Scientific Spring Meeting
Friday April 13, 2018

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 13, 2018
Vergadercentrum Domstad Utrecht

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

09.00 h **Welcome & coffee**

ORAL PRESENTATIONS

09.30 h *M.P.J. van Diemen, C.L. Berends, N. Akram, J. Wezel, W.M. Teeuwisse, E.G. Mik, H.E. Kan, A. Webb, J.W. Beenakker, G.J. Groeneveld* (Leiden): Validation of a pharmacological model for mitochondrial dysfunction in healthy subjects using simvastatin: a proof-of-pharmacology study

09.45 h *S.M. van den Belt, H.J.L. Heerspink, M. Kirchner, V. Gracchi, D. de Zeeuw, E. Wühl, F. Schaefer* (Groningen): Should RAAS inhibition be discontinued in children with severe chronic kidney disease?

10.00 h *N.M.A. Idzerda, F. Persson, M.J. Pena, B.M. Brenner, P. Brunel, N. Chaturvedi, J.J. McMurray, H.-H. Parving, D. de Zeeuw, H.J. L. Heerspink* (Groningen): NT-proBNP predicts the cardio-renal response to aliskiren in patients with type 2 diabetes at high renal and cardiovascular risk

10.15 h *P. Mian, J.N. van den Anker, K. van Calsteren, P. Annaert, D. Tibboel, M. Pfister, K. Allegaert, A. Dallmann* (Leuven): Physiologically-based pharmacokinetic modelling of paracetamol and its metabolites during pregnancy

10.30 h *D. Bury, R. ter Heine, E.M.W. van de Garde, M.R. Nijziel, R.J. Grouls, M.J. Deenen* (Eindhoven): A 25% higher vancomycin maintenance dose is required in haematologic patients with neutropenia

10.45 h *D. Bamps, L. Macours, L. Buntinx, J. de Hoon* (Leuven): Laser speckle contrast imaging, the future for TRP target engagement biomarker assays

11.00 h **Coffee and Tea Break**

11.15 h *S.E. Berends, G.R. D'Haens, K. Bloem, J. Schaap, A. de Vries, T. Rispens, R.A.A. Mathôt* (Amsterdam): Clinical feasibility of dried blood samples for infliximab in IBD-patients

11.30 h *L.Binkhorst, A. Sobels, S.S.S. Jankie, P. van der Zee, L.E. Visser, J.A. Portielje* (Den Haag): Age-related and sex-related differences in use and toxicity of fluoropyrimidine-oxaliplatin therapy for colon cancer

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

12.50 h **LUNCH**

13.30 h **POSTER SESSION**

1. *L.A. Lammers, R. Achterbergh, J.A. Romijn, R.A. Mathôt* (Amsterdam): Short-term fasting alters acetaminophen metabolism in humans

2. *M.M.M. Wilhelmus, A.B. Smit, M. Loos, B. Drukarch* (Amsterdam): Absence of tissue transglutaminase delays amyloid-beta deposition in an Alzheimer's disease mouse model

3. *D.J. Brinkman, J. Tichelaar, L.B. Mokkink, T. Christiaens, R. Likic, R. Maciulaitis, J. Costa, E. Sanz, S.R. Maxwell, M.C. Richir, M.A. van Agtmael* (Amsterdam): Key learning outcomes for clinical pharmacology and therapeutics education in Europe: A modified Delphi study

4. *S.M. van den Belt, H.J.L. Heerspink, V. Gracchi, D. de Zeeuw, E. Wühl, F. Schaefer* (Groningen): Early proteinuria lowering by ACE inhibition predicts renal survival in children with chronic kidney disease

5. *S.L. Groenland, R.A.G. van Eerden, R.B. Verheijen, A.D.R. Huitema, R.H.J. Mathijssen, N. Steeghs* (Amsterdam): Increasing pazopanib exposure by splitting intake moments

6. *N.C.B. de Jager, J.M. Heijdra, C.J. Fijnvandraat, F.W.G. Leebeek, M.H. Cnossen, R.A.A. Mathôt for the "OPTI-CLOT" study group* (Amsterdam): Population pharmacokinetic modelling of factor VIII levels during perioperative dosing of Haemate® P (Humate P) in patients diagnosed with von Willebrand Disease

7. *C.C.J. Dekkers, S. Petrykiv, G. Laverman, D.Z. Cherney, R.T. Gansevoort, H.J.L. Heerspink* (Groningen): Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers

8. *M.Y.A.M. Kroonen, T. Sen, G. Laverman, H.J.L. Heerspink* (Groningen): Predictors of albuminuria lowering response to dapagliflozin

9. *M. Nederlof, T.C.G. Egberts, L. van Londen, M.C.F.J. de Rotte, P.C. Souverein, R.C.M. Herings, E.R. Heerdink* (Utrecht): Guideline adherence for laboratory monitoring of ambulatory patients treated with lithium: a retrospective follow-up study in the Netherlands

10. *K.M. Heinhuis, S.G.J.G. In 't Veld, G. Dwarshuis, D.A. van den Broek, N. Sol, M.G. Best, T. Wurdinger, N. Steeghs* (Amsterdam): RNA-sequencing of tumor-educated platelets, a novel biomarker for blood-based sarcoma diagnostics

11. *M.A. Sikma, C.C. Hunault, E.M. van Maarseveen, A.D.R. Huitema, E.A. van de Graaf, J.H. Kirkels, M.C. Verhaar, J.C. Grutters, J. Kesecioglu, D.W. de Lange* (Utrecht): Extreme variability of oral tacrolimus pharmacokinetics early after thoracic organ transplantation due to excessive fluctuations in bioavailability (NTR 3912)

12. *S. Wilkes, I. van Berlo, J. ten Oever, F. Jansman, R. ter Heine* (Deventer): A pharmacokinetic justification for continuous dosing of flucloxacillin in non-critically ill patients

13. *B. P.S. Belderbos, S. Bins, R.W.F. van Leeuwen, E. Oomen-de Hoop, N. van der Meer,P. de Bruijn, P. Hamberg, E.N.M. Overkleeft, W.M. van der Deure, M.P. Lolkema, R. de Wit, R.H.J. Mathijssen* (Rotterdam): Influence of enzalutamide on cabazitaxel pharmacokinetics; a drug-drug interaction study in metastatic castration resistant prostate cancer (mCRPC) patients

14. *F.A. Berger, I.H. van der Sijs, N.M.S. de Groot, N.G.M. Hunfeld, J.J.H. Bunge, P.M.L.A. van den Bemt, T. van Gelder* (Rotterdam): Dynamics of the QTc-interval during use of intravenous ciprofloxacin in ICU patients

15. *A.H.M. de Vries Schultink, M.-R.B.S. Crombag, E. van Werkhoven, J.H.M. Schellens, A.D.R. Huitema, J.H. Beijnen* (Amsterdam): Neutropenia and exposure to docetaxel in metastatic castrate-resistant prostate cancer patients compared to other solid tumors: a meta-analysis

16. *W.H. Man, I. Wilting, E.R. Heerdink, G.W.K. Hugenholtz, M.J. ten Berg, W.W. van Solinge, A.C.G. Egberts, E.M. van Maarseveen* (Utrecht): The unbound fraction of clozapine significantly decreases with elevated plasma concentrations of the inflammatory acute phase protein alpha-1-acid glycoprotein

17. *A.M. Punt, N.A. Stienstra, A.C. Egas, R. de Jager, W. Spiering, P J. Blankestijn, M.L. Bots, E.M. van Maarseveen* (Utrecht): Screening and quantification method for antihypertensive agents using LC-MS/MS: a valuable tool for medication adherence assessment

18. *J.B. Langenhorst, T.P.C. Dorlo, C. van Kesteren, E.M. van Maarseveen, S. Nierkens, C.A. Lindemans, M.A. De Witte, A. van Rhenen, R. Raijmakers, M. Bierings, J. Kuball, J.J Boelens, A.D.R Huitema* (Utrecht): Association of fludarabine exposure and survival after allogeneic cell transplantation: retrospectively estimated and prospectively simulated

19. *G.E. Benoist, I.M. van Oort, J.A. Schalken, D.M. Burger, N. Mehra , R. ter Heine, N.P. van Erp* (Nijmegen): Pharmacokinetic and clinical predictors of response to abiraterone in a real world setting

20. *G.E. Benoist, I.M. van Oort, J. Schalken, D.M. Burger, N. Mehra, N.P. van Erp* (Nijmegen): Exposure-toxicity analysis of enzalutamide in patients with metastatic castration resistant prostate cancer

21. *R.E. Wasmann, E.M. Svensson, S.J. Schalkwijk, R.J. Brüggemann, R. ter Heine* (Nijmegen): Normal fat mass cannot be reliably estimated in typical pharmacokinetic studies

22. *E. Van Leeuwen, M. Petrovic, M.L. van Driel, A. De Sutter, R. Vander Stichele, T. Declercq, T. Christiaens* (Gent): Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia.

23. *C.J.T. van der Togt, T.S. Sprong, H.W. Fleuren, C. Kramers* (Nijmegen): Evaluation of a continuous infusion protocol for vancomycin: checking protocol adherence and efficacy

24. *R.E. Wasmann, C. Smit, R. ter Heine, A. Colbers, H.P.A. van Dongen, E.J. Hazebroek, D.M. Burger, C.A.J. Knibbe, R.J.M. Brüggemann* (Nijmegen): Micafungin pharmacokinetics and probability of target attainment in obese individuals

25. *M. Saghari, P. Gal, M.L. de Kam, M.B.A. van Doorn, J. Burggraaf, M. Moerland, R. Rissmann* (Leiden): Antera 3D and laser speckle contrast imaging as novel tools to characterize type IV hypersensitivity skin response in healthy volunteers

26. *L. Martial, J. Kerkhoff, N. Martinez, M. Rodríguez, R. Coronel, G. Molinas, M. Roman, R. Gomez, S. Aguirre, E. Jongedijk, J. Huisman, D. Touw, D. Pérez, G. Chaparro, F. Gonzalez, R. Aarnoutse, J.-W. Alffenaar, C. Magis-Escurra* (Nijmegen): Validation of dried blood spot sampling for pharmacokinetic research and therapeutic drug monitoring of anti-tuberculosis drugs in children

27. *M.T.J. van Bussel, D. Pluim, B. Milojkovic Kerklaan, J.H. Beijnen, J.H.M. Schellens, D. Brandsma* (Amsterdam): Circulating tumor cells analysis in cerebrospinal fluid in patients with epithelial tumors with suspected leptomeningeal metastasis

28. *J.J.J. Geenen, G.M.H.E. Dackus, Ph.C. Schouten, S. Marchetti, H. van Tinteren, J.H. Beijnen, G.S. Sonke, S.C. Linn, J.H. Schellens* (Amsterdam): The REVIVAL study: a phase I trial to determine the maximum tolerable dose (MTD) of two cycles olaparib-carboplatin followed by olaparib monotherapy in patients with advanced cancer

29. *S.E.M. Vonk, C.J. Majoor, E.J.M. Weersink, E.M. Kemper for the Amsterdam CF research group* (Amsterdam): Tobramycin and vestibulotoxicity: 4 cases

30. *M.E. Cloesmeijer, E.H.J. Krekels, A.M. Lynn, A. Smits, D.Tibboel, Y. Daali, K.T. Olkkola, K. Allegaert, P. Mian* (Leiden): Population pharmacokinetics of enantiomer specific intravenous ketorolac across the human-age span

31. *P. Mian, M.J. van Esdonk, K.T. Olkkola, B.C.M. de Winter, A. Liukas, I. Spriet, D. Tibboel, M. Petrovic, B.C.P. Koch, K. Allegaert* (Rotterdam): Setting the stage for evidence-based model-informed dosing of intravenous paracetamol in older people

32. *D. Pluim, W. Ros, M.T.J. van Bussel, D. Brandsma, J.H. Beijnen, J.H.M. Schellens* (Amsterdam): Enzyme linked immunosorbent assay for the quantification of nivolumab and pembrolizumab in human serum and cerebrospinal fluid

33. *J.M. Janssen, G.J.L. Kaspers, D. Niewerth, A.J. Wilhelm, C.M. Zwaan, J.H. Beijnen, A.D.R. Huitema* (Amsterdam): Semi-physiological pharmacokinetics of bortezomib in pediatric patients with acute lymphoblastic leukemia

34. *N.A.G. Lankheet, K.R.M. Ferrier, F.G. Jansman, S.E. Gibbons, J.L.M. Martin, K. McAllister, S.H. Khoo, D.M. Burger, N.P. van Erp* (Nijmegen): Development of an online drug-drug interaction resource to support safe prescription of oncolytics

35. *G. Van Lancker, E. Van Bever, B. Delafontaine, M. Azermai, K. Boussery, E.L. Swart, A. Chahbouni, J. Van Bocxlaer, L. Van Bortel, P. Colin* (Gent): Switchability of gabapentin formulations: assessment of bioequivalence between Neurontin® and Gabasandoz® on the individual patient level

36. *K. Eechoute, R.H.J. Mathijssen, T. van Gelder* (Rotterdam): Tamoxifen-induced fatty liver disease in a Caucasian patient

37. *J. Roosendaal, H. Rosing, L. Lucas, A. Oganesian, J.H.M. Schellens, J.H. Beijnen* (Amsterdam): Development and validation of an LC-MS/MS assay for the quantification of intracellular decitabine nucleotides and genomic DNA incorporated decitabine in peripheral blood mononuclear cells and whole blood

38. *E.B. Uitvlugt, M.J.A. Janssen, E.L. Kneepkens, B.J.F. van den Bemt, P.M.L.A. van den Bemt, F. Karapinar-Çarkıt* (Amsterdam): Which part of unplanned hospital readmissions within 30 days after discharge is medication related? A study to assess the percentage and potential preventability and causes

39. *D. Damoiseaux, A. Lalmohamed, M. de Witte, N.K.A. van Eijkelenburg, K. de Kanter, E.M. van Maarseveen* (Utrecht): Switching to a methotrexate immuno-assay with higher specificity compared to its predecessor results in a shorter time period to reach target concentrations

40. *M. El Amrani, C.L. Szanto, C.E. Hack, A.D.R. Huitema, S. Nierkens, E.M. van Maarseveen* (Utrecht): Quantification of total dinutuximab concentrations with liquid chromatography tandem mass-spectrometry

41. *C. Bastida, D. Soy, V. Ruíz, R. Sanmartí, M. Pascal, J. Yagüe, A.D.R. Huitema* (Amsterdam): Different dynamics of composite indexes variables used for disease activity assessment in rheumatoid arthritis patients on tocilizumab treatment

42. *M.A.G.M. Kroon, J.K. Berbee, S. Majait, E.L. Swart, H.W.M. van Laarhoven, O. van Tellingen, E.M. Kemper* (Amsterdam): Plasma concentration of curcumin and its metabolites in subjects using over the counter supplements in daily life is low

43. *A.M. Harmsze, C. de Jong, I. Drubbel, G.A.M. Roelfs, E.L. Swart* (Nieuwegein): Clomipramine toxicity in a CYP2D6 poor metabolizer who suddenly stopped smoking

44. *A. Keyany, J.T.H. Nielen, P.C. Souverein, F. de Vries, B. van den Bemt* (Nijmegen): Use of parenteral glucocorticoids and the risk of new onset type 2 diabetes mellitus: a case-control study

45. *S.A.W. van Moorsel, A.A. van Bodegraven, D.R. Wong* (Sittard): Therapeutic drug monitoring at week 1 and prediction of clinical sustainability of thiopurines in IBD-patients

46. *R. Achterbergh, L.A. Lammers, R.A. Mathôt, J.A. Romijn* (Amsterdam): A short-term high fat increases exposure to acetaminophen metabolites that are related to hepatotoxicity

47. *S. van Oort, F. Rutters, M. van Herwaarden, P. Elders, K. Kramers, on behalf of the Diabetes Pearl from the Chain of Pearls Initiative* (Amsterdam): The characterization of people with type 2 diabetes mellitus and polypharmacy in the Netherlands: The Diabetes Pearl Cohort

48. *S. Crutzen, K. Taxis, P. Denig, on behalf of the ESOM project group* (Groningen): Efficient selection of older patients for medication review: development and validation of a selection algorithm

49. *M.J. Bakkum, J. Tichelaar, A. Wellink, M.C. Richir, M.A. van Agtmael* (Amsterdam): Digital learning to improve prescribing practice: a systematic review

50. *M. Reumerman, J. Tichelaar, R. van Eekeren, M.C. Richir, M.A. van Agtmael* (Amsterdam): Long term and clinical effects of an pharmacovigilance educational intervention in specialist oncology nurses

51. *M. Sjak Shie, A. Sobels, P. de Wolf, L. Binkhorst* (Den Haag): Drug interactions between tyrosine kinase inhibitors and St. John's wort unnoticed in clinical practice

52. *H.A. Crommelin, A.D.M. Vorselaars, C.H.M. van Moorsel, J.H. Proost, J.C. Grutters, V.H.M Deneer* (Nieuwegein): Pharmacokinetics and exposure-response relationship of infliximab in severe sarcoidosis

53. *R.A. Wijma, A. Huttner, S. Harbarth, R.J.M. Brüggemann, J.W. Mouton, A.E. Muller* (Rotterdam): The pharmacokinetics of nitrofurantoin in healthy volunteers using two frequently used dosing regimen

14.15 h Lecture of the winner of the **'NVKFB'-Thesis Award 2017 (1)**

14.35 h Lecture of the winner of the **'NVKFB'-Thesis Award 2017 (2)**

14.55 h Lecture of the winner of the **'NVKFB'-TOP Publication Award 2017**

15.10 h Lecture of the winner of the **`NVKFB´-Education Award 2017**

15.25 h **Coffee and Tea Break**

ORAL PRESENTATIONS

15.45 h *M.-R.B.S. Crombag, A.H.M. de Vries Schultink, S.L.W. Koolen, M. Joerger, J.H.M. Schellens, N.P. van Erp, R.H.J. Mathijssen, J.H. Beijnen, A.D.R. Huitema* (Amsterdam): Older age has minor impact on paclitaxel exposure: a population pharmacokinetic model

16.00 h *A. Sobels, J. Bongers, E.M. Westerman* (Den Haag): The introduction of biosimilar rituximab in clinical practice

16.15 h *L.A. Lammers, R. Achterbergh, J.A. Romijn, R.A. Mathôt* (Amsterdam): Effect of short-term fasting and high fat diet on midazolam metabolism

16.30 h *L.M.A. Favié, F. Groenendaal, C.M.A. Rademaker, T.R. de Haan, T.C.G. Egberts, F. van Bel, M.P.H. van den Broek, A.D.R. Huitema, and the PharmaCool Study Group* (Utrecht): Pharmacokinetics of morphine and its metabolites in neonates with hypoxic-ischemic encephalopathy during and after therapeutic hypothermia

16.45 h Closure

VALIDATION OF A PHARMACOLOGICAL MODEL FOR MITOCHONDRIAL DYSFUNCTION IN HEALTHY SUBJECTS USING SIMVASTATIN: A PROOF-OF-PHARMACOLOGY STUDY

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Aim
Proof-of-pharmacology models to study compounds in healthy subjects offer multiple advantages. Simvastatin is known to induce MD at least partly by depletion of co-enzyme Q10. The goal of this study was to evaluate a model of simvastatin-induced MD in healthy subjects and to determine whether MD could be pharmacologically reversed by treatment with co-enzyme Q10 (ubiquinol).

Methods
Subjects received simvastatin 40 mg/day for 8 weeks. After 4 weeks, subjects were randomized to receive ubiquinol 300 mg/day or placebo in a double-blinded fashion. Mitochondrial function was assessed by measuring the phosphocreatine recovery time (τ-PCr) using phosphorous Magnetic Resonance Spectroscopy (^{31}P-MRS) after in-magnet exercise.

Results
After 4 weeks of simvastatin treatment, τ-PCr prolonged with 15.2% compared to baseline, (95%CI, 2.5 to 29.4%; P=0.018, Figure 3). After 8 weeks, τ-PCr further prolonged to 37.27 seconds in the placebo group (prolongation of 18.5% compared to baseline, still significantly prolonged, 95%CI, 1.1 to 38.9%; P=0.037), but shortened to 33.81 seconds in the ubiquinol group (prolongation of 9.1% compared to baseline, no longer significantly prolonged, 95%CI, -7.9 to 29.2%; P=0.31). At 8 weeks, there was no significant difference between groups (difference of 8.2%, 95%CI, -14.5 to 37.0%; P=0.51).

Conclusion
Simvastatin induces subclinical mitochondrial dysfunction in healthy subjects, which can be partly reversed by treatment with ubiquinol. This model of pharmacologically induced and reversed mitochondrial dysfunction can be used to study the effects of compounds that enhance mitochondrial function in healthy subjects.

SHOULD RAAS INHIBITION BE DISCONTINUED IN CHILDREN WITH SEVERE CHRONIC KIDNEY DISEASE?

S.M. van den Belt[1], H.J.L. Heerspink[1], M. Kirchner[2], V. Gracchi[1], D. de Zeeuw[1], E. Wühl[3], F. Schaefer[3]

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Introduction: Although Renin Angiotensin Aldosterone System inhibition (RAASi) with Angiotensin Converting Enzyme inhibitors or Angiotensin Receptor Blockers is a cornerstone in the treatment of renal complications in children with Chronic Kidney Disease (CKD), it is sometimes discontinued when renal function further declines. However, the effect of RAASi discontinuation on renal disease progression is unknown. Therefore, we studied the reasons and impact of discontinuation of RAASi on important risk markers of CKD progression and on estimated glomerular filtration rate (eGFR) decline.

Study design: Data from the observational Cardiovascular Comorbidity in Children with Chronic kidney disease (4C) cohort study were analysed. Children with CKD who discontinued RAASi before starting renal replacement therapy were included in the analyses. Initial change in systolic blood pressure, albuminuria and potassium were assessed ~6 months after RAASi discontinuation. Rate of eGFR decline (eGFR slope) during a median of 1.9 years before and 1.2 years after discontinuation were estimated using a linear mixed effects model.

Results: Out of 704 children included in the 4C study, 73 children discontinued RAASi before starting renal replacement therapy. eGFR data were available in 69 children (67% male, mean age 13.7 years, mean eGFR 27.3 ml/min/1.73m2). Physician-reported reasons for RAASi discontinuation were increase in serum creatinine (n=23), hyperkalemia (n=16), and symptomatic hypotension (n=12). After discontinuation of RAASi, blood pressure and albuminuria increased, whereas potassium decreased. There was a steeper decline in eGFR after discontinuation of RAASi (-3.9 ml/min/1.73m2/year (95% CI -5.1 to -2.6)), compared to the slope under RAASi treatment (-1.5 ml/min/1.73m2/year (95% CI -2.4 to -0.6); P=0.005).

Conclusions: Discontinuation of RAASi in children with CKD is associated with an acceleration of renal function decline. These results indicate that RAASi is important for renal protection and that stopping this therapy even for good clinical reasons should be weighed against the negative impact on long term renal function.

NT-PROBNP PREDICTS THE CARDIO-RENAL RESPONSE TO ALISKIREN IN PATIENTS WITH TYPE 2 DIABETES AT HIGH RENAL AND CARDIOVASCULAR RISK

Nienke M.A. Idzerda[1], Frederik Persson[2], Michelle J. Pena[1], Barry M. Brenner[3], Patrick Brunel[4], Nish Chaturvedi[5], John J. McMurray[6], Hans-Henrik Parving[7], Dick de Zeeuw[1], Hiddo J. L. Heerspink[1]

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Aims: Extracellular volume restriction by means of diuretic treatment or low sodium diet enhances the blood pressure and albuminuria lowering response to renin-angiotensin-aldosterone system (RAAS) inhibition. N-terminal pro-brain natriuretic peptide (NT-proBNP) is released in the setting of increased cardiac wall stress and volume overload. We investigated whether NT-proBNP can be used as a marker to predict the response to aliskiren.

Methods: Data were used from 5081 (59.4% of total cohort) patients with available NT-proBNP measurements participating in the ALTITUDE trial, a double-blind randomized-controlled trial comparing the effect of aliskiren 300 mg/day versus placebo as adjunct to standard RAAS inhibition on cardio-renal endpoints in patients with type 2 diabetes with increased cardiovascular or renal risk. Safety outcomes included acute kidney injury and hyperkalaemia. The effect of aliskiren on cardio-renal endpoints was estimated according to tertiles and continuous measures of baseline NT-proBNP levels by Cox proportional hazard regression.

Results: Median NT-proBNP levels at baseline in each tertile were 50, 157, and 534 pg/ml, respectively. During a median follow-up of 2.5 years, 840 (16.4%) patients experienced a cardio-renal event. Aliskiren compared to placebo reduced the risk of the primary cardio-renal endpoint events by 20% (95%CI: 16 to 61) and 2% (-42 to 30) in the two lowest NT-proBNP tertiles, and it increased the risk by 25% (-4 to 96) in the highest NT-proBNP tertile (p-value for trend = 0.009). Similar trends were observed for the cardiovascular and ESRD end points. Effects of aliskiren compared to placebo on safety outcomes were independent of NT-proBNP.

Conclusion: Baseline NT-proBNP may be used as a marker to identify a subgroup of patients more likely to benefit from addition of aliskiren to standard therapy with RAAS inhibition.

Physiologically-based pharmacokinetic modelling of paracetamol and its metabolites during pregnancy

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Introduction: Paracetamol (acetaminophen) is one of the most commonly prescribed drugs for acute pain during pregnancy (Marcus *et al.* 2011). Physiological changes during pregnancy can affect pharmacokinetics (PK) (Pariente *et al.* 2016). The aim of this study was to develop and evaluate a physiologically-based pharmacokinetic model that predicts the PK of paracetamol and its metabolites in women at different stages of pregnancy (p-PBPK).

Methods: Whole body (p)-PBPK models were developed for paracetamol and its metabolites in non-pregnant and pregnant populations using physicochemical and *in vitro* PK parameters from the literature. A PBPK model was built for non-pregnant women using the Open Systems Pharmacology software suite (Dallmann *et al.* 2017). Once this model described the observed PK profile well, it was scaled to pregnancy following a previously described workflow (Dallmann *et al.* 2017). Pregnancy-induced changes in the activity of UDP-glucuronosyltransferase (UGT) and sulphotransferase (SULT) were estimated utilizing a scaling approach combining *in vitro* information on hormonal regulation of gene expression with *in vivo* data on hormone levels in pregnant women taken from the literature. PK profiles were simulated and compared with observed clinical data (Kulo *et al.* 2013)

Results: The PBPK model successfully simulated PK of paracetamol and its metabolites in non-pregnant populations. All predicted paracetamol plasma concentrations were within a 2-fold error range and 85% of the predicted concentrations within a 1.25-fold error range. The p-PBPK model successfully predicted the PK of paracetamol and its metabolites in pregnant populations. All predicted paracetamol plasma concentrations were within a 2-fold error range. Pregnancy-induced changes in clearance were adequately predicted by the proposed scaling approach. The maximum clearance increased mainly due to a 4-fold increase in UGT expression. Expressions of SULT and cytochrome P-450 2E1 were marginally changed (1.04- and 1.08-fold increase, respectively).

Conclusion: Developed p-PBPK model accounts for physiological changes and quantifies in silico drug exposure to paracetamol and its metabolites during pregnancy. The clinical usefulness of this model could be further enhanced by investigating and predicting placental transfer of paracetamol and fetal exposure to paracetamol and its metabolites.

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A 25% HIGHER VANCOMYCIN MAINTENANCE DOSE IS REQUIRED IN HAEMATOLOGIC PATIENTS WITH NEUTROPENIA

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Introduction
Vancomycin is an effective antibiotic agent with antimicrobial activity against amongst others methicillin-resistant *S. aureus*. Also in severe septic haematological patients, vancomycin is generally used as first line agent. There is accumulating evidence that patients with haematological disease require much higher dosages vancomycin than non-haematological patients, and that the increased clearance is likely attributed to the presence of neutropenia. To prevent subtherapeutic drug exposure and inefficacy of treatment, it is important to obtain adequate exposure from the first dose onwards with as little as dose titration necessary. We, therefore, aimed to quantify the effect of neutropenia on the pharmacokinetics of vancomycin.

Aim
The aim of this study was to quantify the effect of neutropenia on the pharmacokinetics of vancomycin using non-linear mixed effect modelling.

Methods
We retrospectively collected data of a matched patient cohort of patients known with 1] haematological disease, 2] solid malignancy, and 3] patients not known with cancer were extracted. Patients were selected if they were treated with vancomycin for ≥2 days and from whom at least 1 vancomycin plasma concentration was available. General patient characteristics, vancomycin dose, and peak and trough plasma concentrations were retrospectively collected. Pharmacokinetic analysis was performed using non-linear mixed effect modelling with neutropenia investigated as a binary covariate on clearance and volume of distribution of vancomycin.

Results
A total of 116 patients were included (39 hematologic patients, 39 solid tumor patients and 38 patients not known with cancer). In total, 742 paired time-concentration observations were available for the pharmacokinetic analysis. Presence of neutropenia showed to significantly (p=0.018) increase the clearance of vancomycin by 23% (95%-CI 3%-48%), whereas it did not impact volume of distribution (p=0.20).

Conclusion
Vancomycin clearance is increased in patients with neutropenia by 23%. Therefore, the vancomycin maintenance dose should be pragmatically increased by 25% in neutropenic patients at the start of treatment. Since the volume of distribution appeared unaffected, no adjustment in loading dose is indicated. These dose adjustments do not rule out the necessity of further dose individualization by means of therapeutic drug monitoring.

LASER SPECKLE CONTRAST IMAGING, THE FUTURE FOR TRP TARGET ENGAGEMENT BIOMARKER ASSAYS

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Background: In the field of pain, target engagement biomarker models provide a valuable asset to support early clinical drug development. In the past, topical application of capsaicin and cinnamaldehyde (CA) have been developed as such target engagement biomarker assays for TRPV1 and TRPA1, respectively [1,2]. The capsaicin model for TRPV1 has already proven its value in the PK/PD modelling of small molecules and biologicals targeting the CGRP pathway.
Both TRP target engagement biomarker models employ laser Doppler imaging (LDI) to measure changes in dermal blood flow (DBF) following capsaicin or CA application. However, recently laser speckle contrast imaging (LSCI) is gaining attention as a superior method to image DBF, with increased spatial and temporal resolution. In this study, we aim to validate our target engagement biomarker models with LSCI.

Methods: Fifteen healthy male subjects with a CA-induced and capsaicin-induced increase in DBF of ≥ 100% compared to baseline were included. Three 10 mm rubber rings were placed on the volar surface of subjects' forearms. A 20 µl topical dose of CA (10%) and capsaicin (1000 µg/20 µl) was applied in the two proximal rings on the right and left forearm, respectively. A 20 µl vehicle (i.e. placebo) dose was applied in the distal ring. Changes in DBF were assessed at baseline and at 10, 20, 30, 40 and 60 minutes post application.
At each timepoint, perfusion was first measured with the LSCI instrument (Pericam PSI system, Perimed) followed by LDI (PeriScan PIM 3 system, Perimed). For LSCI, a scan size of 15,0 x 20,0 cm was chosen, incorporating the three rubber rings in one perfusion image. For LDI, three images were required per arm, using a scan size of 3,0 x 3,0 cm.
The response in DBF was expressed in arbitrary perfusion units (PUs). Correlation between LDI and LSCI data was determined using Pearson's correlation. The area under the curve over a 60 minutes period (AUC_{0-60}) was compared between vehicle and challenge application using dependent T-testing.

Results: An excellent correlation between LDI and LSCI was observed, both for capsaicin (n=15, R^2 = 0,92) and CA (n=15, R^2 = 0,85). As expected, lower DBF values were measured using LSCI since LSCI does not penetrate the skin as deep as LDI. However, the increase in DBF measured with LSCI is sufficient to employ as a target engagement biomarker for possible TRPV1 and TRPA1 channel antagonists since a significant difference ($p < 0.001$) was demonstrated between challenge and vehicle AUC_{0-60}.

Conclusion: In the future, LSCI can be used to measure changes in DBF as a non-invasive method to asses target engagement for potential TRPV1 and TRPA1 antagonists.

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CLINICAL FEASIBILITY OF DRIED BLOOD SAMPLES FOR INFLIXIMAB IN IBD-PATIENTS

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Introduction

Therapeutic drug monitoring (TDM) is important to optimize outcome of infliximab (IFX) treatment in patients with inflammatory bowel disease (IBD). Dried blood samples (DBS) using capillary blood obtained via a finger prick could facilitate TDM, since patients can administer this finger prick themselves at any time and away from the hospital. We investigated the predictive performance and the feasibility of DBS for measuring IFX concentrations in IBD-patients.

Methods

We studied 40 adult IBD-patients receiving IFX therapy according to standard guidelines. From each patient blood was obtained simultaneously via venepuncture and DBS via finger prick by a trained employee at 3 different timepoints (trough, peak, 3-5 weeks after infusion). One week before IFX infusion (timepoint 4), patients performed DBS at home and the sample was directly sent to Sanquin laboratories, Amsterdam, The Netherlands. The corresponding serum concentration for this time point was estimated using Bayesian pharmacokinetic analysis. Capillary blood was obtained by a Mitra microsampling device. A fixed hematocrit (Hct) value of 0.42 was used to convert DBS eluate results to values which can be compared to (venous) serum concentrations. Spearman's correlation coefficient was used to assess correlation and Passing-Bablok regression was performed.

Results

Forty IBD patients were included with median [interquartile range] age: 41 [32-50], albumin: 43 mg/L [41-45], and CRP: 1.3 mg/L [0.4-4.4]. IFX concentrations obtained from the DBS method correlated strongly with serum results from the same patient for IFX trough- and mid-interval concentrations (Spearman's correlation coefficient ≥0.867) and moderately for IFX peak concentrations (Spearman correlation coefficient = 0.624). IFX serum concentrations from the DBS performed at home showed strong correlation with the concentrations obtained by Bayesian analysis (Spearman correlation coefficient = 0.697). At timepoint 4, Passing-Bablok regression showed small structural and proportional bias for samples with 95% confidence interval of the intercept of the regression line not enclosing zero (0.215 – 2.71 mg/L), and with 95% confidence interval of the slope of the regression line not enclosing one (0.524 – 0.933)). No bias was shown at timepoint 1, 2, or 3.

Conclusion

DBS via finger prick can be used for the assessment of serum IFX concentrations. We showed the feasibility of using DBS via finger prick at home. This method greatly facilitates the use of TDM in the treatment of IBD patients using IFX.

AGE-RELATED AND SEX-RELATED DIFFERENCES IN USE AND TOXICITY OF FLUOROPYRIMIDINE-OXALIPLATIN THERAPY FOR COLON CANCER

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Aims**:** A fluoropyrimidine plus oxaliplatin is the standard of care for the adjuvant treatment of high risk colon cancer. Both capecitabine and 5-fluorouracil can be used as chemotherapy backbone, as the clinical efficacy is equal. There has been some speculation that fluoropyrimidine-related toxicity differs between men and women.[1] In addition, elderly patients may experience more treatment-related toxicity than younger patients. In this study, we evaluated 'real world' data from three general hospitals to examine sex-related and age-related differences in use and toxicity of fluoropyrimidine (plus oxaliplatin) therapy in patients with colon cancer.

Methods: Data were collected from adult (age ≥ 18) patients who received adjuvant fluoropyrimidine-based chemotherapy for high risk stage II or stage III colon cancer at three hospitals (HagaZiekenhuis, the Hague; Reinier de Graaf Gasthuis, Delft; or IJsselland Ziekenhuis, Capelle ad IJssel) between 2009 and 2016. The collected data included patient demographics, tumor/disease characteristics, stage, fluoropyrimidine therapy (monotherapy or combination therapy with oxaliplatin, dose, number of cycles), toxicity, comorbidity and clinical outcome. The local Medical Ethical Committee waived the requirement for written informed consent [METC ZWH 2015-064].

Results**:** Data were available for a total of 226 patients; 126 (56%) males and 100 (44%) females. Sixty-five patients (29%) were older than 70 years (at start of treatment). Eighty-one percent of the patients received therapy with capecitabine, nineteen percent of the patients with 5-fluorouracil. Older patients received fluoropyrimidine monotherapy more often than younger patients (52% vs. 4%; P=0.01 (χ^2 test)). Although not statistically significant, women received oxaliplatin less frequently compared to men (20% vs. 16%; P= n.s.). Only 41 patients (18%) completed all planned cycles (fluoropyrimidine plus oxaliplatin). Women were more likely to discontinue therapy than men (88% vs. 76%; P=0.033 (χ^2 test)). Therapy was discontinued because of toxicity or disease progression. The most commonly observed toxicities included hand-foot syndrome, gastro-intestinal disturbances, neuropathy and neutropenia. Toxicity was reported more often in women than in men, however, men tended to suffer from neuropathy more frequently (59% vs. 53%, P= n.s.). Hand-foot syndrome was observed more often in older patients than younger patients (35% vs. 17%), while younger patients suffered from neuropathy more frequently (65% vs. 35%).

Conclusions**:** Capecitabine was the most commonly used fluoropyrimidine. Elderly patients and women received standard-of-care therapy with oxaliplatin less frequently. Only a small number of patients completed their whole treatment course, mainly because of premature oxaliplatin discontinuation. Older patients suffered more from toxicity, except neuropathy. Women suffered more than men from toxicity.

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Short-Term Fasting alters Acetaminophen Metabolism in Humans

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Acetaminophen (APAP) hepatotoxicity is caused by the metabolite N-acetyl-p-benzoquinone imine (NAPQI) formed by Cytochrome P450 (CYP)-mediated metabolism. Preclinical studies have shown that fasting is a predisposing factor for acetaminophen-induced hepatotoxicity. Furthermore, previous studies in humans have demonstrated that short-term fasting can alter the activity of CYP enzymes.

Aims

The aim of our study was to assess the effect of short-term fasting (STF) on the pharmacokinetics of acetaminophen and its metabolites.

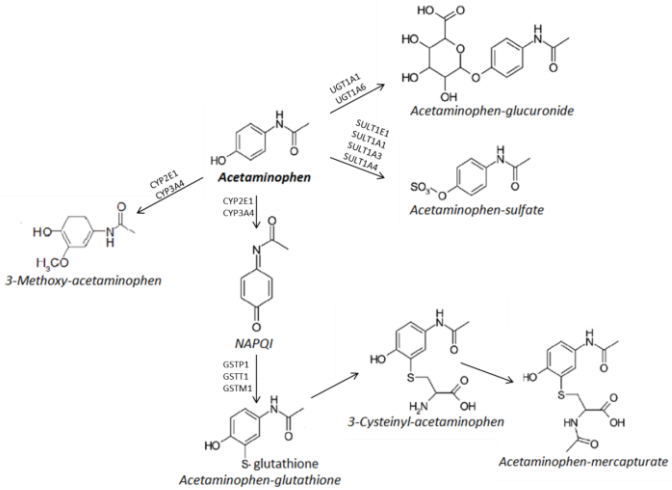
Methods

In a randomized controlled cross-over trial, nine healthy subjects received a single oral administration of 1000 mg acetaminophen after (1) an overnight fast (control) and (2) 36h of fasting. Pharmacokinetics of acetaminophen and its metabolites (acetaminophen-glucuronide (APAP-Glc), acetaminophen-sulfate (APAP-Sul), 3-cysteinyl-acetaminophen (APAP-Cys), acetaminophen-mercapturate (APAP-Cys-NAC) and 3-methoxy-acetaminophen (APAP-OMe) (Figure 1) were analyzed by non-linear mixed-effects modeling (NONMEM). Apparent clearances of acetaminophen (CL_{apap}/F_{apap}) and metabolites ($CL_{met}/(F_{apap} \times f_{met})$) were estimated, where F represents bioavailability and f represents the fraction APAP converted to the metabolite.

Results

Short-term fasting decreased the apparent clearance of APAP ($\Delta CL_{apap}/F_{apap}$ =10%, p<0.01), APAP-Sul ($\Delta CL_{Sul}/(F_{apap} \times f_{Sul})$ =17%, p<0.01), APAP-Cys ($\Delta CL_{Cys}/(F_{apap} \times f_{apap\text{-}Cys})$ =12%, p<0.01) and APAP-OMe ($\Delta CL_{OMe}/(F_{apap} \times f_{OMe})$ =15%, p<0.01) whereas apparent clearance of APAP-Cys-NAC increased by 15% ($\Delta CL_{apap\text{-}Cys\text{-}NAC}/(F_{apap} \times f_{apap\text{-}Cys\text{-}NAC} \times f_{apap\text{-}Cys})$, p<0.01). Fasting did not affect apparent APAP-Glc clearance.

Figure 1: Simplified metabolic pathway of acetaminophen



Conclusions

The study demonstrates that STF increases acetaminophen exposure and the exposure of its CYP-mediated metabolites in humans. Although NAPQI was not determined directly, this implies that fasting increases the risk of acetaminophen induced hepatotoxicity in humans.

Absence of tissue transglutaminase delays amyloid-beta deposition in an Alzheimer's disease mouse model

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Introduction: Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) aggregates in the brain as senile plaques and cerebral amyloid angiopathy. Targeting Aβ aggregates has been one of the major approaches for AD therapies, although these attempts had little to no success so far. Therefore, novel treatment options should focus on blocking the actual formation of neurotoxic Aβ multimers. Evidence is accumulating that the enzyme tissue transglutaminase (tTG) plays a key role in these processes[1]. TTG is abundantly expressed in the human brain and catalyzes post-translational modifications resulting in covalently cross-linked protein complexes[2]. Aβ is a substrate for tTG cross-linking, resulting in stable and neurotoxic Aβ oligomers[3]. As such, tTG activity plays a prominent role in initiating the Aβ cascade in AD. Therefore, *in vivo* absence of tTG in the AD-mimicking mouse model APP23 may provide evidence that tTG is a suitable target in AD to counteract Aβ neurotoxicity.

Methods: Here, we used a crossbreed of the tTG-/- mouse model and the AD-mimicking APP23 mouse model. As a readout, the following analysis were performed: 1)(immuno)histochemical analysis of presence and severity of Aβ pathology, 2) presence of neuroinflammation, 3) mRNA levels of APP and all brain TGs, and 4) amyloid-beta protein analysis.

Results: We found that the absence of tTG in APP23/tTG-/- mice (n=6) resulted in an overall reduction ($p = 0.07$) of Aβ deposits in 12-month-old APP23 mice (n=7), whereas this difference was undetectable in 18-month-old animals (APP23 n=8; APP23/tTG-/- n=10). Analysis of the individual Aβ deposits revealed that the absence of tTG significantly reduced the formation of amyloid plaques ($p=0.03$), small dense plaques ($p=0.049$) and vascular amyloid deposits ($p=0.018$) when compared to aged-matched 12-month-old APP23 mice. This significant difference was undetectable when comparing 18-month-old APP23 mide with APP23/tTG-/- mice. Finally, we found no effects on neuroinflammation associated with the Aβ pathology or beta-pleated sheet formation of the deposited Aβ between APP23 and APP23/tTG-/- mice.

Conclusion: We found that absence of tTG delays the formation of Aβ pathology in the AD-mimicking APP23 mouse model. Therefore, tTG might be a suitable therapeutic target for reducing and/or delaying Aβ deposition in AD.

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EARLY PROTEINURIA LOWERING BY ACE INHIBITION PREDICTS RENAL SURVIVAL IN CHILDREN WITH CHRONIC KIDNEY DISEASE

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Introduction: Proteinuria predicts progression of renal failure in chronic kidney disease (CKD). While pharmacotherapeutic proteinuria lowering was found nephroprotective in adults, the predictive value of early drug-induced proteinuria reduction for long-term renal survival in pediatric CKD is unknown. The goal of this study was to assess the association between the initial antiproteinuric effect of standardized angiotensin converting enzyme (ACE) inhibition and subsequent renal disease progression in children with CKD.

Methods: Data from the Effect of Strict Blood Pressure Control and ACE inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) Trial were analysed. 280 eligible children with CKD stage II-IV (mean age 11.7 years, mean estimated glomerular filtration rate (eGFR) 43 ml/min/1.73m^2, 71% congenital renal malformations) received a fixed dose of ramipril (6 mg/m^2/day) and were subsequently randomized for conventional (<95th percentile for age) or intensified (<50th percentile for age) blood pressure control. Initial proteinuria reduction was assessed from baseline to first measurement on ramipril (at 2.5±1.3 months). A multivariable Cox model was used to estimate the association between initial proteinuria reduction and the risk of reaching a renal end point (50% eGFR decline or end-stage renal disease), which occurred in 80 patients during 5 years observation.

Results: Ramipril therapy lowered proteinuria by a mean of 43.5% (95% CI 36.3 - 49.9%). Relative to proteinuria reduction <30%, 30-60% reduction resulted in a hazard ratio of 0.70 (95% CI 0.40-1.22) and >60% reduction in a hazard ratio of 0.42 (95% CI 0.22-0.79). This association was independent of age, gender, CKD diagnosis, baseline eGFR, baseline proteinuria, baseline blood pressure, and concomitant blood pressure reduction.

Conclusions: The early antiproteinuric effect of ACE inhibition is associated with long-term preservation of renal function in children with CKD. Proteinuria lowering should be considered as an important target in the management of pediatric CKD.

Increasing pazopanib exposure by splitting intake moments

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Background. Pazopanib is an oral anti-angiogenic tyrosine kinase inhibitor, which is indicated for the treatment of advanced renal cell carcinoma and soft tissue sarcoma. Despite the high inter-patient variability in pharmacokinetic exposure (40-70%), pazopanib is still being administered at a fixed dose of 800 mg once daily (QD) (Yu *et al.*, 2017). Pharmacokinetic exposure is linked to efficacy, with patients with a minimum concentration (C_{min}) ≥ 20.5 mg/L having a significantly longer progression-free survival (19.6 versus 52.0 weeks, p = 0.0038) (Suttle *et al.*, 2014). 20-57% of patients do not reach this threshold with the currently used fixed dose of 800 mg QD (Suttle *et al.*, 2014; Verheijen *et al,* 2016). Simulations based on a population pharmacokinetic model show that splitting intake moments into 400 mg twice-daily (BID) leads to an increase in C_{min} and area under the concentration-time curve from time zero to 24 h ($AUC_{0\text{-}24h}$) of 75% and 59%, respectively.

Aim. This study aims to show whether switching patients from a 800 mg QD to a 400 mg BID dose schedule will lead to a significant increase in pharmacokinetic exposure, measured as C_{min} and $AUC_{0\text{-}24h}$.

Methods. We describe a prospective pharmacokinetic cross-over trial in which 10 patients will be included. On day 1 pharmacokinetic sampling occurs at the 800 mg QD dose schedule, after which the intake moments are split into 400 mg BID during one week, followed by pharmacokinetic sampling at day 8. Paired samples t-tests will be used to assess the differences in C_{min} and $AUC_{0\text{-}24h}$ between these two dose schedules.

Results. Currently, six patients are included in the study, of whom five are evaluable for pharmacokinetic analyses. On the 800 mg QD schedule mean C_{min} and $AUC_{0\text{-}24h}$ were 18.5 mg/L (mean percentage coefficient of variation (CV%) 37.5) and 578 mg h/L (CV% 46.0), respectively. Switching to 400 mg BID resulted in an increase of both C_{min} and $AUC_{0\text{-}24h}$ to 39.6 mg/L (CV% 42.5) and 1007 mg h/L (CV% 42.0), respectively.

Conclusion. We demonstrated that splitting intake moments leads to an increase in C_{min} and $AUC_{0\text{-}24h}$, which offers a cost-neutral option to optimize pazopanib treatment for patients with low pharmacokinetic exposure. Five more patients will be included in this study.

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POPULATION PHARMACOKINETIC MODELLING OF FACTOR VIII LEVELS DURING PERIOPERATIVE DOSING OF HAEMATE® P (HUMATE P) IN PATIENTS DIAGNOSED WITH VON WILLEBRAND DISEASE.

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Introduction Von Willebrand factor/factor VIII (VWF/FVIII) concentrate Haemate® P (Humate P) is widely used in the treatment of patients with von Willebrand Disease (VWD). These patients are characterised by a qualitative or quantitative defect of VWF. VWF is essential in primary and secondary hemostasis as it mediates adhesion and aggregation of platelets at sites of vascular injury, and acts as a chaperone protein for FVIII by protecting it from premature clearance. Treatment consists of replacement therapy using clotting factor concentrates in cases of acute or perioperative bleedings aiming to correct the VWF (and FVIII when present) deficiency. Currently, most treated patients reach higher VWF and FVIII levels after administration of clotting factor concentrates than necessary to achieve hemostasis, resulting in a possible risk of thrombosis development and burdening of the national health care budgets. The development of population pharmacokinetic (PK) algorithms could allow more accurate dosing of clotting factors and, using PK-guided dosing, lead to a reduction of consumption of these concentrates without increase of bleeding risk.

Methods VWD patients undergoing minor or major surgery in the Academic Medical Centre Amsterdam, Erasmus university Medical Centre, Leiden University Medical Centre, Radboud University Medical Centre or University Medical Centre Groningen between 2000-2015 and who were treated with Humate P were included. Based on collected FVIII concentrations, population PK modelling was performed using nonlinear mixed-effects modelling. A bootstrap method was used to check the robustness of the PK parameter estimates. Model performance evaluations were based on goodness-of-fit plots and visual predictive checks (VPC).

Results PK parameter estimates are based on 96 adults and 8 children, who underwent 139 and 8 surgeries respectively. PK profiles were best described using a one-compartment model, with a proportional error model. Typical values of the final model for the volume of distribution (Vd) and clearance (CL) were 3.27 L/70 kg and 0.0416 L/h/70 kg respectively. Corresponding inter-individual variability of Vd and CL were 35.1% and 88.4%. Bootstrap results indicate strong robustness of the model. Furthermore, the VPC of the final model, using 1000 replicate simulations of 104 patients, resulted in predictions of the simulated data that were well-matched with the observed concentration-time profiles.

Conclusion Time-courses of obtained perioperative FVIII concentrations after administration of Humate P were described adequately by the developed PK model. This model facilitates PK-guided dosing of Humate P in VWD patients undergoing a minor or major surgical procedure, which potentially results in improvement of quality and cost-effectiveness of care.

EFFECTS OF THE SGLT-2 INHIBITOR DAPAGLIFLOZIN ON GLOMERULAR AND TUBULAR INJURY MARKERS

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Introduction: Sodium-glucose co-transporter 2 (SGLT-2) inhibitors reduce albuminuria and slow kidney function decline in type 2 diabetes. The mechanisms by which SGLT-2 inhibitors lower albuminuria are incompletely understood. The aim of this study was to assess the effects of the SGLT-2 inhibitor dapagliflozin on glomerular, tubular, and inflammatory biomarkers to provide more insight into kidney protective effects of this drug.

Methods: Thirty-one patients with type 2 diabetes and albuminuria ≥100 mg/g were selected from a randomized controlled cross-over trial designed to assess the albuminuria lowering effect of 6-weeks treatment with dapagliflozin 10 mg/day. Renal fractional clearances of IgG to IgG4 and IgG to albumin were used as proxies of glomerular charge and size selectivity. Urinary KIM-1, NGAL, and LFABP were assessed as tubular injury markers; urinary MCP-1 and IL-6 were measured as inflammation markers.

Results: Dapagliflozin decreased albuminuria by 43.9% (95% CI: 30.3 to 54.8%) and as expected there was an initial decline in eGFR by 5.1 (2.0 to 8.1) ml/min/1.73m^2 compared to placebo. Compared to placebo, dapagliflozin did not change glomerular charge or size selectivity index. Dapagliflozin decreased urinary KIM-1 excretion by 22.6% (0.3 to 39.8%; p=0.05) and IL-6 excretion by 23.5% (1.4 to 40.6%; p=0.04) compared to placebo, whereas no changes in NGAL, LFABP, and MCP-1 were observed. During dapagliflozin treatment, the change in albuminuria correlated with changes in eGFR (r=0.36, p=0.05) and KIM-1 (r=0.39, p=0.05). eGFR change during dapagliflozin treatment did not correlate with changes in kidney injury or inflammation markers.

Conclusions: The albuminuria lowering effect of 6 weeks dapagliflozin therapy may be due to a decrease in intraglomerular pressure and/or a reduction in tubular cell injury. Further work is required to elucidate the role of SGLT-2 inhibition in nephroprotection along the entire spectrum of chronic kidney disease.

PREDICTORS OF ALBUMINURIA LOWERING RESPONSE TO DAPAGLIFLOZIN

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Objective: The albuminuria lowering response to sodium glucose co transporter 2 inhibitor dapagliflozin varies between patients. Prior studies have suggested that the degree of renal impairment is a potential determinant of individual responses to renoprotective drugs. The aim of this study was to determine whether the rate of eGFR decline in the two years prior to initiation of dapagliflozin (eGFR slope), the actual eGFR level, degree of proximal tubular injury or inflammation at start of dapagliflozin therapy determines the individual albuminuria lowering response.

Design: Double-blind, randomized, placebo controlled crossover trial. Each patient was randomized to 6-week treatment periods with dapagliflozin (10mg/day) or placebo in random order with a 6-week wash out in between.
elevated albuminuria.

Setting: Outpatient clinic of the Department of Internal Medicine Ziekenhuis-Groep Twente, Almelo/Hengelo, the Netherlands. And retrospective eGFR data collected from patient information system.

Main Outcome Measurement: Percentage difference in change in 24-hour urinary albumin excretion from baseline during placebo and dapagliflozin treatment.

Patients: A total of 33 patients was enrolled (mean age 61, 24,4% female, median 24h UAE of 470 mg/24h).

Results: Dapagliflozin reduced 24 h UAE by 36.2% (95% CI, 22.9 to 47.2; $P < .001$). This effect was consistent in subgroups defined by eGFR slope, baseline eGFR or albuminuria, and baseline values of Kidney Injury Molecule-1, MCP-1, or Interleukin-6 values (Table).

Conclusions: Our data suggest that the degree of renal impairment does not determine the albuminuria lowering response to dapagliflozin in patients with type 2 diabetes and

GUIDELINE ADHERENCE FOR LABORATORY MONITORING OF AMBULATORY PATIENTS TREATED WITH LITHIUM: A RETROSPECTIVE FOLLOW-UP STUDY IN THE NETHERLANDS

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Aims
Laboratory monitoring of patients using lithium is important to prevent harm and to increase effectiveness. The aim of this study was to determine guideline adherence overall and within subgroups for laboratory monitoring of patients using lithium.

Methods
All patients having at least one dispensing for lithium for six months from January 2010 to December 2015 were identified retrospectively using data from the Dutch PHARMO Database Network. Monitoring was defined as adherent to the Dutch Multidisciplinary Clinical Guideline Bipolar Disorders if lithium serum levels and creatinine were measured at least every six months, and thyroid stimulating hormone (TSH) at least annually during lithium use.

Results
Data were analyzed of 1583 patients with a median duration of seven 6-month periods of lithium use. Patients were monitored for lithium serum levels in 65% of the time in 6-month periods and in 73% for creatinine. TSH was monitored in 73% of years of lithium use. Little over one-third (36%) of patients were monitored adherent to the guideline for all three parameters during total follow-up. Especially males, middle-aged patients, patients using <5 medications, patients receiving prescriptions solely from general practitioners, patients without interacting co-medication, and patients without other days with laboratory measurements were less

Conclusion
A considerable number of patients were not monitored adherent to the guideline. To ensure patient safety and effectiveness of lithium treatment, it is important to understand why this is the case.

RNA-sequencing of tumor-educated platelets, a novel biomarker for blood-based sarcoma diagnostics.

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Introduction Sarcoma is a rare and heterogeneous group of malignancies arising from soft tissues. The potential of development of metastases is high and methods for diagnostics are poor. Blood-based liquid biopsies may overcome this clinical problem. Recently, it has been shown that platelets play a major role in tumor microenvironment. Tumor-educated platelets (TEP) can ingest circulating mRNA and they show specific splice events in response to external stimuli. This leads to a highly dynamic mRNA repertoire with potential applicability for cancer diagnostics (Alix *et al*, 2016; Calverley *et al*, 2010*).*
Aim To evaluate the potential of TEPs for blood-based diagnostics and monitoring of patients with sarcoma.
Methods We included active sarcoma patients and former sarcoma patients (cancer free for at least 3 years). RNA-sequencing data was mapped to the human genome, and quantified read counts were subjected to ANOVA statistics and a support vector machine (SVM) classification algorithm. Highly correlating mRNAs of a sarcoma subtype tumor (liposarcoma, leiomyosarcoma, gastrointestinal stroma or 'miscellaneous') were compared to all other tumor subtypes and to healthy donors (HD) to find a sarcoma specific signature.
Results We successfully sequenced the spliced platelet RNA collected from 25 sarcoma patients, 15 former sarcoma patients, and 61 age- and gender-matched healthy donors. Differential splicing ANOVA analysis indicated a distinctive platelet RNA expression pattern of 189 genes (FDR<0.05) in sarcoma (n=15) compared to non-sarcoma; [-HD (n=6) and former sarcoma patients (n=9)]. Development of a machine learning classification algorithm for the blood-based diagnosis of sarcoma reached an accuracy of 85% in the 20-samples sized validation cohort (AUC: 0.84, p<0.001). Analysis of a combined healthy donors plus former sarcoma patients cohort versus sarcoma patients indicated that the platelet RNA of cancer-free patients regresses towards those of healthy donors.
Conclusion Our data indicates that TEP RNA-based liquid biopsies might enable for blood-based sarcoma diagnostics. This technique could potentially be used for the monitoring of tumor recurrence in post-operative sarcoma patients. Thus far, the number of samples analyzed remains small, and potential bias introduced by the two institutes of sample origin needs to be taken into account.

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A pharmacokinetic justification for continuous dosing of flucloxacillin in non-critically ill patients

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Introduction: Flucloxacillin is approved for intermittent dosing (SmPC flucloxacillin). For some patients continuous dosing can have practical benefits. Furthermore, as the efficacy of flucloxacillin is time-dependent, continuous infusion is considered more effective (Drusano, 2004). Flucloxacillin is assumed to be highly protein bound, but this may vary in practice. Furthermore, at high exposure, neurotoxicity may occur (Imani, *et al* 2017). As it stands, the optimal flucloxacillin dosage for continuous infusion is unknown. The primary objective was to determine the optimal dose for continuous flucloxacillin infusion in non-critically ill patients.

Methods: 30 patients, age ≥18, receiving intravenous flucloxacillin were included. Exclusion criteria were: admission to the ICU and pregnancy. An integrated population PK model for total and unbound flucloxacillin concentrations was developed. A Monte-Carlo simulation was performed to quantify pharmacokinetic target attainment for typical S aureus isolates and for development of toxic exposure for different dosing regimens, based on unbound concentrations.

Results: In our population, protein binding varied from 64,4-97,1% and albumin explained variability in the unbound fraction. A dosage of 4 gram/24 hours was sufficient for 93,4% of the population to obtain a target of 100%fT>MIC 0,5 mg/L (figure 1). In 88,9% of the population a dosage of 12 gram/24hours was sufficient for a MIC of 2 mg/L, being the clinical breakpoint for S. aureus. The probability of toxic exposure was 0,2, 2 and 18% for a dosage of 4, 6 and 12gram/24 hours.

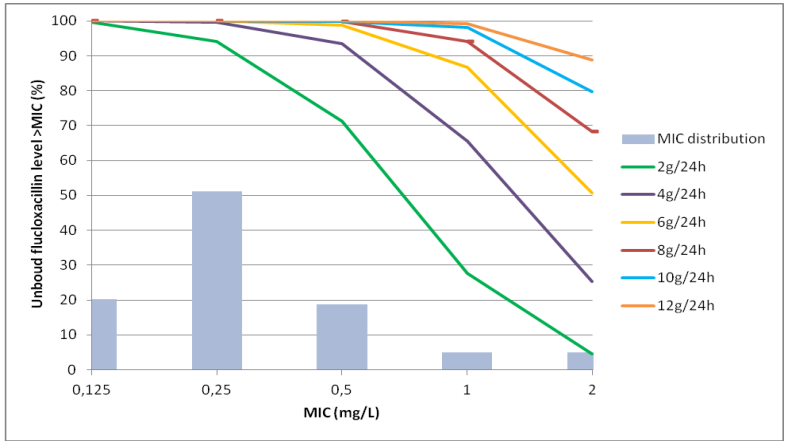

Figure 1: Predicted percentage target attainment and MIC distribution of S. aureus.

Conclusion: Our study showed that 4gram/24hours is sufficient to treat infections caused by the most common MICs found for S. aureus in non-critically ill patients. In doses >12 gram/24h, toxic exposure is likely. In case of poor treatment response or toxicity, we advice to alter the dosage based on unbound flucloxacillin levels.

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Influence of Enzalutamide on Cabazitaxel Pharmacokinetics; a Drug-Drug Interaction Study in Metastatic Castration Resistant Prostate Cancer (mCRPC) Patients

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Background: Cabazitaxel and enzalutamide are effective monotherapy options for men with metastatic castration-resistant prostate cancer (mCRPC). The potential enhanced efficacy of the combination of taxanes with AR-targeted agents, e.g. enzalutamide and abiraterone, is currently being explored.(1) However, since enzalutamide induces the CYP3A4 enzyme and taxanes are metabolized by this enzyme, a potential drug-drug interaction is to be expected. Recently, Morris *et al*, reported a decreased docetaxel concentration by 12% during a short period of co-treatment with enzalutamide.(2) In this pharmacokinetic trial we investigated the influence of long-term enzalutamide on cabazitaxel pharmacokinetics.

Methods: We performed a cross-over study in 14 evaluable mCRPC patients who were scheduled for treatment with cabazitaxel Q3W (25 mg/m^2). Patients were studied for three consecutive cabazitaxel cycles. PK-sampling (over 24h) was conducted on day 1 of each cycle. From day 7-8 of the first cycle until day 7-8 of the third cycle, enzalutamide (160 mg/day) was administered concomitantly. Primary endpoint was the difference in geometric mean area under the curve ($AUC_{0\text{-}24h}$) between the first cycle (cabazitaxel without enzalutamide) and third cycle (cabazitaxel with enzalutamide). Secondary endpoints included safety parameters and PSA response.

Results: A potential clinically relevant 22% (95%CI: 9–34%, p=0.005) reduction in cabazitaxel exposure was found with concomitant enzalutamide use. The geometric mean $AUC_{0\text{-}24h}$ of cabazitaxel was 234 ng*h/mL (95%CI 209-261 ng*h/mL) in cycle 1 and 181 ng*h/mL (95%CI 150-219 ng*h/mL) in cycle 3. The combination of enzalutamide and cabazitaxel did not result in excessive toxicity, while PSA response was promising in these heavily pre-treated patients.

Conclusion: We found a significant decrease in cabazitaxel exposure when combined with enzalutamide. In an era of clinical trials on combination strategies for mCRPC, it is important to be aware of clinically relevant drug-drug interactions between these agents. Recent study results support the use of a lower standard cabazitaxel dose of 20 mg/m^2.(3) The clinical relevance of this interaction may be substantial, since the addition of enzalutamide may result in sub-optimal cabazitaxel exposure. We stimulate clinical studies on this combination, but investigators should be aware of the demonstrated drug-drug interaction.

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Dynamics of the QTc-interval during use of intravenous ciprofloxacin in ICU patients.

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Aims: Prolongation of the QT interval is an adverse effect associated with the use of fluoroquinolones. It is unknown whether or not QTc-prolongation is more pronounced at Cmax. In addition, intravenous administration in critically ill patients might increase the QTc-prolonging effect. Therefore, the aim of this study was to assess the dynamics of the QTc-interval over a 24-hour time interval during intravenous ciprofloxacin in ICU patients.

Methods: An observational study was performed in ICU patients (≥ 18 years) admitted to the Erasmus University Medical Centre receiving ciprofloxacin intravenously. Continuous ECG data were collected from 2 hours before to 24 hours after the first administration. QT-analyses were performed using the high-end holter software Synescope™. Intraindividual changes were analysed using the paired Student's t-test, and the course of the QTc-interval was compared to a control group without QTc-prolonging drugs using the independent Student's t-test.

Results: A total of 30 patients (n = 15 index, n = 15 control) were included for analysis. The mean QTc-interval during administration (405.7 ± 21.6ms) did not statistically significantly differ from baseline (400.4 ± 29.7ms; p = 0.075). No peak QTc-time was found to be related to ciprofloxacin administration. There was no significant difference between the mean QTc-interval of the ciprofloxacin group (403.7 ± 28.9) and the control group (399.2 ± 21.6ms; p = 0.419) (Fig. 1).

Conclusion: Intravenous ciprofloxacin does not have a significant effect on the QTc-interval over a 24-hour time interval in ICU patients.

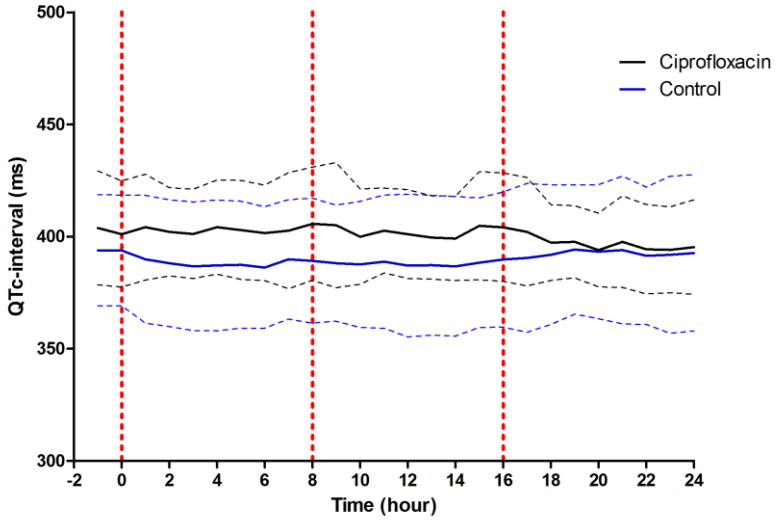

Fig 1. The dynamics of the mean QTc-interval of the ciprofloxacin and control group. *Dotted lines: administration of ciprofloxacin : 3dd400mg.*

NEUTROPENIA AND EXPOSURE TO DOCETAXEL IN METASTATIC CASTRATE-RESISTANT PROSTATE CANCER PATIENTS COMPARED TO OTHER SOLID TUMORS: A META-ANALYSIS.

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Introduction Docetaxel is a chemotherapeutic agent, currently approved for the treatment of various solid tumors, e.g. breast cancer, lung cancer and metastatic castration-resistant prostate cancer (mCRPC). Variability in exposure to docetaxel has been reported, leading to variability in response and toxicity [1]. Particularly, lower incidences of grade 3/4 neutropenia were reported for mCRPC patients in literature, indicating a lower exposure to docetaxel in this patient group. A previous study has reported a 2-fold lower area under the curve (AUC) in mCRPC patients compared to non-castrated prostate cancer patients [2]. Therefore, the aim of this study was to i) evaluate the incidence of neutropenia in patients with mCRPC vs. other solid tumors in a clinical cohort and ii) determine if exposure in mCRPC patients is lower compared to patients with other solid tumors based on literature data.

Methods i) Patients treated with docetaxel (2006-2016) at the Netherlands Cancer institute and the MC Slotervaart were evaluated. Grade 3 (severe) or grade 4 (life-threatening) neutropenia was included as a dichotomous variable (yes/no). Logistic regression was performed to determine if mCRPC was associated with a lower odds of experiencing grade 3/4 neutropenia. ii) Meta-analysis: a PubMed search was conducted. Clinical trials reporting an $AUC_{0\text{-}inf}$ for docetaxel were included in the meta-analysis. AUCs and standard deviations were dose normalized to 75 mg/m^2. Subsequently, a random effects model was used to determine the mean $AUC_{0\text{-}inf}$ value. Bioanalytical method, AUC calculation method and last measured time point were included as covariates, in addition to mCRPC.

Results i) In total, 812 patients were included in the neutropenia analysis. Logistic regression was corrected for dose and demonstrated that patients with mCRPC had a 2.3-fold lower odds of developing grade 3/4 neutropenia compared to patients with other solid tumors (odds ratio [95% confidence interval] 0.46 [0.31-0.90]). ii) The meta-analysis included 19 cohorts from 13 trials and showed that patients with mCRPC had a 1.8-fold lower mean AUC compared to patients with other solid tumors ($p<0.0001$). In the final model residual heterogeneity was high (I^2 = 90.0%), indicating that the differences in AUCs might be due to uncharacterized or unexplained underlying factors. Therefore, a sensitivity analysis was performed with a higher sampling error per cohort, which reduced the heterogeneity to moderate (I^2 = 40.0%). In this analysis, mCRPC remained a significant determinant of having a lower exposure to docetaxel.

Conclusion Patients with mCRPC, treated with docetaxel, have a lower incidence of neutropenia compared to patients with other solid tumors. This is expected to be a result of lower exposure to docetaxel, confirmed by our meta-analysis, demonstrating lower AUCs in mCRPC patients compared to patients with solid tumors. Further studies are required to elucidate the mechanisms and clinical impact behind our observations.

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SCREENING AND QUANTIFICATION METHOD FOR ANTIHYPERTENSIVE AGENTS USING LC-MS/MS: A VALUABLE TOOL FOR MEDICATION ADHERENCE ASSESSMENT

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Introduction and aim

Adherence to antihypertensive agents is of importance to attain blood pressure targets and thereby prevent short and long term cardiovascular events. Recently, LC-MS/MS has gained interest for compound screening in medication adherence assessment. Therefore, we explored screening and semi-quantification of antihypertensive agents in serum using LC-MS/MS in patients with alleged therapy-resistant hypertension.

Methods

A fast and efficient sample preparation was designed based on protein precipitation in combination with LC-MS/MS analysis. 48 compounds and metabolites were included in the screening assay covering over 95% of antihypertensive agents available in Europe. To detect non-adherence, the lower limit of quantification (LLOQ) concentrations, selected for each compound, were based on mean population trough concentrations (PTC). LLOQ and linearity were validated according to EMA guidelines. Next, the method was designed as semi-quantitative assay aiming for optimal accuracy and precision for all compounds. Matrix effects, autosampler- and room temperature stability were investigated. After analytical validation, the assay was clinically tested using samples drawn from patients with resistant hypertension. Patients and physicians were unaware of adherence assessment.

Results

LLOQ and linearity for all compounds complied with EMA guidelines. Furthermore, for 95% of the antihypertensive agents, the LLOQ was lower or equal to the PTC. Moreover, for 44% of the compounds the LLOQ was ≥50 times lower compared to PTC. Only for lercanidipine and captopril the PTC was lower compared to LLOQ. Canrenone, captopril and nefidipine could only reported as positive/negative due to compound instability. Analysis of patients samples showed that no or extremely low supratherapeutic concentrations were retrieved of at least half of prescribed antihypertensive medication in 31 (32%) patients. The median number of antihypertensive agents detected was two while the median number prescribed was four.

Conclusion

A screening and semi-quantification for 48 antihypertensive agents in serum using LC-MS/MS was successfully developed fulfilling predetermined qualifications and semi-quantification validation requirements. Analysis of samples from patients with alleged resistant hypertension indicated non-adherence in a large number of patients. In conclusion, serum screening for antihypertensive drugs with subsequent semi-quantification with LC-MS/MS is a valuable tool for a detailed assessment of adherence in patients with therapy-resistant hypertension.

ASSOCIATION OF FLUDARABINE EXPOSURE AND SURVIVAL AFTER ALLOGENEIC CELL TRANSPLANTATION: RETROSPECTIVELY ESTIMATED AND PROSPECTIVELY SIMULATED

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Introduction: Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for a variety of malignant and benign hematological disorders. Fludarabine combined with busulfan and rabbit-anti-thymocyte globulin (rATG) is a commonly used conditioning regimen for HCT. A dramatic influence of busulfan- and rATG- drug exposure on HCT outcomes has recently been found, but for fludarabine this influence is unknown.
Methods: A pharmacokinetic (PK) model for the circulating metabolite of fludarabine-phosphate (F-ara-A, hereafter referred to as Flu) was developed. Subsequently, a retrospective cohort analysis was performed on patients receiving 160 mg/m^2 Flu combined with busulfan targeted to a cumulative area under the curve (AUC) of 90 mg*h/l. In these patients, Flu AUC was quantitatively linked to outcomes of HCT using parametric survival models. Outcomes of interest were: graft-failure, non-relapse mortality (NRM), and relapse. The Flu AUC corresponding to a minimal probability of having any of these events, was considered the optimum. Next, alternative dosing strategies to attain this target were evaluated in clinical trial simulations (CTS) The aim of CTS was 1) to evaluate the expected survival gain of alternative dosing based on either the developed PK-model or therapeutic drug monitoring (TDM) and 2) to calculate the power of clinical trials comparing 160 mg/m^2 dosing to the alternative dosing strategies. For this, a database was used of patients in the UMC, transplanted for leukemia or lymphoma. Flu PK and subsequent event probabilities were simulated after each different dosing regimen, with the previously developed PK and survival models respectively. In CTS, patients were randomized to receive either 160 mg/m^2, Flu PK-model-based dosing, or TDM-based dosing. 80 patients were included per dosing arm. Events were simulated to calculate event probabilities and p-values per dosing arm.
Results: The incidence of NRM increased with increasing Flu AUC ($p<0.001$), and more graft failures were observed at lower AUC ($p=0.03$). Flu AUC had no significant relationship with relapse ($p=0.63$). This resulted in a minimal event probability at a cumulative Flu exposure of 20 mg*h/L. In the trial simulations, NRM cumulative incidence decreased from 24% to 13% and 9% in the PK-model-based and TDM-based-dosing arm, respectively. Relapse incidence increased slightly after individualized dosing, as more patients were at risk due to lower NRM. Graft failure was similar among treatment arms. The estimated power for NRM was 54% and 78% for the comparison between original dosing and PK-model-based or TDM-based dosing respectively.
Conclusion: These results indicate that a substantial survival benefit can be achieved by individualizing the Flu dose prior to HCT. Furthermore, prospective evaluation is feasible in a clinical trial, when TDM is compared to original dosing.

Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia. Cochrane Review update. *Submitted.*

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Purpose

To evaluate whether withdrawal of antipsychotic agents is successful in older people with dementia in primary care or nursing home settings. This is an update of the Cochrane review published in 2013.

Methods

We searched the literature sources until 11 January 2018. We included all randomised, controlled trials comparing an antipsychotic withdrawal strategy to continuation of antipsychotics in participants with dementia who had been treated with an antipsychotic drug for at least three months.

Results

Ten studies involving 632 participants were included in the review. One new trial (n = 19) was added in this update. Reported data are predominantly from studies at low or unclear risk of bias. We found low quality evidence from nine trials with 575 randomised participants that used a proxy outcome for overall success of withdrawal. Based on assessment of seven studies, discontinuation may make little or no difference in study completion between groups. However, a pilot study of participants with psychosis or agitation/aggression who had responded to haloperidol, time to relapse of a worsening of the symptoms psychosis and and agitation/aggression was shorter in the discontinuation group. Another trial including participants with psychosis or agitation/aggression who had responded to risperidone for four to eight months, reported that discontinuation led to an increase in the Neuropsychiatric Inventory (NPI)-core score of 30% or greater. For the outcome behavioural and psychological symptoms measured in seven studies using various scales, discontinuation may make no difference between groups (7 trials, n = 519, low quality evidence). However, a subgroup analysis in one study suggests that in participants with less severe NPS (NPI score ≤14) discontinuation may improve outcome in terms of agitation (a subscale of the NPI). Two other subgroup analyses suggest that participants with more severe NPS (total NPI >14) may benefit from continuing antipsychotic treatment. Evidence from five trials showed that discontinuation may have little or no effect on adverse events (5 trials, n = 381, low quality evidence). Discontinuation may have little or no effect on quality of life (2 trials, n = 119, low quality evidence). Five trials found that discontinuation may have no impact on cognitive function (5 trials, n = 365, low quality evidence). It is unclear whether discontinuation of antipsychotics leads to a decrease in mortality at short or long-term follow-up (2 trials, n = 275, very low quality evidence).

Conclusions

There is low quality evidence that antipsychotics may be discontinued in older participants with dementia who have been taking them for at least three months and may have little or no important effect on behavioural and psychological symptoms

Evaluation of a continuous infusion protocol for vancomycin: checking protocol adherence and efficacy

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Introduction It is known that dosing vancomycin is difficult, due to the interpatient variations and the risk of toxic and sub-therapeutic levels. No optimal dosing protocol has been yet found. In 2014, the Canisius Wilhelmina Hospital created their own detailed continuous infusion (CI) protocol, based on a loading and daily dose. Still, when using this protocol, several adaptations of the dose are needed, before reaching adequate serum levels.

Aim to perform an evaluation of this protocol, by: (i) determining the protocol adherence; (ii) checking protocol efficacy in both adherence group and non-adherence group and (iii) defining patient factors in the adherence group, associated with insufficient vancomycin levels.

Methods Patients were enrolled, if treated with the vancomycin CI protocol between February 2014 and May 2017. Information was extracted from the patient files and the pharmacy records. Serum vancomycin concentration was taken daily and an adequate concentration was defined as 20-25 mg/L. Differences were assessed using the Chi-squared test, Fisher's exact test, unpaired T-test or Mann-Whitney U test.

Results 88 patients were included. Thirty-six patients received protocol-care up to the first serum concentration (41% of total) and 25 up to the second serum level (29%). In the correctly dosed patients, 92% of the first serum concentrations were below range and 48% of the second. Younger age was associated with insufficient vancomycin levels (68 versus 80 years, p=0.044).

Conclusion The protocol adherence was low and correct application of the protocol resulted in low serum concentrations. Thus, protocol adherence needs to be improved and higher doses are needed to improve the protocol efficacy.

VALIDATION OF DRIED BLOOD SPOT SAMPLING FOR PHARMACOKINETIC RESEARCH AND THERAPEUTIC DRUG MONITORING OF ANTI-TUBERCULOSIS DRUGS IN CHILDREN

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Background Dried blood spot sampling (DBS) for pharmacokinetic (PK) studies and Therapeutic Drug Monitoring has unique advantages over venous sampling, including decreased patient burden. We aimed to clinically validate a DBS method for first-line anti-TB drugs in children, and directly implement DBS to assess PK parameters.

Methods Children were treated according to the revised WHO dosing scheme for children. A 4-point PK curve was performed with DBS and conventional venous sampling for rifampicin, pyrazinamide and ethambutol. Passing-Bablok regression and Bland-Altman plots were used to assess agreement between DBS and plasma concentrations. The percentage of patients attaining (adult) population PK values for C_{max} (rifampicin 8-12; isoniazid 3-6 (only in plasma); pyrazinamide 20-50 and ethambutol 2-6 mg/L) and AUC_{0-24h} was calculated.

Results Fifteen patients completed PK sampling. After use of a conversion factor, Passing-Bablok regression showed no significant proportional or systematic bias. Bland-Altman plots showed that 95% of the ratios of the DBS predicted:observed plasma concentrations lied between 0.6-1.4 for rifampicin, 0.5-1.6 for pyrazinamide and -0.4-2.8 for ethambutol (ideally, this ratio is 1). Good predictive performance was observed for rifampicin and pyrazinamide but not for ethambutol. PK parameters (geometric means) were: isoniazid C_{max} 3.1 mg/L, AUC_{0-24h} 12.7 mg*h/L ; rifampicin C_{max} 5.5 mg/L, AUC_{0-24h} 25 mg*h/L; pyrazinamide C_{max} 40 mg/L, AUC_{0-24h} 519 mg*h/L and ethambutol C_{max} 2.3 mg/L, AUC_{0-24h} 15 mg*h/L. C_{max} target attainment was 62.5% for isoniazid, 25% for rifampicin, 100% for pyrazinamide and 75% for ethambutol.

Conclusion A DBS method for rifampicin and pyrazinamide was clinically validated and successfully used for PK parameter analysis. DBS sampling of ethambutol was associated with too much variability. Despite higher doses, still only 25% of the population reached average targeted adult rifampicin exposures. New paediatric formulations should be made available and procurable worldwide as soon as possible.

CIRCULATING TUMOR CELLS ANALYSIS IN CEREBROSPINAL FLUID IN PATIENTS WITH EPITHELIAL TUMORS 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: 44-67% at first LP, increasing to 84-91% upon second sampling. To improve CSF diagnostics, enumeration of Circulating Tumor Cells (CTC) by immunoflow cytometry has been developed.

Aim

To determine the sensitivity and specificity of a diagnostic immunoflow cytometry method in CSF in patients with epithelial tumors with suspected LM.

Methods

We developed an epithelial cell adhesion molecule (EpCAM) based CTC assay to detect CTC in the CSF. We tested the performance of this assay versus CSF cytology in CSF in a prospective study in 55 patients with solid tumors with a clinical suspicion of LM but a non-confirmatory MRI.

Results

In patients with solid tumors with a clinical suspicion of LM but a non-confirmatory MRI cytology had a sensitivity of 68% (48-83) (95% CI) and a specificity of 100% (84-100). At a cut-off value of >1 CTC/ml the CTC assay had a sensitivity of 93% (76-99) and a specificity of 100% (83-100). The CTC and cytology results are depicted in table 1.

Table 1. CTC and cytology results.

cytology- CTC-	cytology+ CTC-	cytology- CTC+	cytology+ CTC+	final diagnosis
25	0	0	0	no LM
1	0	9	19	LM
1	0	0	0	suspected LM*
0-0.6	0-0.2	2.2-65	34-3550	CTC/ml range

*Based on clinical symptoms and MRI.

Conclusion

The EpCAM-based CTC assay can identify CTC in CSF in patients with LM with a negative cytology.

Tobramycin and vestibulotoxicity: 4 cases

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Introduction - In a short period of time 4 patients in our hospital suffered from vestibulotoxicity after treatment with tobramycin intravenously (IV). Three of them were cystic fibrosis (CF) patients, one patient suffered from Primary Ciliary Dyskinesia (PCD). Vestibulotoxicity is described as a 'common' (≥1/100 to <1/10) adverse reaction of tobramycin, however in our hospital none of the CF physicians had observed this adverse effect of tobramycin in the past years. Since vestibulotoxicity is a serious adverse reaction, which can be irreversible, a team was established to investigate if there was a cause for the toxicity and whether the quality of care had been inadequate. During the investigation, the hospital decided not to use tobramycine due to the severity of the side effect and to prevent occurrence of new cases.

Description of cases - From October 2015 till April 2016 a total of 26 CF patients were treated in the Academic Medical Centre, Amsterdam, with tobramycin according to valid guidelines. Three of them and one patient with PCD suffered from vestibulotoxicity and they experienced acute dizziness which disrupted their daily activities. Two patients experienced irreversible bilateral vestibular hypofunction and the other two unilateral loss of the right labyrinth, with decreasing of dizziness over time.

Results of the investigation - For all four patients the indication for the use of tobramycin, prescriptions and doses were correct and other possible causes (co-medication, co-morbidity) could not be demonstrated.
Therapeutic drug monitoring was performed on a regular basis by the hospital pharmacy on validated equipment. Peak and through concentrations were within the ranges of 25-35 mg/L and <0,5 mg/L, respectively. There were no deviations in the medication and supply chain. Preparation protocols were requested from the company who prepared the IV medication for use at home and no deviations were found. The manufacturer of tobramycin (Centrafarm) and Lareb (Dutch Adverse Reaction Centre) were informed and asked if there had been more reports of this adverse reaction in 2015 and 2016. Only one report (2011) was known by Lareb.

Discussion - The conclusion of the investigation was that there was no apparent cause of the vestibulotoxicity in these four patients and that the simultaneous occurrence in our hospital was not due to a lack in quality of care. Therefore vestibulotoxicity in CF patients can possibly be marked as a type B adverse effect of tobramycin.
Symptoms of dizziness and balance disorders should be recognized by patients and care-takers (e.g. physicians and nurses) in an early stage, so additional diagnostics can be done to prevent further deterioration. In our hospital treatment of patients that did not experience symptoms with tobramycin was restarted, now with extra alertness for those symptoms.

POPULATION PHARMACOKINETICS OF ENANTIOMER SPECIFIC INTRAVENOUS KETOROLAC ACROSS THE HUMAN-AGE SPAN

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Introduction: Ketorolac tromethamine (ketorolac) is a non-steroidal anti-inflammatory drug to treat mild to moderate pain. The drug consists of S- and R enantiomers. Since the pharmacological effect is primarily attributed to the S-enantiomer, the aim of this study was to develop an enantiomer specific population pharmacokinetic (PK) model, to characterize the PK of ketorolac over the human-age span, using published datasets.

Methods: The pooled dataset included 485 plasma samples from 80 patients (median age 23 [range 0.216-49] years and median body weight 56 [range 5.36-99] kg). All received a single racemic ketorolac dose (median dose 0.34 [0.15-0.78] mg/kg). PK model building and evaluation was conducted using nonlinear mixed-effects modelling (NONMEM 7.3). One, two and three compartment models were tested for S- and R-ketorolac. Body weight and age were tested as covariates on model parameters in a linear and power function with a constant exponent or with a variable body weight-dependent exponent.

Results: Given the different sampling schemes, S-ketorolac PK was best described with a two-compartment model for infants and a three–compartment model for adults. R-ketorolac PK was best described with a two-compartment model in both populations. Body weight was a covariate on most of the PK-parameters; for both enantiomers. CL increased exponentially with body weight (exponent 0.764 and 0.787). V1 increased exponentially with bodyweight (exponent 0.572) for S-ketorolac and linearly for R-ketorolac. For S-and R-ketorolac the population parameter values [relative standard error] for CL were 5.4 L/h/56kg [26%] and 1.24 L/h/56kg [8%] respectively, and V1 was 11.1 L/56kg [25%] and 3.47 L/56kg [6%] respectively.

Conclusions: Differences in enantiomer specific PK for ketorolac should be considered when deriving dosing regimen based on a racemic ED50 target.

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Setting the stage for evidence-based model-informed dosing of intravenous paracetamol in older people

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Introduction: Paracetamol is the most commonly used analgesic in older people. In this heterogeneous group, paracetamol is mainly dosed according to empirical dosing guidelines that are mostly based on clinical experience or extrapolation from studies in younger adults. As physiological changes occur with increasing age, the pharmacokinetics (PK) of paracetamol can be influenced. Therefore, the aim of this research was to describe the PK of paracetamol in healthy older people to optimize paracetamol dosing.

Methods: A population PK-analysis, using NONMEM 7.2, was performed based on 601 concentrations of paracetamol from 30 healthy older people (median age 77.3 years, range [61.8-88.5] and body weight 79 kg [60-107]). All received an intravenous paracetamol dose of 1000 mg (over 15 minutes) after elective knee prosthesis operation (Liukas *et al.* 2011). Simulations of standardized dosing regimen (1000 mg every 6 or 8 hours) were modelled to identify the obtained target concentration. Based on the final model, a dosing advice is proposed around a target concentration of 10 mg/L.

Results: A 2-compartment PK-model for paracetamol best described the data. Volume of distribution of paracetamol increased with body weight (population mean 54.9 L/79k g). Clearance (population mean 17 L/h) was not influenced by any covariate. Simulations of the standardized dosing regimens (1000 mg) resulted in a steady state concentration of 8.2 mg/L and 5.5 mg/L, for q6h and q8h respectively, indicating dose increases are appropriate to reach effective concentrations.

Conclusion: A PK model for paracetamol in healthy older people was identified. The resulting steady state simulations for the standardized dosing regimens suggest that the majority of the population remains under the desired target concentration. This population PK model can be used to develop evidence-based dosing of paracetamol in older people.

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ENZYME LINKED IMMUNOSORBENT ASSAY FOR THE QUANTIFICATION OF NIVOLUMAB AND PEMBROLIZUMAB IN HUMAN SERUM AND CEREBROSPINAL FLUID

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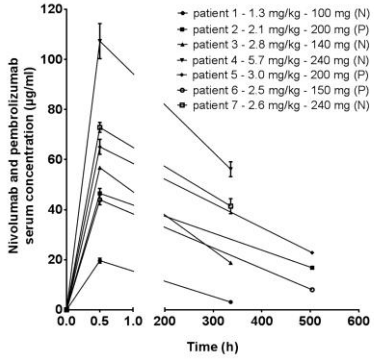
Introduction: Immunotherapy with monoclonal antibodies targeting the programmed-death-1 (PD-1) receptor has become standard of care for an increasing number of tumour types. Assays which accurately determine drug concentrations may help to optimize anti-PD-1 therapy by enabling individualized treatment strategies and by gaining better understanding of pharmacokinetic– pharmacodynamic relationships. Here, we report an enzyme linked immunosorbent assay (ELISA) capable of measuring nivolumab and pembrolizumab concentrations in serum and cerebrospinal fluid (CSF).

Methods: The ELISA was developed based on the specific capture of nivolumab and pembrolizumab by immobilized PD-1, with subsequent enzymatic chemiluminescent detection by anti-IgG4 coupled with horse radish peroxidase (HRP). Validation of the ELISA method was performed based on the guidelines for bioanalytical assays provided by the FDA.

Results: We developed an ELISA with a calibration range of 1 ng/ml – 100 ng/ml. The lower limit of quantification for serum and CSF was 2 ng/ml for both anti-PD-1 agents, which is sufficient to measure serum trough concentration levels and CSF concentrations. The within- and between day precision ranged from 3.3 % to 4.2% and from 4.1% to 4.6%, respectively. The assay shows dilutional linearity and specificity. We showed that ipilimumab (anti-CTLA-4), which is often given concomitantly with nivolumab, does not interfere with the assay. The ELISA method showed long term sample stability of > 1 yr. Clinical applicability was demonstrated by measuring serum and CSF concentrations from patients treated with nivolumab or pembrolizumab. For this, patient samples were diluted 10 – 1000 times. We found nivolumab C_{max} concentrations of 44–65µg/ml, which is within the concentration range reported by EMA. We furthermore showed that minimal nivolumab concentrations reach the brain/CSF, with serum:CSF ratios being between 52 – 299.



Conclusion: We developed and validated a sensitive ELISA for the quantitative determination of nivolumab and pembrolizumab in serum and CSF. The method is accurate, precise, and shows good long-term sample storage stability using standard laboratory equipment and techniques. This quantitative ELISA for nivolumab and pembrolizumab can be used in future clinical trials.

Semi-physiological Pharmacokinetics of Bortezomib in Pediatric Patients with Acute Lymphoblastic Leukemia

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Introduction Bortezomib is a proteasome inhibitor targeting the 20S proteasome used in the treatment of adult multiple myeloma, and is currently under investigation for treatment of children with relapsed acute lymphoblastic leukemia (ALL). The pharmacokinetics (PK) of bortezomib are characterized by a large volume of distribution and a rapid decline in plasma concentrations within the first hour after administration. Furthermore, a marked increase in exposure was observed in the second week of treatment (Horton et al. 2007; Muscal et al. 2013; Blaney et al. 2004). This has previously been explained by extensive binding of bortezomib to proteasomes in erythrocytes and peripheral tissues (Zhang et al. 2015) The objective of the current study was to characterize the time-dependent PK profile of bortezomib in order to evaluate the currently used dosing regimen in pediatric patients.

Methods PK data of 28 patients was available from the ITCC 021/I-BFM-SG-study (EudraCT number: 2009-014037-25). Patients were treated with an intravenous bortezomib dose of 1.3 mg/m^2 in a twice-weekly schedule. PK samples in plasma and cerebrospinal fluid (CSF) were collected after the bortezomib administrations on day 1 and 11 at 7 time points (pre-dose and 15 minutes, 3, 8, 24, 48, 72 hours after dose). A semi-physiological PK model for bortezomib was developed incorporating saturable binding of bortezomib in erythrocytes using nonlinear mixed-effects modelling. Visual assessment of the model was applied by goodness-of-fit plots and prediction-corrected visual predictive check(pcVPC).

Results Bortezomib concentrations in CSF were undetectable in the majority of the samples (83.5%). The plasma data was adequately described by a two-compartment model with large volumes of distribution (V1 = 69.2 L and V2 = 632 L) and systemic clearance of 7.03 L/h. Allometric scaling was applied to all clearance and volume parameters. Increased concentrations were observed on day 11 compared to day 1. Binding to erythrocytes was described by a Langmuir model with a maximal binding capacity (B_{max} = 66.4 ng/mL), inter-individual variability on B_{max} of 48% and an equilibrium dissociation constant (K_D = 74.2 ng/mL). Introduction of between-week variability in B_{max} significantly improved the model (dOFV -20.3) and was estimated as 33%.

Conclusion The semi-physiological model adequately described the nonlinear PK of bortezomib in plasma. The saturable binding to erythrocytes provides an explanation for the increased exposure in the second week of treatment. Additionally, the final model parameters were in agreement with reported adult values.

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SWITCHABILITY OF GABAPENTIN FORMULATIONS: ASSESSMENT OF BIOEQUIVALENCE BETWEEN NEURONTIN® AND GABASANDOZ® ON THE INDIVIDUAL PATIENT LEVEL.

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Purpose

To ensure a stable drug effect, generic substitution of anti-epileptic drugs like gabapentin is generally not advised in patients with epilepsy. The primary aim of this work was to study the switchability of gabapentin (800mg tablets) between a reference listed drug product (RLD; Neurontin®) and its generic counterpart (Gabasandoz®). A secondary objective was to assess whether batch-to-batch differences might play a significant role in the within-subject variability.

Methods

Thirty subjects were included in a cross-over individual bioequivalence study. Subjects received gabapentin of 2 different batches of each formulation (RLD or generic) on 6 occasions. Plasma samples were collected up to 36 hours post dosing and were analysed using LC-MS/MS. For the primary objective, the trial was analysed, using SAS®, according to the Food and Drug Administration (FDA) framework to establish individual bioequivalence (IBE). For the secondary objective the model was extended to estimate the magnitude of between-batch variability.

Results

The 95% upper confidence bound of the IBE criterion was -2.01 and -2.31 for $AUC_{0\text{-}inf}$ and C_{max}, respectively and fulfilling the criteria proposed by the FDA (IBE criterion<0 for both $AUC_{0\text{-}inf}$ and C_{max}). Furthermore, potential batch-to-batch variability slightly changed the 95% upper confidence bound of the IBE criterion to -2.13 and -2.58, respectively, but did not influence the conclusion of individual bioequivalence. High between- and within-subject variability were found in the systemic exposure (26.0% and 23.6%, respectively) following a single oral dose.

Conclusions

This study shows that gabapentin 800mg tablets of 2 different manufacturers are bioequivalent on an individual level and switchable according to FDA criteria. Furthermore, batch-to-batch variability does not significantly contribute to the observed within-subject variability and may therefore be neglected during therapeutic follow-up. It can be concluded that Neurontin® can be substituted by Gabasandoz® and vice versa also in patients with epilepsy.

Tamoxifen-induced fatty liver disease in a Caucasian patient.

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Introduction

Tamoxifen is a well-established hormonal treatment modality for hormone receptor positive breast cancer that is generally well tolerated. Although preclinical data indicate that tamoxifen induces lipid accumulation in the liver, up until now hepatic steatosis has not been reported in Caucasian patients (Lelliott et al., 2005, Larosche et al., 2007). This is in contrast with Asian patients, in whom tamoxifen-induced hepatic steatosis has been demonstrated in more than 40% of the cases (Ogawa et al., 1998, Lin et al., 2014, Yang et al., 2016, Nishino et al., 2003).

Aims

In a patient who received tamoxifen, and who developed jaundice, we assessed liver enzymes during tamoxifen therapy and 6 weeks after cessation. Ultrasound and computed tomographic imaging of the liver were also performed.

Results

We observed a 52-year old Caucasian female patient who had been diagnosed with locoregional hormone receptor positive breast cancer in September 2015. She underwent a mastectomy with a sentinel nodal procedure and subsequently received adjuvant chemotherapy. After completing chemotherapy, she started with tamoxifen 20 mg.

From September 2016 on, she developed progressive fatigue, nausea and vomiting. In April 2017 she suffered from jaundice, recurring fever and abdominal pain. Laboratory tests showed a cholestatic liver panel (see Table 1).

Ultrasound and computed tomography imaging showed steatosis of the liver parenchyma but no evident hepatic duct dilatation or visceral metastases.

Further laboratory investigations and medical history showed no evidence for viral hepatitis, drug- or alcohol-induced etiology or auto-immune disease (see Table 1). After cessation, our patient showed a full recovery of the hepatic enzyme levels and clinical symptoms.

Conclusion

We describe severe steatotic hepatitis in a patient who received tamoxifen. We therefore suggest further observational research to quantify the prevalence of these side effects and to assess the need for possible preventive or screening strategies for fatty liver disease in these patients.

Table 1.

Liver enzymes	During Tamoxifen Therapy	6 weeks after cessation
ASAT[1]	1229 U/L	91 U/L
ALAT[2]	1793 U/L	39 U/L
GGT[3]	261 U/L	80 U/L
Total bilirubin	163 µmol/L	20 µmol/L
AF[4]	112 U/L	60 U/L
Auto-immune disease		
ENA[5]	negative	n.a.[13]
IgA[6]	0,95 g/L	n.a.
IgG[7]	8,9 g/L	n.a.
IgM[8]	2,30 g/L	n.a.
Viral disease		
Anti-CMV[9] IgG/IgM	negative	n.a.
HBs[10] Ag	negative	n.a.
anti HBs[10] Ag	120 IU/L	n.a.
anti HB core AB	negative	n.a.
anti HAV[11] IgG/IgM	negative	n.a.
anti HCV[12] AB	negative	n.a.

Abbreviations: 1 aspartate transaminase, 2 alanine transaminase, 3 gamma-glutamyl transferase, 4 alkaline fosfatase, 5 extractable nuclear antigens, 6 immunoglobuline A, 7 immunoglobuline G, 8 immunoglobuline M, 9 anti-cytomegalie virus, 10 hepatitis B surface, 11 anti-hepatitis A virus, 12 anti-hepatitis C virus, 13 not applicable

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DEVELOPMENT AND VALIDATION OF AN LC-MS/MS ASSAY FOR THE QUANTIFICATION OF INTRACELLULAR DECITABINE NUCLEOTIDES AND GENOMIC DNA INCORPORATED DECITABINE IN PERIPHERAL BLOOD MONONUCLEAR CELLS AND WHOLE BLOOD

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Introduction: Guadecitabine, a dinucleotide of β-decitabine (β-DEC, Dacogen®) and deoxyguanosine, is under clinical investigation for the treatment of hematological malignancies and solid tumors. β-DEC is a registered DNA methyltransferase (DNMT) inhibitor that is used for the treatment of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). β-DEC requires cellular uptake and intracellular metabolic activation to β-DEC triphosphate before it can be incorporated into the DNA. Once incorporated in the DNA, β-DEC can exert its hypomethylating effect by trapping DNMT-1, with a restored gene function as a result. Further insight in the intracellular metabolism of β-DEC in patients may result in a better understanding of the drug's therapeutic effect.

Methods: An LC-MS/MS assay was developed and validated to further explore the intracellular pharmacokinetics of (gua)decitabine. This assay will be used for the indirect quantification of intracellular β-DEC nucleotides in human peripheral blood mononuclear cells (PBMCs), and for the quantitative determination of β-DEC incorporation in genomic DNA isolated from human whole blood. In addition, global DNA methylation, expressed as 5-methyl-2'-deoxycytidine (5mdC) DNA content, can be used as a marker for therapeutic effect. To normalize the β-DEC and 5mdC contents, 2'-deoxycitidine (2dC) amounts can be quantified simultaneously.

Results: The assay was validated using the following concentration ranges: 0.5 – 100 ng/mL for β-DEC, 50 – 10,000 ng/mL for 2dC, and 5 – 1,000 ng/mL for 5mdC. A calibrator at the limit of detection (LOD) was added for ß-DEC at 0.1 ng/mL. To demonstrate the applicability of the validated assay, intracellular β-DEC nucleotide levels, and genomic DNA incorporated β-DEC in PBMCs and whole blood samples obtained from patients (n=4) treated with guadecitabine were analysed. Global DNA methylation status was successfully monitored by analysis of 5mdC DNA content, relative to 2dC content. It was shown that β-DEC DNA incorporation increases over time, which provides evidence that the method is suitable to support clinical studies with β-DEC or β-DEC prodrugs.

Discussion: We successfully developed and validated an accurate, precise, and sensitive LC-MS/MS assay for the quantification of β-DEC nucleotides in human PBMCs and for β-DEC, 2dC and 5mC in genomic DNA isolated from whole blood. To our knowledge, this is the first time that ß-DEC DNA incorporation was determined in patients treated with (gua)decitabine, without making use of a radiolabeled drug.

WHICH PART OF UNPLANNED HOSPITAL READMISSIONS WITHIN 30 DAYS AFTER DISCHARGE IS MEDICATION RELATED? A STUDY TO ASSESS THE PERCENTAGE AND POTENTIAL PREVENTABILITY AND CAUSES

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Objective

Primary aim: to identify the percentage and preventability of unplanned hospital readmissions ≤30 days of discharge due to medication related problems. Secondary aims: to assess which types of medication were responsible for potentially preventable readmissions and potential causes of these readmissions.

Design

Cross-sectional observational study.

Methods

Patients (≥18 years) with an 30-day unplanned hospital readmission after discharge from the departments of pulmonology, surgery, cardiology, internal medicine, gastro-enterology, psychiatry and neurology were included. Residents of these departments and a pharmacist reviewed files of readmitted patients. During multidisciplinary meetings potentially preventable cases were discussed and consensus was reached. Percentage of readmissions that were medication related, and potential preventability were assessed. For potentially preventable readmissions types of medication responsible for the readmission and potential causes were assessed. Potential causes were categorized into three categories: problems due to transitions in care, prescribing and adherence.

Results

426 readmissions were included. Nineteen percent was medication related and 38% was potentially preventable. Most common types of medication responsible for potentially preventable readmissions were: diuretics (20%), drugs used in diabetes (17%) and cardiac therapy/beta blocking agents (13%). Potential causes of these readmissions were problems due to transitions in care (23%), prescribing (43%) and adherence (33%).

Conclusion

Thirty-eight percent of medication related readmissions is potentially preventable. These problems were most often caused by problems with transitions in care, prescribing and adherence. These causes might be good starting points for implementing interventions to reduce medication related hospital readmissions.

SWITCHING TO A METHOTREXATE IMMUNO-ASSAY WITH HIGHER SPECIFICITY COMPARED TO ITS PREDECESSOR RESULTS IN A SHORTER TIME PERIOD TO REACH TARGET CONCENTRATIONS

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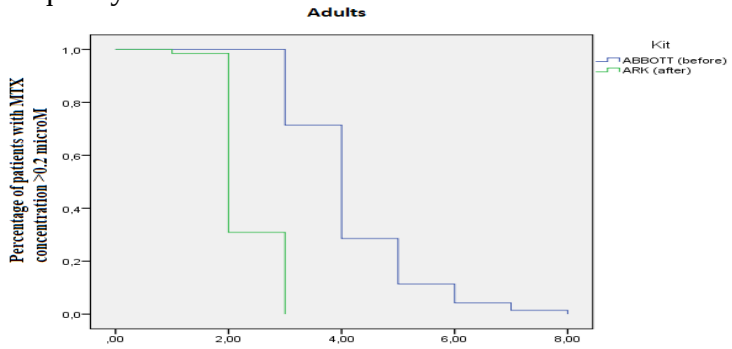
Introduction and aim
High dose methotrexate (MTX) (> 3000 mg/m2) warrants therapeutic drug monitoring (TDM) in oncology patients, since renal toxicity and prolonged exposure can lead to life-threatening side effects, e.g. myelosuppression and mucositis. Serum MTX concentrations, along with serum creatinine and urine output should be monitored with ongoing adjustments in hydration, alkalinization and leucovorin rescue until the target of less than 0.10–0.4 µM is reached. Importantly, cross reactivity of MTX immune-assays with the metabolite 4-diamino-N(10)-methylpteroic acid (DAMPA) results in false elevated levels of MTX causing a redundant elongation of supportive care and hospitalization. Here, we studied the effect of a switch to an assay with a declared lower DAMPA cross reactivity, compared to its predecessor, on the time period to reach MTX concentrations below the above-mentioned target in a mixed pediatric an adult oncology patient cohort.

Methods
In October 2013, the assay switched from the ABBOTT® to the ARK® MTX kit. The first 150 MTX treatments before and after the switch were selected. Data were obtained from the hospital information system. The primary outcome was the number of days between the end of MTX infusion and the first recorded MTX level below the target concentrations of 0.2 µmol/L for adults and 0.4 µmol/L for paediatric patients. For statistical comparison, variables such as age, gender, weight, renal function and dose were assessed in an independent t-test. A multivariate linear regression and a Kaplan-Meier analyses were performed. Adults and children were analysed separately.

Results
278 of 300 treatments were included due to missing data in 15 cases before the switch and 7 after. Baseline characteristics differed in renal function for the adults: 93.7 vs. 101.2 mL/min (p=0.027), and for the children: 109.1 vs 117.7 mL/min (p=0.006 in the pre- and post-switch populations respectively. For children also gender: 78% vs. 49% males (p<0.001), and age: 7.6 vs. 5.4 years (p=0.001) differed between pre- and post-periods. Multivariate linear regression analyses showed a significantly shorter period after the assay switch of 2.0 days (4.2 vs 2.3 days; p<0.001) in the adult population and 1.1 days in children (3.5 vs 2.4 days; p<0.001) to reach an MTX level below the target (see Figure for adult results).

Conclusion
Switching to an assay with higher MTX specificity results in a shorter time to MTX levels under the target concentration in both a paediatric and adult oncology patient cohort. This translates to a shorter period of supportive care and most likely to a shorter length of stay in the hospital which will improve the quality of life and lower the healthcare costs.



QUANTIFICATION OF TOTAL DINUTUXIMAB CONCENTRATIONS WITH LIQUID CHROMATOGRAPHY TANDEM MASS-SPECTROMETRY

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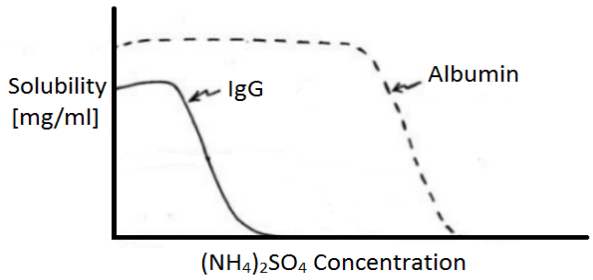
Introduction and aim:
Neuroblastoma is one of the most commonly found solid tumors in children. The monoclonal antibody dinutuximab targets the sialic acid-containing glycosphingolipid GD2 expressed on almost all neuroblastoma tumor cells and induces cell lysis. However, the expression of GD2 is not limited to tumor cells only, but is also present on central nerve tissue and peripheral nerve cells explaining dinutuximab toxicity. The most common adverse reactions are pain and discomfort, which may lead to discontinuation of the treatment. Furthermore, there is little to no data available on exposure and effect relationships of dinutuximab. We, therefore, aimed to develop an easy method to quantify dinutuximab levels in human plasma using LC-MS/MS to facilitate pharmacokinetic and pharmacodynamics studies of this monoclonal antibody.

Methods
Ammonium sulphate was used to precipitate all immunoglobulins (IgG's) in human plasma (Figure 1). After centrifugation, supernatant containing albumin was decanted and the precipitated IgG fraction was re-dissolved in a buffer containing 0.5% SDS. Samples were then reduced, alkylated and digested with trypsin. Finally, a signature peptide in complementarity-determining region 1 of DNX heavy chain was quantified on LC-MS/MS using a stable isotopically labeled peptide as internal standard.

Results
Ammonium sulphate purification efficiently removed 97.5% of the albumin fraction in the supernatant layer. The validation performed on DNX showed that within-run and between- run coefficients of variation (CV's) for LLOQ were 5.5% and 1.4%, respectively. The overall CV's for QC Low, QC Med and QC High levels were <5%. Linearity in the range 1 – 32 mg/L was excellent (r2>0.999). Selectivity, stability parameters and matrix effect were in concordance with EMA guidelines.

Conclusions
In conclusion, a method to quantify DNX in human plasma using LC-MS/MS was successfully developed. In addition, the high and robust process efficiency allows utilization of a stable isotopically labelled (SIL) peptide instead of SIL DNX, which is commercially unavailable.

Figure 1. Principle of Ammonium sulfate precipitation



DIFFERENT DYNAMICS OF COMPOSITE INDEXES VARIABLES USED FOR DISEASE ACTIVITY ASSESSMENT IN RHEUMATOID ARTHRITIS PATIENTS ON TOCILIZUMAB TREATMENT.

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Introduction: Tocilizumab (TCZ) is a humanized anti-IL-6 receptor monoclonal antibody that has shown efficacy in the management of moderate to severe rheumatoid arthritis (RA). Disease activity in RA patients is routinely assessed using composite indexes that include clinical and/or laboratory variables. These composite indexes assume all variables have the same dynamics but on TCZ treatment, it has been reported that inflammatory markers show faster decrease compared to clinical variables.

Objectives: The purpose of the study was to assess the dynamics of different variables included in composite indexes in RA patients on treatment with intravenous (iv) TCZ using a modeling approach.

Methods: Pharmacokinetic and clinical data were obtained from a prospective, observational, single-center study involving 35 subjects with RA treated with iv TCZ at a dose range from 4 to 8 mg/kg every 28 days. Clinical data and levels of inflammation markers such as C-Reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were retrospectively collected from the beginning of TCZ treatment every 28 days until the moment of inclusion at the PK study. A PK/pharmacodynamics (PKPD) model was developed using a previously published PK model and non-linear mixed-effects modeling implemented in NONMEM v7.3.

Results: The relationship between TCZ concentration and disease activity was described using an indirect response model with inhibition of the variable input (K_{in}). Dynamics of the PD data could be adequately described grouping them in slow-decreasing variables (for tender and swollen joint counts and patient and evaluator global health assessment) and fast-decreasing variables (for CRP and ESR). Slow decreasing variables have a higher EC_{50} (EC_{50}: 7.05 µg/mL (RSE 36.2%), IIV: 126%) and a lower maximum effect (E_{max}: 0.811 (RSE 4.6%)) and output constant (K_{out}: 0.00093 h^{-1} (RSE 44.6%), IIV: 98.8%) than the fast decreasing variables, which have an EC_{50} of 1.04 µg/mL (RSE 6.3%), IIV: 103%), E_{max}: 1 and K_{out}: 0.00178 h^{-1} (RSE 22%), IIV: 73.6%).

*EC_{50}: concentration at which 50% of the maximum effect is reached; IIV: inter-individual variability; RSE: relative standard error.

Conclusion: Higher serum TCZ concentrations are needed to normalize tender/swollen joint counts and health assessment values than to normalize inflammation markers such as CRP and ESR. Moreover, composite indexes that include fast-decreasing variables in their formula, would overestimate the number of patients in remission at the beginning of the treatment with TCZ.

References: Bastida et al. Br J Clin Pharmacol. 2018 Jan 4; Nishimoto et al. Mod Rheumatol (2010) 20:539–547

PLASMA CONCENTRATION OF CURCUMIN AND ITS METABOLITES IN SUBJECTS USING OVER THE COUNTER SUPPLEMENTS IN DAILY LIFE IS LOW

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Introduction
The effect of curcumin *in vitro* has been linked to many beneficial effects e.g. anti-inflammatory or anti-cancer. Curcumins effectiveness however, has never been shown clinically and this could be related to the low bioavailability of curcumin. Yet there are still some patients and healthy persons who take curcumin supplements, because they are convinced of the beneficial effects of curcumin.

Aim
To investigate if curcumin and its metabolites are detectable in plasma of patients or healthy persons who use curcumin supplements in daily life.

Method
In this single centre study, 50 persons (patients or healthy) are included and asked to fill in a questionnaire about their use of curcumin and medication. On the day of visit, a blood sample was taken just before patients were asked to take their curcumin (through concentration) and a second blood sample was taken 1,5 hours after intake (expected peak concentration). Curcumin and its metabolites demethoxycurcumin (DEC), bisdemethoxycurcumin (BIC) and tetrahydroxycurcumin (THC) were analyzed in plasma using a sensitive, validated HPLC-MS/MS method ranging from 2 nM to 400 nM. To determine glucoronidated and sulphated curcumin, samples were also treated with β-glucoronidase combined with sulfatase to catalyze the hydrolysis of glucuronidated and sulphated metabolites.

Results
Within 10 months, 50 persons were included of which 2 persons participated twice with different formulations. Thus far, samples of 47 persons have been analyzed. Curcumin formulation dosages ranged from 40 mg to 3000 mg. Curcumin was detectable in 6 persons at peak level varying from 0.9 ng/ml to 97.6 ng/ml. Whereas curcumin through levels were detected in 4 persons varying from 1.2 ng/ml to 18.2 ng/ml. The metabolites DEC and THC were not detectable at peak or through levels. After hydrolysis, curcumin was detectable in 40 persons varying from 0.7 ng/ml to 134.3 ng/ml, DEC was detectable in 23 persons at peak level varying from 0.9 ng/ml to 66.5 ng/ml and THC varied from 1.1 ng/ml to 110.1 ng/ml in 37 persons. BIC was not detectable in persons before hydrolysis .

Conclusion
Our results show that the systemic exposure of curcumin is very poor when used in daily life. Following hydrolysis of glucuronidated and sulphated metabolites curcumin was detectable in more patients, suggesting a rapid first pass metabolism, however, concentrations remain low. Our study indicates the need to be critical towards the claimed beneficial effects of curcumin supplement use in daily life.

CLOMIPRAMINE TOXICITY IN A CYP2D6 POOR METABOLIZER WHO SUDDENLY STOPPED SMOKING

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Introduction

The tricyclic antidepressant clomipramine and its active metabolite N-desmethylclomipramine are mainly metabolized by CYP2D6 and CYP2C19 enzymes and clomipramine to a lesser extent by CYP1A2 and CYP3A4. Factors influencing the capacity of these iso-enzymes can alter drug plasma concentrations leading to differences in clomipramine efficacy and toxicity. We present a case of clomipramine toxicity caused by multiple factors.

Case description

A 70-year-old Caucasian woman underwent an elective total knee arthroplasty. Her psychiatric history was characterized by recurrent episodes of anxiety with OCD and depression. Psychiatric medication consisted of haloperidol 3 mg/day, fluvoxamine 100 mg/day and clomipramine 100 mg/day. She was a heavy smoker, but suddenly discontinued smoking after hospital admission. During hospital admission, the patient was increasingly confused and agitated. Clomipramine and N-desmethylclomipramine trough plasma concentrations were determined (HPLC). This revealed a supratherapeutic clomipramine plasma concentration of 1345 µg/L (therapeutic range 50–200 µg/L) and a N-desmethylclomipramine concentration of 368 µg/L, which was within the therapeutic window (150-400 µg/L). This led to a toxic sum plasma concentration of clomipramine and its active metabolite of 1713 µg/L. The administration of clomipramine was discontinued immediately. In order to elucidate potential causes of the elevated clomipramine levels and the striking clomipramine and metabolite ratio of almost 4:1 (which normally is 1:2), genetic variations in CYP2C19 and CYP2D6 were determined. The patient was found to be a CYP2D6 poor metabolizer (CYP2D6*4/*5) and a CYP2C19 extensive metabolizer (CYP2C19*1/*1). Generally, elimination half-life of clomipramine is 12-36 hours. In our case, the elimination half-life of clomipramine was prolonged to approximately 11 days. Twenty-two days after clomipramine discontinuation, the sum plasma concentration was reduced to <600 µg/L, and patients recovered from her agitated and confused state.

Discussion

We describe a patient with clinical symptoms of clomipramine toxicity. Plasma concentrations of clomipramine were almost 7 times higher than the upper limit of the therapeutic window. We identified multiple factors that were considered to be associated with the elevated plasma concentrations. First, the CYP2D6 poor metabolizer status and second, the concomitant use of the strong CYP1A2 inhibitor fluvoxamine. Third, patient abruptly stopped smoking, which is associated with a rapid down-regulation of CYP1A-enzymes. In literature, plasma concentrations of clomipramine were reported to be twice as high in non-smokers as in smokers.
In conclusion, clinicians should consider that not only genetic variations and drug-drug interactions but also changes in smoking behaviour can affect pharmacokinetics of clomipramine.

Use of parenteral glucocorticoids and the risk of new onset type 2 diabetes mellitus: a case-control study

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Background: Use of oral glucocorticoids (GCs) has been associated with hyperglycaemia and type 2 diabetes mellitus (T2DM). However, unlike oral GCs, there is minimal or no data on the effect of parenteral GC use on T2DM.

Aim: To assess the association between use of parenteral GCs and the risk of receiving a first prescription of a non-insulin antidiabetic drug (NIAD) as a proxy for new onset of T2DM.

Methods: A population based case-control study was performed using the Clinical Practice Research Datalink (CPRD). Cases (n=177,154) were defined as patients >18 years of age who had their first ever NIAD prescription between January 1987 and October 2013. Controls were matched by age, gender and general practitioner practice. Conditional logistic regression analyses were used to estimate the risk of NIAD prescription and use of parenteral GCs. To determine the effect of prolonged use, we stratified current users by number of prescriptions. We also stratified current users by type of GC. Our analyses were statistically adjusted for lifestyle factors, comorbidities and concomitant drug use.

Results: Although this study confirmed that oral GCs increases the risk of receiving a first prescription of a NIAD (OR 2.63 [95% CI 2.53-2.73])**,** there was no association between the use of parenterally administered GCs and the risk of receiving a first prescription of a NIAD (OR 0.88 [95% CI 0.76-1.02]). The number of GC prescriptions was not associated with risk of new onset T2DM compared to no parenteral GCs use; neither the type of GC.

Conclusion: Our study does not demonstrate an association between the use of parenteral GCs and the risk of new onset of T2DM.

Therapeutic Drug Monitoring at week 1 and prediction of clinical sustainability of thiopurines in IBD-patients

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Introduction
Approximately 25% of the patients with inflammatory bowel disease (IBD) who start with conventional thiopurine derivatives discontinue therapy within 3 months due to side effects including hepatotoxicity, gastrointestinal complaints and leukopenia. It is shown that patients with a "skewed" thiopurine metabolism [ratio 6-MMPR/6-TGN > 20] are particularly at risk for therapy failure. We aimed to assess thiopurine metabolite levels at one week after start of therapy (T1) to predict the clinical sustainability in patients.

Methods
In this multicenter observational study, we included adult IBD patients who started azathioprine 2-2.5 mg/kg bodyweight or mercaptopurine 1-1.5 mg/kg bodyweight. Exclusion criteria were baseline leukocytes <3.0 x 10 9 / l, hepatic impairment at baseline (ASAT, ALAT, γ-GT of AF ≥ 2 x upper limit of normal (ULN)) and reduced renal function at baseline (creatinine ≥2 x ULN or MDRD <60 ml/min).
Thiopurine metabolite levels were measured at T1 and T8. After 12 weeks of follow-up discontinuation of thiopurine therapy was determined; discontinuation of therapy between normal and skewed metabolism was assessed. We decribed all patients displaying a skewed metabolism at T1.

Results
Skewing at week 1 does not correlate with discontinuation of therapy within the first 12 weeks of treatment (OR 1.12 (95%CI 0.38–3.31)), as seven out of sixteen patients (44%) with skewed metabolism at T1 discontinued or switched thiopurine therapy in the first 12 weeks, compared to thirty-two out of seventy-eight patients (41%) with normal metabolism.
Six out of sixteen patients with skewed metabolism at T1 also showed skewed metabolism at T8, whereas five patients with skewed metabolism at T1 showed normal metabolism at T8. For the other five patients no metabolite levels at T8 were available due to early discontinuation of treatment.
Reasons for discontinuation in the patients with skewed metabolism were adverse events (N=6), hepatotoxicity (N=2) and high measured metabolite levels at T8 (N=1). The most common adverse events in the patients with skewed metabolism resulting in discontinuation of treatment were flu-like symptoms, nausea, vomiting and rash.

Table 1 Number of patients with skewed metabolism at week 1

	Continued treatment	**Discontinued treatment**	**Total**
Skewed metabolism	9	7	16
Normal metabolism	46	32	78
Total	55	39	94

Skewed metabolism = ratio 6-MMPR/6-TGN > 20,
Discontinuation = stop thiopurine, lower dose or switch to other thiopurine

Conclusion
Surprisingly, a skewed metabolism of conventional thiopurine derivatives at week 1 does not predict clinical sustainability of thiopurine therapy during the first 12 weeks.

A short-term high fat increases exposure to acetaminophen metabolites that are related to hepatotoxicity

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A three-day high fat diet induces hepatic steatotic alterations. Previous studies have indicated that such a diet might alter hepatic drug enzyme activity. This might be relevant since acetaminophen induced liver injury is caused by the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQi) formed by CYP2E1 And CYP3A4 (Figure 1).

Aims

The aim of our study was to assess the effects of a three-day high fat diet on exposure to acetaminophen and its metabolites.

Methods

In a randomized controlled crossover trial, nine healthy subjects received a single oral adminstration of 1000 mg acetaminophen (1) after an overnight fast (control) and (2) after an overnight fast after three days of a high fat diet consisting of 500ml of cream (1700 kcal) supplemented to their regular diet. Pharmacokinetic parameters of acetaminophen and its metabolites (acetaminophen-glucuronide (APAP-Glc), acetaminophen-sulfate (APAP-Sul), 3-cysteinyl-acetaminophen (APAP-Cys), 3-(*N*-acetyl-$_L$-cystein-*S*-yl)-acetaminophen (APAP-Cys-NAC) and 3-methoxy-acetaminophen (APAP-OMe) were determined by non-compartimental analysis via PKsolver.

Results

A short-term high fat diet increased median $AUC_{0\text{-inf}}$ of APAP-Cys from median 11.7 (7.9-15.0) µmol L-1h-1 in the control situation to 14.0 (10.2-17.8) µmol L-1h-1 after the high fat diet (p=0.02). The $AUC_{0\text{-t}}$ of APAP-Cys-Nac increased from 3.3 (2.2-4.2) µmol L-1h-1 in the control situation to 4.6 (2.8-6.0) µmol L-1h-1 after the high fat diet (p=0.01). Exposure to APAP, APAP-Glc or APAP-Sul was not affected by the high fat diet.

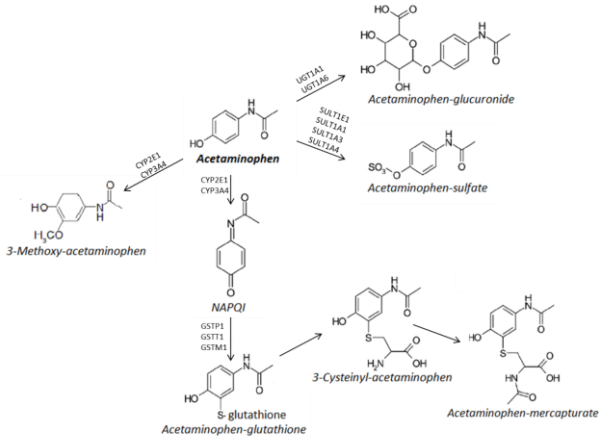

Figure 1: Simplified metabolic pathway of acetaminophen

Conclusions

This study demonstrates that a three-day high fat diet increases exposure to acetaminophen metabolites APAP-Cys and APAP-Cys-Nac. Both metabolites are formed after NAPQi, and are associated with an increased risk to acetaminophen-induced toxicity.

The characterization of people with type 2 diabetes mellitus and polypharmacy in the Netherlands: The Diabetes Pearl Cohort.

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Background: Polypharmacy in people with type 2 diabetes mellitus (T2DM) is highly prevalent and a risk factor for suboptimal glycemic control, possibly due to decreased therapeutic compliance. The aim of this study was to describe the prevalence of polypharmacy, as well as to describe the subject characteristics and drug types associated with polypharmacy in the general Dutch T2DM population.

Methods: The study population consisted of people with T2DM, treated in different geographical areas and all types of care, from the Dutch Diabetes Pearl cohort. Data concerning drug use, as well as sociodemographic, metabolic and complication characteristics were gathered. Linear and logistic regression analyses were performed, stratified by mild polypharmacy (5-9 drugs) and hyperpolypharmacy (≥10 drugs).

Results: 6447 participants were included of which 60% men, mean age 62±10 years. The prevalence of mild polypharmacy and hyperpolypharmacy was 48% and 19%, respectively. Compared to those with mild polypharmacy or no polypharmacy, people with hyperpolypharmacy were characterized by higher age, female sex, lower educational level, longer diabetes duration, treatment in tertiary care, obesity, suboptimal glycemic control (HbA1c>53 mmol/mol) and more diabetes complications. The use of cardiovascular and diabetes drugs was similar in the three groups, while people with hyperpolypharmacy more often use other drugs than those with mild polypharmacy or no polypharmacy.

Conclusions: Hyperpolypharmacy and mild polypharmacy are highly prevalent in the general Dutch T2DM population and were associated with poorer metabolic control. As the other drugs rather than cardiovascular or diabetes drugs were causing the hyperpolypharmacy, this could provide a focus for development of future deprescribing guidelines in the T2DM population.

EFFICIENT SELECTION OF OLDER PATIENTS FOR MEDICATION REVIEW: DEVELOPMENT AND VALIDATION OF A SELECTION ALGORITHM

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Introduction: Performing medication reviews in older patients with multiple chronic medication can increase medication appropriateness as well as adherence of the patients. In the Netherlands there are around 750.000 older patients with at least 5 chronic medications, who may be eligible for medication reviews. To conduct such reviews efficiently, a suitable selection procedure is needed. We aimed to develop and validate an algorithm that is able to select complex patients most in need of a medication review.

Methods: We constructed an algorithm from 80 patient cases. An expert panel of 9 community pharmacists and 7 general practitioners rated the complexity of the cases in a modified Delphi method. Each case was rated by 8 experts. The median of the complexity rating for the cases with consensus was used to develop the selection algorithm. We used backward stepwise linear regression with a minimum number of case characteristics to give good prediction (high adjusted R^2). The resulting algorithm was applied in 4 community pharmacies in the Netherlands to test its feasibility and validity. We selected a random sample of up to 5 complex and 5 simple cases per pharmacy, and compared these on (1) time needed for the review, (2) number of proposed and of implemented interventions, using t-tests. We also compared the complexity rating of the algorithm with the rating of the community pharmacists using kappa statistics, and assessed the need for medication review according to the pharmacists.

Results: The expert panel reached consensus on 75 cases. The cases had a mean age of 79 years, 48% were males, and mean number of prescribed drugs was 10. The final regression model predicted the complexity ratings significantly (adjusted R^2=0.726, P<0.0001), and resulted in the following algorithm: 'number of drugs'×1 + 'number of prescribers'×3 + 'recent fall incident'×7 + 'does not collect own medication'×4. Applying this algorithm in 4 pharmacies resulted in a sample of 170 patients, of which 19 complex and 19 simple cases received a medication review. Medication reviews took on average 77 minutes in the complex and 66 minutes in the simple group (P=0.134). No difference was found in the number of proposed (P=0.658) or implemented (P=0.515) interventions. The pharmacists agreed with the algorithm on complexity of the patients in 71% of the cases (ƙ=0.42). For 58% of the complex cases, the pharmacists assessed the need for a review as high, whereas this was 26% for the simple cases.

Conclusions: We developed an easy-to-apply algorithm including four common case characteristics to identify complex patients for a medication review. The algorithm showed moderate agreement with judgments of community pharmacists.

DIGITAL LEARNING TO IMPROVE PRESCRIBING PRACTICE: A SYSTEMATIC REVIEW

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Background: Recent literature shows that undergraduate prescribing education is often inadequate, leading to up to 10% potential hazardous prescribing error-rates in junior doctors, affecting 50% of all admitted clinical patients. Therefore, efforts are made to improve both undergraduate and graduate prescribing education. Digital learning may have benefits over traditional teaching. Well-designed digital learnings can be used extensively throughout a curriculum and may be distributed at no extra cost. Additionally, digital learning promotes active participation, placing the learner in charge of the timing and pace of his/her training. This flexibility creates opportunities for postgraduate education, teaching busy practicing clinicians.
Novel, multimedia-rich and interactive education is easily praised. However, one should not judge an (e-)book by its cover and much is still unknown about the effects of digital education. The aim of this review is to assess the effect of digital learning for prescribing practice and identify quality-indicators.

Methods: Databases (PubMed, Embase, CINAHL and ERIC) were searched for articles evaluating digital learning strategies for graduate and undergraduate prescribers (physicians, nurse-specialists, dentists and pharmacists). The Medical Education Research Study Quality Instrument (MERSQI) was used to assess study-quality. Outcomes were assessed on the basis of the Kirkpatrick-model.

Results: A total of 56 articles was included in the analysis. Most were e-learnings (n=44), compared to few multimedia-streams (n=3) and simulations (n=3). The majority targeted physicians (n=36), 34 articles described postgraduate courses. The mean MERSQI was 11.2/18 (± 2.9). Highest Kirkpatrick outcome was level 1 (Reaction) for 9 and level 2 (Learning) for 17 articles, outcomes were mainly positive (21/26). 5 studies evaluating higher Kirkpatrick-levels showed mixed results. Qualitative assessment revealed that flexibility (7) and multimedia (5) were most appreciated. Technological issues (9) and extensive time-burden (3 articles) were negatively appraised. Examples of best practices include the multi-institutional UK SCRIPT (http://www.safeprescriber.org) and Dutch Pscribe (https://www.pscribe.nl/en GB/Entrance/Home/Index).

Conclusion Digital learning is well appreciated and appears to effectively create more awareness in appropriate prescribing. A learner-centered approach and rich multimedia are among the most valued features of digital learning, whereas time-burden and technological issues should be avoided.

LONG TERM AND CLINICAL EFFECTS OF AN PHARMACOVIGILANCE EDUCATIONAL INTERVENTION IN SPECIALIST ONCOLOGY NURSES.

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Background: Despite the importance of adverse drug reaction (ADR) reporting the rate of underreporting, especially under (specialist) nurses, is high (0.9% reporting rate/year) and hinders optimal ADR monitoring. Since (specialist oncology) nurses administer most drugs they could play a major role in monitoring and reporting ADRs. Only several interventions in healthcare professionals have proven effective in increasing knowledge, however failed to produce clinical and durable effects. This study therefor aims to investigate the clinical and long-term effects of a pharmacovigilance educational intervention in specialist oncology nurses (SONs).

Methods: A prospective case-control intervention study in the three postgraduate school who offer the course "prescribing qualification" for SONs was initiated. We incorporated an introduction lecture on pharmacovigilance, ADR reporting assignment and group discussion on the self-reported ADRs in one of the postgraduate schools. Clinical value was assessed by analysing the number of reported ADR-reports to the Netherlands pharmacovigilance centre Lareb, one year after the course. Nurses competences on ADR-reporting were evaluated using e-questionnaires direct after the course ended (T0) and after one year (T1).

Results: Thus far, sixty SONs (74% of total) were included in the intervention group and ten nurses (59% of total) in the control group. Seventy ADRs were reported during and after the intervention while the control group did not report any. Six students (10%) completed a report within one year after the course, which showed an 11 time increase compared to baseline nurse ADR reporting rates.
Nurses in the intervention group showed an additional continuous advanced knowledge score one year after the course (T_0: 82% / T_1: 83%) compared to the control group (T_0: 65% / T_1: 69%). Intervention group members were more aware that ADR reporting contributes to the safe use of medicines (Intervention; T_0: 6.55±0.39 vs Control; T_0: 4.13 ±1.11, 1-7 min/max) although a small decrease was seen in the intervention group after one year (T_1: 5.88±0.24, 1-7 min/max). A similar decrease was seen in SONs intentions to report serious ADRs (Intervention; T_0: 5.57±0.39 / T_1: 5.19 ±0.41). All nurses agreed physicians and pharmacist are essential healthcare professionals to report ADRs, whilst only the trained SONs reported themselves to be important in ADR reporting (3.66 ±0.36 vs 1.75 ±0.59, 1-5 min/max).

Conclusion: This is the first study that shows a significant and relevant increase in the quantity of reported ADRs after a single educational intervention. The intervention also produces a sustainable long-term increase in pharmacovigilance competences. Although, the intention and attitudes scores in the intervention group decrease marginally after one year, students still outperform non-trained SONs. Further research is needed to analyse a larger group and study the qualitative clinical effects of this intervention.

DRUG INTERACTIONS BETWEEN TYROSINE KINASE INHIBITORS AND ST. JOHN'S WORT UNNOTICED IN CLINICAL PRACTICE

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Aims: Many tyrosine-kinase inhibitors (TKIs) have been introduced in (hemato-)oncology recently. Most TKIs are substrate for CYP3A4 and P-glycoprotein (P-gp). These pharmacokinetic characteristics make TKIs susceptible for clinical relevant drug interactions as with St. John's wort (SJW). SJW constituents induce CYP3A4 and P-gp expression via PXR. This can result in lower TKI exposure, leading to treatment failure. SJW (composed of dried flower leafs of hypericum perforatum) is available as over the counter herbal medicine for symptoms of depression and anxiety. Depression is more prevalent in patients with cancer than in the general population but data on the use of SJW in patients treated with TKIs are scarce. We evaluated whether TKI-treated patients who use SJW would be identified as patients at risk for clinical relevant pharmacokinetic drug interactions in our clinic.

Methods**:** First we checked whether our medication reconciliation protocol identifies the use of SJW. We also checked whether SJW is listed in medication lists. Secondly, we searched for literature to identify which TKI interacts with SJW (PubMed). In addition, we checked which TKIs are substrate for CYP3A4 and/or P-gp using databases from KNMP Kennisbank, Farmacotherapeutisch Kompas, and MICROMEDEX and if an interaction was mentioned (databases and www.drugs.com). At last we checked whether our electronic prescribing system (HIX 6.0 standard content) generates alerts when TKI are prescribed in combination with SJW.

Results**:** According to the medication history database of HIX and Pharmacom SJW is not used in our population. Our medication reconciliation protocol does specifically address herbal medicine, particularly SJW. Data on pharmacokinetic interactions were established (table not shown in abstract). The effects of SJW on imatinib pharmacokinetics have been studied and there is strong evidence for a significant pharmacokinetic drug interaction. However, data for other TKIs are lacking. Electronic prescribing in HIX results in an alert in the case of imatinib in combination with SJW. For other TKIs, like nilotinib and osimertinib, no alert is generated although a significant pharmacokinetic interaction can be expected.

Conclusions**:** We conclude that most TKIs are probably at risk for a clinical relevant drug interaction when used in combination with SJW, which may remain unrecognized in our setting. Creating more awareness among patients, pharmacy technicians, pharmacists and oncologists about a potential drug interaction between TKIs and SJW, and tuning our electronic prescribing system to yield an alert when co-prescribed, can improve medication safety and treatment efficacy for patients treated with TKIs.

PHARMACOKINETICS AND EXPOSURE-RESPONSE RELATIONSHIP OF INFLIXIMAB IN SEVERE SARCOIDOSIS

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Aims
Sarcoidosis is a multi-organ disease characterised by inflammation and non-caseating granulomas. In severe sarcoidosis, infliximab is an effective off-label third-line therapeutic. The aim of this study was to describe the pharmacokinetics and exposure-response relationship of infliximab in severe sarcoidosis.

Methods
Sarcoidosis patients treated with infliximab (n=68) 5 mg/kg at week 0, 2 and every four weeks thereafter, were studied for two years. Serum samples were collected at every dose just before and one hour after the end of infusion during the first six months and thereafter every three months. Response on clinical and inflammatory parameters and a composite response score were determined after six months of treatment. A pharmacokinetic model was developed using NONMEM.

Results
Population pharmacokinetic estimates (typical value (relative standard error)) in the final covariate model were clearance (CL) 0.276 L/day (3.2%), volume of central compartment (V1) 3.16 L (1.6%), intercompartmental clearance (Q) 0.177 L/day (21%) and volume of peripheral compartment (V2) 1.49 L (11%). Interindividual variability for CL, V1 and V2 were 23.5%, 10.9% and 75.4%, respectively. Covariate analyses showed that V1 increased with baseline body surface area and CL increased with positive antibodies against infliximab status, low baseline serum albumin and high body weight. No association with inflammatory activity or genotype and no exposure-response relationship were found.

Conclusions
Baseline body surface area, body weight, serum albumin and antibodies against infliximab status were found to influence the pharmacokinetics of infliximab in severe sarcoidosis. No exposure-response relationship was found, indicating overdosing in the current treatment protocol.

The pharmacokinetics of nitrofurantoin in healthy volunteers using two frequently used dosing regimen.

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Background: Nitrofurantoin has been used in the treatment of lower urinary tract infections for more than 50 years. Despite the paucity of pharmacokinetic data, there has been a recent resurgence of interest in the drug due to emerging resistance and lack of new antibiotics. We investigated the pharmacokinetics after a frequently used dosing regimen of 50 mg qid or 100 mg tid.

Materials/methods: Nitrofurantoin (100 mg Furabid® or 50 mg Furadantine®) was administered to 12 healthy, female volunteers (age 18-46 years, weight 50-85 kg, eGFR>90 mL/min) to examine two dosing regimens in a crossover design with a washout period of one month. Eleven plasma samples were collected during 6h (50 mg qid) or 8h (100 mg tid) after administrating nitrofurantoin with food together with one sample before administration. Urine was collected during the same time periods.

Nitrofurantoin concentrations were quantified with a validated HPLC-UV method. Relevant pharmacokinetic parameters for each matrix were calculated with *Phoenix WinNonlin® 6.4*.

Results: The calculated pharmacokinetic parameters (± standard deviation) are presented in the table below. Plasma pharmacokinetics are dose proportional based on the maximum plasma concentration (C_{max}) and the area-under-the-concentration-time-curve from 0 to infinity ($AUC_{0-\infty}$) values which are doubled when comparing the 50 mg to the 100 mg dose, but this is not reflected in the urinary PK .

	Plasma	Plasma	Urine	Urine
PK parameter	50 mg qid	100 mg tid	50 mg qid	100 mg tid
C_{max}	325.9 ± 80.7 µg/L	687.8 ± 350.8 µg/L	94.4 ± 47.8 mg/L	94.1 ± 49.9 mg/L
T_{max} (h)	2.4 ± 1.4	2.1 ± 1.4	0.6 ± 1.4	1.9 ± 3.2
V_d (L)	0.100 ± 0.050	0.104 ± 0.066	-	-
CL (L/h)	42.4 ± 9.1	48.5 ± 19.4	-	-
$T_{1/2}$ (h)	2.3 ± 1.8	1.7 ± 0.6	5.2 ± 7.1	4.0 ± 4.5
$AUC_{0-\infty}$	1228.4 ± 252.2 µg/L*h	2162.3 ± 958.4 µg/L*h	260.5 ± 111.9 mg/L*h	285.3 ± 193.7 mg/L*h

Conclusions: Plasma pharmacokinetics of NF are dose proportional changing, but urinary pharmacokinetics are comparable for the two dosing regimens. This points to the hypothesis that the excretion in urine of NF is saturable.

OLDER AGE HAS MINOR IMPACT ON PACLITAXEL EXPOSURE: A POPULATION PHARMACOKINETIC MODEL

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Introduction: Limited available data suggest that older patients may be more prone to developing paclitaxel-induced toxicity compared to their younger peers. It remains unclear whether this is underscored by age-dependent pharmacokinetics (PK) of paclitaxel.

Aims: Primary objective of this study was to determine the influence of older age on the PK of paclitaxel, by evaluating difference in Objective Function Value (dOFV) and interindividual variability (IIV). Hereafter, the impact of multiple covariates, including age, on model predictions was assessed.

Methods: Plasma concentration-time data of patients aged ≥70 years receiving paclitaxel at the Netherlands Cancer Institute (NKI) and the Radboud University Medical Center between September 2012 and May 2017 were collected according to a flexible sampling scheme. These prospectively collected data were pooled with previously published databases from multiple clinical trials conducted at the NKI and Erasmus MC Cancer Institute. A previously developed 3-compartment population PK model with saturable distribution and saturable elimination (Joerger *et al.*, 2012) was fitted to paclitaxel plasma concentration-time data of the total cohort. Hereafter, the following covariates that may distort the influence of age on paclitaxel PK were assessed using forward-backward evaluation: gender, body surface area (BSA), total bilirubin (BILI), albumin, and performance status (PS). The impact of older age on paclitaxel PK was evaluated on maximal elimination capacity (VM_{EL}) and time-above-threshold-concentration of 0.05 µmol/L ($T_{c>0.05\mu M}$).

Results: In total, we evaluated paclitaxel PK data from 684 patients, consisting of 166 patients ≥70 years (24%). Median age of our total cohort was 61 years, ranging from 18 to 84 years old. The final model included BSA, bilirubin, age, gender, and albumin as significant covariates on VM_{EL}. The impact of age, either treated as a continuous or dichotomous covariate, on paclitaxel PK was very small but statistically significant (dOFV -32 with IIV -0.2%, and dOFV -13 without a decrease in IIV, resp.). The VM_{EL} decreased by 4% with a 10-year increment of age for a typical male patient with median values for BSA, bilirubin, and albumin. Simulations revealed no relevant influence of older age on $T_{c>0.05\mu M}$.

Conclusion: In this extensive dataset including a considerable number of older patients, older age had only a minor impact on paclitaxel PK.

References: Joerger *et al.* (2012), Clin Pharmacokinet. 51(9):607-7.

THE INTRODUCTION OF BIOSIMILAR RITUXIMAB IN CLINICAL PRACTICE

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Aims: The biological rituximab is widely used for treating various types of autoimmune disease and cancer (e.g. rheumatoid arthritis, idiopathic thrombocytopenic purpura and non-Hodgkin's lymphoma). For these indications rituximab is an effective treatment, but it is also highly expensive. The introduction of rituximab biosimilars can reduce healthcare costs. Switching from an originator to a biosimilar is possible according to the Medicines Evaluation Board (CBG-MEB) and Dutch Federation of Medical Specialists, provided that adequate clinical monitoring takes place. We evaluated the controlled switching of patients from originator MabThera® to the biosimilar Truxima® in Farma-XL* affiliated hospitals Franciscus Gasthuis & Vlietland and HagaZiekenhuis.

Methods: In collaboration with haematologists and rheumatologists, Farma-XL created a monitoring plan to evaluate the introduction of biosimilar rituximab. Rituximab-naïve patients, as well as switching patients were eligible for inclusion in the monitoring plan, which includes data until mid-August 2017. Follow-up lasted from the first administration of the biosimilar until the second administration or discontinuation. Switching patients were identified by using prescription data generated by the electronic prescribing system (Chipsoft HiX) and Cytostatica Management System (CMS).

A switching patient was defined as a patient who had an administration of biosimilar rituximab less than one year after the last administration of the biological. Using the electronic patient data registry, the following data were collected: medical indication, former infusion reactions on the originator, infusion reactions after the first and second biosimilar administration, treatment of infusion reactions and other noteworthy side effects that could be attributed to the administration of rituximab.

Results: 101 patients were included in the monitoring plan. Of these patients 26 (25,7%) were rituximab-naïve and 75 (74,3%) switched from the originator to the biosimilar. 15 of the switching patients (20,0%) formerly experienced an infusion reaction on the originator. Two of the switching patients (2,6%) and six of the rituximab-naïve patients (23,1%) experienced an infusion reaction during their first administration of the biosimilar. This is less than reported in clinical trials. None of the patients who experienced infusion reactions discontinued their medication. Reactions were successfully treated by reducing infusion flow or administration of either clemastine and prednisolone, or both. 62 patients were observed during a second administration of the biosimilar. None of these patients experienced infusion reactions.

Conclusions: Switching of rituximab originator to biosimilar in clinical practice did not raise any specific concerns with regard to infusion reactions or side effects.

Effect of Short-Term Fasting and High Fat Diet on Midazolam Metabolism

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Previous studies have shown that the nutritional status, such as short-term fasting (STF) or a high fat diet (HFD), can alter drug metabolism by affecting the activity of metabolizing enzymes. Consequently, the nutritional status may result in treatment failure or, conversely, in side effects.

Aims

The aim of our study was to assess the effect of two nutritional conditions, STF and a short-term HFD, on CYP3A4-mediated hydroxylation (phase I metabolism) and UGT-mediated glucuronidation (phase II metabolism) by studying the pharmacokinetics of midazolam (MDZ) and its main metabolites.

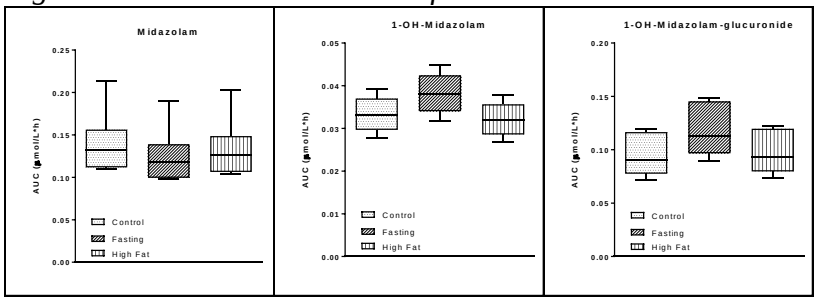
Methods

In a randomized controlled crossover trial, nine healthy subjects received a single intravenous administration of 0.015 $mgkg^{-1}$ MDZ after (1) an overnight fast (control), (2) 36h of fasting and (3) an overnight fast after three days of a HFD consisting of 500ml of cream supplemented to their regular diet. Pharmacokinetics of MDZ, 1-OH-midazolam (1-OH-MDZ) and 1-OH-midazolam-*O*-glucuronide (1-OH-MDZ-gluc) were analysed using the non-linear mixed-effects modeling (NONMEM).

Results

STF increased CYP3A4 mediated CL_{MDZ} by 12% ($p<0.01$) and decreased UGT-mediated metabolism apparent 1-OH-MDZ clearance by 13% ($p<0.01$) by decreasing the ratio of clearance and the fraction metabolite formed ($(\Delta CL_{1\text{-}OH\text{-}MDZ}/f_{1\text{-}OH\text{-}MDZ}$). Furthermore, STF decreased apparent clearance of 1-OH-MDZ-gluc ($CL_{1\text{-}OH\text{-}MDZ\text{-}gluc}/(f_{1\text{-}OH\text{-}MDZ\text{-}gluc} * f_{1\text{-}OH\text{-}MDZ})$) by 20% ($p<0.01$). A short-term HFD did not affect systemic clearance of midazolam or metabolites. Individual area under the plasma concentration-time curve (AUC) values were obtained by post-hoc analysis. STF decreased midazolam exposure and increased the exposure of its metabolites 1-OH-midazolam and 1-OH-midazolam-*O*-glucuronide (Figure 1).

Figure 1: Post hoc AUC values of midazolam and metabolites



Conclusions

Short-term fasting differentially alters phase I and II midazolam metabolism by increasing CYP3A4-mediated metabolism but by decreasing UGT-mediated metabolism. In contrast, a short-term HFD did not affect systemic clearance of midazolam.

Pharmacokinetics of morphine and its metabolites in neonates with hypoxic-ischemic encephalopathy during and after therapeutic hypothermia

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Background: morphine is a routinely used drug in (near) term neonates undergoing therapeutic hypothermia (TH, body temperature of 33.5°C for 72h) as treatment for hypoxic-ischemic encephalopathy (HIE). Little is known about the effect of TH on pharmacokinetics (PK) of morphine in this population.

Aim: to study the effect of hypothermia on the pharmacokinetics of morphine in neonates with HIE.

Methods: data was collected in two prospective cohort studies in the Netherlands. (Near) term neonates who received morphine while treated with TH for HIE were eligible for inclusion. A maximum of four plasma samples per neonate were obtained of four consecutive days during and after TH. Plasma concentrations for morphine and metabolites M3G and M6G were analysed using LC-MS/MS. PK analyses were performed using NONMEM (version 7.3). A dynamic model of temperature over time was included, which took the timing and the rate of cooling and rewarming into account.
The predicted body temperature was subsequently included in the PK model. A model for serum creatinine (SCr) was developed and parameters related to renal function from this model were included in the PK model.

Results: 244 patients (gestational age 39.8 ± 1.6 wk; birth weight 3428 ± 613 g) were assessed. Morphine was administered as continuous infusion; dose varied between 0.1 and 0.5 mg/kg/day. 832 plasma samples were analysed; 66% were drawn during TH. Morphine levels varied between 10 and 371 ng/ml. In one patient (0.4%) plasma levels exceeded the potentially toxic upper limit of 300 ng/ml[1].
PK parameters were best described with a one-compartment model for morphine and subsequent one-compartment models for both metabolites using birth weight based allometric scaling for body size and postnatal age for maturation. Rewarming increased morphine clearance by 5.3% (relative standard error (RSE) of 25%) per one °C and metabolite clearance by 7.3% (RSE 11%) per one °C. SCr derived renal function parameters were not related to metabolite clearance.

Conclusion: clearance of morphine, M3G and M6G is reduced in neonates undergoing TH compared to normothermia. Morphine dosing is based on clinical need and a therapeutic window for morphine plasma concentrations has not been firmly established. The present study suggests that morphine dosing according to current practice rarely leads to undesirable high plasma levels in this population.

References: [1]Pacifici.; Clinics 2016;71(5):474-480