are largely based on extrapolation of results of adult trials. As a result, the availability of these drugs for children is delayed for several years.

Methods:
Experts in paediatrics, pharmaceutical sciences, veterinary medicine and ethics (of three Belgian universities: Ghent University KULeuven and KULeuven) collaborated to develop a research consortium that will focus mainly on generating paediatric pharmacokinetic and pharmacodynamic (PK/PD) knowledge before the actual human trials are performed. National and international stakeholders (including industry, regulatory authorities and patient organisations) support this consortium in the valorisation of results.

Results:
The above-mentioned networking resulted in the SAFE-PEDRUG project, funded by the Agency for Innovation by Science and Technology Flanders (now managed by the Research Foundation – Flanders). This program will explore the value of the porcine juvenile animal model *(ref 1)* and PK modelling (population pharmacokinetics and physiologically based pharmacokinetic modelling, *ref 2*) in providing prior paediatric PK/PD knowledge. For the evaluation of this approach, three case compounds were selected: desmopressin, lisinopril, and fluoroquinolones. The results of the models are plotted against human paediatric data. Furthermore, PK/PD in neonates and critically ill children will also be explored.

Conclusion:
A close collaboration of experts and stakeholders is mandatory for the future of paediatric pharmacology. Exchange of ideas and knowledge can help to tailor paediatric clinical trials to the PK/PD-characteristics and needs of children.

References:
1. Gasthuys E, Vandecasteele T, De Bruyne P, et al. Pediatric drug design: The potential use of piglets as an animal model. Current Pharmaceutical Design 2016; 22(26): 4069-85.
2. Michelet R, Dossche L, De Bruyne P, et al. Effect of food and pharmaceutical formulation on desmopressin pharmacokinetics in children. Clinical Pharmacokinetics 2016; 55(9): 1159-70.

VORICONAZOLE DOSING STRATEGIES IN YOUNG CHILDREN: CHALLENGES AND RECOMMENDATIONS

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Aims

The aim of this case series is to evaluate the effectiveness of dosing guidelines in combination with routine therapeutic drug monitoring (TDM) to achieve therapeutic serum concentrations of voriconazole in young cancer patients (age 0-6 years old).

Background

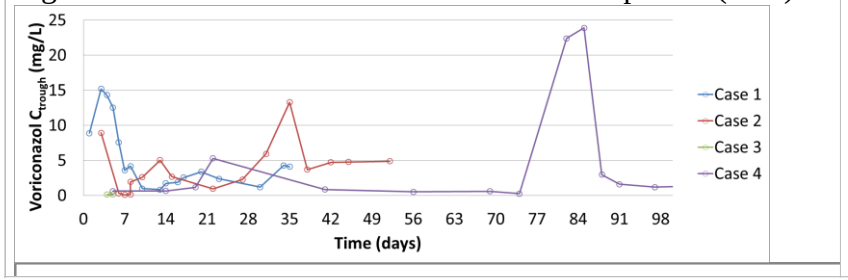
Voriconazole pharmacokinetics (PK) have been studied in pediatric studies and described by population pharmacokinetic modeling.[1]. Using the currently approved intravenous (IV) dosing regimen, 23 pediatric patients provided 30 trough samples resulting in a observed median (range) of 1.2 (0.11-17.4) mg/L.[1] This illustrates the highly variable pharmacokinetic (PK) profile of voriconazole in children.

Methods

At the VUmc, pediatric patients are treated using TDM. Voriconazole plasma concentrations are monitored and dosing regimens are individualized, aiming at trough levels of 1,5-6 mg/L. A case series of 4 children (age 0-6 yrs) is presented.

Results

Figure 1 illustrates the variable voriconazole exposure (N=4).



Case 1 Boy, 13 months, acute myeloid leukemia

- Loading dose 9 mg/kg tid (IV), maintenance 8 mg/kg tid (IV) resulted in supratherapeutic levels and hepatic toxicity. Root cause: CYP2C inhibition by previous Itraconazole treatment.
- Therapeutic levels achieved at 6 mg/kg tid (IV).

Case 2 Boy, 5 years, acute lymphatic leukemia

-Doses varying between 7 mg/kg tid IVand 11 mg/kg tid IV. Highly variable trough concentrations.

Case 3 Girl, 7 months, mixed phenotype acute leukemia

- Loading dose 6 mg/kg bid (IV), maintenance 9 mg/kg bid (PO) resulted in subtherapeutic trough levels (0,1-0,2 mg/L), possibly due to high first pass metabolism.

Case 4 Girl, 5 years, acute lymphatic leukemia

-Loading dose 10 mg/kg bid (PO), high maintenance dose of 23 mg/kg bid (PO) resulted in therapeutic levels. Higher doses of 30 mg/kg bid resulted in a more than dose-proportional increase of exposure (trough level 22 mg/L), suggesting non-linear PK.

Conclusion

Voriconazole PK is highly variable in pediatric cancer patients, which can only partly be attributed to drug interactions and co-morbidities. A starting dose of 18 mg/kg (IV) is recommended and could be administered as 6 mg/kg tid (IV).[2] Intensive TDM (at least twice weekly) and daily in-depth status reviews are recommended to achieve therapeutic drug levels.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000387/WC500186844.pdf
[2] An optimized voriconazole dosing strategy to achieve therapeutic serum concentrations in children younger than 2 years old. T.N. Zembles, Thompson N.E., Havens P.L. eta al. Pharmacotherapy 2016

MATURATION OF HUMAN HEPATIC MEMBRANE TRANSPORTER PROTEINS IN THE FIRST FOUR MONTHS OF LIFE.

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Background
Hepatic membrane-embedded proteins are involved in trafficking endogenous and exogenous compounds and may influence the pharmacokinetics of drugs. Transporter-specific age-related changes in protein abundance were found in a pilot study (n=24), but now we aimed to elucidate the exact developmental pattern of clinically relevant hepatic transporters in a larger cohort of 63 fetuses, preterm and term neonates and infants and compare it with adults.

Methods
Protein expression of BCRP, BSEP, GLUT1, MCT1, MDR1, MRP1-3, NTCP, OCT1, OATP1B1, OATP1B3, and OATP2B1 was quantified using UPLC-MS/MS, on snap-frozen post mortem fetal and infant liver samples and adult surgical liver samples. Protein expression was quantified in isolated crude membrane fractions. Pairwise comparison Kruskal-Wallis test was used to analyze a possible age-related difference.

Results
Thirty-six fetal [median GA 23.4 weeks (range 15.3-41.3), no PNA], 12 premature neonatal [GA 30.2 weeks (24.9-36.7), PNA 1.0 weeks (0.14-11.4)], 11 term neonatal [GA 40.0 weeks (39.7-41.3), PNA 4.14 weeks (0.29-18.1)], 4 pediatric [PNA 4.13 years (1.08-7.44)] and 8 adult liver samples were studied. Expressions of BCRP, MCT1, OATP1B3, and OATP2B1 were similar in all age groups. MDR1, MRP1, MRP2, MRP3 and OCT1 expressions were low in fetus and high in adults (all $p<0.05$). Expression of BSEP increased from fetal to term newborn and to adult age (both $p<0.01$) and of NCTP increased over the whole age range (all $p<0.05$). GLUT1 and OATP1B1 expressions were high in fetuses and decreased towards newborns age (both $p<0.01$). GLUT1 expression decreased further in children's and adult age (both $p<0.05$).

Conclusion
These data further delineate transporter specific changes in protein abundance across the first months of age.

PEDIATRIC MICRODOSE STUDY OF [^{14}C]MIDAZOLAM TO STUDY THE ONTOGENY OF CYP3A MEDIATED DRUG METABOLISM.

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Background
Microdose studies present an interesting innovation to study age-related changes in drug metabolism in young children. To further delineate maturation of intestinal and hepatic CYP3A activity, we aimed to study the feasibility for an oral [^{14}C]midazolam (MDZ) microdosing study in children.

Methods
Children admitted to the pediatric intensive care were eligible to receive a single oral [^{14}C]MDZ microdose when they received IV midazolam for therapeutic reasons and had arterial line in place. Blood samples were taken up to 24 hrs after dosing from a indwelling catheter. Plasma concentrations of [^{14}C]MDZ and the metabolite [^{14}C]OH-MDZ were determined by AMS. PK parameters were estimated using non-compartmental PK with PK solver software.

Results
Of 139 eligible patients, informed consent was obtained from parents of nine children [median age 3.3 months (range 12 days – 4.2 years)] who received a midazolam microdose (19.3 [18.7-21.3] ng/kg; 58 [56-64] Bq/kg). [^{14}C]MDZ and [^{14}C]OH-MDZ were detectable at expected-concentrations: plasma [^{14}C]MDZ $AUC_{0-\infty}$ was 49.9 (4.0-107.7) ng/L*h, C_{max} was 7.5 (1.5-22.2) ng/L, T_{max} was 0.5 (0.3-3.1) h, $T_{0.5}$ was 4.6 (1.1-14.0) h, CL/*F* was 0.4 (0.2-5.3) L/h/kg and V_{ss}/F was 3.1 (1.7-10.7) L/kg. Plasma [^{14}C]OH-MDZ $AUC_{0-\infty}$ 7.8 (1.3-28.3) ng/L*h and CL/*F* was 2.4 (0.7-14.6) L/h/kg. Plasma C_{max} of [^{14}C]MDZ normalized to a dose of 0.1 mg/kg was 39.9 (7.0-114.9) ng/ml.

Conclusion
We demonstrate the feasibility of an oral [^{14}C]MDZ microdose to study MDZ and 1-OHM disposition in young infants and children. This method can be used to study developmental changes in intestinal and hepatic CYP3A activity.

Population Pharmacokinetics of Amoxicillin and Gentamicin in Term Neonates Undergoing Moderate Hypothermia

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Introduction

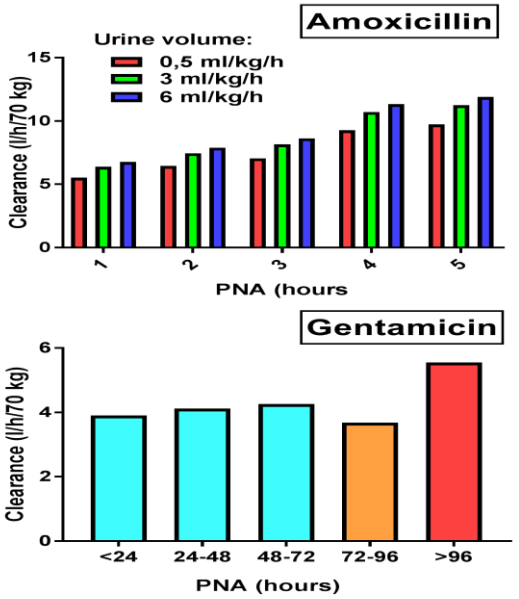
Little is known about the pharmacokinetics (PK) of amoxicillin (AMX) and gentamicin (GNT) in newborns undergoing moderate hypothermia. This study prospectively evaluates and describes the population PK of these antibiotics in this specific patient population.

Methods

Data of patients included in a multicenter prospective observational cohort study (the "PharmaCool Study"(1)) were collected. Non-linear mixed-effects regression analyses (NONMEM®) were performed to describe the population PK of GNT and AMX. The optimal dosing regimens were evaluated based on Monte Carlo simulations of the final PK models.

Results

Forty-seven patients (median gestational age (GA) 40 (range 36-42) weeks, birth weight (BW) 3400 (range 2090-5070) grams, 58.7% male) and 125 patients (median GA 40 (range 36-42) weeks, BW 3340 (range 2090-5070) grams, 59.2% male) received GNT and AMX, respectively. The PK of both antibiotics were best described by an allometric 2-compartment model with first order elimination. AMX clearance (Cl_{AMX}) increased with increasing postnatal age (PNA), GA, TEMP and urine volume (UV) (for all covariates $p<0.001$). GNT clearance (Cl_{GNT}) increased with increasing GA and PNA for both covariates $p<0.001$). Cl was constant during hypothermia and rewarming, but increased with 29% after reaching normothermia (>96 hours PNA).
The Cl_{AMX} and Cl_{GNT} for a patient with GA 40 weeks and BW of 3 kg is shown in figure 1:



Conclusion:

We recommend an empiric dose of 50 or 75 mg/kg/24h amoxicillin in 3 doses for patients with GA 36 or 38-42 weeks, respectively. For GNT we recommend 5 mg/kg every 36 or every 24 hours for patients with GA 36-40 weeks and GA 42 weeks, respectively.

References:

1. de Haan, T. R. *et al. BMC Pediatr.* **12,** 45 (2012).

PENFLURIDOL (ORAL LONG ACTING ANTIPSYCHOTIC AGENT) AS COMPARED TO SECOND-GENERATION ANTIPSYCHOTICS: AN ONGOING RANDOMIZED CONTROLLED TRIAL ON EFFECTIVENESS

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Introduction: Non-adherence to drug medication is unfortunately common in patients with a psychotic disorder and is associated with higher relapse-rates, hospitalizations, and higher healthcare costs. Penfluridol is a first generation antipsychotic drug (FGA) and currently the only long-acting oral agent that can be taken once a week. Second generation oral antipsychotic drugs (treatment as usual: TAU), including olanzapine and risperidone, have to be taken daily. Literature has shown that penfluridol has a similar clinical effect as compared to other FGA. However, no studies have been conducted comparing the clinical effect of penfluridol and TAU. Due to ample evidence, current guidelines do not recommend penfluridol in the treatment of patients with psychotic disorders, even though treatment adherence and other clinical outcomes/ healthcare related costs may be superior to TAU. In this abstract we present a study protocol.**Objectives:**
- The primary aim of this study is to determine the time to all-cause discontinuation of penfluridol as compared to TAU.
- The secondary aim is to determine the healthcare related costs, reason for drug discontinuation, efficacy, safety and tolerability, drug attitude, subjective well-being, insight and quality of life in patients on penfluridol as compared to TAU.

Methods/Design: An open label multicenter randomized controlled trial will be conducted in 180 patients studying the effectiveness of penfluridol as compared to TAU. Adult outpatients with a psychotic disorder will be assigned to one of the three groups; (a) oral penfluridol once a week, (b) oral olanzapine daily, or (c) oral risperidone daily. At 2, 4, 6, 8, 10, and 12 weeks and 6, 9 and 12 months, information on adherence to drug medication will be collected by pill count and the BARS questionnaire. At baseline, three and twelve months of follow-up additional information will be derived through questionnaires on efficacy (PANSS, WHODAS), safety and tolerability (LUNSERS, SHRS), drug attitude (DAI-10), health-related costs (TIC-P, EQ-5D), well-being (SWN-20), and insight (BIS).

Results/Conclusion: The results of this trial will provide an initial insight into 1) the adherence to several antipsychotic drugs and 2) the effectiveness of penfluridol in terms of clinical and economical outcomes as compared to TAU. This information will provide an indication whether the clinical guideline for the treatment of psychotic disorders can be updated, and subsequently a potential extended and safeguarded use of penfluridol for future patients.

References:

- Acosta FJ et al. Medication adherence in schizophrenia. World J Psychiatry 2012;2:74-82
- Lacro JP et. al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 2002;63:892-909.
- Soares BG et al. Penfluridol for schizophrenia. Cochrane Database Syst Rev. 2006;2:CD002923.

DEVELOPMENT OF A MODEL TO PREDICT QTc PROLONGATION IN PATIENTS WHO USE ONE OR MORE QT-PROLONGING DRUGS

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Introduction
Several drugs can induce QTc interval prolongation, which could lead to sudden cardiac death. Healthcare providers receive warnings for interactions between two QT-prolonging drugs. However, it is debatable whether these signals are clinically relevant. The aim of this study is to develop a model to predict QTc interval prolongation based on risk factors in patients who use ≥1 QT-prolonging drugs. This model is for hospital use and a simplified model can be used in primary care.

Method
This retrospective cohort study included 12,949 ECGs of in- and outpatients of 18 years of age and older who used one or more QT prolonging drugs when their ECG was recorded. On 880 (6.9%) ECGs the patient showed QTc prolongation (QTc interval >500ms, corrected with the Bazett's formula). ECGs with a QRS interval > 120 ms were excluded. The independent risk factors were determined using backwards conditional stepwise multivariate logistic regression. The continuous variables were categorized based on their odds ratios. Significant variables (P≤0.050) were considered independent risk factors. Risk scores were assigned to the independent risk factors based on their regression coefficient, and the area under the ROC-curve was determined.

Results
The variables analysed were serum electrolytes, age, eGFR (MDRD), serum ALAT level, number of QT prolonging drugs in use, the maximum QTc measured in the past year, gender, diabetes mellitus, and the use of antiarrhythmics, loop diuretics, thyroid hormones, beta-blockers, verapamil and/or diltiazem and acetylsalicylic acid. For the simplified model the maximum QTc measured, serum calcium levels and serum magnesium levels were not included in the model.
The independent risk factors for the hospital model, with the accompanying risk score, are age >70 years (P=0.009), risk score 1; use of antiarrhythmics (P<0.001), 1; use of loop diuretics (P<0.001), 2; eGFR ≤60 ml/min/1.73m^2 (P<0.001), 2; serum calcium level ≤2.14 mmol/L (P<0.001), 2; serum potassium level between 3 and 3.4 mmol/L (P<0.001), 3; maximal QTc measured between 480ms and 500ms (P<0.001), 3; serum potassium level ≤2.9 mmol/L (P<0.001), 7; and a maximal QTc measured of >500ms (P<0.001), 7. The area under the ROC curve is 0.728.
For the simplified model the risk factors and risk scores are age >70 years (P=0.012), 1; use of beta-blockers (P=0.030), 1; eGFR ≤60 ml/min/1.73m^2 (P<0.001), 2; use of antiarrhythmics (P<0.001), 3; use of loop diuretics (P<0.001), 4; and serum potassium level between 3-3.4 mmol/L (P<0.001), 4 and ≤2.9 mmol/L (P<0.001), 8. The area under the ROC curve is 0.658.

Conclusion
The risk models predict QTc prolongation, although a substantial part of the variation is not predictable from these risk models.

PERINATAL DRUG EXPOSURE IN EXTREME LOW BIRTH WEIGHT INFANTS AND SUBSEQUENT RENAL OUTCOME IN CHILDHOOD: A SAFETY STUDY IS FEASIBLE

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Introduction:
Long term safety studies on renal safety following drug exposure in extreme low birth weight infants (ELBW, < 1000 g) are relevant, but difficult to perform. It is hereby reasonable to focus on compounds with short term safety signals, like ibuprofen that results in acute transient renal dysfunction but without data on long-term renal safety.

Methods:
The PREMATCH study also generated data on renal outcome in former ELBW infants compared to term born controls in young (11 year) adolescence (Raaijmakers *et al*, 2015). Renal length and estimated glomerular filtration rate Cystatin C ($eGFR_{Cys}$) in ELBW cases were hereby one standard deviation lower compared to term born controls [8.73 (0.66) *vs* 9.1 (0.59) cm and 97.2 (13.6) *vs* 108.7 (15.3) ml/min.1.73m^2, at least p<0.01] (Raaijmakers *et al*, 2016). We here aimed to link renal outcome in cases to perinatal drug exposure using an earlier published perinatal dataset on these cases (George *et al*, 2011) and applying univariate (Mann-Withney U, Chi square, Rank correlation) and – if applicable - multivariate statistics.

Results: 84 renal ultrasound length measurements and 59 Cystatin C samples were available. *Renal length*: 41/84 of ELBW cases were exposed to ibuprofen in neonatal life, but there was no difference in renal length for the left kidney [ibuprofen = 8.44 (7.50-10.32) *vs* 8.76 (7.3-10.72) cm, p=0.38] nor right kidney [ibuprofen = 8.57 (7.58-10.39) *vs* 8.82 (7.49-11.01) cm, p=0.28]. None of the other perinatal drug exposure characteristics (prenatal steroids, tocolytics, postnatal steroids, duration parenteral nutrition), were associated with differences in renal length in young adolescence. *$eGFR_{Cys}$*: 36/59 of the former ELBW cases were exposed to ibuprofen in early neonatal life. There was no difference between cases exposed or not to ibuprofen [95 (73-130) *vs* 96.8 (70.2-120.6) ml/min.1.73m^2,p=0.92). Similar, none of the other perinatal drug exposure characteristics were associated with differences in $eGFR_{Cys}$ in young adolescence. Since there were no significant covariates in the univariate analysis, a multiple regression model was not performed.

Conclusions: The absence of a renal safety signal for ibuprofen is somewhat reassuring. However, since renal length and eGFRCys are significantly different (-1 SD) in former ELBW cases, larger safety studies are needed to explore the covariates of variability in $eGFR_{Cys}$ in former ELBW cases. This matters, since this relates to risk for hypertension, cardiovascular events and renal disease in later life.

References: Raaijmakers *et al*, Blood Pressure 2015; Raaijmakers *et al*, Hypertension (in press); George *et al*, Pediatr Nephrol 2011. Research supported by the "Agency for Innovation, Science and Technology in Flanders (IWT) through the "SAFEDRUG" project (IWT/SBO 120033).

BRAF MUTATIONS AS PREDICTIVE BIOMARKER FOR RESPONSE TO ANTI-EGFR MONOCLONAL ANTIBODIES: PROPOSAL FOR AN UPDATE OF THE DRUG LABEL OF PANITUMUMAB AND CETUXIMAB

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Aims Recent guidelines state that patients with metastatic colorectal cancer (mCRC) could be treated with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) such as cetuximab and panitumumab, only in absence of Rat-Sarcoma (*RAS)* mutations. In line with the resistance caused by *RAS* mutations, also *BRAF* mutations may cause treatment resistance (figure 1). However, *BRAF* is not used as predictive biomarker yet because the evidence for the impact of *BRAF* mutations on treatment outcome is considered insufficient[1,2]. We reviewed the evidence for *BRAF* as predictive marker, in order to answer the question if evidence is really insufficient and if so, what information is lacking exactly.

Methods Based on a systematic review of literature, 8 meta-analyses were included that described the impact of *BRAF* mutations on progression and survival in mCRC patients treated with cetuximab or panitumumab. The quality and quantity of evidence was compared to the evidence that is available for *RAS* mutations as predictive biomarker.

Results In all meta-analyses, *BRAF* mutations consistently predict a lack of benefit from anti-EGFR mAb treatment in terms of overall response, progression-free survival and overall survival. High quality clinical evidence comes from a population of 628 patients with *BRAF* mutations.

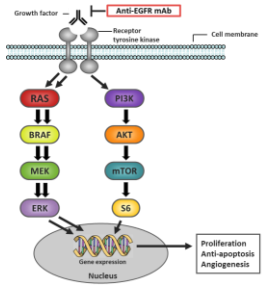

Figure 1. Schematic overview of the MAPK and PI3K signalling pathway. Adapted from van Geel et al[3].

In comparison, the evidence for *KRAS* exon 3,4 and *NRAS* exon 2,3,4 is based on only 360 patients.

Conclusion We conclude that the evidence for *BRAF* is of sufficient quality. All studies show a strong trend towards a negative benefit-risk ratio of anti-EFGR mAbs in patients with *BRAF* mutations. We therefore ask the regulatory agencies Food and Drug Administration and European Medicines Agency to reconsider *BRAF* status as predictive biomarker for response and we propose to update cetuximab and panitumumab labels.

1. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J Clin Oncol*. 2016;34(2):179-185. doi:10.1200/JCO.2015.63.9674. **2.** Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;(July):mdw235. doi:10.1093/annonc/mdw235. **3.** van Geel RMJM, Beijnen JH, Bernards R, Schellens JHM. Treatment Individualization in Colorectal Cancer. *Curr Colorectal Cancer Rep*. 11(6):335-344. doi:10.1007/s11888-015-0288-z.

PREVALENCE OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS SUPPRESSION BY INHALATION OR NASAL CORTICOSTEROIDS IN HIV-INFECTED PATIENTS

Authors/researchers:
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Introduction:
Prevalence of hypothalamic-pituitary-adrenal (HPA)-axis suppression by inhalation or local corticosteroids is unclear, theoretically the risk is higher when a CYP3A4 inhibitor is used. Cases of symptomatic patients have been published. It is important to detect HPA-axis suppression in asymptomatic patients, since it can lead to adrenal insufficiency or iatrogenic Cushing. Patients using a CYP3A4 inhibitor should be treated with beclomethasone, which is not metabolized by CYP3A4.

Aims:
How often do nasal or inhalation corticosteroids lead to suppression of the HPA- axis?
Secondary aim: does this HPA-axis suppression occur more often in patients using a CYP3A4 inhibitor in combination with a local corticosteroid?

Methods:
We selected adult HIV-patients who used antiretroviral therapy and an inhalation or nasal corticosteroid for at least two weeks. They were excluded if they used topical corticosteroids, oral corticosteroids in the last three months, intramuscular or intra-articular corticosteroid injections in the last year. Other exclusion criteria were: known adrenal insufficiency, allergy or contra-indication for tetracosactide. Women were excluded if they were pregnant, lactating or if they used oral contraceptives. A morning plasma cortisol was measured and it was determined 60 and 90 minutes after ACTH injection. Suppression of HPA-axis was defined as a morning plasma cortisol below 80 nmol/L or a cortisol below 550 nmol/L after the ACTH injection.

Results
12 patients were included. Nine of them used inhalation corticosteroids and six used nasal corticosteroids.

Medication use	HPA-axis suppression
No CYP3A4 inhibitor /booster	3/8
Booster and beclomethasone(ICS/NCS)	0/2
Booster and another ICS/NCS	0/2

(ICS= inhalation corticosteroid, NCS= nasal corticosteroid)

Conclusion:
We showed a risk of 25 % on HPA-axis suppression in asymptomatic patients who used inhalation or nasal corticosteroids. This risk is similar to that found in other studies. (broersen et al, 2015) We could not assess our secondary aim, because our group was too small, which can be explained by the fact that the combination of a CYP3A4 inhibitor and local corticosteroids is already avoided.

References:
Broersen, et al. Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism. 2015;100(6):2171-80.
Funding: This research was partly funded by AIDS fonds

SAFE TREATMENT OF HOMOZYGOUS OR COMPOUND HETEROZYGOUS *DPYD* VARIANT ALLELE CARRIERS WITH LOW DOSE FLUOROPYRIMIDINES IS FEASIBLE

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Introduction: The fluoropyrimidine anti-cancer drugs 5-fluorouracil (5-FU) and its pro-drug capecitabine are the cornerstone of treatment for several types of cancer. Reduced activity of the main 5-FU metabolizing enzyme dihydropyrimidine dehydrogenase (DPD) is known to be associated with increased risk of severe, potentially lethal, fluoropyrimidine-related toxicity. This reduced DPD-activity is most often caused by genetic polymorphisms in *DPYD*, the gene encoding DPD. Screening for *DPYD* variants and dose reductions in *DPYD* variant allele carriers can therefore improve patient safety. For heterozygous carriers of *DPYD* variant alleles, dosing recommendations are available. However, for homozygous carriers or compound heterozygous carriers, clear treatment recommendations are lacking, as the occurrence of this genotype is very rare.

Aims: The aim of this study was to gain more insight in the clinical and functional effects of a homozygous or compound heterozygous *DPYD* genotype.

Methods: In this case series, seven patients with a homozygous or compound heterozygous *DPYD* genotype are described. All patients were identified as a carrier of this *DPYD* genotype before start of fluoropyrimidine-containing chemotherapy. The DPD phenotype of these patients was determined (based on measuring DPD enzyme activity in peripheral blood mononuclear cells (PBMCs)). In 3 out of 7 patients, pharmacokinetic analyses were also performed after intake of a reduced dose of capecitabine.

Results: Two homozygous c.2846A>T carriers were identified with a remaining DPD enzyme activity in PBMCs of 10-30%. Three homozygous c.1236G>A carriers were found that had large variations in DPD enzyme activity in PBMCs (40% and 75% remaining activity, and one patient with increased DPD activity). One compound heterozygous carrier (c.1236G>A/ c.2846A>T) had a remaining activity of 45%. These patients could all be safely treated with a reduced dose of fluoropyrimidines. However, in a patient with complete DPD deficiency (a homozygous *DPYD**2A genotype), pharmacokinetic analyses showed that, as 5-FU could not be further metabolized due to absence of DPD activity, exposure to 5-FU was dramatically increased. This patient was eventually successfully treated with a capecitabine dose that was <1% of the originally planned dose.

Conclusions: This unique series of patients with rare *DPYD* genotypes showed that patients with a reduced, but not completely absent DPD activity, caused by a homozygous or compound heterozygous *DPYD* genotype, can be safely treated with a tailored dose of fluoropyrimidines. In a patient with complete DPD deficiency, caused by a homozygous *DPYD**2A genotype, treatment with an extremely reduced dose of capecitabine was well tolerated.

HUMAN MASS BALANCE AND METABOLITE PROFILING OF ^{14}C-NIRAPARIB IN PATIENTS WITH CANCER

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Background: Niraparib is an investigational oral, once daily, selective poly(ADP-Ribose) polymerase (PARP)-1 and PARP-2 inhibitor. In the pivotal Phase 3 NOVA/ENGOT/OV16 study, niraparib met its primary endpoint of improving progression-free survival (PFS) for adult patients with recurrent, ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to platinum-based chemotherapy. Significant improvements in PFS were seen in all patient cohorts regardless of biomarker status[1].

Aim: To conduct a mass balance study to evaluate the absorption, metabolism and excretion of ^{14}C-niraparib, administered to six patients as a single oral dose of 300 mg with a radioactivity of 100 µCi. To identify and quantify niraparib metabolites formed.

Methods: Total radioactivity (TRA) in whole blood, plasma, urine and faeces was measured using liquid scintillation counting (LSC) to obtain the mass balance of niraparib. In addition, metabolite profiling was performed on selected plasma, urine and faecal samples using liquid chromatography – tandem mass spectrometry (LC-MS/MS) coupled to off-line LSC.

Results: Mean TRA recovered over 504 hours was 86.3%, of which 47.5% was recovered in urine and 38.8% in faeces. Two major metabolites were found: the known metabolite M1 (amide hydrolysed niraparib) and the glucuronide of M1 (M10). M1 (2.4%) was detected in faecal samples, and M1 (20.0%) and M10 (6.2%) were quantified in urine. The majority of ^{14}C-radioactivity in plasma was accounted for by M10 (55.7%) and M1 (9.3%). A few minor metabolites were also identified: Mono-oxygenated dehydrogenated M1 (M9) was excreted via the urine, but levels were too low to allow for accurate quantification, and Methylated M1 was only detected in the plasma matrix and accounted for 2.5% of the ^{14}C-radioactivity. Only 2.4% of ^{14}C-radioactivity in plasma was accounted for by the parent drug.

Conclusion: Based on this study it was shown that niraparib undergoes hydrolytic, and conjugative metabolic conversions, with the oxidative pathway being minimal. Mass balance results indicate that both renal and hepatic pathways are comparably involved in excretion of niraparib and its metabolites. Apart from the previously discovered metabolite M1, only the glucuronide of M1 (M10) was identified as a major metabolite.

[1]Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M,Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Mądry R, Christensen RD, Berek JS, Dørum A, Tinker A V., du Bois A, González-Martín A, Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, and Matulonis UA (2016) Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 375:2154–216

A MULTIFACETED INTERVENTION TO IMPROVE GUIDELINE ADHERENCE AMONG PRESCRIBING PHYSICIANS AT SURGICAL WARDS

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Aim

The P-REVIEW study, a prospective, multicentre, open intervention study, has shown that an approach of education of the prescriber combined with audit and feedback by the hospital pharmacist can lead to a reduction of drug-related complications among patients at surgical wards.[1]
In this study we also determined whether such approach improves adherence of prescribing physicians to key pharmacotherapeutic guidelines.

Methods

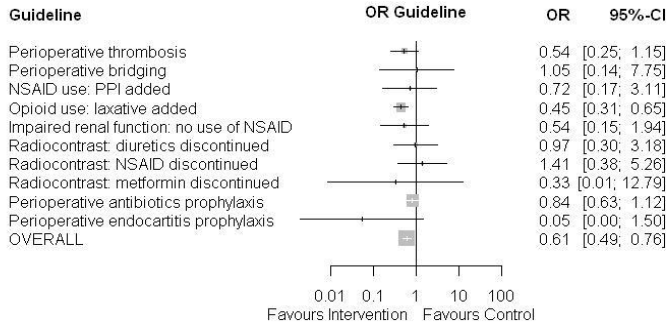
1435 Admissions of 1378 patients who were admitted to surgical, urological or orthopaedic wards during the usual care period and 1195 admissions of 1090 patients during the intervention period were included.
An educational program covering pain management, antithrombotics, fluid and electrolyte management, prescribing in the case of renal insufficiency, application of radiographic contrast agents and surgical antibiotic prophylaxis was presented to all prescribers on the participating wards. National and local hospital guidelines were part of this program. Hospital pharmacists performed medication safety consultations, combining medication review of high-risk patients and visits to ward physicians.

Primary outcome of the study was the proportion of patients in which the physician did not adhere to one or more of the included guidelines (overall non-adherence).

Results

Overall non-adherence decreased significantly during the intervention period (21.8% (193/886)) compared to the usual care period (30.5% (332/1089)). The adjusted odds ratio (OR) was 0.61 (95% CI 0.49-0.76).

Figure 1. Forest plot of nonadherence of prescribers to pharmacotherapeutic measures based on prevailing guidelines



Conclusions

The P-REVIEW study shows that education and support of the prescribing physician with respect to high-risk patients in surgical departments can improve guideline adherence among prescribing physicians at surgical wards.

1. Bos JM, van den Bemt PM, Kievit W, Pot JL, Nagtegaal JE, Wieringa A, Van der Westerlaken MML, Van der Wilt GJ, De Smet PAGM, Kramers C. A multifaceted intervention to reduce drug-related complications in surgical patients. Br J Clin Pharmacol. 2016. DOI:10.1111/bcp.13114

Effects of a single-dose fampridine on internuclear ophthalmoplegia (INO) severity in patients with multiple sclerosis (MS).

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Introduction

Fampridine is a potassium channel blocker that improves nerve conduction in demyelinated axons by enhancing action potential formation. It is currently approved for the improvement of walking capacity in multiple sclerosis (MS) patients. Internuclear ophthalmoplegia (INO) is characterized by slowed eye adduction during horizontal saccades and is a common cause of visual symptoms in patients with MS. The aim of this study was to determine the effects of fampridine on eye movements in MS patients with INO.

Methods

This was a randomized, double-blind, placebo-controlled, cross-over study with fampridine in 24 MS patients with INO. Patients had 2 visits and received either 20 mg fampridine or placebo. We analyzed eye movements recorded by the EyeLink1000 at baseline and post-dose. The primary outcome measures were Versional Dysconjugacy Index (VDI) peak velocity and first pass amplitude (FPA). Higher VDI and FPA values indicate delay in eye adduction associated with INO. These values were compared with a mixed model analysis of variance.

Results

All patients completed the study. A significant change of -17.4% (95% CI: -22.4%, -12.1%; $p<0.0001$) in VDI and -12.5% (95% CI: -18.9%, -5.5%; $p<0.01$) in FPA were observed after fampridine administration compared with placebo, showing a significant improvement in eye adduction. The main adverse event reported after administration of fampridine was dizziness (61%).

Conclusion

Fampridine was associated with a significant decrease in VDI and FPA, corresponding with an improvement in INO severity in comparison with placebo. This study also shows that the current method can be used to investigate pharmacological effects of compounds on nerve conduction in demyelinated fibers.

POPULATION PHARMACOKINETIC ANALYSIS OF INTRAVENOUS TOCILIZUMAB IN RHEUMATOID ARTHRITIS PATIENTS

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Introduction: Tocilizumab (TCZ) is a humanized anti-IL-6R monoclonal antibody that has shown efficacy in the management of moderate to severe rheumatoid arthritis (RA).

Objectives: The purpose of the study was to develop a population pharmacokinetic (PK) model using nonlinear mixed effect modeling to describe the PK characteristics of intravenous (iv) TCZ, estimate interindividual variability (IIV) and assess the influence of different covariates that contribute to this variability.

Methods: We performed a prospective, observational, single-center study conducted in a tertiary hospital. Enrolled subjects received treatment for their RA with iv TCZ at a dose range from 8 to 4 mg/kg every 28 days. Demographic characteristics and clinical laboratory data were obtained at the moment of inclusion and disease activity was assessed. Blood samples for drug concentration testing were collected before TZC administration and, when possible, once a week until the next administration. Informed consent was obtained from all included subjects.

Results: A total of 109 samples were collected from 35 patients with RA on iv TCZ. Overall, 88.6% were women and 80% Caucasian. Mean age ± standard deviation (SD) was 54.1 ± 12.3 and the median [range] of years of RA diagnosis was 11.1 [2.9-48.5]. TCZ serum concentrations were adequately described by a one-compartment disposition model with parallel first-order (linear) and Michaelis-Menten (nonlinear) elimination kinetics. IIV was incorporated on clearance (CL) and volume of distribution (V) parameters. Weight and C-reactive protein (CRP) levels (inflammatory biomarker) significantly affected CL. An increase in weight from 40 to 100 kg led to a 34% increase in CL and an increase of CRP levels from 0.05 to 20 mg/dL led to a 88% increase in CL. Inclusion of weight and CRP in the final model decreased the IIV for from 25.7% to 19.8%. PK parameter estimates and the impact of the covariates are summarized in the following table.

Parameter	Estimate	IIV	Estimate
CL, L/h	0.0138	VAR(η_{CL}), CV%	19.8
V, L	4.78	VAR(η_{V}), CV%	31.6
V_M, mg/h	0.178		
K_M, µg/mL	3.07	Residual error	
WT (kg) on CL	0.319	Additive, µg/mL	0.165
CRP (mg/dL) on CL	0.105	Proportional, %	24.19

K_M, Michaelis-Menten constant; V_M, maximum elimination rate; WT: weight, CRP: C-reactive protein.

Conclusion: A valid population PK model was developed to describe the PK of iv TCZ in RA patients. Drug disposition was affected by weight and an inflammatory biomarker.

References: Shetty A et al. Drug Des Devel Ther 2014;8:349–64; Beal S et al. NONMEM user's guides (1989–2009), v. 7.3. Icon Development Solutions, Ellicott City, MD.

PHARMACOKINETICS OF MOXIFLOXACIN AND LINEZOLID DURING AND AFTER PREGNANCY IN A MDR-TB PATIENT

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Worldwide, TB is among the top 5 causes of death for woman aged 15 to 44. While pregnancy is a risk factor for reactivation of TB, data about MDR-TB in pregnant women is lacking. Also there is only little data about the efficacy and safety of second-line anti-TB drugs during pregnancy both for mother and child. During pregnancy, pharmacokinetic (PK) parameters might change over time, due to dynamic physiological changes in different stages of pregnancy, in turn leading to inadequate treatment and poor outcome. In this case study, we aimed to describe the pharmacokinetics of moxifloxacin (Mfx) and linezolid (Lzd) during and after pregnancy in a patient with MDR-TB.

A 25 year old, pregnant HIV-negative female from Somalia presented with a complaint of cough for several months. After being diagnosed with MDR-TB, she was transferred to our TB reference center at 11 weeks gestation. As the risk to harm the foetus is highest in the first trimester of pregnancy, treatment was started at week 20 of gestation based on drug susceptibility testing. Treatment was commenced with pyrazinamide, Mfx (400 mg od), prothionamide, and Lzd (300mg bd). TDM is standard care in our center for patients with MDR-TB. We hypothesized that her pregnancy would cause changes in her volume of distribution, we therefore performed TDM at three different time-points (see Figure 1).

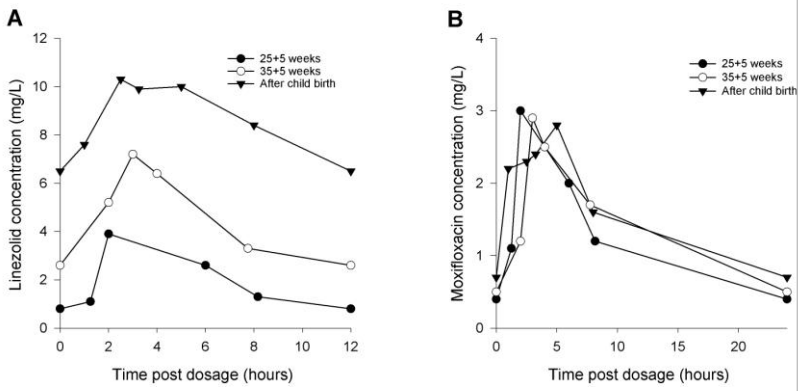

Figure 1: linezolid (A) and moxifloxacin (B) concentration-time curves at 25+5 weeks weighing 75.5 kg (solid circles); 35+5 weeks weighing 74 kg (open circles); and 18 weeks post-partum weighing 68 kg (solid triangles).

In our patient we observed a decreased exposure of Lzd and Mfx during pregnancy compared to post-partum measurements. The linezolid $AUC_{0\text{-}24h}$ was 106 mg*h/L at 35+5 and 203 mg*h/L post-partum and the Mfx $AUC_{0\text{-}24h}$ was 32 and 34.9 mg*h/L respectively. We saw a trend towards an increased exposure of Lzd and, to a lesser extent of Mfx from 25+5 to 35+5 weeks of pregnancy. The observed PK variability might be caused by physiological changes during pregnancy, e.g. increased volume of distribution, increased hepatic blood flow perhaps resulting in enhanced metabolism, and increased renal plasma flow.

In conclusion, TDM of MDR-TB drugs is warranted during all trimesters of pregnancy and 2 and 6 weeks post-partum. Further research is needed.

Population pharmacokinetic modelling of paracetamol after cardiac surgery in children with and without Down syndrome.

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Nearly half of children with Down Syndrome (DS) who undergo cardiac surgery, receive paracetamol as part of their post-operative pain treatment (Fudge *et al.*,2010). Differences have been reported in paracetamol metabolism in children with or without DS (Griener *et al.*,1990). The aim of the study was to determine the population pharmacokinetics of intravenous paracetamol after cardiac surgery in two groups of children – those with and those without DS.

The model was based on 161 plasma samples from 30 children of whom 17 (median age 176 days [92-300] and weight 6.1 kg [4.2-12.9]) had DS and 13 (median age 204 days [105-944] and weight 5.9 kg [4.0-8.2]) did not. All received three paracetamol doses of 7.5 mg/kg (<10kg) or 15 mg/kg (>10kg) at 8 hourly intervals. Population pharmacokinetic modelling for paracetamol was performed using NONMEM 7.2. One, two and three compartment models were evaluated and the influence of different covariates such as age, weight and DS was investigated. Model selection criteria were decrease in objective function and evaluation of diagnostic plots.

Paracetamol pharmacokinetics was best described with a one-compartment model. Paracetamol clearance and volume of distribution increased exponentially and linearly with weight respectively. The population mean[relative standard error]) was (16 ml/min [12%]) and (3780 ml [30%]) respectively. DS did not have a statistically significant influence on any model parameter.

Population pharmacokinetic analysis revealed that body weight influenced both clearance and volume of distribution of paracetamol in children from 3-36 months of age. However, no statistically significant differences in any of the pharmacokinetic parameters of paracetamol between children with and without DS after cardiac surgery were observed. As paracetamol is metabolized through glucuronidation, sulphation and to a lesser extent through cytochrome P450 2E1 oxidation, the following steps will be to incorporate paracetamol-metabolites in this model to evaluate potential differences in paracetamol metabolism between children with or without DS.

(1) Fudge *et al.* Congenital heart surgery outcomes in Down syndrome: Analysis of a national clinical database
(2) Griener *et al.* Noninvasive determination of acetaminophen disposition in Down's syndrome.

Clinical trial simulations in paediatric oncology: a feasibility study with bosutinib in paediatric CML

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Introduction. Paediatric dose finding studies are very difficult to perform due to ethical reasons, the limited number of available patients and the limitation in the number of blood withdrawals. Phase I trials in paediatrics usually start with knowledge about the recommended phase II dose, safety and pharmacokinetics (PK) of the investigated drug in adults. In certain cases, the adult PK exposure can be used as target for dose finding in paediatrics. The aim of this study was to investigate the power of a paediatric phase I trial to show similar PK exposure as observed in adults.

Methods. A previously developed population pharmacokinetic model for the anti-cancer drug bosutinib was used to simulate individual predicted pharmacokinetic curves in paediatrics (Hsyu *et al.*, 2014). Allometric scaling was applied to scale the adult PK parameters to paediatrics. Subsequently, a clinical trial simulation was performed to determine the power of a proposed clinical trial design, consisting of 6 paediatric patients and blood withdrawals at six time points (pre-dose and 1, 3, 6, 8 and 24 hours post-dose). The power was defined as the fraction of 1000 clinical trials with a geometric mean area under the plasma concentration-time curve at steady-state ($AUC_{24,SS}$) within the target range (±20% of the adult geometric mean $AUC_{24,SS}$, i.e. 3640 h*ng/mL). Sample schedules with more, less and different time points for blood withdrawal were tested to optimize the clinical trial design.

Results. A population of 6000 paediatric patients was simulated. At the paediatric starting dose of 300 mg/m^2 (which is equivalent to the approved 500 mg dose in adults), the power of the clinical trial design was 66.9%. The geometric mean exposure on this dose level was 3442 h*ng/mL. The power did not improve when the dose was increased to 350 mg/m^2 (65.3%). Simulations of two different sample schedules showed that addition of one sample resulted in similar results as the original sample schedule (67.5% and 67.7% versus 66.9%). Separate removal of one sample in the absorption and elimination phase of the curve did not improve the power (64.8% and 57.9% versus 66.9%). Increasing the number of patients to 10 patients per trial resulted in an increased power of 78.9% for the starting dose.

Conclusion. A simulation method has been developed and applied to predict the PK of bosutinib in paediatrics. The power of a paediatric clinical trial can be predicted and optimized using this simulation method. With this method, clinical trials in paediatrics can be performed as efficient as possible while protecting the child from unnecessary harm.

Hsyu *et al.* Drug Metab Pharmacokinet. 2014;29(6):441-8

TREATMENT OF HYPERTENSION IN THE FRAIL ELDERLY

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Background
Treatment of hypertension in frail people 80 years and older is not that straightforward.

Aim
The evidence for treatment of arterial hypertension in frail elderly of 80 years and older was assessed.

Methods. Randomized controlled trials (RCTs) in hypertensive octogenarians were selected.

Results. The *Hypertension in the very elderly trial* (HYVET) showed a significant reduction in mortality in the actively treated group. However, selected post-hoc analyses and other studies could not confirm this reduction in mortality and even noticed an increased mortality with an intensive treatment of hypertension. There is a clear heterogeneity between the HYVET-study and the other studies. The current international guidelines recommend treatment of hypertension in patients 80 years and older who have a systolic blood pressure (SBP) of $\geq$ 160 mm Hg aiming at a SBP lower than 150 mm Hg.

These guidelines, however, are mainly based on studies that do not include frail elderly or elderly with multiple comorbidities. For this reason these guidelines cannot be applied in the frail patients of 80 years and older.

Conclusion and discussion. People of 80 years and older in good general condition and functionally independent should be treated following the general guidelines. For the group of frail elderly of 80 years and older there is limited evidence for the treatment of hypertension and therefore the general clinical and functional condition of the patient should be considered, stressing the need for an individualized treatment and avoiding polypharmacy.

References

1. Benetos A, Rossignol P, Cherubini A, et al. Polypharmacy in the aging patient: management of hypertension in octogenarians. JAMA 2015;314:170–180.
2. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887-1898.
3. Benetos A, Gautier S, Labat C, et al. Mortality and cardiovascular events are best predicted by low central/peripheral pulse pressure amplification but not by high blood pressure levels in elderly nursing home subjects. J Am Coll Cardiol. 2012;60(16): 1503-1511.
4. Detremerie C, De Backer T, Petrovic M. Polyfarmacie bij de oudere patiënt: behandeling van hypertensie bij kwetsbare 80-plussers. Tijdschrift voor Geneeskunde 2017; 73, 3: 121-130

The REVIVAL study: olaparib and carboplatin as first line treatment in advanced BRCA mutated breast cancer.

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Introduction: Preclinical studies show additive and even synergistic effects of the combination of platinum compounds and PARP-inhibitors, such as olaparib in cell models with BRCA -1 or -2 mutations. In several non-randomized studies in patients with BRCA-1 and -2 mutation, treatment with olaparib has resulted in stable disease or even partial or complete response and coinciding with longer progression free survival.Yet, there is no clinical evidence that carboplatin-olaparib has a superior benefit-risk compared to standard therapy in advanced BRCA mutated breast cancer patients. Therefore the two-part REVIVAL study is currently being performed.

Aim: Primary objective part 1: to assess the Maximum Tolerable Dose (MTD) of the combination of olaparib and carboplatin followed by olaparib monotherapy in patients possibly benefiting from this combination regimen. Secondary objectives part 1 are to investigate the preliminary response rate, the pharmacodynamics and the systemic exposure of the tablet formulation of olaparib.

Methods: Dose-escalation to predefined dose-levels of two cycles carboplatin-olaparib followed by olaparib monotherapy.

Results: Patients were included in a 3+3 dose-escalation schedule to the following dose-levels: dose-level -1: olaparib 25 mg BID and carboplatin AUC 3, dose-level 1: olaparib 25 mg BID and carboplatin AUC 4, dose-level 2: olaparib 50 mg BID and carboplatin AUC 4, dose-level 3: olaparib 75 mg and carboplatin AUC 4 and dose-level 4: olaparib 100 mg BID and carboplatin AUC 4. We are currently including patients in dose-level 4. To date 19 patients have been included in this phase I trial, fifteen patients with breast cancer, one with ovarian cancer, one with melanoma, one with colorectal cancer and one patient with oesophageal cancer. Twelve patients had a germline BRCA mutation. Thirteen out of 19 patients (68%) have a partial response as best response. Two patients developed a grade 3 platelet count decrease, one patient a grade 3 neutrophil count decrease. All other toxicities were mild (grade 1-2). Pharmacokinetic assessments show that the systemic exposure of the olaparib tablet formulation is comparable to the exposure of the previous capsule formulation.

Conclusion: Preliminary results show promising anti-tumor effects with manageable side-effects. The MTD has not been reached yet and will be determined in phase I before starting the randomized phase II part. In the phase II part of this study patients will be randomised between two cycles of carboplatin-olaparib followed by olaparib monotherapy, or to capecitabine monotherapy 1250 mg/m2 BID day 1-14, q day 22. Upon progression these patients will receive eribulin, vinorelbine, paclitaxel or capecitabine (if randomized to carboplatin-olaparib in first line).

This study is supported by an unrestricted grant from Astrazeneca Inc., UK.

NEW POPULATION PHARMACOKINETIC MODEL THAT PREDICTS THE STARTING DOSE OF TACROLIMUS FOLLOWING PEDIATRIC RENAL TRANSPLANTATION

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Introduction: Multiple clinical, demographic and genetic factors affect the pharmacokinetics (PK) of tacrolimus (Tac) in children, yet in daily practice the starting dose is based solely on bodyweight. TDM limits the time a patient is exposed to concentrations outside the target range, but it can take two weeks to reach the target Tac concentration. The aim of this study was to describe the population PK the first weeks after pediatric renal transplantation.

Methods: Clinical, demographic, PK and genetic data were collected for the first six weeks after renal transplantation. All children were treated with basiliximab, Tac, mycophenolic acid and glucocorticoids. Every child had at least one Tac PK profile performed over 4 h. A population PK analysis was conducted using NONMEM. Demographic, clinical and genetic parameters were evaluated as covariates for all PK parameters containing interpatient variability (IIV). The final model was validated using visual predictive checks.

Results: 46 children with a median age of 9.1 years (range 2.4-17.9) were included. Population PK was best described by a two compartment model. The mean absorption rate was 0.56 h^{-1} (188% IIV), clearance (CL) was 50.5 L/h (25% IIV), central volume of distribution (V_d) was 206 L (69% IIV) and the peripheral V_d 1520 L (62% IIV). Inter-occasion variability was added to CL (18%) and the peripheral V_d (35%). Allometric scaling was used to adjust for differences in bodyweight. Smaller children had a higher Tac CL. CYP3A5 expressers had a 2 times higher CL. An increase in eGFR from 30 to 90 ml/min resulted in a 19% higher CL, whereas a decrease in hematocrit levels from 0.3 to 0.25 L/L corresponded with a 20% higher Tac CL. Transplantation with a kidney from a deceased donor was associated with a higher Tac CL than living donor. In total, these covariates explained 41% of the variability in CL. No co-medications or time after transplantation were associated with Tac PK. The model was externally validated using an independent dataset.

Conclusion: During the first 6 weeks after transplantation, the tacrolimus weight-normalized starting dose should be higher in patients with a lower bodyweight, lower hematocrit, higher eGFR, who express CYP3A5 and those who receive a kidney from a deceased donor. Using these parameters an individualized dosing regimen can be developed for the initial dosage.

REPEATED TIME-TO-EVENT MODELING OF RESCUE MORPHINE DURING RECOVERY FROM CARDIAC SURGERY

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Introduction

To alleviate postoperative pain, many patients still require rescue analgesia in addition to the standardized analgesia protocols. The aim of this study was to characterize the occurrence of rescue analgesia after cardiac surgery using pharmacokinetic-pharmacodynamic modeling and repeated time to event modeling, ultimately to get to individualized analgesia protocols.

Methods

The time and dose of (rescue) morphine administrations were collected in 118 adult patients after cardiac surgery with a median follow-up 42 hours. Morphine pharmacokinetics in these patients were previously modelled by Ahlers et al. (2015). A population pharmacokinetic-pharmacodynamic model was developed with NONMEM using repeated time-to-event modelling to characterize the hazard of rescue morphine (Juul et al., 2016). Morphine concentration and clock time were tested as predictors of this hazard.

Results

The data were best described using a model with an exponential function (half-life of 64 hours) for the hazard for rescue medication after surgery. A significant circadian variation of the hazard was found and implemented as a sine wave with an estimated amplitude of 30.3%, a fixed period of 24 hours, and an estimated peak hazard at 22:42. The effect of morphine in reducing the hazard for rescue morphine was statistically significant ($p<10^{-5}$) and best described with an exponential function. The morphine concentration that reduced the hazard by 50% was estimated at 13.3 ng/ml. Despite accounting for inter-individual differences in morphine pharmacokinetics, the inter-individual variability of the baseline hazard rate (or frailty) was high (CV=123%).

Conclusion

Here, we characterized the effect of morphine and circadian rhythm on the hazard of rescue morphine after cardiac surgery. Because of large variability in pain and morphine pharmacodynamics, future research should focus on the identification of patient-specific predictors in order to individualize management of pain after cardiac surgery.

References

Ahlers *et al*. Anesth Analg 2015;121:1261-73.
Juul *et al*. Pharm Res 2016;33:1093-103.

EFFICACY OF A STANDARDIZED ORAL VITAMIN D DOSING REGIMEN IN SOMATIC AND PSYCHOGERIATRIC NURSING HOME RESIDENTS

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Background
The prevalence of vitamin D deficiency in nursing home residents (NHR) ranges from 79 to 98% (Lips *et al*., 1988; Chel *et al.*, 2008). The aim of this cross-sectional observational study in somatic and psychogeriatric NHR was to determine the efficacy of a standardized oral vitamin D dosing regimen (VDDR) consisting of a loading dose (LD) of 200,000 IU followed by a maintenance dose (MD) of 100,000 IU every 13 weeks in obtaining and maintaining an adequate and safe vitamin D trough level (VDTL), defined as 75-220 nmol/l (Vieth *et al*., 1999; Holick *et al*., 2011).

Methods
Blood samples of NHR who had received the LD followed by at least one MD were analyzed for VDTL, calcium, PTH, and creatinine. Data on age, sex, race, body weight, length, co-morbidity, co-medication, number of MDs, calcium supplementation, smoking and use of alcohol were obtained from patient charts.

According to the Dutch Medical Research Involving Human Subjects Act (WMO) no ethical approval was needed, since the drawing of blood for measurement of laboratory parameters is standard of care for NHR who receive the VDDR.
The primary outcome for the efficacy of the VDDR was defined as the percentage of NHR with a VDTL 75-220 nmol/l. A percentage of 75.31% was considered to be non-inferior to the aimed percentage of 85% (α 0.05; β 0.0881). Secondary outcomes were analyzed as dichotomous variables using logistic regression.

Results
In 91 (58.3%) of 156 included NHR, a VDTL of 75-220 nmol/l was measured (average [SD] 81 [28] nmol/l, range 13-150 nmol/l). Data were abstracted from the charts of 138 (88%) NHR. The only variable found to be a significant predictor for obtaining a VDTL ≥75 nmol/l was a larger number of MDs (≥4 vs 4; OR 2.69; 95% C.I. 1.357-5.328).

Conclusion
The VDDR was not efficacious in obtaining and maintaining an adequate VDTL in somatic and psychogeriatric NHR.

References
Chel *et al*. Osteoporos Int. 2008;19:663–71.
Holick *et al*. J Clin Endocrinol Metab. 2011;96:1911–30.
Lips *et al*. J Clin Endocrinol Metab. 1988;67:644–50.
Vieth *et al*. Am J Clin Nutr 1999; 69: 842-56.

AMIKACIN PHARMACOKINETICS TO OPTIMIZE DOSING RECOMMENDATIONS IN NEONATES WITH PERINATAL ASPHYXIA TREATED WITH HYPOTHERMIA

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Introduction

Pharmacokinetics (PK) of aminoglycosides are expected to be different in neonates with perinatal asphyxia (PA) treated with hypothermia (HT). For amikacin dosing in neonates a recent guideline was proposed[1] but without adjustments in case of PA with HT. Our goal is to quantify the differences in amikacin PK between neonates with and without PA and HT and translate this information in dosing recommendations.

Methods

Amikacin therapeutic drug monitoring data were collected retrospectively from 55 term neonates with PA and HT at the neonatal intensive care units of VUmc Amsterdam and UZ Leuven. Data were added to a published PK dataset of 930 neonates[2]. A data- driven covariate analysis was performed to assess the impact of PA and HT on amikacin clearance, which was translated into an increase in the dosing interval of the current guideline[1]. Monte Carlo simulations facilitated the comparison of simulated exposures with both the current guideline[1] and the proposed adjustments for PA and HT. Stochastic simulations were used to investigate the differences in exposure among typical neonates with PA and HT with varying birth weights (1965–4220 g).

Results

Our analysis showed a 40.6% (RSE 9%) decrease in amikacin clearance for neonates with PA and HT which was translated in a 12 h increase in the dosing interval of the current guidelines[1]. Monte Carlo simulations show that, using the current dosing guidelines in this special population would result in 40 - 57% of patients having trough concentrations above the therapeutic trough range (>5mg/L), whereas, the proposed adjustment is expected to lower this percentage to 14%. Stochastic simulations show that among typical neonates the percentage of patients with trough concentrations above 5 mg/L is between 14 to 25%.

Conclusion

We found that amikacin clearance is reduced with 40.6% in neonates with PA and HT. The performed simulations suggest that an increase in dosing interval of 12 h is needed to decrease the chances of adverse events. Amikacin is mainly eliminated through glomerular filtration, hence, other drugs eliminated primarily via this route could have affected clearances and might require similar dosing adjustments.

References

1. Smits, A. et al. A. A. C. **59,** 6344–6351 (2015).
2. De Cock, R. F. W. et al. Clin. Pharm.. **51,** 105–117 (2012).

Clinical validation of a Dried Blood Spot method for determination of risperidone, aripiprazole, pipamperone and their major metabolites

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Introduction Risperidone, aripiprazole and pipamperone are the three most frequently prescribed antipsychotic drugs for the treatment of comorbid behavioural problems in children with autism spectrum disorders. Therapeutic Drug Monitoring (TDM) might reduce the side effects and improve patient outcome for these drugs (Hiemke *et al.*,2011). The Dried Blood Spot (DBS) method offers a minimally invasive sampling method for TDM which is of particular interest for the paediatric population. The aim of this study was to validate the use of the DBS method for risperidone, aripiprazole, pipamperone and its major metabolites 9-OH risperidone and dehydroaropiprazole in a clinical setting.

Methods We simultaneously collected DBS samples and venous plasma samples in adult patients treated with one of the drugs under study, as we expected adults to have a same correlation between DBS and plasma samples as children. Informed consent was given by all participants. Venous sampling was performed by venipuncture. The haematocrit (Hct) was measured in venous samples. Drug plasma levels were measured in both matrices by a previously validated UHPLC-MS/MS method. Estimated plasma concentrations (EPC) were calculated from DBS concentrations (DC) using the formula EPC= DC/[1-Hct]. Agreement between methods was evaluated using Deming-regression and Bland-Altman difference plots. For Bland Altman, acceptable agreement was predefined as 67% of the samples being within 20% of the mean of the 2 samples. The influence of hematocrit, protein status and C-reactive Protein (CRP) was investigated by Pearson's correlation and explorative plots.

Results
Paired samples were obtained for risperidone (n=20), aripiprazole (n=12) and pipamperone (n=5). Mean recovery rates were 0.67 (metabolite 0.66), 0.52 (metabolite 0.51) and 0.20 respectively. For aripiprazole, dehydroaripiprazole, risperidone and 9-OH risperidone there was no constant or proportional bias observed between EPC and plasma levels. For pipamperone, with application of a correction factor of 0.2, no bias was observed. For risperidone and pipamperone the limits of agreement by Bland-Altman were fulfilled. Haematocrit did not significantly influence the results for pipamperone. No correlation with protein status or level of inflammation (CRP) and DBS-plasma agreement could be found.

Conclusion
Our results demonstrate that DBS is a valid alternative for conventional venous sampling which enables patient friendly TDM-sampling in clinical practice.

1.Hiemke C et al, AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry, 2011 Sep;44(6):195–235.

Prevalence estimation of alcohol consumption by pregnant women using the new biomarker phosphatidylethanol (PEth)

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Introduction: Alcohol consumption by pregnant women may result in mild to severe damage to the unborn child. These symptoms are referred to as Fetal Alcohol Spectrum Disorders, of which the Fetal Alcohol Syndrome (FAS) is the most severe one. Children with FAS experience lifelong physical, behavioral, and cognitive disabilities. To improve preventive actions, we should know which and how many women continue alcohol consumption during pregnancy. Compared to the more conventional markers for alcohol consumption, phosphatidylethanol (PEth) is a more reliable marker to study this subject. We conducted a study in which PEth measurements were performed anonymously in all pregnant women visiting the outpatient obstetrics department.
Methods: We conducted a two-phase study; in phase 1 the women were asked to give informed consent for withdrawal of an extra blood sample. When the inclusion-ratio turned out to be <95%, phase 2 was started in which residual material was used anonymously. The study was approved by the MEC of Erasmus MC. All women that visited the outpatient obstetrics department and by whom a blood sample was taken for routine care 12th week screening, were eligible for the study. Women were excluded in case they 1) were registered as non-Dutch speaking; 2) objected to the use of residual material by the department or inclusion in this study; 3) had more than one 12th week screening (in that case only the first one was used). PEth-analysis was performed using a validated UPC2/MS-method. A result of at least 5,0 µg/L for POPEth, 4,0 µg/L for PLPEth or 2,5 µg/L for DOPEth resulted in a positive PEth-test. Primary endpoint was the percentage of women with a positive PEth-test. Secondary endpoint was the relation between a positive PEth-test and potential predictive variables (age, date and country of birth, ethnicity, postal code numbers, gestation, gravidity, parity, reported alcohol consumption and smoking). All data were collected from the patients' record.
Results: Inclusion-ratio in phase 1 was 84%; phase 2 started in August 2016 in which 336 women were included until this interim-analysis. Only 6 women objected to the use of residual material. We found that 6,9% of the women had a positive PEth-test in the first trimester of pregnancy (n=248). Creole ethnicity was found as potential predictive variable for a positive PEth-test (OR 4,52; CI 1,47 – 13,83). Furthermore, smoking at time of conception seems a potential predictive variable (OR 3,22; CI 0,96 – 10,79). Multivariate analysis for Creole ethnicity and smoking at time of conception, did not result in higher OR's.
Discussion and conclusion: The percentage of women with a positive PEth-test was 6,9%. This percentage is probably higher in a general population, since the PEth-test also remains a snapshot and many women in our population have fertility problems. We assume that these women tend to have a healthier lifestyle. On the other hand, our population is highly multicultural. So, it would be interesting to extend this study with a cohort from a more representative population for the Netherlands. Strength of this study is the fact that 98,2% of the eligible women were included. Creole ethnicity and smoking at time of conception seem to be important variables.

CRUSHING OF DOLUTEGRAVIR COMBINATION TABLETS INCREASES DOLUTEGRAVIR EXPOSURE

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BACKGROUND:
If HIV-patients are unconscious or cannot swallow tablets for other reasons, antiretroviral medication is often crushed and dissolved prior to administration. Crushing can influence pharmacokinetics (PK) leading to altered drug exposure, possibly leading to treatment failure, development of resistance or toxicity. Currently, there is no information about crushing the branded fixed-dose combination of dolutegravir/abacavir/lamivudine (Triumeq®, TRI), therefore crushing TRI is not recommended. In addition, a PK interaction between dolutegravir (DTG) and enteral nutrition is possible, based on the known interaction between DTG and cations in antacids and supplements.

METHODS:
An open-label, 3-period, randomized, cross-over, trial in 22 healthy volunteers was conducted. Subjects randomly received a single dose of TRI with a 7-day washout period. Reference treatment A: TRI whole tablet fasting, intervention treatments B: crushed and suspended TRI fasting and C: crushed and suspended TRI, followed by drinking enteral nutrition (250kcal) within 5 minutes after TRI intake. To show bioequivalence between reference A and B and C a 48-h PK profile was measured for DTG. Geometric mean ratios (GMR) with 90% confidence interval (CI) for $AUC_{0\text{-}inf}$ and C_{max} were calculated. Bioequivalence was accepted when the 90% CI was within 80-125% for AUC and C_{max}. Safety and tolerability were evaluated.

RESULTS:
22 healthy volunteers (21 Caucasian and 1 mixed-race, 10 female), 25 (18-54) years and BMI 23 (20-27) kg/m^2 (median (range)) completed the trial.
For crushed TRI vs whole tablet, the GMR (90% CI) of DTG C_{max} was 129% (123-136), of DTG $AUC_{0\text{-}inf}$ 126% (119-132) and DTG half-life 101% (97-104). For crushed TRI with enteral nutrition vs whole tablet, the GMR (90% CI) of DTG C_{max} was 122% (115-128), of DTG $AUC_{0\text{-}inf}$ 118% (112-125) and DTG half-life 98% (95-102). No SAEs were reported during the trial.

CONCLUSIONS:
A crushed tablet and a crushed tablet with enteral nutrition are not bio-equivalent to a whole TRI tablet (in fasting conditions), since the 90%CI of $AUC_{0\text{-}inf}$ and/or C_{max} fell outside the predefined bioequivalence range. Crushing TRI leads to higher dolutegravir exposure, but does not exceed exposures after intake with food or in BID dosing. Cations in enteral nutrition do not have a relevant negative impact on absorption of dolutegravir from a crushed tablet fasting. In our opinion TRI can be crushed for patients with swallowing difficulties or with an enteral feeding tube and can be combined with enteral nutrition without separating intake in time. Although no dose-limiting toxicity of DTG is observed to date, crushing dolutegravir is advised against if BID dosing and intake with food is needed.

TRANSITION STUDY OF BIOSIMILAR INFLIXIMAB IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Aims: The recent introduction of biosimilar alternatives reduces costs and provides financial headroom to new innovations. Due to the evidence based medicine driven nature of guidelines based on RCTs, EMA's biosimilar approval process that is focused on preclinical similarity evidence, will not be sufficient to gain full trust in the medical field. The principle of "first do no harm (primum nil nocere)" is challenged in a financially driven transition from an originator biological into a similar version. These developments demand clinical infrastructures that facilitate the registration on efficacy and safety to maintain or improve insights in treatment quality.

Methods: The infliximab biosimilar (BS-IFX) consensus team started with a robust long-term business case to facilitate supportive personal to collect and document outcomes. We performed a 52 weeks during observational study in the routine treatment of patients with Morbus Crohn (MC) and Colitis Ulcerosa (CU) treated with originator infliximab (IFX) and transited to BS-IFX. Assessment of CRP, fecal calprotectin, neutralizing antibodies (NABs) against IFX, IFX trough levels, and disease activity measures (patient HAQ) were executed according to routine treatment during treatment visits 1, 2, 4 and 7. The protocol was reviewed by the local medical ethics review committee as not subject to medical research on human subjects due to its observational character of clinical routine care.

Results: In the period between July 2016 and January 2017, 77 patients were informed about the IFX transition project. After given their informed consent a group of 65 (24/41 CU/MC) patients enrolled the project. Twelve patients preferred to continue their treatment on originator IFX. Eight participating patients ceased their therapy. Four patients ceased IFX therapy due to NABs formation (1/3; CU/MC) against originator IFX (detected upon the transition) and later against BS-IFX in combination with loss of response and or adverse drug effects (AEs).

A group of three (1/2; CU/MC) patients ceased BS-IFX therapy without NABs formation because of experienced loss of response and one MC patient because of AEs.

In one CU patient this was objectified after three BS-IFX gifts in a diminished quality of life (QoL) score and increased levels of fecal calprotectin with normal CRP without side effects.

After two gifts the other two MC patients had atypical complaints about ineffectiveness without QoL and laboratory abnormalities and or side effects. In these two patients (3%) the complaints could be attributed to nocebo-effects.

Despite premedication upon infusion, one MC patient had shivers and chills during two subsequent gifts with BS-IFX and switched back to originator IFX upon which infusion reactions remained. None of the patients newly developed NABs on BS-IFX.

Conclusions: Implementation of biosimilars in an observational study secures the documentation of treatment parameters and provides structured insight in outcome. Clinical study wise patient counseling could be an explanation for the relative low nocebo-effect rate in this project. Nocebo-effect rate could be a benchmark for good clinical practice.

PROSPECTIVE VALIDATION OF AN AUTOMATED DELIRIUM PREDICTION MODEL

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Aims Delirium is an under-diagnosed, severe, and costly disorder. In 30-40% of the cases it can be prevented. Different screening tools have been developed and are widely used to detect delirium so treatment measures (pharmacological and non-pharmacological) can be started in time. A fully automated model to predict delirium in older people was developed in 2013 at Zuyderland MC (1). The DElirium MOdel (DEMO) was retrospectively developed, but has not yet been prospectively validated; the objective of this study is to prospectively validate DEMO in the hospital setting.

Methods The DEMO analyses daily all hospitalized patients ≥ 60 years and predicts whether a patient is at risk of developing a delirium within 24 hours after the analysis. Afterwards it was checked in the Electronic Patient Record if the patient had actually developed a delirium. In this way, patients were classified as True Positive, True Negative, False Positive, False Negative. Three analysis were performed in order to validate the model, delirium within 1 day, 3 days and 5 days from the DEMO analysis.

Results The study lasted eight months. A total of 383 patients was included in this study. Each set was independently analysed.

1 day	Est. value	95% confidence interval	
Prevalence	**8.6%**	0.061	0.120
Sensitivity	**87.9%**	0.709	0.960
Specificity	**72.6%**	0.675	0.771
LR+	**3.204**	2.59	3.962
LR-	**0.167**	0.067	0.419
3 days			
Prevalence	**11.5%**	0.086	0.152
Sensitivity	**90,9%**	0.774	0.971
Specificity	**74,9%**	0.699	0.794
LR+	**0.471**	0.355	0.624
LR-	**0.016**	0.006	0.042
5 days			
Prevalence	**13.1%**	0.099	0.169
Sensitivity	**92,0%**	0.799	0.974
Specificity	**76,3%**	0.713	0.807
LR+	**0.582**	0.446	0.760
LR-	**0.016**	0.006	0.042

Table 2. Estimates of the prevalence, sensitivity, specificity, and likelihood ratios with corresponding 95% confidence intervals

Conclusions Given the results, we can conclude that the DEMO is a good predictive model with a high sensitivity and a relatively high specificity, being the highest when the DEMO is used to predict a delirium within 5 days. The next step is applying the DEMO in the clinical practice so physicians are alerted when a patient is at risk of developing a delirium so that preventive measures can be started.

References 1.de Wit et al. Int J Clin Pharm.2016 Aug;38(4):915-23

One size does not fit all: How to adjust the dose of anidulafungin in obesity

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Background: In 2025 approximately one in five individuals will be obese. Physiological changes associated with obesity may influence the pharmacokinetics (PK) of drugs. In a previous study we demonstrated lower exposure to anidulafungin in morbid obese subjects. A direct comparison with non-obese subjects as well as an investigation which PK parameters were impacted by obesity were lacking. Here, we combined data from obese subjects with data from two clinical trials in non-obese subjects. Population-PK modeling and simulation were used to determine an optimal dosing regimen for anidulafungin in obese patients.
Methods: Twenty adult individuals, of which twelve were normal-weight healthy volunteers (median [range] weight of 67.7kg [60.5-93.6]) and eight morbidly obese patients undergoing bariatric surgery (BMI > 40kg/m^2; 149.7kg [124.1-166.5]) were included. Subjects received a single dose of 100mg anidulafungin i.v. over 90 minutes and were sampled up to 168 hours for non-obese and 48 hours for obese. PK analysis was performed by means of non-linear mixed effects modeling. Several body size descriptors were investigated as covariates, using linear or allometric functions with fixed or estimated allometric exponents. Covariates were added stepwise with forward inclusion backward elimination. The final model was selected by objective-function-value, goodness-of-fit plots and ETA-plots. Internal model validation was performed with prediction-corrected visual-predictive-checks and non-parametric bootstrap. Monte Carlo simulations with 5000 subjects per 10kg weight bands (range:60-170kg) were defined to simulate three dosing regimens: 1) licensed dose (200mg loading/ 100mg maintenance); 2) 25% higher dose (250mg/125mg) and; 3) 50% higher dose (300mg/150mg).
Results: A 3-compartment model with a proportional error and equal volumes of distribution (Vd) described the data best. Clearance and Vd were 1.00L/h (95% confidence interval [CI] 0.9-1.1) and 16.6L (95%CI 15.6-17.6) for a 70kg individual, respectively. Both were found to change with TBW using an allometric function with an estimated exponent of 0.322 (95%CI 0.17-0.50) and 0.631 (95%CI 0.39-0.83), respectively. Inter-compartmental clearances between central and peripheral compartments were 0.15L/h (95%CI 0.13-0.18) and 14.1L/h (95%CI 12.2-16.0), respectively. Inter-individual variability of clearance and central Vd were 12.5% (95%CI 4.5-17.7%) and 10.1% (95%CI 5.5-14.2%). We predicted that >85% of patients with a weight above 100kg will be exposed to an AUC_{0-24} lower than 100mg*h/L due to higher clearance. In these patients Vd was 25% higher compared to normal weight individuals.
Conclusion: Our investigations illustrate to what extend overweight influences both Vd and clearance and therefore overweight patients will have a lower exposure to anidulafungin. As a result, a 25% increase in both loading and maintenance dose should be considered in patients >100kg.

REDUCTION OF CALCULATION ERRORS WITH THE DUTCH PEDIATRIC FORMULARY'S WEB-BASED PAEDIATRIC DOSING CALCULATOR

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INTRODUCTION Calculating a paediatric dose is complex due to a variety of parameters influencing the dose and therefore error prone, ultimately resulting in incorrect dosing, lack of efficacy and/or adverse effects. The development and implementation of a paediatric dosing calculator could reduce calculating errors.

OBJECTIVES
1. To develop a clinical decision tool for calculating an individual paediatric dose, using the comprehensive Dutch paediatric formulary as dosing reference.
2. To show a 50% reduction of calculation errors by establishing an individualized paediatric dose through a paediatric dosing module.

METHODS
The Paediatric Dosing Calculator consists of a calculation interface which integrates the dosing recommendations of the Dutch paediatric Formulary with clinical patient variables, thus resulting in an individual recommended dose. After establishing the functional requirements and risk minimization measures the dosing calculator was developed by using a test-retest approach. The alfa version was validated by performing 2 calculations for an aselect sample of 230 drugs of the formulary.Two groups of healthcare professionals were presented with 15 cases for which they were asked to calculate a dose. One group (n=37) was instructed to calculate with conventional tools i.e. a mathematical calculator and the dosing recommendations as listed in the Dutch Paediatric Formulary. The second group (n=36) was instructed to use the integrated paediatric dosing calculator interface. The time for the calculating tasks was limited to 2 minutes per case as to mimic the stressful circumstances of daily practice. The % of calculating errors was compared between groups.

RESULTS
Of the 460 test calculations of the first calculator version 5% contained a calculation error. After analyzing, correction and re-testing an error-free beta version was launched Using the calculator interface resulted in a 35% reduction of calculating errors compared to manual calculations (18,7 %/(range 0-83%) vs 28,4% (range 9-61%), respectively.

CONCLUSIONS
We successfully developed a web-based dose calculator. The use of this calculator appears to reduce dosing errors by approximately one third.
Healthcare providers may benefit from using the calculator interface provided that they carefully enter and select the parameters required.

PHASE I DOSE-FINDING STUDIES WITH THE ORAL DOCETAXEL FORMULATION MODRADOC006 CO-ADMINISTERED WITH RITONAVIR (ModraDoc006/r)

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Introduction: The oral bioavailability of docetaxel has been improved by the development of a novel solid dispersion tablet (ModraDoc006) co-administered with the CYP3A4 and P-glycoprotein inhibitor ritonavir (r). ModraDoc006/r was tested in two phase I studies exploring 1) a once daily weekly (QW) administration, and 2) a bi-daily (BID) QW (BIDW) administration. Safety, maximum tolerated dose (MTD), pharmacokinetics (PK) and preliminary activity were explored.

Methods: A classic 3+3 dose-escalation design was employed in both studies. Patients with advanced solid tumours with a WHO performance status (PS) ≤2 and adequate bone marrow, renal and liver function were included. ModraDoc006 was co-administered with 100 mg ritonavir. Safety was assessed using CTCAE v3.0. PK sampling was performed in the first two cycles 0-48 hours after the first intake. Response was determined every 6 weeks using RECIST v1.0.

Results: In total 46 patients were included in the two studies. Mean age was 58 (range 47-76) years and most had a PS ≤1. Most common toxicities were: diarrhoea, nausea, vomiting and fatigue. Neutropenia was rare and hypersensitivity reactions did not occur. PK was linear with dose, the area under the plasma concentration-time curve ($AUC_{0\text{-}inf}$) reached at the MTDs was1173 and 1247 ng/ml*h and the maximum concentration (C_{max}) 161 and 104 ng/ml for the QW and BIDW schedule, respectively. Partial responses (PR) were observed in 7 patients. Five patients (1x PR, 4x stable disease) continued treatment for >6 months. The MTD was defined as 60 mg ModraDoc006/r for QW and 30/20 mg ModraDoc006/r for BIDW.

Conclusion: ModraDoc006/r was well tolerated in both administration schedules. The BIDW schedule had less inter-patient variability in AUC and was therefore chosen for further development. Anti-tumour activity is promising.

ModraDoc006/r is commercially developed by Modra Pharmaceuticals BV of which Jos Beijnen and Jan Schellens are founders and employees

VANCOMYCING PROTEIN BINDING IN NEONATES AND YOUNG INFANTS

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Introduction Vancomycin, a glycopeptide, is often administered to treat (suspected) serious gram-positive infections caused by Staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococci* (CoNS). Vancomycin pharmacokinetic (PK) and pharmacodynamic (PD) data in neonates are based on total concentrations. However, only unbound vancomycin is pharmacologically active and available for elimination.

Aim The aim was to determine vancomycin protein binding and the covariates impacting unbound vancomycin concentration in neonates and young infants.

Methods In neonates and young infants to whom vancomycin was administered intermittently for medical indications, total and unbound vancomycin plasma concentrations were determined using a validated LC-MS/MS method (Oyaert et al, 2015). Sampling occurred randomly during vancomycin exposure, covering a broad range of vancomycin concentrations. Impact of covariates on unbound concentration was determined using Spearman correlation, linear regression or Mann Whitney U test. Significant results of the univariate regression were entered in a multiple regression.

Results Thirty-seven samples in 33 patients [median (interquartile range) gestational age 35 (29-39) weeks and postnatal age 14 (8-29) days] were collected. Median total and unbound vancomycin concentrations were 14.3 (7.4-20.6) and 13.6 (7.2-22.5) mg/L, respectively. Median unbound fraction was 0.90 (0.77-0.98). Multiple regression revealed total vancomycin concentration (β=0.88, $p<0.001$) and albumin (β=-0.32, $p=0.007$) as most important covariates of unbound vancomycin concentrations, resulting in an R^2 adjusted of 0.95 ($p<0.0001$).

Conclusions The unbound vancomycin fraction in neonates is higher compared to children and adults and total vancomycin concentration and albumin were the most important covariates of unbound vancomycin concentration. Integration of protein binding in future PK/PD analyses is appropriate to optimize vancomycin dosing and to determine population-specific vancomycin PD targets for neonates.

Ref: Oyaert et al, Clinica Chimica Acta 441 (2015), 63-70.

AUGMENTED VANCOMYCIN CLEARANCE IN NEUTROPENIC PATIENTS: ASSESSING PREDICTORS AND ADEQUATE TREATMENT

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Introduction: Previously, we found augmented vancomycin clearance (CLva) in a small study in neutropenic patients [1]. The aim of this study is determine the factors associated with CLva in a large group of haematological patients.

Methods: Hospitalized patients older than 18 years treated with vancomycin intravenously were included from May 2011-July 2013 and from January-December 2015. Univariable and multivariable analyses were used to analyse the association between CLva and co-variables, such as, hematological malignancy, neutropenic period, full laboratory parameters and SIRS-criteria. The pharmacokinetic parameters were calculated with mean a posteriori (MAP) Bayesian estimation computer program (MW/Pharm 3.60, Mediware, the Netherlands) as has been described before [1].

Results: A total of 282 patients with mean(±SD) age 60(±14) years were included. Mean CLva was 55(±26) mL/min, estimated creatinine clearance (eCLcr) 96(±63) mL/min and serum creatinine 96(±78) µmol/mL. The pharmacokinetic parameters are shown in Table 1.

Table 1: Mean (±SD) Age, eCLcr, CLva, $Dose_{24}$ and AUC_{24} in neutropenic and non-neutropenic patients.

Neutro-penia	N	Age years	eCLcr mL/min	CLva mL/min	$Dose_{24}$ mg	AUC_{24} mg.h/L
No	202	61(±15)	93(±66)	50(±25)	1501(±726)	510(±153)
Yes	80	57(±12)	109(±58)	66(±26)	1955(±713)	501(±119)
P		0.032	0.012	<0.001	<0.001	0.935

In the univariable analysis, eCLcr, hematologic malignancy, neutropenia, leucocytes, Ht, thromobocytes and urea levels were significantly associated with CLva. In the multivariable analysis both eCLcr (B:0.232, 95%CI 0.194-0.270), P<0.001 and neutropenia (B:11.6, 95%CI 2.3-30.9, P=0.014) were significantly and independently associated with CLva.

Discussion: Neutropenia is associated with a significantly higher CLva in this large population of patients with hematological malignancies. Our data support the advise for administration of a higher than usual 24h dose of vancomycin and for TDM in these patients. No other co-variables were found to be significantly associated with augmented CLva in neutropenic patients. The cause of augmented CLva remains unknown and further studies are needed to understand the mechanism of the augmented CLva in neutropenic patients.

*References:*1. Haeseker *et al.*, 2014, PLoS One e112008