Scientific Spring Meeting
Friday April 1, 2016

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 1, 2016
Jeroen Bosch Hospital, 's-Hertogenbosch

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

09.00 h **Welcome & coffee**

ORAL PRESENTATIONS

09.30 h *P.E. Spies, J.L.W. Pot, R.P.J. Willems, J.M. Bos, C. Kramers* ('s-Hertogenbosch): Interaction between tramadol and SSRI's: do doctors care?

09.45 h *E.C. Vasbinder, L.M.A. Goossens, M.P.M.H. Rutten-van Mölken, B.C.M. de Winter, L. van Dijk, A.G. Vulto, E.I.M. Blankman, N. Dahhan, M.T.M. Veenstra-van Schie, F.G.A. Versteegh, B.H.M. Wolf, H.M. Janssens, P.M.L.A. van den Bemt* (Rotterdam): e-Monitoring of Asthma Therapy to Improve Compliance in children: a randomised controlled trial (e-MATIC)

10.00 h *L.M. Henricks, D. Meulendijks, U. Amstutz, T.K. Froehlich, C.R. Largiadèr, J.H. Beijnen, A. de Boer, M.J. Deenen, A. Cats, J.H.M. Schellens* (Amsterdam): RS895819 in *MIR27A* improves the predictive value of *DPYD* variants to identify patients at risk of severe fluoropyrimidine-associated toxicity

10.15 h *I. Gesquiere, B. Hens, B. Van der Schueren, R. Mols, J. de Hoon, M. Lannoo, Ch. Matthys, V. Foulon, P. Augustijns* (Leuven): Influence of Roux-en-Y gastric bypass on oral disposition of fenofibrate and posaconazole

10.30 h *L. Stolk, F. de Vries, C. Ebbelaar, A. de Boer, T. Schalekamp, P. Souverein, A. ten Cate-Hoek, A. Burden* (Maastricht): Risk of myocardial infarction in patients with atrial fibrillation using vitamin k antagonists, aspirin or direct acting oral anticoagulants

10.45 h *W.H. Man, J.C.A. de Koning, P.F.J. Schulte, W. Cahn, I.M.M. van Haelst, H.J. Doodeman, A.C.G. Egberts, E.R. Heerdink, I. Wilting* (Utrecht): The effect of glycopyrrolate on clozapine-induced nocturnal sialorrhea in psychiatric patients: a randomized, crossover, double-blind, placebo-controlled trial

11.00 h **Coffee and Tea Break**

PHARMACOTHERAPY IN THE ELDERLY

11.15 h *Prof. dr. R. van Marum*: Clinical perspective

11.45 h *Prof. dr. A. Egberts*: Pharmacy perspective

12.15 h **LUNCH and POSTER SESSION**

1. *X. Liu, M.H.M. Diekstra, J.J. Swen, E. Boven, D. Castellano, H. Gelderblom, R.H.J. Mathijssen, C. Rodríguez-Antona, J. García-Donas, B.I. Rini, H-J. Guchelaar* (Leiden): Association of single nucleotide polymorphisms in *IL8* and *IL13* with sunitinib-induced toxicity in patients with metastatic renal cell carcinoma

2. *F.A.R. Franssen, J.E. de Haan, N.G.M. Hunfeld* (Rotterdam): Acute liver failure after molybdenum ingestion

3. *E. Ista, M.A. Baarslag, D.Tibboel, M. van Dijk, S.N. de Wildt* (Rotterdam): IV Paracetamol as first choice analgesic in infants after major surgery: RCT versus clinical practice findings

4. *M. van Luin, B. Klok, K. de Jong, M. de Maat, N. van Erp, S. Stalpers-Konijnenburg, A.W.G. Essink* (Arnhem): Clinical benefit from monitoring protein-unbound valproic acid plasma concentrations in selected patients

5. *D. Brinkman, J. Tichelaar, S. Benemei, Y. Böttiger, B. Chamontin, T. Christiaens, R. Likic, R. Maciulatis, M. Monteiro, P. Papaionnidou, Y.M. Pers, C. Pontes, R. Raskovic, R. Regenthal, R. Rissmann, E. Sanz, B. Tamba, K. Wilson, T. Schutte, T. de Vries, M.C. Richir, M. van Agtmael, On behalf of the Working Group Research on Education of the European Association for Clinical Pharmacology and Therapeutics (EACPT)* (Amsterdam): 837 European nearly graduates: a first multinational study of essential knowledge, skills and attitudes in clinical pharmacology and therapeutics

6. *P.E. Spies, R.P.J. Willems, J.L.W. Pot, J.M. Bos, C. Kramers* (’s-Hertogenbosch): Interaction between opioids and SSRIs: what do pharmacists do?

7. *L.G.W. Franken, A.D. Masman, B.C.M de Winter, B.C.P. Koch, F.P.M. Baar, D. Tibboel, T. van Gelder, R.A.A. Mathôt* (Rotterdam): Pharmacokinetics of midazolam and its metabolites in terminally ill patients

8. *E.A.M. Calvier, E.H.J. Krekels, P.A. Välitalo, A. Rostami-Hodjegan, D. Tibboel, M. Danhof, C.A.J. Knibbe* (Leiden): Allometric scaling of clearance in paediatrics : when does the magic of 0.75 fade?

9. *E.H.M. Schmitz, M.A.C. Broeren, L. Merry-Meier, R. Traksel, L.J.J. Derijks* (Veldhoven): Comparison of infliximab innovator (Remicade®) and biosimilar (Inflectra®) in rheumatic patients: an interim analysis of a switch-study

10. *G. Sidorenkov, K.P.J. Smits, J. Voorham, P. Denig* (Groningen): Association between prescribing quality indicators and surrogate outcomes in patients with type 2 diabetes

11. *N.T. Jessurun, R.J. van Marum, E.P. van Puijenbroek* (’s-Hertogenbosch): Faster onset of proton pump inhibitor induced hypomagnesemia when diuretics are concomitantly used

12. *H.J. Blussé van Oud-Alblas, M.J.E. Brill, M.Y.M. Peeters, D. Tibboel, M. Danhof, C.A.J. Knibbe* (Rotterdam): Propofol population pharmacokinetics and pharmacodynamics using Bispectral Index and composite A-line ARX index in adolescents undergoing scoliosis surgery with intraoperative wake-up test

13. *A.A. Blenke, R.J. van Marum, A.M. Vermeulen Windsant, W.A. Hermens, H.J. Derijks* (’s-Hertogenbosch): Success rate of advices and effectuated changes based on a structured medication review in psychogeriatric patients admitted to a nursing home: a prospective cohort study

14. *E.M.J. v. Brummelen, W. Ros, G.J. Wolbink, J.H. Beijnen, J.H.M. Schellens* (Amsterdam): The clinical relevance of anti-drug antibody formation in oncology

15. *S. Hadi, J. Hartstra, A. Stockis, P. Singh* (Zuidlaren): Brivaracetam bioavailability/bioequivalence comparison between 10, 50, 75 and 100 mg tablets and 100 mg intravenous bolus in healthy volunteers

16. *B. Schievink, T. Kröpelin, S. Mulder, P. Vemer, D. de Zeeuw, H. Lambers Heerspink* (Groningen): Early renin-angiotensin-system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes

17. *M.P. van der Aa, V. Hoving, E.M.W. van de Garde, A. de Boer, C.A.J. Knibbe, M.M.J. van der Vorst* (Nieuwegein): Eighteen-month treatment with metformin in obese adolescents: results on change in BMI in an outpatient clinic compared to results obtained in a clinical trial

18. *J.M. Penning de Vries, B.C.P. Koch, E. Wildschut, B.C.M. de Winter, M. de Hoog* (Rotterdam): Pharmacokinetics of pentobarbital in pediatric status epilepticus patients

19. *A. Sobels, L.Binkhorst, L.E.Visser, E.B. Wilms, J.E.A. Portielje* (Den Haag): Treatment variation of stage III colorectal cancer among hospitals

20. *S. Petrykiv, D. de Zeeuw, F.I. Persson, P. Rossing, H-H. Parving, G.D. Laverman, H.J. Lambers Heerspink* (Groningen): Optimizing between-patient variability in response to renoprotective drugs: meta-analysis of rotation trials

21. *C.E. van Ewijk, G.E. Jacobs, A.R.J. Girbes* (Amsterdam): Unsuspected serotonin toxicity in the ICU

22. *C.A.T.C. Lunenburg, M.C. van Staveren, H. Gelderblom, H.-J. Guchelaar, J.J. Swen* (Leiden): Clinical implementation of prospective *DPYD* genotyping in 5-fluorouracil or capecitabine treated patients

23. *E. Vandael, B. Vandenberk, R. Willems, J. Reyntens, J. Vandenberghe, V. Foulon* (Leuven): Risk management of hospitalized psychiatric patients taking multiple qt-prolonging drugs

24. *H. van Meir, M.J.P. Welters, T.C. van der Sluis, N.M. Loof, V.J. van Ham, S. van Duikeren, S.J. Santegoets, R. Arens, M.L. de Kam, A.F. Cohen, M.I.E. van Poelgeest, G.G. Kenter, J.R. Kroep, J. Burggraaf, C.J. Melief, S.H. van der Burg* (Leiden): Favorable immune response after properly timed HPV16-SLP vaccination during chemotherapy for advanced cervical cancer

25. *M.R. Dillingh, E.P. van Poelgeest, K.E. Malone, E.M. Kemper, E.S.G. Stroes, J. Burggraaf, M. Moerland* (Leiden): Human endotoxemia model: the effect of a single low dose of lipopolysaccharide on systemic inflammation, vascular activation and renal function

26. *M.J. Henstra, L. Wong, A. Chahbouni, F. Sombogaard* (Amsterdam): Pharmacokinetics of ibogaïne and noribogaine in a 46-yrs old woman with prolonged multiple cardiac arrhythmias after ingestion of internet purchased ibogaine

27. *R.M.J.M. van Geel, S. Leijen, G.S. Sonke, D. de Jong, E.H. Rosenberg, S. Marchetti, D. Pluim, E. van Werkhoven, S. Rose, M.A. Lee, T. Freshwater, J.H. Beijnen, J.H.M. Schellens* (Amsterdam): Wee1 inhibitor AZD1775 plus carboplatin in patients with *TP53* mutated ovarian cancer refractory or resistant to first-line therapy: a phase II study

28. *P.C.D. Bank, J.J. Swen, H.J. Guchelaar* (Leiden): An evaluation of Dutch pharmacists' knowledge, experience and attitudes towards pharmacogenetic testing: results of a nationwide survey

29. *R.B. Verheijen, L.E. Swart, H. Yu, J.H.M. Schellens, J.H. Beijnen, N. Steeghs, A.D.R. Huitema* (Amsterdam): Pharmacokinetic exposure of pazopanib in routine patient care: opportunities for dose optimization

30. *A.H.M. de Vries Schultink, R.P. Doornbos, A.B.H. Bakker, S. Shamsili, M. Throsby, J.H. Schellens, J.H. Beijnen, A.D.R. Huitema* (Amsterdam): Pharmacokinetics of MCLA-128 in monkeys and extrapolation to humans to support selection of first-in-human dose

31. *I.H. van der Sijs, L.C.P. Borra, F. de Velde* (Rotterdam): Medication review in paediatric outpatient cystic fibrosis patients; a new useful role for the hospital pharmacist

32. *M. Nabiollah, R. Admiraal, S.N. de Wildt, I.H. van der Sijs* (Rotterdam): Drug-drug interactions in a paediatric intensive care unit: a pilot study

33. *A.G.J Engbers, E.H.J. Krekels, E. Olofsen, A.P.J. de Vries, M.E.J. Reinders, J.W. de Fijter, J. den Hartig, H.J. Guchelaar, D.J.A.R. Moes* (Leiden): Population pharmacokinetics and limited sampling of once-daily tacrolimus in unstable renal transplant recipients

34. *A.G. Kalpoe, A. Sobels, L.E. Visser, R. Stuyt, N. Srivastava, E.B. Wilms* (Utrecht): The current therapeutic drug monitoring practice of infliximab in patients with Inflammatory Bowel Disease

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

14.15 h *Prof. dr. L.M.A.B. Van Bortel:* **Lifetime Achievement Lecture**

14.35 h Lecture of the winner of the **'NVKFB'-Thesis Award 2015:** *Dr. P.C. van Rijn-Bikker*

15.00 h Lecture of the winner of the **'NVKFB'-TOP Publication Award 2015:** *Dr. M. Brill*

15.15 h **Coffee and Tea Break**

ORAL PRESENTATIONS

15.30 h *M.M. van Weissenbruch, E. de Kort, S.A. Prins, P.G. van het Verlaat, A. Chahbouni, P. Andriessen, I.K.M. Reiss, E.L. Swart, S.H.P. Simons* (Amsterdam): Propofol for endotracheal intubation in preterm newborns: first data of a multicenter dose finding study

15.45 h *M.P. van der Aa, M.A.J. Elst, E.M.W. van de Garde, E.G.A.H. van Mil, C.A.J. Knibbe, M.M.J. van der Vorst* (Nieuwegein): Long-term treatment with metformin is effective in stabilizing BMI in obese, insulin resistant adolescents

16.00 h *K. Langenberg-Ververgaert, N. Broos, R. Lammers* (Ede): Subtherapeutic vancomycin levels in pediatric oncology patients: current initial dosing regimen does not suffice

16.15 h *F.J. van den Oever, C.F.M. Heetman-Meijer, E. Birnie, Y.C. Schrama* (Rotterdam): Pharmacy based dosing of darbepoetin: a randomized controlled trial in hemodialysis patients

16.30 h *S.C.A. Sparla, J.M.G. Coppens, I.M. Evers, C. Stramrood, P.C.M. Pasker-de Jong, M.M.L. van der Westerlaken, [E.L. Swart], P.H.G. Hogeman, M.M. Malingré* (Amersfoort): Plasmaconcentrations of psychotropic drugs in neonates as prognostic factor for admission to neonatology ward and withdrawal symptoms (proof-1)

16.45 h *E.P 't Hart, R. Alvarez, S. Prins, M. de Kam, G.J. Groeneveld* (Leiden): Validation of a cognitive challenge model with mecamylamine

17.00 h Closure and drinks

INTERACTION BETWEEN TRAMADOL AND SSRI'S: DO DOCTORS CARE?

Petra E. Spies, MD, PhD[1], J.L.W. (Hans) Pot, PharmD[2], Roel P.J. Willems, MD[3], Jacqueline M. Bos, PharmD[4], Cornelis Kramers, MD, PhD[4,5]

1 Jeroen Bosch hospital, 's-Hertogenbosch, The Netherlands
2 Meander medical center, Amersfoort, The Netherlands
3 Amphia hospital, Breda, The Netherlands
4 Canisius-Wilhelmina hospital, Nijmegen, The Netherlands
5 Radboud university medical center, Nijmegen, The Netherlands

Introduction: The combination of a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) with tramadol can result in serotonin syndrome, characterized by neuromuscular excitation, autonomic nervous system excitation, and altered mental state. The serotonin syndrome can range from mild to life-threatening and is more easily prevented than treated. Most overview articles consider awareness of the serotonin syndrome the most important step to prevent it (Boyer *et al* 2005; Buckley *et al* 2014), yet research among GP's showed that a mere 15% was aware of this potentially dangerous syndrome (Mackey *et al*, 1999).

Aim: To investigate whether prescribers in a general hospital were aware of this risk and if it influenced their prescribing behavior in clinical practice.

Methods: A questionnaire was sent to 185 physicians and 9 physician assistants in a general teaching hospital with over 650 beds in the Netherlands. The questionnaire presented four cases, two of whom used an SSRI or SNRI among other medications, and asked the respondent to prescribe an opioid in each case. The respondents were not aware of the focus of our research. In addition, actual prescription rates of tramadol in admitted patients who did or did not use an SSRI or SNRI were assessed by using the hospital pharmacy database.

Results: Seventy-one questionnaires were available for analysis. About one-third of respondents who prescribed tramadol indicated they were aware of the interaction with SSRI's or SNRI's. About one-fifth deliberately avoided tramadol because an interaction with SSRI's or SNRI's was identified. However, there was no difference in actual tramadol prescriptions: 23.8% of SSRI/SNRI-users received tramadol, versus 24.6% of non-SSRI/SNRI-users, calculated odds ratio 0.96 (95% CI 0.78-1.17).

Conclusions: A small part of prescribers in a general hospital is aware of the interaction between tramadol and SSRI's or SNRI's, yet this does not translate to a difference in tramadol prescriptions in clinical practice. Education could be one way to enhance the knowledge of prescribers, but hospital pharmacies may play an important role as well in signalling the interaction and advising prescribers.

References:
Boyer EW et al, New Engl J Med 2005;352:1112-20.
Buckley NA et al, BMJ 2014;348:g1626.
Mackay FJ et al, Br J Gen Pract 1999;49:871-4.

e-Monitoring of Asthma Therapy to Improve Compliance in children: a randomised controlled trial (e-MATIC)

EC Vasbinder[1,2], LMA Goossens[3], MPMH Rutten – van Mölken[3], BCM de Winter[1], L van Dijk[4], AG Vulto[1], EIM Blankman[5], N Dahhan[6], MTM Veenstra – van Schie[7], FGA Versteegh[2], BHM Wolf[8], HM Janssens[1], PMLA van den Bemt[1]

[1]Erasmus University Medical Center [2]Groene Hart Ziekenhuis [3]Institute for Medical Technology Assessment [4]NIVEL [5]BovenIJ Ziekenhuis [6]Academic Medical Center / Emma Children's Hospita l [8]Sint Lucas Andreas Ziekenhuis

Real time medication monitoring (RTMM) is a promising tool for improving adherence to inhaled corticosteroids (ICS), but has not been sufficiently tested in children with asthma. We aimed to study the effects of RTMM with SMS reminders on adherence to ICS, asthma control, asthma-specific quality of life, and asthma exacerbation rate; and to study the associated cost-effectiveness.

In a multicenter, randomised controlled trial, children (4-11 years) using ICS were recruited from five outpatient clinics and were given an RTMM device for 12 months. In a multicenter, randomised controlled trial, children (4-11 years) using ICS were recruited from five outpatient clinics and were given an RTMM device for 12 months. The intervention group also received tailored SMS reminders, sent only when a dose was at risk of omission. Outcome measures: adherence to ICS (RTMM data), asthma control (c-ACT questionnaire), quality of life (PAQLQ questionnaire) and asthma exacerbations. Costs were calculated from a healthcare and societal perspective.

We included 209 children. Mean adherence was higher in the intervention group: 69.3% vs. 57.3% (difference 12.0%; 95%CI: 6.7%-17.7%). No differences were found for asthma control, quality of life or asthma exacerbations. Costs were higher in the intervention group, but not statistically significant.

RTMM with tailored SMS reminders improved adherence to ICS, but not asthma control, quality of life or exacerbations in children using ICS for asthma.

Corresponding and presenting author:
p.vandenbemt@erasmusmc.nl

RS895819 IN *MIR27A* IMPROVES THE PREDICTIVE VALUE OF *DPYD* VARIANTS TO IDENTIFY PATIENTS AT RISK OF SEVERE FLUOROPYRIMIDINE-ASSOCIATED TOXICITY

Linda M. Henricks*[1], Didier Meulendijks*[1], Ursula Amstutz[2], Tanja K. Froehlich[2], Carlo R. Largiadèr[2], Jos H. Beijnen[1,3], Anthonius de Boer[3], Maarten J. Deenen[1], Annemieke Cats[1], Jan H.M. Schellens[1,3]

*Contributed equally
[1]Netherlands Cancer Institute, Amsterdam, the Netherlands
[2]Inselspital Bern University Hospital, Bern, Switzerland
[3]Utrecht University, Utrecht, the Netherlands

Introduction: Fluoropyrimidines are frequently used anticancer drugs. A critical determinant of fluoropyrimidine-associated toxicity (FP-toxicity) is dihydropyrimidine dehydrogenase (DPD) deficiency, often due to risk variants in the encoding gene *DPYD*. DPD activity is regulated at the post-transcriptional level by microRNA-27-a, encoded by *MIR27A*, and polymorphisms in *MIR27A* have been shown to affect DPD activity (Offer *et al*. 2014) and FP-toxicity in *DPYD* risk variant carriers (Amstutz *et al.* 2015).

Aim: The objective of this study was to determine whether genotyping of the *MIR27A* polymorphisms rs895819A>G and rs11671784C>T can be used to improve the predictive value of *DPYD* variants to identify patients at risk of severe FP-toxicity.

Methods: Patients (*N*=1592) treated with fluoropyrimidine-based chemotherapy in a previous prospective study (Deenen *et al.* 2015) were genotyped for *MIR27A* variants rs895819 and rs11671784, and *DPYD* variants c.2846A>T, c.1679T>G, c.1129-5923C>G, and c.1601G>A. The predictive value of *MIR27A* variants for early-onset grade ≥3 FP-toxicity, alone or in combination with *DPYD* variants, was tested in multi-variable logistic regression models. Random-effects meta-analysis was performed, including previously published data (Amstutz *et al.* 2015).

Results: Allele frequencies of rs895819 and rs11671784 were 0.331 and 0.020, respectively. In *DPYD* wild type patients, *MIR27A* variants did not affect risk of FP-toxicity (OR 1.3 for ≥1 variant *MIR27A* allele vs. none, 95% CI 0.87-1.82, *p*=0.228). In contrast, in patients carrying any of the genotyped *DPYD* variants, the presence of ≥1 rs895819 variant allele was associated with increased risk of FP-toxicity (OR 4.9, 95% CI 1.24-19.7, *p*=0.023). Rs11671784 was not associated with FP-toxicity (OR 2.9, 95% CI 0.47-18.0, *p*=0.253). Patients carrying a *DPYD* variant and rs895819 were at increased risk of FP-toxicity compared to patients wild type for rs895819 and *DPYD* (OR 2.4, 95% CI 1.27-4.37, *p*=0.007), while patients with a *DPYD* variant but without a *MIR27A* variant were not (OR 0.3, 95% CI 0.06-1.17, *p*=0.081). In meta-analysis, rs895819 remained significantly associated with FP-toxicity in *DPYD* variant carriers (OR 5.4, 95% CI 1.83-15.7, *p*=0.002).

Conclusion: In this study, we show that *MIR27A* variants can be used to improve the predictive value of *DPYD* variants c.2846A>T, c.1679T>G, and c.1129-5923C>G to identify patients at risk of severe FP-toxicity, and suggests a relevant effect of c.1601G>A on FP-toxicity risk in combination with rs895819. Combined *MIR27A*/*DPYD* screening could lead to better selection of patients who require a dose reduction of fluoropyrimidines.

References: Amstutz *et al.* Clin Cancer Res 2015;21(9):2038-44. Deenen *et al.* J Clin Oncol 2016;34(3):227-34. Offer *et al.* Mol Cancer Ther 2014;13(3):742-51.

RISK OF MYOCARDIAL INFARCTION IN PATIENTS WITH ATRIAL FIBRILLATION USING VITAMIN K ANTAGONISTS, ASPIRIN OR DIRECT ACTING ORAL ANTICOAGULANTS

L Stolk[1], F de Vries[13] , C Ebbelaar[3], A de Boer[3], T Schalekamp[3], P Souverein[3], A ten Cate-Hoek[2], A Burden[13]
Dpts of [1]Clinical Pharmacy and Toxicology, [2] Internal Medicine, Maastricht University Medical Centre, The Netherlands [3] Dpt of Pharmaceutical Sciences, Utrecht University, The Netherlands.

Introduction. Since 2009 direct acting oral anticoagulants (DOACs) have become available, for the prevention of stroke in patients with atrial fibrillation (AF). Conflicting results have been published on the risk of acute myocardial infarction (AMI) with the use of DOACs in comparison with vitamin k antagonists (VKAs). Objective of this study was to evaluate the risk of AMI in patients with AF who are exposed to either VKAs, DOACs or low dose (< 325 mg) aspirin.

Methods. We conducted a population based cohort study using data of the Clinical Practice Research Datalink (2008-2014). The study population (n = 30146) consisted of all patients > 18 years with diagnosis atrial fibrillation and new users of either VKAs, or DOACs, or aspirin. Cox proportional hazards models were used to estimate the hazard ratio (HR) of AMI for users of DOACs or aspirin versus VKA users. Adjustments were made for age, sex, lifestyle risk factors, comorbidity and other drugs.

Results. Following the inclusion and exclusion criteria, we identified 30,146 new users of DOACs (n=1266), VKAs (n= 13098) , low dose aspirin (n = 15400) or mixed users (n=382) at index date. The DOACs were rivaroxaban (71.6%) and dabigatran (28.4%).

Results are presented in table 1. Risk for AMI was doubled when we compared current use of DOACs with current use of VKAs (adj. HR 2.11; 95% CI 1.08 – 4.12). A similar increase was observed among users of aspirin versus VKAs users (adj. HR 1.91; 95% CI 1.45-2.51 CI 1.45-2.51). Among patients with past aspirin use, use was associated with increased risk.

Table 1**:**

Exposure	Number of AMI	IR 1000 PY	Age/Sex adjusted HR (95% CI)	Adjusted HR final (95% CI)
Current VKAs	81	2.90	reference	reference
Current DOAC	10	5.00	2.10 (1.08-4.10)*	2.11 (1.08-4.12)*
Current Aspirin	114	6.05	1.84 (1.40-2.42)*	1.91 (1.45-2.51)*
Current Mixed	5	5.27	1.80 (0.73-4.42)	1.69 (0.69-4.16)

Abbreviations: AMI acute myocardial infarction, DOACs direct acting oral anti coagulants , IR incident rate, PY per Year. * p < 0.05. Adjusted for: age, sex, bmi, alcohol status, smoking status, antihypertensives, congestive heart failure, statins.

Conclusion. Our cohort study identified a twofold increase of risk for AMI when using the DOACs, rivaroxaban or dabigatran, in comparison with VKAs in AF therapy of real world patients. In addition, results suggest that in patients with AF the relative risk of aspirin, as monotherapy, versus VKAs is higher.

The effect of glycopyrrolate on clozapine-induced nocturnal sialorrhea in psychiatric patients: a randomized, crossover, double-blind, placebo-controlled trial

W.H. Man*[1], J.C.A. de Koning*[2], P.F.J. Schulte[3], W. Cahn[4], I.M.M. van Haelst[2], H.J. Doodeman[2], A.C.G. Egberts[1], E.R. Heerdink[1], I. Wilting[1]. [1]Department of Clinical Pharmacy, University Medical Center Utrecht, The Netherlands, [2] Department of Clinical Pharmacy, Medical Centrum Alkmaar, The Netherlands,[3] Mental Health Services North-Holland North, Heerhugowaard, The Netherlands,[4] Department of Psychiatry, University Medical Center Utrecht, The Netherlands. * Both authors contributed equally to this work.

Introduction: Clozapine-induced (nocturnal) sialorrhea (CIS) is one of the most frequent adverse effects of clozapine. Glycopyrrolate, in contrast to most anticholinergic drugs, does not cross the blood-brain barrier and is therefore not associated with central anticholinergic adverse effects (1). The objective of the study was to evaluate the therapeutic and adverse effects of glycopyrrolate in psychiatric patients with CIS.

Methods: This four week, randomized, double-blind, cross-over study compared glycopyrrolate with placebo, included an optional open-label extension of glycopyrrolate during two weeks and was conducted in two medical centers in The Netherlands from April 2013 to June 2015. Patients with a psychiatric disorder according to DSM-IV treated with clozapine and suffering from CIS were randomly assigned to receive once daily one mg glycopyrrolate or placebo before bedtime in two periods of six consecutive days. During the open-label phase the subjects received two mg glycopyrrolate before bedtime once daily. The primary outcome was clinical improvement of CIS assessed by the Patient Global Impression of Improvement (PGI-I). Secondary outcomes were severity of CIS (PGI-S), extent of nocturnal hypersalivation (NHRS) and patients' satisfaction with clozapine (MSQ). After each treatment week adverse event monitoring was done through patient questionnaires and lab results. Patients were asked to identify their treatment preference.

Results: 32 patients were included. Glycopyrrolate one mg once daily compared to placebo did not significantly differ according to PGI-I (18.8% vs 6.3%, p=0.289), but significantly more patients reported improvement in glycopyrrolate two mg once daily vs placebo (43.5% vs 6.3%, p=0.039). Significant reductions in PGI-I (2.65 vs 3.75), PGI-S (2.13 vs 3.34) and NHRS (1.52 vs 2.66) were observed in glycopyrrolate two mg vs placebo. Significantly more patients preferred one mg over placebo after the double-blinded phase (46.9% vs 6.3%), and significantly more patients preferred two mg over placebo after the open label phase (56.5% vs 0%). Glycopyrrolate was not associated with severe adverse events and worsening of central adverse events.

Conclusion: Glycopyrrolate two mg but not one mg once daily showed a clinical significant improvement of nocturnal CIS compared to placebo in psychiatric patients. Both glycopyrrolate one mg and two mg were not associated with severe adverse events nor any central adverse events and therefore seemed to be a tolerable anticholinergic agent in the treatment of CIS.

Reference: (1) Paton et al,(1952). The methonium. Pharmacol Rev. 4(3):219–53.

ASSOCIATION OF SINGLE NUCLEOTIDE POLYMORPHISMS IN *IL8* AND *IL13* WITH SUNITINIB-INDUCED TOXICITY IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Xiaoyan Liu[1,2,3,*], Meta H.M. Diekstra[1,2,*], Jesse J. Swen[1,2], Epie Boven[2,4], Daniel Castellano[5,6], Hans Gelderblom[2,7], Ron H.J. Mathijssen[2,8], Cristina Rodríguez-Antona[9,10], Jesus García-Donas[6,11], Brian I. Rini[12], Henk-Jan Guchelaar[1,2]

*Both authors contributed equally

[1]Dept. of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands,
[2]Dutch SUTOX consortium,
[3]Institute of Clinical Pharmacology, Qilu Hospital of Shandong University, Jinan, China,
[4]Dept. of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands,
[5]Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain,
[6]Spanish Oncology Genitourinary Group (SOGUG), Madrid, Spain,
[7]Dept. of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands,
[8]Dept. of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands,
[9]Hereditary Endocrine Cancer Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain,
[10]ISCIII Center for Biomedical Research on Rare Diseases (CIBERER), Madrid, Spain,
[11]Oncology Unit, Clara Campal Comprehensive Cancer Center, Madrid, Spain,
[12]Dept. of Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute (CCF), Cleveland, Ohio, USA.

Aims Earlier, the association of Single Nucleotide Polymorphisms (SNPs) with toxicity and efficacy of sunitinib has been explored in patients with metastatic renal cell carcinoma (mRCC). Recently, additional SNPs have been suggested as potential biomarkers. We investigated these novel SNPs for association with sunitinib treatment outcome in mRCC patients.

Methods In this exploratory study, we selected SNPs in genes *CYP3A4*, *NR1I2*, *POR*, *IL8*, *IL13*, *IL4-R*, *HIF1A* and *MET* that might possibly be associated with sunitinib treatment outcome. Each SNP was tested for association with progression-free survival (PFS) and overall survival (OS) by Cox-regression analysis, and for clinical response and toxicity using logistic regression.

Results We included 374 patients for toxicity analyses, of which 38 patients with non-clear cell renal cell cancer were excluded from efficacy analyses. The risk for hypertension was increased in presence of the T allele in *IL8* rs1126647 (OR=1.69, 95%CI=1.07-2.67, *P*=0.024). The T allele in *IL13* rs1800925 was associated with an increase in the risk of leukopenia (OR=6.76, 95%CI=1.35-33.9, *P*=0.020) and increased prevalence of any toxicity > grade 2 (OR=1.75, 95%CI=1.06-2.88, *P*=0.028). No significant associations were found with PFS, OS or clinical response.

Conclusions We show that polymorphisms in *IL8* rs1126647 and *IL13* rs1800925 are associated with sunitinib-induced toxicities. Validation in an independent cohort is required.

ACUTE LIVER FAILURE AFTER MOLYBDENUM INGESTION

FAR Franssen[1], JE de Haan[1] and NGM Hunfeld[1,2]
1) Intensive Care Unit and 2) Pharmacy, ErasmusMC, Rotterdam, the Netherlands

Molybdenum is a heavy metal and essential dietary trace element. Molybdenum intoxication is extremely rare and its clinical course and treatment are unknown.

Presenting symptoms
A 31-year old patient, known with a delusional psychiatric disorder, thought he suffered from Wilson's disease and started treating himself with 10g molybdenum once daily. Two days prior to referral to our center, the patient was admitted to the ICU because of severe hypokalemia following vomiting and diarrhea. Subsequently distributive shock, acute kidney injury and acute liver failure developed. At referral, he was grade III encephalopathic, in severe distributive shock and anuric. Laboratory evaluation revealed severe lactic acidosis (27mmol/L), elevated transaminases, hyperbilirubinemia, severe coagulopathy and hypoglycemia.

Clinical Course
After admission to our ICU, intravenous chelation therapy (dimercaptopropanesulfonate, DMPS) and hemofiltration was initiated. Patient fulfilled King's College Criteria for poor prognosis in acute liver failure and was listed for high-urgency liver transplantation. The night following admission, the patient developed progressive hepatic encephalopathy requiring intubation. Despite high-volume hemofiltration and chelation the patient's condition deteriorated. Twenty hours after admission he developed refractory shock leading to cardiac arrest. The patient died three days after presentation. Post-mortem examination revealed extensive internal petechiae and remarkable stiff liver. Microscopy showed extensive liver necrosis. Molybdenum level in blood was 23 mg/L (reference 0.9-1.8µg/L), in liver tissue 12µg/g and in hemofiltration fluid 4.4 mg/L.

Discussion
Molybdenum is a trace element, its highest concentrations are found in serum, liver and kidneys; there is no evidence of bioaccumulation in other human tissue. Our patient ingested a massive amount of molybdenum leading to a 10000-fold increased serum level causing acute liver failure and kidney injury. Since little is known about molybdenum toxicity, we based our treatment on literature of heavy metal intoxications, therefore hemofiltration and chelator therapy were initiated. We argued that liver transplantation was the only possible therapeutic intervention. Despite aggressive supportive care, the patient's condition failed to improve and he died awaiting a liver transplantation. Post mortem examination revealed high molybdenum levels in the liver, suggesting it to be the causing agent of liver necrosis. It remained unclear whether kidney failure was also due to molybdenum intoxication or secondary to acute liver failure and shock.

Conclusion
This is the first well documented case of acute liver failure after molybdenum intoxication. Supportive treatment should comprehend intravenous chelation in combination with high-volume hemofiltration. Given its fulminant clinical course, early referral and listing for liver transplantation is crucial.

IV PARACETAMOL AS FIRST CHOICE ANALGESIC IN INFANTS AFTER MAJOR SURGERY: RCT VERSUS CLINICAL PRACTICE FINDINGS

Authors:
Erwin Ista, Manuel A Baarslag, Dick Tibboel, Monique van Dijk and Saskia N de Wildt
Department of Intensive Care and Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands.

Background and aim:
Opioids are the first choice of analgesic treatment after major surgery in infants. In a previous RCT we showed that paracetamol IV as primary analgesic reduced morphine requirements by 66% with comparable pain scores. Now we aimed to study if these results could be confirmed in daily practice.

Methods:
In a prospective study, from February 2014 to December 2015, we included infants up to the age of 1 year, after major non-cardiac thoracic or abdominal surgery. As part of the revised clinical protocol, they received a loading dose IV paracetamol after arrival in the PICU, followed by q4h paracetamol IV. When pain was suspected (COMFORT-B ≥17 and NRS≥4), a morphine rescue bolus was administered with dose adjusted for postnatal age (10 mcg/kg if ≤10 days vs. 15 mcg/kg if >10 days) which could be repeated twice within one hour. If pain persisted, continuous morphine was to be started. Protocol adherence and morphine consumption were documented. Findings were compared to the original results of our RCT.

Results:
We included 77 patients; 64 were ≤10days of age (83%). Seventy-five (97.4%) received IV paracetamol of whom 42 (56%) did not need rescue morphine. The two other patients received rectal paracetamol. 35 infants (46.7%) needed rescue morphine, with a median of 2 boluses (IQR 1-4), 27 also needed continuous morphine infusion with median dosage of 7.9 mcg/kg/u (IQR 5-10). After implementation, the median cumulative morphine consumption across the first 48 hours postoperatively [111 mcg/kg (IQR 0-279)] was not different from that in the RCT paracetamol condition [121 mcg/kg (IQR 99-264)] ($p<0.05$).

Conclusion:
The results of our study confirm that IV paracetamol as first-choice analgesic after major surgery works well in daily practice. Adherence to IV paracetamol was high, while continuous morphine was started sooner and higher than the revised clinical protocol dictated.

CLINICAL BENEFIT FROM MONITORING PROTEIN-UNBOUND VALPROIC ACID PLASMA CONCENTRATIONS IN SELECTED PATIENTS

Authors:
M. van Luin[1], PhD, PharmD; B.Klok[1], PharmD, K. de Jong[1], M. de Maat[1], Pharm D, PhD, N. van Erp[2], PhD, PharmD, S. Stalpers-Konijnenburg[3,4,] MD, AWG Essink[1], PharmD
Affiliations:
1.Department of Clinical Pharmacy, Hospital Rijnstate, Arnhem, 2. Department of Clinical Pharmacy, Radboudumc, Nijmegen, 3. Department of Geriatrics, Hospital Rijnstate Arnhem, 4. Stichting Pro Persona, Arnhem

INTRODUCTION
Valproic acid (VPA) is an effective anti-epileptic drug, which is also used as mood stabilizer. A key characteristic of VPA is its high binding of approximately 90% to plasma proteins, predominantly albumin. While the 10% protein-unbound concentration of VPA is responsible for its pharmacological activity, total drug concentrations are monitored in routine clinical practice, mainly for feasibility reasons. In our local therapeutic drug monitoring (TDM) protocol, TDM of unbound VPA is recommended for specific clinical scenarios, such as decreased renal function or hypo-albuminemia. The goal of our study was to evaluate the use of TDM of unbound VPA.

METHODS
We evaluated all TDM requests for unbound VPA in 2014 and 2015. In patients with potentially toxic unbound VPA concentrations (i.e., > 12 mg/L), we evaluated whether toxicity was noted and whether the TDM result was followed by a VPA dose reduction. Unbound VPA concentrations were measured by means of a validated immune-assay at the laboratory of the Department of Clinical Pharmacy from the Radboudumc.

RESULTS
In 2014 and 2015, we analyzed 273 unbound VPA plasma concentrations in 132 different patients. The median age of these patients was 65 years (range 10-93); 52% of them were men. The main reasons for requesting TDM of unbound VPA were decreased renal function (34%) and a low serum albumin (27%). In the initial concentration measurement in these 132 patients, the median (range) unbound VPA concentration was 9.8 (2.5-47.6) mg/L (therapeutic concentration range 4-12 mg/L).
In 49 of the 132 patients (37%), the initial unbound VPA concentration was above the threshold of 12 mg/L, potentially resulting in toxicity. Of note, only 4 of these 49 patients had elevated total VPA concentrations (i.e., >100 mg/L). Clinical toxicity was noted in 37 of the 49 patients with elevated unbound VPA concentrations. Reported toxicities varied from drowsiness (n=28) to rigidity (n=2), lethargy (n=2), hypotension (n=1) and even decreased consciousness (n=4). In 36 of the 37 patients with elevated unbound VPA concentrations and clinical toxicity, a dose reduction was applied (median dose reduction 40%). In the majority of patients who had their dose reduced (28 out of the 36 patients), dose reduction was associated with improvement or resolution of suspected VPA toxicity.

CONCLUSION
TDM of unbound VPA is an important tool to manage VPA therapy in selected, vulnerable patients

837 European nearly graduates: a first multinational study of essential knowledge, skills and attitudes in clinical pharmacology and therapeutics

D. Brinkman, J. Tichelaar, S. Benemei, Y. Böttiger, B. Chamontin, T. Christiaens, R. Likic, R. Maciulatis, M. Monteiro, P. Papaionnidou, Y.M. Pers, C. Pontes, R. Raskovic, R. Regenthal, R. Rissmann, E. Sanz, B. Tamba, K. Wilson, T. Schutte, T. de Vries, M.C. Richir, M. van Agtmael
On behalf of the Working Group Research on Education of the European Association for Clinical Pharmacology and Therapeutics (EACPT)

Introduction
In order to prescribe safely and effectively, European medical students should have acquired a minimum set of prescribing competencies at the point of graduation (Maxwell *et al*., 2007). However, it has never been investigated whether this requirement is met. Therefore, the aim of this multinational study is to evaluate the essential knowledge, skills and attitudes in clinical pharmacology and therapeutics (CPT) of final-year medical students across European medical schools.

Methods
In this descriptive, cross-sectional study, a formative standardized assessment and survey was conducted of 827 final-year students from 17 medical schools across 14 European countries (BE, DE, ES, GR, FR, HR, IT, LT, NL, PT, RS, RO, SE, UK). The assessment (web-based) consisted of 24 MCQs and 5 patient case descriptions. The assessment and survey was developed with all participating European schools and reflected knowledge, skills and attitudes in CPT that medical graduates should possess. Universities are equally weighted in reported results. Ethical approval was given by the Dutch Ethics Review Board of Medical Education.

Results
Overall, students had a mean knowledge score of 69.2% (SD 15.1), with lowest score in subdomain drug interactions and contraindications (49.8% [SD 21]). Regarding the patient cases, only 26.8% (range 3-43) of students' therapy choices was classified as appropriate. The remaining therapy choices (73.2%) were incorrect, with 9,4% (range 6-15) being potentially harmful and 2.2% (range 1-4) potentially lethal for the patient. Additionally, at least one prescribing error was found in 69.4% of the items prescribed. Students showed a general lack of confidence about essential prescribing skills. Only one-third of the students felt adequately prepared for their future prescribing task as a doctor. And lastly, the majority of students (≥75%) was not satisfied about the undergraduate teaching in clinical pharmacology and pharmacotherapy and believed that the overall amount of teaching in both subjects was insufficient.

Conclusion
Although there exist variation between medical schools, our findings show an overall lack of essential prescribing competencies among European nearly graduates. This suggest that the undergraduate education in CPT throughout Europe is insufficient leading to incompetent prescribers and potentially unsafe medical care. Our results emphasize the urgent need to collaboratively develop a core curriculum in CPT that should be used throughout European medical schools.

References
Maxwell *et al.* Basic Clin Pharmacol Toxicol 2007;101(6): 391-400.

INTERACTION BETWEEN OPIOIDS AND SSRIS: WHAT DO PHARMACISTS DO?

Petra E. Spies, MD, PhD[1], Roel P.J. Willems, MD[2], J.L.W. (Hans) Pot, PharmD[3], Jacqueline M. Bos, PharmD[4], Cornelis Kramers, MD, PhD[4,5]

1 Jeroen Bosch hospital, 's-Hertogenbosch, 2 Amphia hospital, Breda, 3 Meander medical center, Amersfoort, 4 Canisius-Wilhelmina hospital, Nijmegen, 5 Radboud university medical center, Nijmegen, The Netherlands

Introduction: The combination of a selective serotonin or serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) with certain opioids can result in serotonin syndrome, a potentially life-threatening syndrome that is more easily prevented than treated. There are no published case reports that describe this syndrome as a result of an SSRI or SNRI combined with morphine, but concurrent use with fentanyl, oxycodone and tramadol have all been associated with serotonin syndrome. Problems with tramadol are most often reported, whereas the mechanistic evidence for oxycodone is most scarce. Current guidelines, however, do not make a clear distinction between fentanyl, oxycodone and tramadol where combinations with serotonergic agents are concerned and generally advise to inform the patient and consider replacing serotonergic opioids with non-serotonergic opioids.

Aim: To investigate the policy of hospital pharmacies and general pharmacies regarding the combination of different opioids and SSRIs/SNRIs.

Methods : We approached 11 hospital pharmacies and 60 general pharmacies in the Netherlands by e-mail to fill out a questionnaire. A reminder was sent after 4 weeks. Eleven hospital pharmacies (100%) and 18 general pharmacies (30%) returned the questionnaire.

Results: Half of hospital and general pharmacies described an action when an SSRI/SNRI was combined with fentanyl or oxycodone, whereas more than 80% reacted when an SSRI/SNRI was combined with tramadol. If an SSRI/SNRI was prescribed coincidentally with tramadol, prescribers and patients would be more often informed by the pharmacy and receive advice about alternative drugs.

	Hospital pharmacies (n=11)	**General pharmacies (n=18)**
SSRI/SNRI + tramadol		
No action	2 (18%)	3 (17%)
Inform prescriber	6 (55%)	5 (28%)
Inform patient	n.a.	13 (72%)
Advise about alternative	4 (36%)	2 (11%)
Other	3 (27%)	0
SSRI/SNRI + oxycodon/fentanyl		
No action	6 (55%)	9 (50%)
Inform prescriber	3 (27%)	4 (22%)
Inform patient	n.a.	7 (39%)
Advise about alternative	1 (9%)	1 (6%)
Other	3 (27%)	0

Conclusions: Although guidelines do not clearly differ in their advice when an SSRI/SNRI is combined with either fentanyl, oxycodone or tramadol, both hospital pharmacies and general pharmacies give more emphasis to the combination with tramadol. This suggests that empirical evidence or evidence from case reports adds importantly to current guidelines.

PHARMACOKINETICS OF MIDAZOLAM AND ITS METABOLITES IN TERMINALLY ILL PATIENTS.

L.G.W. Franken (1), A.D. Masman (2,3), B.C.M de Winter (1), B.C.P. Koch (1), F.P.M. Baar (2), D. Tibboel (3,4), T. van Gelder (1) and R.A.A. Mathôt (5)

1 Department of Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, the Netherlands
2 Palliative Care Centre, Laurens Cadenza, Rotterdam, the Netherlands
3 Intensive Care, Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands
4 Pain Expertise Centre, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands
5 Hospital Pharmacy – Clinical Pharmacology, Academic Medical Centre, Amsterdam, the Netherlands

Background: Midazolam is a commonly used sedative drug in terminally ill patients and is titrated to achieve the desired level of sedation. In the case of refractory symptoms it is of great clinical importance to achieve adequate sedation as soon as possible. As the terminally ill are a very heterogeneous population with severe co-morbidity, including hepatic and renal impairment, it would be preferential if an individualised dose could be determined beforehand. To find clinical relevant parameters for dose individualisation we performed a pharmacokinetic study on midazolam, 1OH-midazolam (1OH-M) and 1OH-midazolam-glucuronide (1OH-MG) in terminally ill patients.

Methods: A population pharmacokinetic analysis was conducted with 192 samples, using non-linear mixed effects modelling (NONMEM 7.2). The covariates analysed were patient characteristic, co-medication and blood chemistry levels.

Results: The data were best described by a one-compartment model for midazolam, 1OH- midazolam and 1OH-midazolam-glucuronide. Between-subject variability (BSV) was shown for the bioavailability of midazolam, clearance of midazolam, 1OH-M and 1OH-MG and for the volume of distribution of midazolam. The population mean estimates for midazolam, 1OH-M and 1OH-MG clearance were 9.1 L/h (BSV 46.3%), 47.5 L/h (BSV 57.5%) and 5.7L/h (BSV 48.6%) respectively. Low albumin levels corresponded with low midazolam clearance and explained 19.1% of the BSV in midazolam clearance. 1OH-MG clearance was correlated with the estimated glomular filtration rate explaining 40% of the BSV in 1OH-MG clearance.

Conclusion: The population pharmacokinetics of midazolam and its two major metabolites were accurately quantified. A decreased eGFR resulted in lower clearance of 1OH-midazolam-glucuronidine and could therefore result in increased sedation. Low albumin levels resulted in decreased midazolam clearance, which is probably an effect inflammatory response, as CRP as a covariate had a similar effect yet less significant. eGFR and albumin might therefore be useful clinical parameters to develop an individualized dosing regimen, however before this can be achieved the pharmacodynamics effects requires further study.

ALLOMETRIC SCALING OF CLEARANCE IN PAEDIATRICS : WHEN DOES THE MAGIC OF 0.75 FADE?

Calvier EAM[1], Krekels EHJ[1], Välitalo PA[1], Rostami-Hodjegan A[2], Tibboel D[3], Danhof M[1], Knibbe CAJ[1,4]

[1] Division of Pharmacology, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands
[2] Manchester Pharmacy School, University of Manchester, Manchester, UK
[3] Intensive Care and Department of Pediatric Surgery, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, The Netherlands
[4] Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands

Allometric scaling on the basis of bodyweight raised to the power of 0.75 (AS) (Anderson *et al*., 1997) is frequently used to scale size-related changes in plasma clearance (CLp) from adults to children. A systematic assessment of its applicability is undertaken for drugs cleared through hepatic metabolism or glomerular filtration (GF).

A physiologically-based pharmacokinetic (PBPK) simulation workflow was developed in R for 12620 hypothetical drugs. In one scenario, only size-related changes in liver weight, hepatic blood flow, and glomerular filtration rate were included in simulations of 'true' paediatric CLp (Johnson *et al*., 2006). In a second scenario, also maturation in unbound microsomal intrinsic clearance (CLint,mic), plasma protein concentration (Johnson *et al*., 2006), and haematocrit (Irwin *et al*., 2001) were included in these simulated 'true' paediatric CLp values. For the first scenario, an allometric exponent was estimated based on 'true' CLp, while for both scenarios, the prediction error (PE) of AS-based paediatric CLp predictions was assessed.

In the first scenario, the estimated allometric exponent ranged from 0.50 to 1.20 depending on age and drug properties, with PE of AS-based paediatric CLp predictions reaching up to 253% in neonates. In the second scenario, the PE sensitivity to drug properties and maturation was higher in the youngest children, with AS resulting in accurate CLp predictions above five years of age.

Using PBPK principles, it was shown that there is no evidence for one unique allometric exponent in paediatrics, even in scenarios that only consider size-related changes. As PE is most sensitive to the exponent, drug properties and maturation in younger children, AS leads to increasingly worse predictions with decreasing age.

Anderson BJ *et al*. (1997). Clin. Pharmacokinet., 33(5):313–27
Irwin JJ *et al*. (2001). Am. Fam. Physician, 64(8):1379–86
Johnson TN *et al*. (2006). Clin. Pharmacokinet., 45(9):931–56

COMPARISON OF INFLIXIMAB INNOVATOR (REMICADE®) AND BIOSIMILAR (INFLECTRA®) IN RHEUMATIC PATIENTS: AN INTERIM ANALYSIS OF A SWITCH-STUDY

EHM Schmitz[2], MAC Broeren[2], L Merry-Meier[3], R Traksel[3], LJJ Derijks[1]

Departments of [1]Clinical Pharmacy, [2]Clinical Chemistry and [3]Rheumatology, Máxima Medical Center, Veldhoven, The Netherlands

Introduction: Infliximab (IFX) has been successfully used to treat inflammatory diseases for many years. Since 2015, IFX biosimilars (Inflectra® and Remsima®) have entered the market. Registration studies in rheumatic populations have demonstrated pharmacokinetics, efficacy, safety and immunogenicity to be comparable to IFX innovator (Remicade®)[1,2]. To determine comparability in clinical practice we studied the controlled switch from Remicade® to Inflectra® in our cohort of rheumatic patients.

Methods: All rheumatic patients treated with Remicade® of the Department of Rheumatology of Máxima Medical Center were included. Infliximab trough levels, antibodies to IFX (ATI's), CRP, ESR, and validated disease activity scores were determined just before the first, second, fourth and seventh infusion of Inflectra®. Infliximab levels were measured using the apDia IFX ELISA kit, ATI levels were measured at Sanquin Diagnostics (Amsterdam) only if IFX levels were < 1 μg/ml. Correlation was determined using Spearman's correlation, equality using the Wilcoxon signed rank analysis.

Results: Firstly, we showed that the apDia IFX ELISA kit yielded similar results for spiked samples containing Remicade® or Inflectra®. Twenty-eight patients were included. At the moment of interim-analysis, the second IFX trough level was determined in 22 patients. Median IFX levels were 2.4 [IQR 1.5-7.3] and 2.4 [IQR 1.4-4.9] μg/ml for Remicade and Inflectra respectively (p=0.610). IFX levels correlated well (R^2=0.91, p<0.0001)(Figure 1). No significant differences in IFX level, CRP, ESR and disease activity scores could be observed after the switch from Remicade® to Inflectra®.

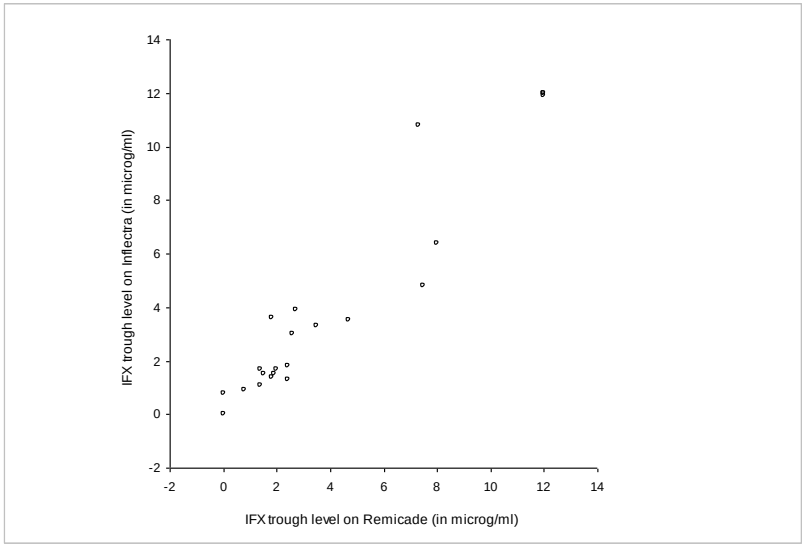


Figure 1. Scatterplot of IFX trough levels on Remicade® versus Inflectra®

Conclusion: The first interim results of this switch study indicate that Remicade and Inflectra are indeed comparable in the treatment of rheumatic patients.

References

[1] Park W *et al.*, Ann Rheum Dis 2013;72:1605-12.
[2] Yoo DH *et al.*, Ann Rheum Dis 2013;72:1613-20.

Association between prescribing quality indicators and surrogate outcomes in patients with type 2 diabetes

G. Sidorenkov[1], K.P.J. Smits[1], J. Voorham[1], P. Denig[1]
[1] Department of Clinical Pharmacy & Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Introduction Clinical guidelines provide the recommendations for optimal treatment for patients with type 2 diabetes mellitus (T2DM). To measure whether the optimal treatment is actually delivered in practice a set of novel longitudinal prescribing quality indicators (PQIs) was developed in the Netherlands by a group of experts. The aim of this study is to assess whether the developed PQIs for treatment of cardiovascular and renal risk factors are associated with better surrogate outcomes in patients with T2DM.
Methods For this cohort study data were used from >20,000 patients with T2DM in the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT). Included PQIs measured the quality of treatment with glucose-lowering drugs, statins, antihypertensives and RAAS-blockers in the year 2012. The surrogate outcomes were follow-up measurements of HbA1c, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP), and micro/macro-albuminuria in the next year. Associations were tested between receiving the recommended treatment as measured by each PQI (yes/no) and the related surrogate outcome using linear regression for HbA1c, LDL-C and SBP and logistic regression for albuminuria while adjusting for baseline values, age, gender and diabetes duration. Effect sizes with 95% confidence intervals (95%CI) are reported for linear regression and odds ratios (OR) with 95%CI for logistic regression.
Results In total, eleven PQIs were tested. The PQIs measuring initiation and intensification of glucose-lowering drugs, and initiation of insulin were all associated with better follow up HbA1c (resp. −0.57% (95%CI −0.16 to −0.99); −0.61% (95%CI −0.49 to −0.74); −0.78% (95%CI −0.67 to −0.90)). The PQIs measuring initiation and intensification of statins were associated with better LDL-C (resp. −0.90 mmol/l (95%CI −0.85 to −0.96); −0.58 mmol/l (95%CI −0.51 to −0.64)). The PQI measuring prevalent statin use was also associated with better LDL-C (−0.24 mmol/l (95%CI −0.21 to −0.26)). The PQIs measuring initiation and intensification of antihypertensives were associated with better SBP (resp. −7.92 mmHg (95%CI −5.93 to −9.90); −7.81 mmHg (95%CI −5.93 to −9.69)). The PQI measuring initiation of RAAS-blockers (either ACE-i or ARB) was associated with lower risk of micro/macro-albuminuria (OR: 0.21 (95%CI 0.10-0.44)). The PQIs measuring the preference of treatment with RAAS-blockers among T2DM patients with micro/macro-albuminuria treated with antihypertensives or among T2DM patients treated with 2 or more antihypertensives were not associated with a risk of micro/macro-albuminuria.
Conclusions Nine of the novel PQIs for treatment with glucose-lowering drugs, statins and antihypertensives in T2DM patients were associated with better surrogate cardiovascular and renal outcomes, which supports their validity for clinical practice.

Faster onset of proton pump inhibitor induced hypomagnesemia when diuretics are concomitantly used

N.T. Jessurun[1], R.J. van Marum[2,3], E.P. van Puijenbroek[1,4]
[1]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, [2]Jeroen Bosch Hospital, 's-Hertogenbosch, [3]Department of General Practice & Elderly Care Medicine / EMGO Institute for Health and Care Research, VU University Medical Center Amsterdam, [4]Pharmacotherapy and Pharmaceutical Care, Department of Pharmacy, University of Groningen

Hypomagnesaemia is a an adverse drug reaction (ADR) of proton pump inhibitors (PPIs) which is often seen after years of use. PPI induced hypomagnesemia is poorly understood but may reflect impaired gastrointestinal absorption of magnesium by inhibition of intestinal TRPM 6 and 7 cation channels which are responsible for active transport of magnesium; renal magnesium handling is often preserved. It is generally accepted that diuretics, due to increased urinary excretion, can also cause hypomagnesemia.

Aim: To assess whether the use of diuretics impacts the timing of the occurrence of PPI induced hypomagnesaemia.

Methods: The Netherlands Pharmacovigilance Centre Lareb (NPCL) maintains the spontaneous ADR database of the Netherlands. ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA®; version 18.1) and the drugs are classified according to the WHO Anatomical Therapeutics Chemical classification system. All reports of hypomagnesemia in the database of the NPCL up to 31 December 2015 are included for this study and are systematically assessed.

Results: On 31 December 2015 the database of NPCL contained 92 ADR reports of hypomagnesaemia. When PPIs are used without a diuretic the average time between start of the drug and diagnosis of hypomagnesemia is about 89 months (median 55, q25% 24, and q75% 122 months). When a diuretic is concomitantly used the average latency time is shortened to 33 months (median 23, q25% 5.5, q75% 67 months) for concomitant use of loop diuretics and to an average of 43 months (median 24, q25% 1.5 months, q75% 97 months) for concomitant use of thiazide diuretics.

Discussion and conclusions: Our findings show that hypomagnesemia is an ADR that is associated with long term use of PPIs. Concomitant use of diuretics seems to shorten the average time between start of the PPI and the diagnosis of hypomagnesaemia which points to an additive effect. Since the number of our reports of hypomagnesemia associated with PPI and diuretic use is small, we will continue our research on this topic to verify our findings.

Propofol population pharmacokinetics and pharmacodynamics using Bispectral Index and composite A-line ARX index in adolescents undergoing scoliosis surgery with intraoperative wake-up test

HJ Blussé van Oud-Alblas [1,2], MJE Brill [3], MYM Peeters [4], D Tibboel [2], M Danhof [3], and CAJ Knibbe [2,3,4]
[1] Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands

Introduction: Adolescent scoliosis surgery with an intraoperative wake-up test is often performed with propofol-remifentanil anesthesia because of the shortacting properties of this combination. To avoid potential problems from inadequate anesthesia and to predict return of cognition to allow immediate neurological evaluation during the intraoperative wake-up test, the pharmacokinetics (PK) and pharmacodynamics (PD) for propofol during propofol-remifentanil anesthesia are characterized in adolescents.
Methods: Fourteen adolescents (median age 14.7 years, median bodyweight 51 kg) were evaluated during standardized propofol-remifentanil anesthesia for scoliosis surgery with an intraoperative wake-up test and reinduction of anesthesia using Bispectral index (BIS) monitoring and composite A-line ARX index (cAAI) as PD endpoints. A population PK and PD model was developed.

Results: Propofol pharmacokinetics were best described by a two-compartment model with a total clearance of 1.37 L/min, central volume of 3.6 L, intercompartmental clearance of 1.15 L/min and peripheral volume of 76.8 L. Propofol PKPD was characterized using a sigmoid Emax model. Hill coefficient (1.43 for BIS and 6.85 for cAAI) and EC50 (3.51 mg/L for BIS and 2.14 mg/L for cAAI) differed largely between both endpoints. The effect-compartment equilibrium rate constant between the central and effect compartment (k_{eo}) during infusion and bolus administration were 0.18 and 0.055 min^{-1}, respectively (CV=54%).

Conclusions: A population PKPD model for propofol in adolescents undergoing scoliosis surgery with intraoperative wake-up test was described using BIS and cAAI as endpoints. Large differences were demonstrated between both monitors. This may imply that BIS and cAAI measure fundamentally different endpoints in the brain.

Success rate of advices and effectuated changes based on a structured medication review in psychogeriatric patients admitted to a nursing home: a prospective cohort study

Blenke AA[1], van Marum RJ[2], Vermeulen Windsant AM[1], Hermens WA[1], Derijks HJ[1]
[1] Department of Clinical Pharmacy, ZANOB, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands, [2]Geriatric Department, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands

Aim

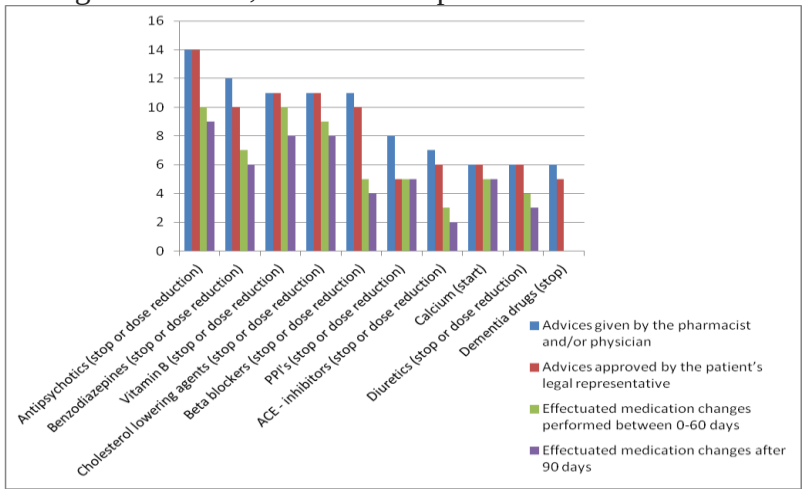
Determination of the success rate of advices and effectuated changes based on a structured medication review in psychogeriatric patients.

Methods

We conducted a prospective cohort study, involving psychogeriatric patients who were admitted to 3 Dutch nursing homes. The inclusion criteria were: age ≥65 years and admission to a psychogeriatric ward. Patients with a life expectancy <90 or an expected follow-up period <90 days were excluded. Within 42 days after admission, an elderly care physician and hospital pharmacist performed a structured medication review according to the "Systematic Tool to Reduce Inappropriate Prescribing-methodology" resulting in a pharmacotherapeutic treatment plan, which was approved by the patient's legal representative. After approval (t=0) medication changes were effectuated. A change was defined as starting or stopping medication, substitution or change of dose, time of administration, pharmaceutical form and frequency of dosing. An advice was defined successful if it was approved by the patient's legal representative. An effectuated change had to take place between t=0-60 days and was defined successful if was still present at t=90 days.

Results

Between March 2014 en July 2015 45 patients were included. 168 medication advices were given, 150 advices were approved (success rate advices: 89.3%). 105 changes were performed and 89 were successful after a follow up of 90 days (success rate effectuated changes: 84.8%). The most common reasons for failure for an advice were: presence or absence of an indication based on additional information, which did not justify changing medication or no approval of the patient's legal representative. The most common reason for uneffectuated changes was restarting medication due to increase or return of complaints. The figure presents the top 10 most given advices, which encompasses 54.8% of all advices.



Discussion and conclusion

The success rates of advices and effectuated changes were respectively 89.3% and 84.8%. The top 10 most given advices encompasses more than 50% of all advices, which raises the question for further research if a structured medication review could be performed more efficiently by focussing on most common problems.

THE CLINICAL RELEVANCE OF ANTI-DRUG ANTIBODY FORMATION IN ONCOLOGY

E.M.J. v. Brummelen[1]; W. Ros[1]; G.J. Wolbink[2]; J.H. Beijnen[13]; J.H.M. Schellens[13] (*[1]The Netherlands Cancer Institute, Department of Clinical Pharmacology [2] Sanquin Research Immunopathology and Reade Amsterdam Rheumatology and Immunology Center [3] University Institute for Pharmaceutical Sciences, Utrecht University)*

Aims In oncology, targeted anticancer agents and immunotherapies are increasingly of biological origin. Biological drugs, such as (monoclonal) antibodies or fusion proteins, may trigger immune responses leading to the formation of anti-drug antibodies (ADAs). ADAs are directed against immunogenic parts of the drug and can affect the drugs' efficacy and safety. In other medical fields, such as rheumatology and hematology, the relevance of ADA formation is well established. However, the relevance of ADA formation in oncology is just starting to be recognized and literature on this topic is scarce. In an attempt to fill this gap, we provide an up-to-date status of the relevance of ADA formation in oncology.

Methods A focused review of literature was done on clinical trials investigating the immunogenicity of biological anticancer agents which yielded 174 results. Of these, 81 were included for review. For 67 monoclonal antibodies, 10 immunotoxins and 4 proteins, data were extracted on the type of drug, drug target, patient population, incidence of ADA formation, the consequences and detection of ADAs.

Results Among 81 clinical trials with biological anticancer agents, ADAs were detected in 63%. Most of the patients in which ADAs were detected had received non-human monoclonal antibodies (murine, chimeric or humanized). The formation of ADAs was related to alterations in pharmacokinetics (decreased exposure), efficacy (reduced) or toxicity (infusion related reactions) in respectively 16 %, 27% and 20%. We found that the assays used for ADA detection are often described poorly, making it difficult to interpret which types of ADAs are detected and how clinically relevant these are. Despite the high incidence of ADA formation, not many strategies to prevent immunogenicity in the clinic have been explored. Although evidence is conflicting, adaptations to the treatment regimens and targeted immunosuppression can be considered.

Conclusion Despite the development of human biologicals, immunogenicity is still a challenge for the majority of biological anticancer agents. However, data on ADA formation is highly inconsistent which makes it difficult to establish the clinical relevance of ADAs. To determine the relevance of ADA formation, it is essential to routinely investigate the effect of ADAs on PK, efficacy and toxicity and to standardize ADA assays. To improve quality of the data, we encourage garnering more attention to investigations on immunogenicity. Also, clinical trials are urgently needed to investigate strategies for the prevention of ADA formation in oncology.

Brivaracetam bioavailability/bioequivalence comparison between 10, 50, 75 and 100 mg tablets and 100 mg intravenous bolus in healthy volunteers.		
Authors: Hadi S, Hartstra J, Stockis A, Singh P, PRA International, Zuidlaren, The Netherlands UCB Pharma, Braine-L'Alleud, Belgium Purpose: To determine the bioequivalence of three brivaracetam (BRV) oral tablet formulations (10 mg, 75 mg and 100 mg) vs BRV 50 mg oral tablet and to compare the bioavailability of BRV 100 mg intravenous (iv) bolus vs BRV 50 mg and 100 mg oral tablets, in healthy volunteers. Method: This Phase I, randomised, open-label, crossover study comprised five treatment periods, separated by a one-week wash-out. All participants received single doses of BRV (10 mg, 50 mg, 75 mg and 100 mg oral tablets and 100 mg iv bolus injection), according to a 5-way Latin square crossover design, under fasting conditions. Pharmacokinetic parameters, dose-normalised to 50 mg (Cmax, AUC(0-inf) and AUC(0-t)), were analysed by ANOVA.		Results: Twenty-five participants (age: 20–54 years; 13 male) were randomised. The 90% confidence intervals (CIs) around the Cmax, AUC(0-inf) and AUC(0-t) ratios for BRV 10 mg, 75 mg and 100 mg vs BRV 50 mg were entirely contained within the standard bioequivalence limits (0.80−1.25). For BRV 100 mg iv bolus, bioequivalence vs BRV 50 mg and 100 mg oral tablets was met for AUC(0-inf) and AUC(0-t) (90% CIs: 0.95–1.01), but iv Cmax was partly outside the limit (90% CIs: 1.19–1.39). Conclusion: Based on dose-normalised pharmacokinetic parameters, BRV 10 mg, 75 mg and 100 mg oral tablets were bioequivalent with BRV 50 mg. BRV 100 mg iv bolus injection had similar bioavailability to BRV 50 mg and 100 mg oral tablets.

Eighteen-month treatment with metformin in obese adolescents: results on change in BMI in an outpatient clinic compared to results obtained in a clinical trial

Authors: M.P. van der Aa[1], V. Hoving[1], E.M.W. van de Garde[2], A. de Boer[3], C.A.J. Knibbe[2], M.M.J. van der Vorst[1]

Affiliations: [1] Department of Pediatrics, St Antonius Hospital, Nieuwegein/Utrecht, The Netherlands; [2] Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein/Utrecht, The Netherlands; [3] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands.

***Background*:** The effect of metformin treatment on change in BMI in obese adolescents has been studied in several clinical trials.[1,2] Because treatment effects from clinical trials may differ from the effects in daily clinical practice, the aim of the present study is to compare the effects of metformin on change in BMI between obese adolescents treated with metformin in daily clinical practice and patients who participated in a randomized placebo controlled trial (RCT).

Methods: In our pediatric obesity outpatient clinic, all obese adolescents treated off-label with metformin and with a clinical follow up of at least 18 months from start of treatment were identified. Anthropometric data (age, height, weight, body mass index) and laboratory parameters (fasted plasma glucose, fasted plasma insulin and HbA1c) were collected at baseline and at t=18 months. Data from patients treated with metformin in a RCT of 18 months were used for comparison.[3,4] Change in BMI after 18 months was compared between the two groups.

Results: Nineteen patients (median age 14.3 (interquartile range 11.7-15.7) years, BMI 31.3 (28.8-33.8) kg/m^2, BMI-SDS 3.23 (3.05-3.64)) in the daily clinical practice group were compared to 23 patients receiving metformin during the RCT (age 13.6 (12.6-15.3) years, BMI 29.8 (28.1-34.5) kg/m^2, BMI-SDS 3.10 (2.72-3.52). Change in BMI after 18 months was -0.36 (-2.10-1.58) vs +0.22 (-2.87-1.27) kg/m^2 for the two groups, respectively. In the multivariable model, the changes in BMI were not statistically significantly different between the two groups (p=0.61).

Conclusion: Treatment with metformin in obese adolescents in daily clinical practice results in a change in BMI comparable to the results observed in a RCT. This finding provides further evidence to the potential place of metformin as an add-on therapy next to lifestyle intervention.

References:

1. Park MH, Kinra S, Ward KJ, White B, Viner RM. Metformin for obesity in children and adolescents: A systematic review. *Diabetes Care.* 2009;32(9):1743-1745.
2. McDonagh MS, Selph S, Ozpinar A, Foley C. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. *JAMA Pediatr. 2014*;168(2):178-184.
3. Van der Aa MP, Elst MA, van Mil EG, Knibbe CA, van der Vorst MM. METFORMIN: An efficacy, safety and pharmacokinetic study on the short-term and long-term use in obese children and adolescents - study protocol of a randomized controlled study. *Trials*. 2014;15:207-6215-15-207.
4. Van der Aa MP, Elst MA, van de Garde EMW, van Mil EG, Knibbe CA, van der Vorst MM. Long-term treatment with metformin is effective in stabilizing BMI in obese, insulin resistant adolescents. *Submitted*

Pharmacokinetics of Pentobarbital in Pediatric Status Epilepticus Patients

Julia M. Penning de Vries[1], Birgit C.P. Koch[2], Enno Wildschut[1], Brenda.C.M. de Winter[2], Matthijs de Hoog[1]
[1] Erasmus MC, Department Intensive Care, Sophia Children's Hospital; Rotterdam
[2] Erasmus MC, Department of Hospital Pharmacy, Rotterdam

Introduction
Status epilepticus (SE) is an acute, life threatening event which requires immediate medical intervention. The overall mortality in children treated for refractory generalized convulsive status epilepticus is 16%-64% [1]. Little consensus consists regarding treatment of refractory SE and there are no randomized, blinded studies in either adults or children. Pentobarbital is the last resource to treat SE. In daily practice dosing is adjusted based on EEG and pentobarbital drug level. However, too low or too high drug levels are often seen.

Aims
The aim of this study was to design a pharmacokinetic model of pentobarbital, which can be incorporated in TDM.

Methods
The design of the study was a retrospective, single-center analysis of medical records of all consecutive pediatric patients who received pentobarbital-coma for refractory generalized convulsive status epilepticus from 2007 through 2012 at the Department of Pediatric Intensive Care, Sophia Children's Hospital, Rotterdam for the primary dataset and between 2013 and February 2015 for de validation set. Inclusion: age 1 week - 18 years, exclusion all patients receiving pentobarbital for other reasons than SE. For pharmacokinetic analysis NONMEM® version 7.2 was used. Demographic and laboratory parameters were evaluated as covariates. Allometric scaling was used to adjust for differences in bodyweight. After formulation of the final model the parameters were introduced in MW-Pharm to use in daily practice. Between subject variability (BSV%) was analysed for PK parameters.

Results
16 patients were included in the primary set (median age 75.5 [17-1363] days, median weight 5.4 [3-19] kg. Mean loading dose was 8.8[0-15.65] mg/kg, mean maintenance dose 4 [1-10] mg/kg. In the validation set 6 patients were included (median age 120.3 [63-460] days, median weight 6.1 [6-10] kg). Mean loading dose was 15.4 [15-16.6] mg/kg and mean maintenance dose 4.5 [3-7] mg/kg.
The data was best described in a two-compartment model (V1 0.89 L/kg (57.9 % BSV), V2 1.46 L/kg, with clearance of 5.12 L/h (44.9 % BSV). In children below 1 year, clearance increased with age (explaining 8 % of BSV).
NPDE of the validation dataset using the final model showed accurate results. Finally, prediction of the final data point of the validation set and comparing it with the real data set, resulted in all predicted data being < 20% different than the real data.

Conclusion
The PK model was validated and has been incorporated in MWPharm to be used in daily practice

References
[1]Kim SJ, Lee DY, Kim JS. Pediatr Neurol 2001;25:217–220

Treatment variation of stage III colorectal cancer among hospitals

A.Sobels[1,2], L.Binkhorst[1,2], L.E.Visser[1,2], E.B. Wilms[1,2], J.E.A. Portielje[1]
[1]HagaZiekenhuis, The Hague, the Netherlands;
[2]Apotheek Haagse Ziekenhuizen, The Hague, the Netherlands.

Aim: Therapy with a fluoropyrimidine (FP) and oxaliplatin is the standard of care for the adjuvant treatment of stage III colon cancer. Both capecitabine (cape) and 5-fluorouracil (5FU) can be used as chemotherapy backbone, as the clinical efficacy of cape is equal to 5FU. Adverse effect profiles are comparable, although differences in incidence of adverse effects exist. In addition to the FP backbone, the use of oxaliplatin in elderly (>70yr) is subject to debate (benefit less clear). The aim of this study was to evaluate variations in treatment of stage III colon cancer among different hospitals.

Methods: Variations in treatment of colon cancer were evaluated among three teaching Hospitals. Patients who were adjuvantly treated with cape or 5FU, as monotherapy or in combination with oxaliplatin, for stage III colon cancer in the period between January 2011 and June 2015 were included. Data on disease stage, treatment regimen, clinical outcome, adverse effects and demographics were obtained from electronic medical records. Differences in treatment, outcome, and toxicity were evaluated.

Results: Data of 181 patients were available (81:51:49). Sex and disease stage (ANOVA; p=0.25) were comparable among the hospitals. The percentage of patients over age 70 differed among hospitals (38% versus 22%, and 18%). Differences in FP use were observed among the hospitals. Most patients received cape treatment, however, 5FU was used in 42.0%, 15.7%, and 6.1% of the patients. In two hospitals, a relatively high number of patients (14.8-23.5%) were switched from cape to 5FU during treatment. No patients were switched from 5FU to cape. Patients were switched because of toxicity, or problems related to cape use. Combination therapy with Oxaliplatin was given in 70.4%, 86.3%, and 79.6% of the patients. Elderly patients (>70yr) received oxaliplatin less frequent (32.3%, 63.6%, and 33.3% of the patients). 65% of the individuals did not receive all planned cycles of oxaliplatin, neuropathy was the dominant reason to interrupt oxaliplatin treatment. FP therapy was discontinued in 32.1%, 49%, and 32.7% of the patients. Regarding toxicity, neuropathy (range, 32.7-76.5%), hand-foot syndrome (6.1-39.2%), and gastro-intestinal abnormalities (13.7-32.1%) were the most observed adverse effects in all three hospitals. Neuropathy was observed slightly more in oxaliplatin-based therapy with 5FU than with cape (71.8 vs. 62.2%). Disease recurrence (10.2-24.7%) and mortality rates (2-13.7%) did not substantially differ among the hospitals; however, because of the small number of patients no conclusions can be made.

Discussion: The treatment of stage III colon cancer among the hospitals varied, with more 5FU use in one hospital. The mean age of the patients was higher in this hospital. The observation of switching from cape to 5FU is remarkable, suggesting less toxicity or problems related to 5FU therapy. The number of patients that stopped FP therapy differed among the hospitals, which may be explained by patient characteristics or co-morbidities. Although FP treatment differed, toxicity seemed to be comparable. The effect of FP on outcome has to be evaluated in a larger cohort.

UNSUSPECTED SEROTONIN TOXICITY IN THE ICU

ABSTRACT

Catharina E. van Ewijk, MD[1]; Gabriel E. Jacobs MD, PhD[2,3]; Armand R.J. Girbes, MD, PhD[1] ([1]Department of Intensive Care, VU University Medical Center Amsterdam, the Netherlands [2]Department of Psychiatry, VU University Medical Center Amsterdam, the Netherlands [3]Centre for Human Drug Research, Leiden, the Netherlands)

Purpose: Delirium is a frequently occurring syndrome in patients admitted to the Intensive Care Unit (ICU) or Medium Care Unit (MCU), yet the pathophysiology remains poorly understood. An excess of central serotonin can lead to an altered mental status, associated with autonomic hyperactivity, and neuromuscular excitation. (Boyer EW *et al*. 2005, Buckley NA *et al.* 2014) Drugs with serotonergic properties are frequently and for prolonged periods administered to ICU/MCU patients. Therefore central serotonergic toxicity may constitute a predisposing, contributing or precipitating factor in the emergence of delirium. The purpose of the present study is to determine the number of patients admitted to the ICU or MCU who are diagnosed with delirium, and who show characteristics of serotonin toxicity (Sternbach 1991, Dunkley EJC *et al.* 2003) in association with the administration of serotonergic drugs.

Methods: During a 10-week prospective observational cohort study in the ICU and MCU, patients aged 18 or older, diagnosed with delirium in the ICU or MCU were included. Patients were considered as delirious in case of a positive CAM-ICU and/or at the start of haloperidol prescription on suspicion of delirium. Once included, patients were screened for recent administered serotonergic drugs and screened for physical signs associated with serotonin toxicity by a standardized physical examination by a specifically trained physician.

Results: A total of 61 patients diagnosed with delirium were enrolled. In 44 out of 61 patients (72,1%) the use of drugs potentially contributing to serotonergic toxicity was recorded. Out of 44 patients, 7 (16%) patients showed physical signs of serotonin toxicity and in addition met the Hunter serotonin toxicity criteria, suggesting the presence of serotonergic toxicity. None of these patients were recognized as such by the treating physicians.

Conclusions: A significant proportion of delirious patients in the ICU might in fact be classified as suffering from central serotonin toxicity. The awareness of potential serotonin toxicity is low among physicians.

References:

Boyer EW, Shannon M (2005) The serotonin syndrome. N Engl J Med 352:1112–20.

Buckley NA et al. (2014) Serotonin syndrome. Bmj 1626(February):15–8.

Sternbach H (1991) The Serotonin Syndrome. Am J Psychiatry 148(June):705–13

Dunkley EJC et al. (2003) The hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. QJM - Mon J Assoc Physicians 96:635–42.

CLINICAL IMPLEMENTATION OF PROSPECTIVE *DPYD* GENOTYPING IN 5-FLUOROURACIL OR CAPECITABINE TREATED PATIENTS

C.A.T.C. Lunenburg[1]*, M.C. van Staveren[2,3]*, H. Gelderblom[1], H.-J. Guchelaar[3], J.J. Swen[3]
[1] Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands [2] Department of Pharmacy, Treant Healthgroup, The Netherlands [3] Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands

Introduction: 5-fluorouracil (5FU) and its oral pro-drug capecitabine (CAP) are commonly used anti-cancer drugs. 10-30% of patients experience severe (grade ≥3) toxicity during treatment. Dihydropyrimidine dehydrogenase (DPD) is the key enzyme in the detoxification of 5FU/CAP. While patients with reduced DPD enzyme activity have an increased risk for toxicity, they can be safely and effectively treated with a reduced dose of 5FU/CAP. Prospective screening for genetic variants in *DPYD* (gene encoding DPD) is a well-known strategy to detect patients who have reduced DPD enzyme activity (DPD deficient). Therefore, prospective *DPYD* screening with pharmacogenetically guided dose recommendation prior to prescribing 5FU/CAP was implemented at the Leiden University Medical Center in April 2013. In this retrospective study we evaluated the physician's acceptance of prospective *DPYD* screening for patients who were prescribed 5FU/CAP in LUMC and the adherence of the recommended dose reduction. Reductions are according to CPIC and DPWG guidelines.

Methods: Starting April 15th 2013, all patients at LUMC with an indication for a fluoropyrimidine containing therapy were aimed to be routinely screened for common *DPYD* variants. In this study the proportion of patients who were screened was determined using prescription and laboratory electronic databases. The follow-up of the recommended dose reductions by the oncologists was determined by screening medical records of patients carrying a variant in *DPYD*. An explorative analysis was executed in order to describe the course of toxicity in relation to the provided dose recommendations.

Results: From April 15th 2013 until December 31st 2014 529 patients were genotyped for *DPYD* variants, of which 275 patients were LUMC patients. 2,498 records of 5FU and CAP prescriptions were retrieved, of which 337 patients remained, who were prescribed 5FU (16%) or CAP (84%) for the first time at LUMC within the study period. After data cleaning, 314 patients with a newly 5FU or CAP prescription remained in the dataset and 273 (86,9%) of these patients were genotyped. **Dose reduction recommendations:** Fourteen patients (5.1%) were found to carry one or more variants. Two patients received a retrospective dose reduction recommendation, which could be adhered to in one patient. Twelve patients received a prospective dose reduction recommendation, which led to an initial adjusted dose in eight patients. One patient did not receive the recommended dose reduction and the recommendations could not be applied in the other three patients. Therefore, the adherence to the dose recommendations (prospective and retrospective) is 90% (9 out of 10). **Toxicity assessments:** In *DPYD* carrying patients, grade ≥3 toxicity was only seen in patients who had not received a prospective dose reduction, or in patients who received a dose increase in later cycles.

Conclusions: Follow-up of dose recommendations given by the pharmacist was possible in most cases and were applied in all cases except one, resulting in a high acceptance rate. Implementation of prospective *DPYD* screening in clinical practice is feasible, results in low toxicity in *DPYD* carriers and is well accepted by physicians.

RISK MANAGEMENT OF HOSPITALIZED PSYCHIATRIC PATIENTS TAKING MULTIPLE QT-PROLONGING DRUGS

Eline Vandael[1], Bert Vandenberk[2], Rik Willems[2], Johan Reyntens[3], Joris Vandenberghe[4], Veerle Foulon[1]

1. Clinical Pharmacology and Pharmacotherapy, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, 3000 Leuven, Belgium.
2. Department of Cardiovascular Sciences, KU Leuven, 3000 Leuven, Belgium.
3. Sint-Jan Hospital, 9900 Eeklo, Belgium.
4. Department of Neurosciences, KU Leuven, 3000 Leuven, Belgium.

Background and objective:
The risk of drug-induced QTc-prolongation has been linked with severe outcomes including Torsade de Pointes and sudden cardiac death. The objective of this study was to investigate the impact of starting an additional QTc-prolonging drug on the QTc-interval of psychiatric inpatients.

Methods:
An observational study was performed between May 2011 and December 2014 in six Belgian psychiatric hospitals. In-patients who were already taking one or more QTc-prolonging drugs could be included in the study when an additional QTc-prolonging drug was started. Twelve-lead electrocardiograms were performed at baseline and follow-up (at steady state). Demographic, medical, medication and laboratory data were collected. A risk score was used to estimate the risk of QTc-prolongation based on patient-specific risk factors. A cut-off value of 8 points was set as high risk for QTc-prolongation.

Results:
During the study period, 152 patients (44.7% female; mean age 44±17 years) were included. One-third of the patients was treated with one or more QTc-prolonging drugs of list 1 of Crediblemeds with a known risk of Torsade de Pointes (Woosley *et al.*, 2015). A significant correlation was found between the number of QTc-prolonging drugs and the QTc-interval in a follow-up ECG. There was a small but significant difference (p=0.032) in mean QTc-interval between baseline (409.1ms±21.8) and follow-up (411.8ms±21.7). Three patients developed a prolonged QTc-interval in the follow-up ECG (QTc ≥450(♂)/470(♀)ms). Fifty-eight patients (38.2%) had a risk score ≥8; these patients had a significant higher QTc-interval in the follow-up ECG than patients with a risk score <8 (p<0.001).

Conclusion:
Although only a limited number of patients developed a prolonged QTc-interval after the start of an additional QTc-prolonging drug, it is still important to screen for high-risk patients at baseline. A risk score as used in this study can help to select patients at risk and to enhance an appropriate and feasible risk management of QTc-prolongation in psychiatry.

References:
Woosley RL, Romero KA. QTdrugs List, December 2015, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755. www.crediblemeds.org. Accessed 7 December 2015.

Favorable immune response after properly timed HPV16-SLP vaccination during chemotherapy for advanced cervical cancer

H. van Meir[1,2], M.J.P. Welters[3], T.C. van der Sluis[4], N.M. Loof[3], V.J. van Ham[3], S. van Duikeren[4], S.J. Santegoets[3], R. Arens[5], M.L. de Kam[1], A.F. Cohen[1], M.I.E. van Poelgeest[2], G.G. Kenter[6], J.R. Kroep[3], J. Burggraaf[1], C.J. Melief[4,5], S.H. van der Burg[3]

[1]Centre for Human Drug Research, Leiden. [2]Department of Gynecology, Leiden University Medical Center, Leiden. [3]Department of Clinical Oncology, Leiden University Medical Center, Leiden. [4]Department of Immunohematology and Blood transfusion, Leiden University Medical Center, Leiden. [5]ISA Pharmaceuticals, Leiden. [6]Center for Gynecologic Oncology, Amsterdam.

Introduction. A previously developed synthetic long peptide (SLP) vaccine against HPV16 oncoproteins, was clinically active in patients with HPV16+ high-grade vulvar intraepithelial neoplasia and correlated with strong HPV16-specific T cell response.[1] When therapeutic vaccination with the HPV16-SLP vaccine is used as monotherapy in patients with HPV16-induced advanced cervical cancer, it fails to properly restore immunity.[2,3] We explored whether HPV16-SLP vaccination could be combined with carboplatin - paclitaxel (standard chemotherapy for advanced cervical cancer) to improve immunity. We studied the effect of standard chemotherapy on the frequency and function of immune cells, to identify the optimal time window to apply immunotherapy.

Methods. We serially sampled blood from 18 patients with stage IV or recurrent cervical cancer treated with carboplatin-paclitaxel. The first 6 patients were studied during chemotherapy only, and the subsequent 12 patients received HPV16-SLP vaccination 2 weeks after the second cycle of chemotherapy. Circulating immune cells including effector T cells, regulatory T cells, macrophages and myeloid derived suppressor cells were profiled by flow cytometry. Proliferation assays were used to determine T cell and antigen presenting capacity. Antigen-specific T-cell responses were measured in response to HPV16 E6 and E7 peptide pools.

Results. Chemotherapy with carboplatin-paclitaxel showed normalization of tumor-induced abnormally high myeloid cell frequencies (median of 32% myeloid cells at baseline, decrease to 7%, $p<0.001$), and an increase of lymphoid cells (median of 67% lymphoid cells at baseline, increase to 93%; $p=0.0002$). In addition, chemotherapy conserved an optimal antigen presenting cell function and general T-cell responses. This effect on the immune system was most distinct within a specific time window, 1-2 weeks after the second cycle of chemotherapy. When HPV16-SLP vaccination was administered within this best immunological window, unexpected strong HPV16-specific proliferative immune responses to E6 and E7 peptide pools were observed. Median stimulation index at baseline amounted 0.8 (range 0.1-6.5), and 25.0 (range 4.3-133.4) 3 weeks after vaccination ($p<0.001$).

Conclusions. Standard carboplatin-paclitaxel chemotherapy has an immune stimulatory effect by the deletion of suppressive myeloid cells in cervical cancer patients. In addition, this chemotherapy sustains vigorous vaccine-induced T-cell responses when vaccination is given at the point that chemotherapy has reset the tumor-induced abnormal myeloid cell composition to normal values.

References

1. Kenter GG et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med. 2009 Nov 5;361(19)1838-47

2. Kenter GG et al. Phase I immunotherapeutic trial with long peptides spanning the E6 and E7 sequences of high-risk human papillomavirus 16 in end-stage cervical cancer patients shows low toxicity and robust immunogenicity. Clin Cancer Res. 2008 Jan 1;14(1):169-77

3. van Poelgeest MI et al. HPV16 synthetic long peptide (HPV16-SLP) vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carcinoma, a phase II trial. J Trans Med. 2013 Apr 4;11:88

HUMAN ENDOTOXEMIA MODEL: THE EFFECT OF A SINGLE LOW DOSE OF LIPOPOLYSACCHARIDE ON SYSTEMIC INFLAMMATION, VASCULAR ACTIVATION AND RENAL FUNCTION

Dillingh M.R.[1], van Poelgeest E.P.[1], Malone K.E.[2], Kemper E.M.[3], Stroes E.S.G.[3], Burggraaf J.[1]. and Moerland M.[1]

[1] Centre for Human Drug Research, Zernikedreef 8, 2333 CL, Leiden, The Netherlands.
[2] Good Biomarker Sciences, Zernikedreef 8, 2333 CL, Leiden, The Netherlands.
[3] Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

INTRODUCTION
Administration of a single dose of lipopolysaccharide (LPS), as low as 0.5 ng/kg, elicits a distinct and transient cytokine response in healthy human subjects. However, clinical data on the activation of the human microvasculature upon low-dose endotoxin exposure, and the effect on kidney function are not readily available in the public domain. Such data would improve the understanding of endotoxin-induced inflammation and organ damage, and support the application of the low-dose LPS challenge as methodological tool in clinical (pharmacology) studies.

METHODS
In a randomized, double-blind, placebo-controlled study in healthy male volunteers, the effects of single low doses of LPS (0.5, 1 or 2 ng/kg; 6 subjects per dose level) were assessed on systemic inflammation (cytokines, CRP), vascular activation (e.g. selectins, cell adhesion molecules), and renal markers (function/activation/injury).

RESULTS
Dose-dependent increases in circulating cytokine levels were observed after LPS dose administration, showing substantial increases from placebo already at the lowest dose level (contrast for timeframe 0-6 hours: TNF-alpha +413%, IL-6 +288%, IL-8 +254%; $p \leq 0.0001$). Also, dose-dependent increases were observed for E-selectin/P-selectin (maximum levels at 6 hours post-dose, followed by a slow return to baseline levels) and ICAM-1/VCAM-1 levels (maximum levels at 24 hours post-dose). Administration of 2 ng/kg LPS resulted in an elevated excretion of urinary KIM-1 and beta-2-microglobulin compared to placebo (corrected for creatinine, 44% ($p=0.0055$) and 37% ($p=0.0149$), respectively). This may suggest that sub-clinical renal damage may occur after 2 ng/kg LPS, however urinary creatinine excretion, serum creatinine and GFR were unchanged.

CONCLUSION
These data demonstrate that endotoxemia elicited by a single low LPS dose ($\leq$2 ng/kg) induces an inflammatory reaction and vascular activation, not translating into functional renal impairment. Therefore, this human endotoxemia model could be applied as methodological tool in early clinical studies for demonstration of the intended pharmacological activity of anti-inflammatory or vasculoprotective compounds.

Pharmacokinetics of ibogaïne and noribogaine in a 46-yrs old woman with prolonged multiple cardiac arrhythmias after ingestion of internet purchased ibogaine.

MJ. Henstra[1] L. Wong[2] A. Chahbouni[3], F. Sombogaard[3]
1 Dept of Internal Medicine, Geriatrics, AMC Amsterdam 2 Dept of Cardiology, VUmc Amsterdam 3 Clinical Pharmacy VUmc Amsterdam

Introduction: Ibogaine, not licensed as a therapeutic drug, is widely used as anti-addictive for multiple types of addiction, although it has been associated with sudden cardiac death. (Maciulaitis et al. 2008; Schenberg et al. 2014)

Aim: To describe pharmacokinetics of ibogaine and its metabolite noribogaine using blood samples of a 46-yrs old woman admitted to our hospital with prolonged multiple cardiac arrhythmias after ingestion of internet purchased ibogaine.

Methods: We developed a LC-MS/MS method to measure plasma-concentrations of ibogain and its metabolite. We describe the pharmacokinetics of ibogaine and noribogaine using a two-compartment model.

Results: Shortly after admission, our patient developed multiple cardiac arrhythmias requiring a temporary pacemaker lead for high frequency pacing during 72 hours. The lead was removed after 5 days and QTc-prolongation remained present till 12 days after ingestion. This implicates clinically relevant noribogaine-concentrations long after ibogaine had been cleared from the plasma. The ratio k12/k21 for noribogaine was 21.55 and 4.28 for ibogaine, which implicates a lower distribution of noribogaine from the peripheral compartment into the central compartment compared to ibogaine.

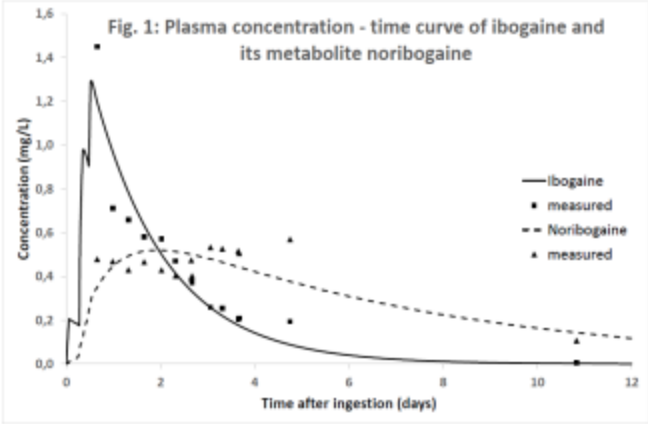


Table 1. PK of Ibogaine and Noribogaine in a two compartment model.

Parameter	Ibogaine	Noribogaine
CL (L/h)	4,66	2,30
V1 (L)	185	48
V2 (L)	789	1.022
t1/2,1 (h)	26,06	12,59
t1/2,2 (h)	2.285	2.540
k12/k21	4,28	21,55

Conclusion: Fat tissue serves as a reservoir for both ibogaine and noribogaine due to their highly lipophilic structure. We demonstrated a direct relationship between the concentration of the metabolite and long duration of action, rather than ibogaine. Therefore, after (prolonged) intake of ibogaine, clinicians should beware of long-term effects due to its metabolite.

Maciulaitis, R. et al. 2008. *Hum Exp Toxicol*, 27: 181-94
Schenberg, E. et al. 2014. , *J Psychopharmacol*, 28: 993-1000.

WEE1 INHIBITOR AZD1775 PLUS CARBOPLATIN IN PATIENTS WITH *TP53* MUTATED OVARIAN CANCER REFRACTORY OR RESISTANT TO FIRST-LINE THERAPY: A PHASE II STUDY

Robin M.J.M. van Geel[1], Suzanne Leijen[1], Gabe S. Sonke[1], Daphne de Jong[1], Efraim H. Rosenberg[1], Serena Marchetti[1], Dick Pluim[1], Erik van Werkhoven[1], Shelonitda Rose[2], Mark A. Lee[2], Tomoko Freshwater[2], Jos H. Beijnen[1,3], Jan H.M. Schellens[1,3]

[1]Netherlands Cancer Institute, The Netherlands; [2] Merck & Co, USA; [3]Utrecht University, The Netherlands

Background:
The *TP53* tumor suppressor gene plays a critical role in the cellular response to DNA damage in order to maintain genome integrity. Mutations in *TP53* are common in cancer and frequently result in a dysfunctional G1 checkpoint. This leaves cells highly dependent on the G2 checkpoint to achieve cell cycle arrest in response to DNA damage. Inhibition of Wee1, a tyrosine kinase that governs the G2 checkpoint, results in G2 checkpoint abrogation. Given the increased G2 checkpoint dependency of *TP53* mutated tumor cells, these are, in contrast to *TP53* proficient cells, particularly sensitive to Wee1 inhibition combined with DNA damaging chemotherapy. A previous phase I study investigating AZD1775, a selective small molecule inhibitor of Wee1, combined with carboplatin demonstrated target engagement and established the recommended phase II dose.

Methods:
We conducted an open-label, proof of principle, phase II study with AZD1775 plus carboplatin in patients with *TP53* mutated ovarian cancer refractory or resistant (within 3 months) to first-line standard carboplatin plus paclitaxel chemotherapy. Patients were treated with carboplatin (AUC 5) in combination with 5 oral twice-daily doses of 225 mg AZD1775 in 21-day cycles. Overall response rate (ORR) was the primary endpoint. Secondary endpoints included toxicity, progression-free survival (PFS) and overall survival (OS).

Results:
Twenty-one out of 24 patients enrolled, were evaluable for tumor response assessment. One patient (5%) achieved a complete response and 8 patients (38%) had a partial response, resulting in an ORR of 43%. Seven patients (33%) had stable disease as their best response and 5 patients (24%) had progressive disease on the first evaluation after 2 treatment cycles. The median PFS and OS were 5.4 months and 12.6 months, respectively. At data cut off, two patients remained on treatment for over 35 and 45 months. Bone marrow toxicity, including thrombocytopenia (48%), neutropenia (39%) and anemia (9%) was the most common grade 3/4 treatment-related adverse event.

Conclusion:
This is the first study providing clinical evidence of AZD1775 acting as a chemosensitizer by the inhibition of Wee1. Given the median PFS of less than 3 months upon first-line treatment in this difficult-to-treat patient population with platinum-resistant *TP53* mutated ovarian cancer, the AZD1775 plus carboplatin combination outperformed the current standard of care warranting further clinical investigation.

AN EVALUATION OF DUTCH PHARMACISTS' KNOWLEDGE, EXPERIENCE AND ATTITUDES TOWARDS PHARMACOGENETIC TESTING: RESULTS OF A NATIONWIDE SURVEY

P.C.D. Bank[1], J.J. Swen[1]& H.J. Guchelaar[1]
[1] Department of Clinical Pharmacy & Toxicology, Leiden University Medical Centre (LUMC), Leiden, The Netherlands

Pharmacists routinely interface with patients and health care providers in providing medication education, selecting and monitoring drug therapy for patients, and ensuring safe and appropriate use of therapies (de Denus et al). Pharmacists could therefore play an important role in the integration of genotype-guided drug therapy into routine practice, but they must be knowledgeable about PGx and be willing to communicate PGx information to the patient.

A web-based survey with 42 questions was sent to all Dutch pharmacists either in a community, hospital or outpatient setting using the website Netq-enquete. The survey was divided into two sections: section 1 was designed to obtain demographic information about the participants and contained questions about age, gender, possession of specialty, practice environment, attended university, whether PGx was part of their (post) academic education and section 2 was related to specific PGx topics such as education & training, adoption, belief in the concept, expectations & worries toward PGx testing, access to and use of PGx information, privacy & coverage of testing. Statistical analysis was performed with chi^2 analysis using SPSS software.Out of the 3550 invited pharmacist a total of 667 (18.8%) completed the survey. Of the participants 54.3% was female and the median age was 41. Virtually all respondents believed in the concept of pharmacogenetics (99.7%) and had high expectations of PGx testing to improve efficacy, reduce toxicity and prevent erroneous drug therapy. With respect to privacy almost 70.0% of the surveyed pharmacists was at least moderately worried that results of a PGx test could come in hands of an unauthorized individual and the majority of pharmacist (91.4%) was at least moderately concerned that that a health-insurance company could determine a patients' genotype based on the drug or dose that he or she is prescribed. Only 14.1% of the participants felt adequately informed about the availability of PGx tests and how to apply PGx in relation to drug therapy. Approximately 40% of the pharmacists had received any education on PGx in their curriculum; however the majority of the responders (88.8%) would like to receive additional training on the subject. Although 74.1% of the responders are aware that dosing guidelines on Drug-Gene Interactions are available in the handbooks, a minority of 27.0% of the participants consider themselves qualified to interpret a PGx test result. Furthermore, only 14.7% the respondents had recommended PGx testing in the previous 6 months. Significant differences in experience, attitudes and knowledge of PGx were observed between community, outpatient and hospital based pharmacists.

All pharmacists believe in the concept of PGx and have high hopes that PGx can improve efficacy, reduce toxicity and prevent erroneous drug choice or dosing. However, only a minority of pharmacists feel qualified to interpret PGx test results and there is a need for training on the subject.

de Denus S et al. Pharmacogenomics. 2013 Jan;14(2):165-75

NetQuestionnaires. http://www.netq-enquete.nl/nl

Pharmacokinetic exposure of pazopanib in routine patient care: opportunities for dose optimization

R.B. Verheijen[1], L.E. Swart[2], H. Yu[1], J.H.M. Schellens[2,3], J.H. Beijnen[1,2], N. Steeghs[3], A.D.R. Huitema[1]

[1]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, The Netherlands. [2]Dept. of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands. [3]Department of Medical Oncology and Clinical Pharmacology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

Background: Pazopanib is an angiogenesis inhibitor, approved for the treatment of renal cell carcinoma (RCC) and soft tissue sarcoma (STS). Pazopanib trough level (C_{min}), has been linked to tumour shrinkage and progression free survival in renal cell carcinoma.

Methods: An observational cohort study was performed from April 2013 to February 2016 in RCC and STS patients treated with pazopanib. Visits were planned in accordance with respective treatment guidelines. Clinical characteristics e.g. demographic data, tumour characteristics, medical history, treatment dose, duration and time to progression (TTP) of these patients were collected retrospectively from medical records. Date and time of last intake of pazopanib dose and time of blood sampling were recorded. Plasma pazopanib levels were determined each week using a validated LC-MS/MS assay. An estimate of the C_{min} was calculated based on the measured concentration and interval between last ingested dose and sample time, using the algorithm developed by Wang et al[1]. Statistical analyses were performed in R 3.2.2. Mean C_{min} per patient was used as a measure of pazopanib exposure during treatment, for the purpose of exposure-response analyses.

Results: 45 patients were included, of which 28 had RCC and 17 STS. Median age was 66 years (range 33-79). In total 145 C_{min} levels were calculated (median 3, range 1 – 16). The average of the mean C_{min} per patient was 27.4 mg/L (CV 39.5%). 17.8% of patients were at risk of suboptimal treatment due to low exposure (mean C_{min} <20 mg/L). At the time of analysis, 22.2% of patients were still on treatment, 6.7% had discontinued due to toxicity and 71.1% due to progressive disease. Toxicities leading to treatment discontinuation were hepatotoxicity (n=1, mean C_{min} 18.6 mg/L) and hypertension (n=2, mean C_{min} 30.5 mg/L).
In RCC, patients with C_{min} (<20 mg/L) had a median TTP of 21.9 weeks (n=5), compared to 37.9 weeks for RCC patients with a higher C_{min} (n=23), p=0.08 (log-rank test). STS patients with C_{min} (<20 mg/L) had a median TTP of 8.7 weeks (n=3), while higher C_{min} patients' TTP was 20.1 weeks (n=14), p=0.30 (log-rank test). In a combined analysis of RCC and STS patients C_{min} ≥20 mg/L also showed a trend toward higher TTP, with 15.3 weeks (n=8) versus 29.9 weeks (n=37), p=0.05 (log-rank test).

Conclusion: In our cohort, 17.8% of patients treated with pazopanib in routine care were underexposed using the current fixed dose paradigm. Moreover, we found that patients with a higher C_{min} showed a trend toward better TTP. This finding, in combination with previous studies showing benefit of higher C_{min}, shows that a relevant subset of patients treated with pazopanib may benefit from a personalized dosing approach.

[1]Wang et al, A therapeutic drug monitoring algorithm for refining the imatinib trough level obtained at different sampling times. Ther. Drug. Monit. 2009, Oct 31(5):579-84.

PHARMACOKINETICS OF MCLA-128 IN MONKEYS AND EXTRAPOLATION TO HUMANS TO SUPPORT SELECTION OF FIRST-IN-HUMAN DOSE.

AHM de Vries Schultink[1], RP Doornbos[2], ABH Bakker[2], S Shamsili[2], M Throsby[2], JH Schellens[1,3], JH Beijnen[1,3], ADR Huitema[1] *[1]The Netherlands Cancer Institute, Amsterdam, the Netherlands [2]Merus B.V., Utrecht, the Netherlands [3]Utrecht University, Utrecht, the Netherlands*

Introduction MCLA-128 is a full length IgG1 bispecific monoclonal antibody (mAb) targeting receptor tyrosine kinases HER2 and HER3 to overcome HER3-mediated resistance to HER2 or EGFR targeted therapies. MAbs of the IgG1 subclass follow primarily linear clearance through cellular uptake followed by lysosomal degradation. The pharmacokinetics (PK) of mAbs are characterized by target mediated drug disposition, leading to saturation of the target and a co-existing nonlinear degradation. MCLA-128 was preclincally tested in cynomolgus monkeys to estimate PK parameters of MCLA-128 using a model based approach and to predict exposure to MCLA-128 in humans in order to support selection of first-in-human dose.

Methods PK data was obtained from a single-dose toxicity study (n=6) and the first week of a repeated dose toxicity study (n=32) in cynomolgus monkeys. MCLA-128 was quantified in serum using a validated electrochemilumin-escence immunoassay. PK parameters were estimated using NONMEM (v.7.3) and parameters were scaled to humans using allometric scaling. A two-compartment model with parallel linear and nonlinear elimination was tested. For model evaluation, parameter estimate plausibility, parameter precision, visual predictive checks and goodness of fit plots were examined. The safety margins for different proposed starting dose levels were obtained by dividing the AUC in cynomolgus monkeys at the NOAEL (no observed adverse effect level), which was found at the highest dose evaluated (100 mg/kg), by the predicted AUC in human.

Results PK profiles were well described by a two-compartment model with parallel linear and nonlinear elimination pathways. Parameter estimates scaled to 70 kg human are shown (Table 1).

Table 1: PK parameters scaled to a 70 kg human

Parameter	Estimate	RSE(%)	IIV	RSE(%)
CL (L/h)	0.0122	9.3	0.0172	13.1
V_1 (L)	3.18	2.8	0.0207	14.4
Q (L/h)	0.0312	6.6	-	-
V_2 (L)	3.59	14	-	-
K_m (mg/L)	0.273	65.2	1.19	109
V_{max} (mg/h)	0.527	13.1	-	-
RV_{prop}	0.106	10.1		
RV_{add}	0.039 FIX			

The estimated parameters were consistent with the general PK characteristics of therapeutic mAbs as expected based on the full length IgG1 format of MCLA-128 [1]. Proposed starting dose levels of 10 mg and 40 mg flat dose had associated safety margins of 6655 and 623, respectively.

Conclusion MCLA-128 showed coexisting linear and nonlinear clearance pathways in cynomolgus monkeys. Based on calculated safety margins the proposed First-in-Human starting doses of 10 and 40 mg every three weeks have a large safety margin.

Reference

[1] Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin. Pharmacokinet. 2010;49:633-59

MEDICATION REVIEW IN PAEDIATRIC OUTPATIENT CYSTIC FIBROSIS PATIENTS; A NEW USEFUL ROLE FOR THE HOSPITAL PHARMACIST

IH van der Sijs, LCP Borra, F de Velde
Department of Hospital Pharmacy, Erasmus MC Rotterdam

Aim

Medication review is currently being advocated by the Dutch Healthcare Inspectorate (IGZ) for elderly patients (≥75 years) with polypharmacy (≥7 drugs) and renal impairment (eGFR <50 ml/min)[1]. Cystic fibrosis (CF) patients generally use many drugs from different prescribers, but do not belong to the group for whom medication review is generally performed, as their life expectancy is about 40 years. We aimed to develop a method for medication review during the annual check-up of paediatric CF-patients and analyse its usefulness.

Methods

Since March 2015, medication review is performed by a hospital pharmacist for every CF-patient in Erasmus MC-Sophia children's hospital during the annual check-up. The (parents of the) patient fill out a list with drugs and doses they use. The hospital pharmacist compares this with the hospital computerised prescriber order entry system (CPOE) and the medication overviews from community pharmacy and outpatient hospital pharmacy. In a patient-pharmacist telephone interview, medication use is verified, and drug use problems and allergies are discussed. Type and number of discrepancies and drug-related problems (DRPs: additional therapy required, unnecessary or ineffective therapy, under- or overdosing, adverse drug event, drug use problem, monitoring required, drug-drug interaction, contra-indicated drug, duplication) are registered. After medication reconciliation and review, the hospital pharmacist proposes drug-therapy adjustments, which are discussed in the multidisciplinary CF-team, as well as parameters related to disease severity, hospital admission, and CF-treatment outside the CF-centre.

Results

52 CF-patients (median 7.1 years, range 0.3-17.2) were reviewed from March to July 2015. Median number of orders per patient in the hospital CPOE was 11.1 (range 1-24). 374 potential problems (median 7.2, range 2-22) were registered. 78% of these problems were discrepancies discovered by medication reconciliation, e.g. missing diabetic or psychiatric medication prescribed outside the CF-team, and antibiotic courses not in use anymore. 22% were DRPs, e.g. under dosing, drug-use problems, missing serum level measurements, and unregistered allergies. Disease severity was relatively low: 13% had a recent hospital admission, 13% had CF-related diabetes and none of the patients had renal impairment. Only 12% of the patients were treated by medical specialists outside the CF-centre.

Conclusions

A medication review is useful in a paediatric outpatient CF-population, although age and renal function do not correspond to the IGZ criteria. Per patient, a median of 5 discrepancies (range 1-19) and 1 drug-related problem (range 0-5) were detected.

References

1. Health Inspectorate www.igz.nl/Vastgesteldenormenmedicatiebeoordeling.pdf, accessed February 10th 2016

DRUG-DRUG INTERACTIONS IN A PAEDIATRIC INTENSIVE CARE UNIT: A PILOT STUDY

M Nabiollah[1], R Admiraal[2,3], SN de Wildt[2], IH van der Sijs[1]
Erasmus MC, 1. Dept of Hospital Pharmacy, 2. Erasmus MC Dept of Paediatric Surgery and Intensive Care, 3. UMCU, Department of Paediatric Blood and Marrow Transplantation

Aim

Drug-drug interactions (DDIs) are common in hospitalised patients and may result in adverse events, for which critically ill patients, due to multiple medications, may be even be more at risk. The incidence of DDIs in critically ill children is unknown. The aim of this study is to describe the prevalence, characteristics and clinical relevance of DDI's in a paediatric intensive care unit (PICU).

Methods

This prospective, observational pilot study was performed in the 28 bed PICU of Erasmus MC, during a seven-day period in July 2015. Daily medication overviews were extracted from the computerised prescriber order entry system (PDMS, Picis). For each patient, all drugs were entered daily in a DDI-checker (www.drugs.com). Next, all major and moderate DDIs were categorized with respect to type of effect and severity. Relevance was scored in three ways: presence on the unit's DDI-trigger list, in the Dutch drug database (G-standard), and by expert opinion by a clinical pharmacist and physician, both fellows in clinical pharmacology.

Results

During the 7-day period, 1967 orders were prescribed in the PICU (281 per day, 14 per patient per day). A total of 1316 major (6%) and moderate (94%) DDIs were identified by the DDI-checker (9.4 per patient per day). The majority of DDIs potentially affect drug levels by CYP450-mediated DDIs (16%), serum electrolyte levels (10%), or had a potential nephrotoxic effect (4.0%). Serotonin syndrome was a potential adverse effect in 1.7% of DDIs. Only 56% of all identified DDIs was mentioned in the G-standard, and only 7.5% could by identified by the unit's DDI trigger list. As ICU patients are extensively monitored, experts scored only 4.7% of DDIs as clinically relevant. Of these relevant DDIs 48% were identified by the unit's DDI trigger list, addition of diclofenac would identify 82% of the relevant DDIs.

Discussion and Conclusion

Many DDIs are identified in paediatric ICU patients. Only 5% are considered relevant in this setting as these patients are extensively monitored (e.g. blood pressure) and often sedated. It remains to be determined if medical interventions like electrolyte administration, respiratory and cardiovascular support could be minimized by a greater awareness of these DDIs by physicians. The DDI-checker includes mechanism-based DDIs including therapeutic duplication as opposed to the literature-based G-standard, categorising duplication as a different class. Both DDI-checker and G-standard are over inclusive, and a trigger list can identify the majority of clinically relevant DDIs.

References

1. DDI-checker, www.drugs.com, accessed Feb 10th 2016
2. G-standard, www.kennisbank.knmp.nl, accessed Feb 10th 2016

Population Pharmacokinetics and Limited Sampling of Once-daily Tacrolimus in Unstable Renal Transplant Recipients

AUTHORS: A.G.J Engbers[1,2], E.H.J. Krekels[2], E. Olofsen[3], A.P.J. de Vries[4], M.E.J. Reinders[4], J.W. de Fijter [4], J. den Hartig [1], H.J. Guchelaar [1], D.J.A.R. Moes [1]
[1]: Clinical Pharmacy & Toxicology, Leiden University Medical Centre
[2]: Systems Pharmacology, Leiden Academic Centre for Drug Research
[3]: Anaesthesiology, Leiden University Medical Centre
[4]: Nephrology, Leiden University Medical Centre

AIM: The purpose of this study was to develop a population pharmacokinetic (PK) model for the once-daily formulation of tacrolimus (Advagraf®, Astellas) which was started directly after transplantation in renal transplant recipients and to develop a limited sampling method (LSM) .

METHODS: A total of 1098 tacrolimus concentration-time data points from 90 patients were available for the building of a structural PK model using NONMEM®. All patients underwent therapeutic drug monitoring-based tacrolimus doses and mycophenolic acid, a subgroup received concomitant low prednisolone doses (n=61). 90 full AUC measurements were available. Different limited sampling methods (LSMs) were tested using posthoc estimation of the PK parameters based on the structural PK model. Estimated clearance (CL) values were used to calculate full exposure (AUC=((Dose*bioavailability)/CL)). Performance of the LSMs was judged by calculating R^2 Pearson coefficient, percentage of AUC's predicted within 15% of the full AUC, discordance (percentage of AUC's predicted outside the 20% range of the full AUC), mean predictive error (MPE), mean percentage predictive error (MPPE), root mean squared prediction error (RMSE) and mean absolute percentage prediction error (MAPE).

RESULTS: PK of the once-daily formulation of tacrolimus was best described by a 2-compartment model with a numerically estimated number of transit compartments. Interindividual variability could be identified for CL, distribution volume of the central compartment (V_c), absorption rate constant (k_a) and mean transit time (MTT). Inter-occasion variability was determined on CL. Tacrolimus concentrations measured at 0, 2 and 4 hours postdose predicted full AUC most accurately (R^2=0.91, discordance = 4.44% and MAPE = 13.4%).

CONCLUSION: Good predictive performance using limited sampling could be obtained for predicting full AUC of the once-daily formulation of tacrolimus.

The current therapeutic drug monitoring practice of infliximab in patients with Inflammatory Bowel Disease

A.G. Kalpoe[1], A. Sobels[2], L.E. Visser[2], R. Stuyt[3], N. Srivastava[4] & E.B. Wilms[2]
[1] Master student, Utrecht University; [2] Hospital Pharmacist, Apotheek Haagse Ziekenhuizen; [3] Gastroenterologist, HagaHospital; [4] Gastroenterologist, MCH-Westeinde Hospital.

BACKGROUND

Treatment with infliximab (IFX) of patients with Inflammatory Bowel Disease (IBD) can be accompanied with the formation of antibodies towards infliximab (ATI), resulting in reduced clinical efficacy of the treatment. Therapeutic Drug Monitoring (TDM) can be a useful method to monitor IFX and ATI levels to optimize the treatment. However, it's debated when TDM should be applied and how TDM should affect treatment. We studied the current TDM policy and accessed the available literature to optimize IFX therapy with TDM.

METHODS

This was an observational multicenter study of IBD-patients in the HagaHospital and the MCH Westeinde hospital. IBD-patients treated with IFX between 1 January 2012 and 31 December 2014 were included. TDM data and medication related data were retrospectively collected from the databases of both hospitals.

RESULTS

We included 309 IBD-patients treated with IFX. Of these, TDM was applied to 196 IFX-patients and the remaining patients were only clinically monitored. Of the IFX-patients monitored via TDM, 274 serum samples were included to describe the current TDM policy. Four main arguments to start TDM were identified: Loss of response to IFX (53,8%), inadequate response to IFX (17,9%), remission or improvement of IBD (5,9%) and infusion reactions (4,8%). In general, an inadequate IFX level (<3 µg/mL) and the absence of ATI (<12 AE/mL) resulted in a shorter dosage interval, an IFX level <3 µg/mL and ATI >12 AE/mL resulted in the stop of IFX therapy and an IFX level >3 µg/mL and ATI <12 AE/mL did not result in changes of the therapy.
Furthermore, an IFX level >3 µg/mL was rarely accompanied with the presence of ATI (>12 AE/mL, n=4 serum samples). In these cases, no changes were made in the treatment with IFX.

CONCLUSION

Loss of response was identified as the main argument for initiation of TDM. In patients with infliximab >3 µg/mL, ATI's were rarely detected above a level of 12 AE/ml. Description of the current use of TDM and comparison to literature data was used to recommend an optimized TDM decision tree.

PROPOFOL FOR ENDOTRACHEAL INTUBATION IN PRETERM NEWBORNS: FIRST DATA OF A MULTICENTER DOSE FINDING STUDY

M.M. van Weissenbruch[1], E. de Kort[2], S.A. Prins[1], P.G. van het Verlaat[3], A. Chahbouni[4] , P. Andriessen[2], I.K.M. Reiss[3], E.L. Swart[4], S.H.P. Simons[3]

1. Department of Pediatrics, Division of Neonatology, VU University Medical Center, Amsterdam, the Netherlands
2. Department of Pediatrics, Division of Neonatology, Máxima Medical Centre, Veldhoven, The Netherlands
3. Department of Pediatrics, Division of Neonatology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands
4. Department of Clinical Pharmacology and Pharmacy, VU University Medical Center, Amsterdam, the Netherlands

Background:
Propofol monotherapy is used as sedative for endotracheal intubation at many neonatal intensive care units. Important data about correct dosages and PK/PD and safety are missing.

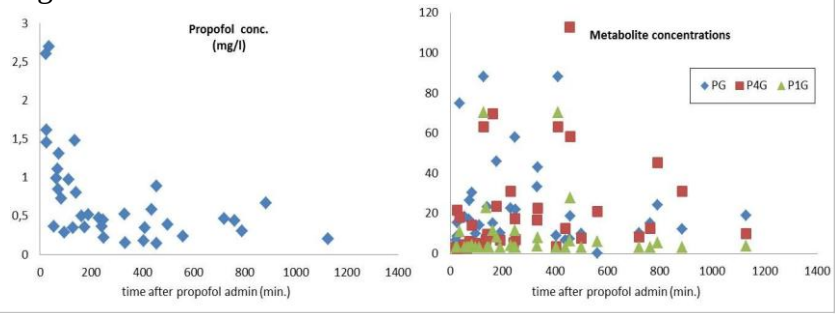
Aim:
To find gestational age and postnatal age dependent effective and safe propofol dosages for endotracheal intubation in newborn infants.

Methods:
In a multicenter dose finding study newborns were stratified to receive propofol with increasing starting dosages. The level of sedation was assessed every 30 seconds after propofol with a 4 point intubation readiness score (IRS) and an intubation score. Blood was taken for propofol (P), propofol glucuronide (PG), 4-OH-propofol-4-glucuronide (P4G) and 4-OH-propofol-1-glucuronide (P1G) using LCMS analyses.

Results:
Up till now 37 newborns were included with a median gestational age of 28+2 (range 24 – 38+6) weeks and median birth weight of 1140 (range 580 -3945) grams. Median postnatal age at intubation was 24.0 (IQR 6.2 – 155.8) hours. The median propofol dose required to achieve adequate IRS scores was 2.20 (1.86-3.48) mg/kg and median time to first intubation was 4 (2-10.5) minutes. Figure 1 shows propofol and metabolite concentrations. First PK/PD data will be presented at the NVKFB meeting.

Conclusions:
Relatively high dosages of propofol were needed to achieve adequate sedation in newborns with a large variability in gestational and postnatal age. Further analyses of patient characteristics, genotype and pharmacokinetics is needed to improve the predictability of propofol pharmacodynamics in newborn infants.

Fig1.



LONG-TERM TREATMENT WITH METFORMIN IS EFFECTIVE IN STABILIZING BMI IN OBESE, INSULIN RESISTANT ADOLESCENTS

Authors: Marloes P. van der Aa[a], MD, Marieke A.J. Elst[a], MD, Ewoudt M.W. van de Garde[b], PharmD, PhD, Edgar G.A.H. van Mil[c], MD, PhD, Catherijne A.J. Knibbe[b], PharmD, PhD, Marja M.J. van der Vorst[a] MD, PhD

Affiliations: [a]Department of Pediatrics, St Antonius Hospital, Nieuwegein/Utrecht, The Netherlands; [b] Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein/Utrecht, The Netherlands; [c] Department of Pediatrics, Jeroen Bosch Hospital, 's Hertogenbosch, the Netherlands.

Objective:
As obese adolescents with insulin resistance may be refractory to lifestyle intervention therapy alone[1], additional off-label metformin therapy is often applied.[2-4] In this study, the long-term efficacy and safety of metformin *versus* placebo in obese insulin resistant adolescents is studied.

Methods:
In a randomized placebo controlled double blinded trial, 62 obese adolescents aged 10-16 years old with insulin resistance received 2000mg of metformin or placebo daily and physical training during 18 months. Primary endpoints were change in BMI and insulin resistance measured by the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Secondary endpoints were safety and tolerability of metformin. Other endpoints were body fat percentage and HbA1c.

Results:
Forty-two patients completed the 18 month-study (66% girls, median age 13 (12-15) years, BMI 30.0 (28.3-35.0) kg/m^2 and HOMA-IR 4.08 (2.40-5.88)). Median ΔBMI was +0.2 (-2.9-1.3) kg/m^2 (metformin) versus +1.2 (-0.3-2.4) kg/m^2 (placebo) (p 0.015). No significant difference was observed for HOMA-IR. No serious adverse events were reported. Median change in fat percentage was -3.1 (-4.8-0.3) vs -0.8 (-3.2-1.6)% (p 0.150), in fat mass -0.2 (-5.2-2.1) vs +2.0 (1.2-6.4) kg (p 0.007), in fat free mass +2.0 (-0.1-4.0) vs +4.5 (1.3-11.6) kg (p 0.047), and in ΔHbA1c +1.0 (-1.0-2.3) vs +3.0 (0.0-5.0) mmol/mol (p 0.020) (metformin vs placebo).

Conclusions:
Long-term treatment with metformin in obese, insulin resistant adolescents results in stabilisation of BMI and improved body composition compared to placebo. Therefore, metformin may be useful as additional therapy next to lifestyle intervention in obese adolescents with insulin resistance.

References:

1. Chiavaroli V, Giannini C, D'Adamo E, et al. Weight loss in obese prepubertal children: The influence of insulin resistance. *Endocr Res*. 2013;38(1):48-57
2. Fazeli Farsani S, Souverein PC, Overbeek JA, et al. Long term trends in oral antidiabetic drug use among children and adolescents in the netherlands. *Br J Clin Pharmacol*. 2015;80(2):294-303.
3. Hsia Y, Dawoud D, Sutcliffe AG, Viner RM, Kinra S, Wong IC. Unlicensed use of metformin in children and adolescents in the UK. *Br J Clin Pharmacol*. 2012;73(1):135-139.
4. Kostev K, Richter H. Unlicensed use of metformin in children and adolescents in Germany and France. *Br J Clin Pharmacol*. 2012;73(2):307-308.

SUBTHERAPEUTIC VANCOMYCIN LEVELS IN PEDIATRIC ONCOLOGY PATIENTS: CURRENT INITIAL DOSING REGIMEN DOES NOT SUFFICE

Karin Langenberg-Ververgaert[1], Nancy Broos[1] and Rick Lammers[2]
Gelderse Vallei Hospital, Ede, the Netherlands. 1. Department of Pediatrics and 2. Department of Hospital Pharmacy

Aim of the study Pediatric oncology patients presenting with febrile neutropenia are empirically treated with vancomycin for Gram-positive coverage. We evaluated the efficacy of the current national dosing regimen[1] with respect to reaching an adequate plasma trough level after 18 hours.

Methods We performed a retrospective cohort study. All pediatric oncology patients with febrile neutropenia between October 2014 and July 2015 were included. According to national guidelines, vancomycin was administered intravenously at a starting dose of 60 mg/kg/day qid. Data on gender, age, height, weight and serum creatinin levels were collected from their medical record. Vancomycin trough levels after 18 hours were compared to the target range for plasma vancomycin trough levels (10-15 mg/L)[2]. Descriptive statistics were used to analyze the collected data.

Results 10 episodes of treatment with vancomycin in 8 different patients with febrile neutropenia were included. One patient was treated thrice for different episodes. The median age was 4.4 years (range: 2.4 – 16.8). Only in one episode (10%) an effective vancomycin trough level was measured (10.8 mg/L). In 80% of the episodes the vancomycin plasma trough level was too low (see table). In one case an elevated vancomycin plasma trough level was measured, despite normal renal function. The median plasma vancomycin trough level in our cohort was 5.85 mg/L (range 2.4-23.5).

Patient	Episode	Age (years)	Plasma trough vancomycin level (mg/L)
1	1	2.4	6.9
2	2	3.7	2.8
	3	3.8	3.2
	4	3.9	2.7
3	5	16.6	5.3
4	6	4.5	10.8
5	7	4.3	6.4
6	8	10.9	2.4
7	9	7.8	7.7
8	10	16.8	23.5

Conclusion Current initial dosing regimen of vancomycin in pediatric febrile neutropenia does not suffice. In 80% of the episodes plasma levels are below the target level. Consequently there is a delay in reaching adequate plasma vancomycin levels in these high risk patients. Furthermore, low plasma vancomycin concentrations are associated with an increased risk of developing antibiotic resistance. We hypothesize that continuous intravenous infusion with vancomycin may be more effective in reaching adequate plasma levels.

References:

1. Stichting Kinderoncologie Nederland. Supportive care guidelines. www.skion.nl

2. Hoang et al. Achieving Therapeutic Vancomycin Levels in Pediatric Patients. Can J Hosp Pharm 2014;67(6):416-22

Pharmacy Based Dosing of Darbepoetin: a randomized controlled trial in hemodialysis patients

F.J. van den Oever[1], C.F.M. Heetman-Meijer[1], E. Birnie[2], Y.C. Schrama[3]
[1]Department of Clinical Pharmacy, Sint Franciscus Gasthuis, Rotterdam
[2]Department of Statistics, Sint Franciscus Gasthuis, Rotterdam
[3]Department of Nephrology, Sint Franciscus Gasthuis, Rotterdam

Aims
In patients with chronic kidney disease, anemia is treated with erythropoietin analogues. For erythropoietin analogues to be most effective, adequate iron levels are required. Treatment guidelines suggest a target range for hemoglobin levels in hemodialysis patients of 6.8 to 7.4 mmol/l. Lower hemoglobin levels are associated with diminished quality of life and increased cardiovascular problems in patients with cardiovascular comorbidity. Higher levels, especially values above 8.1 mmol/l, are associated with increased cardiovascular mortality. Previously, only 23% of all hemodialysis patients in our hospital had actual hemoglobin levels within target range. In this randomized, controlled trial, a treatment algorithm was developed for darbepoetin and intravenous iron sucrose, with the intention to improve the percentage of hemodialysis patients within hemoglobin target range. Secondary end points were percentage of patients with hemoglobin levels above 8.1 mmol/l, and percentage of patients with adequate iron levels.

Methods
Two hundred patients were randomized (n=100 for intervention and control group). Study duration was thirteen months. Adequate iron levels were defined as transferrin saturation of at least 20% combined with serum ferritin levels between 200 and 500 mcg/l. In the control group, darbepoetin and iron sucrose dosages were adjusted by the treating nephrologist as usual. In the intervention group, dosages of darbepoetin and iron sucrose were adjusted by the pharmacist, based on a treatment algorithm developed by three of the authors (FJO, CFMH, and YCS). In this algorithm previous and actual dosages of darbepoetin and iron, and serum levels of hemoglobin, transferrin saturation and ferritin were included. Statistical analysis was performed with SPSS. Median and non-parametric tests (Mann-Whitney U test) were used, as data were not distributed normally. As defined in the protocol, fifteen patients were excluded from analysis due to missing data (n=6 in the intervention group, n=9 in the control group).

Results
In the intervention group 38.5% of patients had hemoglobin levels within target range, as compared to 23.1% in the control group (p=0.001). Hemoglobin levels above 8.1 nmol/l were more frequent in the control group versus the intervention group (7.7 versus 0.0% p=0.034). Adequate iron status was 21.1% in the intervention group compared with 8.3% in the control group (p=0.003).

Conclusions
In hemodialysis patients, darbepoetin and iron sucrose dosing by treatment algorithm increases the percentage of patients within target range for hemoglobin levels as well as with adequate iron storage.

PLASMACONCENTRATIONS OF PSYCHOTROPIC DRUGS IN NEONATES AS PROGNOSTIC FACTOR FOR ADMISSION TO NEONATOLOGY WARD AND WITHDRAWAL SYMPTOMS (PROOF-1)

S.C.A. Sparla[1], J.M.G. Coppens[2], I.M. Evers[3], C. Stramrood[4], P.C.M. Pasker-de Jong[5], M.M.L. van der Westerlaken[1], [E.L. Swart][6], P.H.G. Hogeman[7], [M.M. Malingré][1].

[1]Hospital pharmacy, Meander Medical Centre, Amersfoort, [2]Psychiatrist Meander Medical Centre, [3]Gynaecologist Meander Medical Centre, [4]Gynaecologist resident UMC Utrecht ,[5]Statistician Meander Medical Centre,[6]Hospital pharmacy, VU Medical Centre, Amsterdam,[7]Pediatrician, Meander Medical Centre

Introduction: Untreated psychiatric illnesses in pregnant women are associated with complications, e.g. low birth weight, prematurity and poor interaction between mother and child (Kieviet *et al*., 2013). Infants are also at risk of developing withdrawal symptoms after in utero exposure to psychotropic drugs (Hendrick *et al*., 2003). Observation of the neonates after birth is essential to capture the symptoms and start early symptomatic treatment.
The aim of the study is to determine if plasma levels obtained from neonates' umbilical cord can be used as a prognostic factor for admission to the neonatology ward (with extra observation) and occurrence of withdrawal symptoms.

Method: A retrospective observational mono-center quality of care study was conducted in 186 neonates of mothers using psychotropic drugs and delivering at the Meander Medical Center between 2006-2013. Binary logistic regression was used to determine which of the following parameters were prognostic factors; Apgar-scores after 5 minutes, birthweight (percentiles), gender, childbirth complications, umbilical venous blood pH, gestational age, prematurity, plasma levels in the neonate and mother and (co)medication (SSRI, SNRI, antipsychotic and mood stabilizers) use of the mother.

Results: The main results are shown in the table. Birthweight (BW) differed significantly between not detectable (ND), subtherapeutic (ST) and therapeutic (T) levels (p=0,028), average BW 3333.5 gram, 3388.5 gram and 3058.5 gram respectively. Multivariate analysis showed a 20,5 times [OR, 95%CI 2.2-186.1] higher odd for occurrence of withdrawal symptoms with T plasma levels compared to ND plasma levels. For admission to the neonatology ward 3.1 times [OR<95%CI 1.1-8.6] higher odd was found with T plasma levels compared to ND plasma levels. Other prognostic factors for admission to neonatology ward were prematurity (OR:19.3; 95% CI 3.6-101.6) and Apgar score after 5 minutes (OR:5.1; 95% BI 1.0-26.0). For withdrawal symptoms no other factors were found. There was a positive correlation between plasma levels of the neonate and the mother for citalopram (r =0.908, n=6, p =0.012) and fluoxetine (r=0.898, n=12, p=0.000).

Plasma levels (range)	Admission neonatology ward (% (n))	Withdrawal symptoms (%(n))	Apgar 5 min (% < Agar7 (n))	Gestational age μ (SD)
N.D.	19.5 (17)	1.1 (1)	2.4 (2)	38.9 (1.8)
ST	19.2 (14)	8.2 (6)	4.2 (3)	38.9 (1.5)
T	42.3 (11)	20.0 (5)	7.7 (2)	38.3 (1.4)

Conclusion: Umbilical cord plasma levels of the neonate contributed to the general clinical assessment to predict the necessity of admission to the neonatology ward for extra observation. Furthermore the plasma levels were a prognostic factor for occurrence of withdrawal symptoms.

Hendrick V, et al. Am J Obstet Gynecol 2003; 188(3): 812–5.
Kieviet N, et al. Neuropsychiatric disease and treatment 2013: 9 1257-1266

Validation of a cognitive challenge model with mecamylamine

E.P 't Hart[1], R. Alvarez[1], S. Prins[1], M. de Kam[1], G.J. Groeneveld[1].
[1]Centre for Human Drug Research, Zernikedreef 8, Leiden, the Netherlands.

Introduction. Anti-cholinergic pharmacological challenges can induce cognitive disturbances in healthy subjects and can be used for proof of pharmacology of centrally acting cholinergic drugs. The anti-muscarinic drug scopolamine is mostly used, but for proof-of-pharmacology of nicotinic agonists that are currently developed, a nicotinic anti-cholinergic challenge would be more rational. Mecamylamine is a centrally acting nicotinic acetylcholine (nACh) receptor antagonist We previously showed reversible cognitive disturbances in healthy subjects after administration of 10 and 20mg. In the current study a higher dose of 30mg was investigated and the potential of a nACh receptor agonist (nicotine) and a cholinesterase inhibitor (galantamine) to reverse the cognitive effects of mecamylamine were determined. **Methods**. This was a randomized, double-blind, double-dummy placebo-controlled, four-way cross-over study in 28 healthy male volunteers (age: 18-45 yrs), with oral mecamylamine (30mg) administered on three occasions, and transdermal nicotine (21mg) oral galantamine (16mg) or placebo. Safety, PK and PD assessments were performed frequently. PD effects were measured using a CNS test battery (NeuroCart®), including adaptive tracking, finger tapping, reaction time, n-back (0/1/2-back), visual verbal learning (VVLT; 30 words), and Milner maze tests, pharmaco-EEG, pupillometry and visual analogue scales (VAS) Bond and Lader and VAS nausea. **Results**. Administration of 30mg mecamylamine was well tolerated and safe. Primarily, cardiovascular AEs were observed. Most were mild, some moderate, all were transient of nature. The main PD results are described. Following administration of mecamylamine a 3.27% decrease in score on the adaptive tracking test was observed compared to placebo (95%CI -4.58- -1.97). Co-administration of mecamylamine and nicotine resulted in an increased score of 1.47% (95%CI 0.15-2.78). Mean reaction time (RT) on N-back (2-back condition) was increased following mecamylamine (28.3 msec, 95%CI 2.0-54.6). Co-administration of mecamylamine and nicotine resulted in decreased RT (-36.0 msec, 95%CI -62.2 - -9.7). On the quantitative EEG (qEEG), α power (Pz-Oz) was decreased by mecamylamine (-6.2%, 95%CI -13.4 – 1.6) compared to placebo. Co-administration with nicotine resulted in increase in α power (14.9%, 95%CI 6-24.6).
Discussion. Administration of 30mg mecamylamine resulted in a significant disturbance of attention, executive functioning and a significant decrease in alpha power on EEG. This effect could be partially reversed by the co-administration of nicotine, but not of galantamine (data not shown). qEEG results following mecamylamine were comparable to effects observed in AD (decreased occipital α-power and increased frontal/occipital θ-power), reversed by nicotine administration. Overall, compared to administration of 10 and 20mg mecamylamine, 30mg showed larger negative cognitive effects. Furthermore, these effects could be reversed by co-administration of the nACh receptor agonist nicotine, validating the mecamylamine model as a cognitive challenge model for diseases such as AD. We are currently combining the 30mg data with data from the previous study, to investigate possible concentration-effect relationships.