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Introduction: Randomized clinical trials (RCTs) showed that low-dose glucocorticoid (GC) therapy in patients with rheumatoid arthritis (RA) was associated with less bone mineral density (BMD) loss in hand or hip [1,2]. However, the effect on osteoporotic fractures is not yet clear and observational studies mostly reported contrasting results compared to the BMD studies [3,4,5]. Thus, we investigated the use of low-dose oral GCs on osteoporotic fracture risk among patients with RA in the UK.

Methods: This was a cohort study including all RA patients aged 50+ from Clinical Practice Research Datalink (CPRD) between 1997-2017. Exposure to oral GCs was stratified into current (<6 months), recent (7-12 months), and past use (>1 year), based on the time since the most recent prescription. Current use was further stratified by average daily and cumulative doses.
Time-dependent Cox proportional-hazards models estimated risk of osteoporotic fracture (included hip, vertebrae, humerus, forearm, pelvis, or ribs) in RA patients with current use of low-dose oral GCs (average daily dose ≤7.5mg prednisolone equivalent dose [PED]/d) versus past use. The analyses were statistically adjusted for life-style parameters, comorbidities and comedications.

Results: Among 15,123 patients with RA (mean age 68.8 years, 68% females), 1640 osteoporotic fractures occurred. Low-dose oral GC therapy (≤7.5mg PED/d) in RA patients was associated with no increased risk of OP fractures compared with past GC use (adjusted hazard ratio 1.14, 95%CI 0.98-1.33). The only individual fracture site that observed increased rates with low-dose GC therapy was the clinical vertebrae. Cumulative GC use ≥1g PED in current users was associated with an increased OP fracture risk. However, low-dose oral GC use (≤7.5mg PED/d) was not associated with an increased risk, regardless of the cumulative use.

Conclusion: Low-dose GC therapy did not increase the OP fracture risk in RA patients compared with past GC use. Our results are in line with findings from RCTs reporting a similar effect of low-dose GC use on BMD in various anatomical sites. No extra fracture assessment for OP fracture sites other than the clinical vertebrae is recommended when a RA patient is receiving GCs in low daily doses (≤7.5mg PED/d).

References:

1. Haugeberg G, ey al. Arch Intern Med. 2005 Jun 13;165(11):1293-7.
2. Engvall IL, et al. Arthritis Res Ther. 2008;10(6):R128.
3. Balasubramanian A, et al. J Bone Miner Res. 2018 Oct;33(10):1881-1888.
4. Robinson DE, et al. Bone. 2018 Dec;117:83-90.
5. Saag KG. Ann N Y Acad Sci. 2014 May;1318:55-64.

INFLUENCE OF GENETIC POLYMORPHISMS IN *COMT* ON CISPLATIN-INDUCED NEPHROTOXICITY IN CANCER PATIENTS

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Background: Cisplatin is a widely used chemotherapeutic agent for multiple indications. Unfortunately, in many patients treated with cisplatin acute kidney injury (AKI) occurs. A recent case report suggested single nucleotide polymorphisms (SNPs) in the *COMT* gene might be associated with increased cisplatin-induced nephrotoxicity (de Jong, 2017). Here, we assessed the association of 3 SNPs in this gene with cisplatin-induced nephrotoxicity in our patient population.

Methods: Whole blood samples and serum creatinine concentrations (S_{cr}) of patients who received cisplatin and who had provided informed consent to perform DNA genotyping were included in this analysis. (Erasmus MC study number MEC 02.1002) The 1947 G>A (Val158Met, rs4680), c.615 + 310 C>T (rs4646316) and c.616 – 367 C>T (rs9332377) SNPs were associated with AKI grade 3 (CTCAE v4.03) using Fisher's exact test up to 2 weeks prior to and up to 6 weeks after cisplatin treatment was described.

Results: A total of 551 patients were included in this study. The presence of a variant of *COMT* c.616-367C>T was significantly associated with a decreased incidence of AKI grade 3 when performing a recessive analysis (CC vs CT + TT; OR: 0.201; 95%CI: 0.047-0.861; p=0.014). AKI grade 3 was also significantly associated with age ≥65 years (OR:2.464; 95%CI: 1.095-5.542; p=0.025). Due to the low incidence of AKI grade 3 multivariable testing was not possible. In 25 of the 27 patients that suffered from AKI grade 3, we could not exclude dehydration as a potential cause of AKI, which potentially affected our results. Patients that received chemoradiation (with cisplatin) to treat head/neck cancers were overrepresented in the group of patients that experienced AKI grade 3 (52%). In this subgroup the incidence of mucositis, which lowers fluid intake and therefore is a causal factor for dehydration, is much higher. This underlines the plausibility that AKI grade 3 in most of the patients was caused by dehydration. *COMT* 1947 G>A and c.615+310 C>T SNPs were not associated with AKI grade 3.
Conclusion: This study showed that variation in *COMT* c.616+367 C>T potentially affects the development of AKI grade ≥3, although these results appear to be confounded by dehydration. Therefore, the value of this finding for daily practice is currently unclear and needs to be explored in a prospective setting. This study does not provide a rationale for pre-emptive genotyping of *COMT* SNPs to prevent AKI.

Reference: de Jong C *et al*. Pharmacogenetic analysis of irreversible severe cisplatin-induced nephropathy: a case report of a 27-year-old woman. Br J Clin Pharm 2017; 83: 2120-22.

MODEL-INFORMED PRECISION DOSING OF ECULIZUMAB FOR A PATIENT FRIENDLY TREATMENT REGIMEN RESULTING IN BETTER TREATMENT RESPONSE AND REDUCED COSTS

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Introduction: Eculizumab is a very expensive humanized monoclonal antibody against complement protein C5 for the treatment of atypical hemolytic uremic syndrome (aHUS). Today, it is the only effective and lifesaving drug for this disease. The approved dosing regimen of eculizumab in adults consists of an initial weekly loading dose of 900 mg (4 weeks) followed by a maintenance phase (1200 mg in the fifth week and every 14 days thereafter). Recent data show that exposure is often sub-therapeutic after the first dose, while being supra-therapeutic when starting the maintenance phase. Early adequate therapy is of utmost importance to stop thrombotic microangiopathy and to prevent chronic sequelae. Therefore, we aimed to develop a dosing strategy to improve early treatment response and patient-friendliness at, preferably, lower costs.

Methods: We evaluated the pharmacokinetics and pharmacodynamics (classical pathway (CP) activity levels) in 30 aHUS patients, consisting of 849 eculizumab time-concentration data and 569 CP activity levels. PK-PD modeling was performed by means of non-linear mixed effects modeling. The final model was used to investigate alternative dosing strategies through Monte Carlo simulations. The optimal strategy was defined as the regimen with the highest percentage of patients with a CP <10%, without increasing the cumulative dose.

Results: A PK-PD model with parallel first order and Michaelis-Menten elimination rates best described the PK data. The estimates of the model were clearance 0.163 L/day (RSE 8%), volume of distribution 6.42 L (RSE 6%), maximum rate (Vmax) 29.6 mg/day (RSE 7%), plasma concentration for 50% of maximum rate (Km) 37.9 mg/L (RSE 19%). The PK-PD relation was described with an Emax model, with an estimated baseline of 101% (RSE 6%), maximum inhibition (Imax) of 0.959 (RSE 0.3%), a plasma concentration for 50% inhibition (IC50) of 22.0 mg/L (RSE 9%) and Hill Coefficient (γ) of 5.42 (RSE 5%). To improve therapy, a weight-based loading on day 1, followed by the maintenance dose on day 14 was found to improve the effectiveness of treatment with eculizumab. Therapy could be further improved by individualizing the dose interval, based on the estimated half-life after the first dose. We predict that with this new regimen 99.95% patients reach the efficacy target on day 7, compared to 94.75% with standard dosing. During maintenance phase, comparable percentages of target attainment were predicted, while the dose interval could be prolonged in 28.8% of the patients. This new dosing regimen also resulted in an overall dose reductions of 13.6% compared to the standard dosing regimen in the first 133 days of treatment.

Conclusion: A patient-friendly individualized dosing strategy of eculizumab results in better treatment response and lower costs.

AN EDUCATIONAL ESCAPE ROOM ABOUT THE OPIOID EPIDEMIC, DESIGNED BY STUDENTS FOR AN OPEN EDUCATION PLATFORM

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Aims: Educational escape rooms provide an interesting combination of active, experiential, peer-group and game-based learning. Due to their engaging nature, they are exceptionally suited to create long-lasting awareness about sensitive themes. Together with our students, we have created an educational escape room about the "opioid crisis". The escape room was designed as an open educational resource to be used by international medical faculties. Moreover, it was designed to be relevant for healthcare professionals and students with different backgrounds (doctors, pharmacists, nurses etc.). The design-process, as well as the first evaluations are described here.

Methods: 39 third-year medical students were divided in three groups (n=13). Each of these groups was given the assignment to create an escape experience. Therefore, the groups were subdivided and each team (n=3 or 4) was assigned to create a puzzle about one of the learning objectives. These objectives were co-created with the Dutch Institute for Rational Use of Medicine (IVM, www.opiaten.nl) and were: Opioid addiction, Legal and illegal ways to acquire opioids, The treatment of an acutely overdosed patient and Patient education. Students were instructed to use preferably digital, and otherwise only portable and readily available materials such as small boxes and locks. During the assignment of four weeks, the students were intensively supervised, but received full freedom in the design of their puzzle. On the last day escape rooms were played and the puzzles were judged by a jury of professionals, including professors in clinical pharmacology and a representative of IVM. Students evaluated both designing and playing the room.

Results: 79% of students agreed that playing the escape room was an enjoyable experience, but only 37% agreed that the importance of safe prescribing of opioids has become more clear due to the escape room. Students answered the question "what did you learn" predominantly with the opioid related learning objectives, but also with skills such as teamwork and performing under pressure. 45% of students agreed designing the escape rooms was an enjoyable assignment and 42% found it educational. The freedom and creative thinking of this assignment were praised. Unfortunately, the timing in relation to other assignments and the large amount of work were heavily criticized. Moreover, the students disliked that this was an extra assignment that was not tested in the final exam. The professional jurors were very positive about the creative and educational escape rooms that the students designed and feel that they provide a promising tool for creating awareness about opioid-related problems among health professionals.

Conclusion: Our students have created entertaining first versions of escape rooms about the opioid epidemic. However, the assignment was met with unexpected negativity, revolving largely around the amount of work and planning Together with motivated students, we aim to further develop the puzzles into one escape room. We then plan to publish its design for others to copy on the (planned) open educational platform of the European Association for Clinical Pharmacology and Therapeutics (EACPT).

AN OVERVIEW AND CLASSIFICATION OF DIGITAL EDUCATIONAL RESOURCES USED FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS IN EUROPE

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Background
With the goal to promote international improvement and harmonization of clinical pharmacology and therapeutics education, the European Association for Clinical Pharmacology and Therapeutics (EACPT) aims to create an online platform for collaboration and open educational resources. As a first step in this project, this study aimed to provide an overview of digital educational resources and evaluate their suitability for online sharing and internationalization.

Methods
The principal clinical pharmacology teachers of 279/304 European medical schools were invited to describe their best-practice digital educational resources in a cross-sectional online survey. These were classified and assessed for their internationalization potential.

Results
Teachers from 95 (34%) medical schools in 26 of 28 EU countries responded, 66% of whom used digital educational resources in their clinical pharmacology curriculum. A total of 89 of such resources were described in detail, including e-learning (24%), simulators to teach pharmacokinetics and/or pharmacodynamics (10%), virtual patients (8%), and serious games (5%). Together, these resources covered 235 knowledge-based learning objectives, 88 skills, and 13 attitudes. Only one third (27) of the resources were in-part or totally free and only 2 were licensed open educational resources (free to use, distribute and adapt). The largest, free and most novel resources were highlighted.

Conclusion
Digital educational resources, ranging from e-learning to virtual patients and serious games, are widely used for CPT education in EU medical schools. Learning objectives are based largely on knowledge rather than skills or attitudes. This may be improved by including more real life clinical case scenarios. Moreover, the majority of resources are not free or open. Therefore, with a view to harmonizing international CPT education, more needs to be learned about why CPT teachers are not currently sharing their educational materials.

OPENING UP CLINICAL PHARMACOLOGY AND THERAPEUTICS EDUCATION: AN INTERNATIONAL CONSENSUS STUDY ON THE ADVANTAGES, BARRIERS AND SOLUTIONS TO THE USE OF OPEN EDUCATIONAL RESOURCES

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Background
Clinical pharmacology and therapeutics (CPT) teachers often use digital educational resources in their curriculum. However, they rarely make these resources openly available. This study aimed to assess the advantages and barriers that CPT teachers perceive about sharing their materials. Moreover, the second part of this study aimed to reach consensus on solutions for these barriers to include in the development of an international online platform for collaboration and open education.

Methods
For the first part of this study, a cross-sectional survey was sent to the principal CPT teachers of 279/304 European medical schools. Advantages and barriers perceived about sharing educational materials were questioned using a combination of 5-point Likert type questions and open questions. The latter were analyzed using thematic analysis. For the second part, the results were presented during the education meeting of the bi-annual EACPT congress and discussed by the participants until consensus was reached. This session was audio-recorded and subsequently transcribed verbatim, results are described narratively.

Results
93 CPT teachers (33%) have answered the survey. 92 (99%) feel that openly sharing resources is beneficial. The perceived advantages and barriers were classified in 7 themes each. The three most mentioned advantages were: access to more resources, inspiration from others and quality of teaching materials. The three most mentioned barriers were: Language issues, local differences and expected costs of the platform. During the consensus meeting, approximately 60 international attendees agreed that the main language of the platform should be English and that local differences may be minimized by clearly explaining them, and by largely teaching the uniform basics of prescribing. Moreover, it was agreed upon that the platform should primarily aid teachers in finding suitable educational resources, should be free of charge and should include creative commons licenses.

Conclusion
European CPT teachers almost uniformly see the advantages of openly sharing digital resources, but perceive barriers that revolve largely around differences in language and prescribing ethics. Consensus was reached on potential solutions for these barriers to include in our proposed online platform.

OVERT THYROID DYSFUNCTION AND ANTI-THYROID ANTIBODIES PREDICT RESPONSE TO ANTI-PD-1 IMMUNOTHERAPY IN CANCER PATIENTS

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Introduction: Thyroid dysfunction is among the most common adverse effects during anti-PD-1 immunotherapy, and alongside correlations with elevated anti-thyroid antibodies (ATAb), studies have found correlations with survival. However, the exact relations remain to be clarified. We therefore aimed to clarify relations between thyroid dysfunction, ATAbs and survival in anti-PD-1 treated cancer patients.

Methods: We included 168 non-small-cell lung carcinoma, renal cell carcinoma, and metastatic melanoma patients treated with nivolumab or pembrolizumab. TSH and FT4 levels were measured before each anti-PD-1 infusion. ATAb levels (anti-TPO and anti-Tg) were measured at baseline and after 2 months of treatment. Although the vast majority of patients had detectable levels of ATABs, only few patients had positive ATAbs when using conventional cut-offs. To study the consequences of detectable ATABs, the cut-off levels were a priori set on the median concentrations at baseline in the study population. Tumor progression was classified according to RECISTv1.1.

Results: Patients who acquired overt thyroid dysfunction during treatment had significantly higher overall survival (OS) (HR=0.18 [95%CI: 0.04-0.76]; p=0.020) and progression free survival (PFS) (HR=0.39 [0.15-0.998]; p=0.050) than patients without thyroid dysfunction with one-year OS rates of 94% vs 59% and one-year PFS rates of 64% vs 34%. During treatment, patients with ATAb levels above the median had a higher OS (HR=0.39 [0.21-0.72]; p=0.003) and PFS (HR=0.52 [0.33-0.81]; p=0.004) than patients with ATAb levels below the median, with one-year OS rates of 83% vs 49% and PFS rates of 54% vs 20%, respectively. When analyzing ATAb levels over time, patients with a persistent ATAb level above the median had a higher OS (HR=0.41 [0.19-0.89], p=0.025) and PFS (HR=0.54 [0.31-0.95], p=0.032) compared to patients with a persistent ATAb level below the median.

Conclusions: Acquired overt thyroid toxicity and above median ATAb levels during anti-PD-1 treatment are associated with improved PFS and OS. Additionally, our results suggest that ATAb levels at baseline are of clinical relevance for PFS and OS.

PREVALENCE AND FOLLOW-UP OF POTENTIALLY INAPPROPRIATE MEDICATION AND POTENTIALLY OMITTED MEDICATION IN OLDER PATIENTS WITH CANCER – THE PIM POM STUDY

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Introduction: Older patients with cancer are a vulnerable group of medication users. Pharmacist-led medication reviews may optimize treatment and thereby reduce the risk of harmful effects from medication use. This study aims to determine the prevalence of Potentially Inappropriate Medication (PIMs) and Potentially Omitted Medication (POMs) in older patients with cancer.

Methods: In this prospective observational study (hospital) pharmacists conducted medication reviews with older patients with cancer (aged ≥65 years) treated with parenteral chemo and/or immunotherapy in the Deventer Hospital to determine the prevalence of PIMs and POMs. PIMs and POMs were identified using the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP), the Screening Tool to Alert doctors to the Right Treatment (START) and pharmacists' expert opinion. Recommendations regarding PIMs and POMs were made to the patients' oncologist/haematologist and follow-up was measured. Associations between covariates and the prevalence of PIMs and POMs were statistically analysed.

Results: One hundred seventeen (78%) of the 150 patients included (median age 72 years, 59% male, 68% solid tumours, mean number of medicines 11) had at least one PIM and/or POM. In total 266 PIMs and POMs were identified and these led to 195 (73%) follow-up actions (table 1). Number of medicines and Charlson Comorbidity Index score were both independently associated with having at least one PIM and/or POM (OR (95% CI) = 1.125 (1.003-1.262) and OR (95% CI) = 1.305 (1.094-1.556) respectively).

Table 1. Identification and follow-up of PIMs and POMs

	PIMs and POMs *n* (%)
PIMs, total	**180**
Using STOPP	89 (49)
Using expert opinion	85 (47)
Using both	6 (3)
POMs, total	**86**
Using START	66 (77)
Using expert opinion	20 (23)
Follow-up actions	**266**
By oncologist/haematologist	77 (29)
By general practitioner	118 (44)
No follow-up action	71 (27)

Conclusion: The prevalence of PIMs and POMs and subsequent follow-up in older patients with cancer is high. A pharmacist-led medication review is a good instrument to identify these PIMs and POMs and to optimize patients' treatment. A comprehensive approach, including pharmacists' expert opinion, is recommended to identify all PIMs and POMs in clinical practice.

ENABLING PEMETREXED TREATMENT IN PATIENTS WITH RENAL DYSFUNCTION: TIME TO REVISE THE PK-TOXICITY RELATIONSHIP.

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Introduction: Pemetrexed is a widely used cytostatic agent for the treatment of non-small cell lung cancer (NSCLC), mesothelioma and thymoma. Dosing of pemetrexed is currently based on body surface area although renal function is the only parameter determining systemic exposure. Pemetrexed is currently contraindicated in patients with a creatinine clearance <45ml/min and a large patient group is therefore withheld effective treatment. We recently found severe hematological toxicities in patients with renal dysfunction with pemetrexed in a study where the dose was adjusted to renal function, indicating that the exposure/toxicity relationship is different than previously thought. To allow safe dosing of pemetrexed in this patient group, it is pivotal to unravel the exposure/toxicity relationship of pemetrexed.

Aim: To investigate the pemetrexed exposure/neutropenia relationship and to ultimately allow safe dosing of pemetrexed in renally impaired patients.

Methods: Phase I pharmacokinetic data of pemetrexed were obtained from Eli Lilly. The dataset included 549 pemetrexed plasma concentrations (PK) and 1505 neutrophil counts (PD) in 106 patients with varying renal functions. A previously built PK model with renal function as a covariate on clearance described the plasma concentrations. This model was expanded with a chemotherapy-induced myelosuppression model. The drug effect on the proliferation of the neutrophils was modelled either as a slope (as previously suggested by the manufacturer) or a threshold relation. Model building and evaluations were conducted using nonlinear mixed effect modelling. The prediction capability for both models were tested using the outcome of early phase I study results, where pemetrexed was given in a dose of 0.2-5.2mg/m2 for 5 consecutive days in a Q3W cycle.

Results: The data are well fitted in both our threshold model as the slope model of Latz *et al*. However, when compared with the slope model the threshold model predicted the development of neutropenia as described in the phase I study with low dose daily pemetrexed treatment far more accurate. In the simulations the slope model predicts a low probability for development of neutropenia, in contrast with clinical results, whereas this toxicity predicted by the threshold model is more in line with the study results. In addition, the enhanced hematological toxicity seen in patients with impaired renal function is adequately captured by our model.

Conclusions: We developed a PK/PD threshold model for pemetrexed associated neutropenia which, based on clinical study results, better describes the suppression of neutrophils than the model presented in literature, especially in patients with renal dysfunction. We are currently developing a new dosing regimen based on this improved mechanistic model.

References:
1. Latz et al. Cancer Chemother. Pharmacol. 2006; 57(4):401-11.
2. McDonald et al. Clin. Cancer Res. 1998; 4(3):605-10

SYSTEMATIC REVIEW: THE ABSORPTION OF AND EXPOSURE TO ORALLY ADMINISTERED ANTIBIOTICS DURING THE INITIAL PHASE OF A SYSTEMIC INFECTION IN NON-ICU PATIENTS

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Background: Guidelines recommend to treat non-ICU patients hospitalized because of an infection with intravenously administered antibiotics for at least 48 hours to make sure that adequate systemic antibiotic exposure is achieved, and only to switch to oral antibiotics when the condition has improved and the fever has abated. Currently, there is an increased interest in an earlier IV-to-oral switch in such patients, so that they can benefit even earlier from the advantages of oral therapy: decreased length of hospital stay, risk of new infections and healthcare costs. We performed a systematic review to assess the effect of the initial phase of a systemic infection on the absorption of orally administered antibiotics in febrile non-ICU, hospitalized patients, to evaluate the possibility of an earlier (<24 hours) IV-to-oral switch in such patients.

Methods: An electronic search was conducted in MEDLINE and Embase for all relevant studies up to May 2019. Studies were selected when outcome data were collected during the initial stage of a febrile disease. Outcome data were (maximum) serum concentrations, time of achieving maximum serum concentration, the area-under-the-plasma-concentration-time curve or bioavailability of orally administered antibiotics. Risk of bias was assessed.

Results: We identified 10 studies on 6 antibiotics. Ciprofloxacin was the most frequently studied drug. Outcomes of the studies were heterogeneous and generally had a high risk of bias. Four studies compared the pharmacokinetics of febrile patients with those of clinically recovered patients, of which two studies with a low risk of bias suggested that absorption was not altered in these patients. Other studies either compared the pharmacokinetics from febrile patients with reported pharmacokinetic values from earlier studies in healthy volunteers (n=2), or provided no comparison at all and were non-conclusive (n=4).

Conclusions: There is a clear knowledge gap regarding the pharmacokinetics of oral antibiotics during the initial phase of a systemic infection in non-ICU patients: it is unclear whether the initial phase of a systemic infection alters the absorption of oral antibiotics in such patients. This gap needs to be covered to provide the evidence that an early switch still ensures high enough antibiotic exposure for effective treatment with the accompanying benefits of oral therapy.

CREATININE OR CYSTATIN-C AS A MARKER FOR RENAL FUNCTION IN PATIENTS USING OLAPARIB?

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Background. Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor approved for the treatment of ovarian- and metastatic breast cancer. In patients receiving olaparib, elevated serum creatinine levels were observed returning to baseline after treatment discontinuation (SmPC olaparib). Inhibition of renal uptake and efflux transporters can decrease the creatinine clearance causing elevated serum creatinine levels. This can falsely decrease the calculated eGFR without clinically meaningful alterations in renal function (Chappell *et al.* 2019). *In vitro*, olaparib causes inhibition of the renal uptake (OCT2) and efflux transporters (MATE1/MATE2K) at clinically relevant concentrations (McCormick *et al.* 2017). This study aimed to investigate if patients receiving olaparib have elevated creatinine levels during olaparib treatment and if the elevated creatinine levels are caused by inhibition of active tubular secretion of creatinine or by a reduction in renal function.

Methods. We retrospectively identified patients using olaparib at the Netherlands Cancer Institute from 2012 until 2020. Patients with at least one plasma or serum sample before- and during olaparib treatment were included. Creatinine- and cystatin-c levels were measured and renal function was determined by calculating the eGFR using the CKD-EPI Creatinine Equation and CKD-EPI Cystatin C Equation. Wilcoxon signed rank tests were used to assess differences in creatinine, cystatin-c and calculated eGFR with both equations before- and during treatment of olaparib.

Results. In total, 70 patients were included with available samples. Olaparib treatment increased the median creatinine level with 13.9% from 72 (Inter Quartile Range (IQR): 64-86) µmol/L before treatment to 82 (IQR:71-91) µmol/L during treatment ($p<0.001$) and decreased the median eGFR using creatinine with 12.9% from 85 (IQR: 73-99) mL/min/1.73m^2 before treatment to 74 (IQR: 62-90) mL/min/1.73m^2 during treatment ($p<0.001$). Olaparib treatment had no significant effect on cystatin-c levels ($p=0.52$) and the calculated eGFR using cystatin-c ($p=0.92$).

Conclusion. This study demonstrates that olaparib treatment leads to a significant increase in creatinine levels. Olaparib likely causes inhibition of renal transporters and does not affect renal function, since the eGFR values calculated with CKD-EPI Cystatin C Equation were comparable before- and during treatment of olaparib. Therefore, in patients taking olaparib, an alternative renal marker such as cystatin-c should be used to accurately measure renal function.

References.

Summary of product characteristics, Olaparib, EMA, 2019
McCormick, *et al.* Xenobiotica. 2017;47(10):903-91
Chappell, *et al.* CPT. 2019;105(5):1187-1195

PHARMACOKINETIC EVALUATION OF MICAFUNGIN PROPHYLAXIS FOR INVASIVE MOULD DISEASE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: PART OF THE OPTIMA STUDY

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Introduction: The Princess Máxima Center for pediatric oncology recently introduced a new biweekly prophylactic regimen of micafungin for invasive mould disease, based on experience in adults. Extended dose intervals of micafungin could overcome the need of frequent hospital visits. As part of this new strategy, we aimed to determine the pharmacokinetics of micafungin and to simulate various dose regimens that could be deployed as a mould active prophylactic regimen.

Methods: Micafungin was given biweekly at 9 mg/kg as a two hour infusion during the first five weeks of the induction treatment in pediatric patients with newly diagnosed acute lymphoblastic leukemia (ALL). A five-point sample curve was obtained (t=0,2.5,4,5 and 24h). The PK of micafungin was analysed using nonlinear mixed effects modeling, with clearance (Cl) and volume of distribution (Vd) allometrically scaled to a total body weight of 70kg. Monte Carlo simulations with four different dosage regimens were performed: 5 mg/kg, 7 mg/kg and 9 mg/kg with a maximum dose of 300 mg and flat dose per weight band (0-10kg received 50mg, 10-20kg received 100mg; 20-40kg received 150 mg and >40kg received 300 mg). Simulated pediatric exposure was compared to exposure in adults after 100mg daily.

Results: 62 patients were included with a total of 270 observations. Median age and weight were 4 (range 1-17) years and 19.3 (range 8.6-177.2) kg. A two-compartment model with intravenous administration and linear elimination best fitted the data. Typical parameter values with relative standard error (RSE%) were for clearance (Cl) 0.668(3%) L/h, central Vd (V1) 9.87(15%) L, peripheral Vd (V2) 7.15(17%) L and intercompartmental Cl (Q) 2.65(35%) L/h. Simulated micafungin exposure (i.e. median area under the curve (AUC0-168) with interquartile range (IQR)) for the 5 mg/kg, 7 mg/kg, 9 mg/kg and flat dosing regimens were respectively 783(245) mg·h/L, 1043(301) mg·h/L, 1251(380) mg·h/L and 951(323) mg·h/L. All simulated regimens exceeded the micafungin exposure in adults of 690(244) mg·h/L.

Conclusion: Our 9mg/kg biweekly dose suggests an above average micafungin exposure compared to adults receiving 100mg daily. Our clinical study has currently enrolled 100 patients and will provide the knowledge for efficacy and safety of this 9 mg/kg regimen. A flat dose per weight band may be a suitable alternate.

BIOAVAILABILITY AND VARIABILITY OF POSACONAZOLE EXPOSURE IN CHINESE PATIENTS USING A POPULATION PHARMACOKINETIC ANALYSIS

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Introduction: It is known that large differences exist in the pharmacokinetic (PK) profile of posaconazole suspension between healthy volunteers and patients and potentially also between patients of different races. Our aim is to, for the first time, develop a population PK model of posaconazole oral suspension for Chinese patients and compare their PK parameters to Caucasian healthy volunteers.

Methods: 292 posaconazole serum concentrations were obtained from 80 Chinese patients receiving oral suspension for prophylaxis or treatment of invasive fungal diseases. 85% patients had haematological diseases, including 56% patients with acute myelocytic leukemia or myelodysplastic syndromes or/and stem cell transplantation. Dense data from 28 Caucasian healthy volunteers (20 receiving oral suspension[1] and 8 receiving iv dosing[2]) were added to inform the model. NONMEM 7.3 was used to perform the analysis. A structural and stochastic model were based on a previous analysis in Caucasian healthy volunteers and it was subsequently assessed whether and how parameter values in Chinese patients deviated from these healthy volunteers.

Results: A two-compartment model with first-order absorption and lag time and first-order elimination best described the data. The bioavailability in Chinese patients was demonstrated to be approximately 2.5 (95% confidence interval [CI], 1.82 - 4.13) times lower compared to Caucasian healthy volunteers (mean, 18.2% vs. 46.0%). The absolute clearance in Chinese patients was found to be 61.9% (95% CI, 10.5 - 113.3%) higher than in healthy Caucasians (mean value of 5.85 L/h vs. 9.47 L/h). A difference in absolute volume of distribution or absorption parameters for Chinese patients could not be identified. Inter-individual variability (IIV) was identified for bioavailability and clearance. The IIV for bioavailability and clearance in Chinese patients were almost three (162.3% vs. 50.4%) and two times (48.5% vs. 26.8%) larger than in healthy volunteers, respectively. The proportional residual unexplained variability in Chinese patients was also significantly higher than in healthy volunteers (58.2% vs. 8.1%), which might result from the larger uncertainties in recorded time of drug dosing.

Conclusion: A significantly lower bioavailability and a faster absolute clearance with high IIV were demonstrated in Chinese patients in comparison to the Caucasian healthy volunteers, which is expected to be driven by the disease rather than the race. Future investigation could help identify which patients' demographic and clinical factors predict the IIV in Chinese patients.

References: [1] Brüggemann RJ, *et al.* Journal of antimicrobial chemotherapy 65(10): 2188-2194 (2010); [2] Wasmann RE, *et al.* Journal of Antimicrobial Chemotherapy [published online ahead of print] (2020).

POPULATION PHARMACOKINETICS OF ALLOPURINOL AND OXYPURINOL IN ASPHYXIATED NEONATES EITHER OR NOT TREATED WITH THERAPEUTIC HYPOTHERMIA

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Introduction: Hypoxic-ischemic encephalopathy following birth asphyxia is a major cause of neonatal death and long-term disability. At present, therapeutic hypothermia (TH) is the only established therapy. Allopurinol, a xanthine-oxidase inhibitor, is a promising agent to reduce the incidence of death and improve the neurodevelopmental outcome after perinatal hypoxic-ischemic insults. To investigate the neuroprotective effect of early allopurinol, a double blind placebo controlled study was designed (ALBINO study[1]). This analysis aimed to assess whether the target AUC of allopurinol and oxypurinol in the ALBINO study were reached.

Methods: Neonates were included in the pharmacokinetics (PK) ALBINO substudy. All neonates received a first dose of allopurinol 20 mg/kg within 60 minutes after birth. A second dose of allopurinol 10 mg/kg was only administered to neonates treated with TH at 12 ± 0.5 hours after the first dose. A population PK model was developed for allopurinol and oxypurinol using nonlinear mixed effects modeling (NONMEM, version 7.3). Birth weight (BW) was used as a description of body size and was related to PK parameters using allometric relationships. Measurements below the lower limit of quantification (LLOQ) were included, and the values were set to LLOQ/2 (0.05 mg/L for allopurinol and 0.0467 mg/L for oxypurinol). The model was used to evaluate whether more than two thirds (>66%) of patients in ALBINO study reached the target AUC between 0-12 hours (43.5 mg/L*h for allopurinol and 26.5 mg/L*h for oxypurinol). The adequacy of the developed models was evaluated using goodness-of-fit plots and precision of parameter estimates.

Results: A total of 15 neonates were included in this PK study. A one-compartment model for allopurinol and a subsequent one-compartment model for the metabolite oxypurinol were used to describe the data. Estimated PK parameters were total body clearance (CL) and volume of distribution (V) in neonates normalised to a BW of 3.5 kg. Allopurinol parameter estimates were CL 0.34 ± 0.05 L/h and V 3.55 ± 0.30 L. Oxypurinol parameter estimates were relative to formation fraction (f_m), which were CL/f_m 0.37 ± 0.09 L/h and V/f_m 5.51 ± 0.59 L. The interindividual variability for CL was 38.9% for allopurinol and 57.7% for oxypurinol. In total, 15 (100%) and 12 (80%) patients reached the target AUC for allopurinol and oxypurinol, respectively.

Conclusion: The dosing regimens used in ALBINO study fulfilled the study targets. The effects of TH and HIE severity on allopurinol and oxypurinol will be explored in future studies.

References*:* 1. Maiwald et al. BMC Pediatr. 2019 Jun 27;19(1):210 (study is funded by European Union's Horizon 2020, grant agreement No 667224)

GENETIC VARIANTS IN *TNFRSF1A, TNFRSF1B* AND *HLA-DRB1* ARE ASSOCIATED WITH RESPONSE PARAMETERS OF INFLIXIMAB IN SEVERE SARCOIDOSIS

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Introduction: Sarcoidosis is a systemic, granulomatous disease with a variable and sometimes chronic, progressive clinical course. The anti-tumor necrosis factor (TNF) agent infliximab can be an effective treatment option in severe sarcoidosis, but response is highly variable. In autoimmune diseases, genetic variation in TNF, TNF receptors, Fcγ-receptors and HLA has been associated with response to infliximab therapy. We tested whether genetic variations associated with change in clinical response parameters in a cohort of severe sarcoidosis patients treated with infliximab.

Methods: Patients (n=106) were genotyped for *TNFRSF1A* rs1800693, *TNFRSF1B* T196G (rs1061622), *FCGR2A* G131A (rs1801274), *FCGR3A* V158F (rs396991) and HLA tag SNPs rs2040410A and rs3135388T to capture *HLA-DRB1*03* and *HLA-DRB1*15,* respectively. Pulmonary function tests and inflammatory biomarkers were evaluated at baseline and after six months of treatment. Change from baseline of pulmonary function tests and inflammatory biomarkers soluble interleukin-2 receptor (sIL-2R) and angiotensin-converting enzyme (ACE) were compared between carriers and non-carriers of a genetic variation.

Results: The mean improvement in the diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DLCOc) was better in patients with the *TNFRSF1A* rs1800693 AA genotype than in patients carrying the G allele (AG+GG, 6.2 vs 0.5% predicted, p=0.001). And patients with *TNFRSF1A* rs1800693 AA genotype showed a larger mean decrease in both sIL-2R (6273 vs 2473 pg/ml, p=0.004) and ACE (38 vs 16 U/L, p=0.03). Differences in baseline outcome parameters between patients with *TNFRSF1A* rs1800639 AA genotype and carriers of the G allele were indicative of more severe disease in AA carriers (data not shown). Regarding *TNFRSF1B* T196G, patients with the GG genotype showed a mean increase in ACE of 15 U/L whereas carriers of the T allele showed a mean decrease in ACE of 25 U/L (p=0.02). Finally, *HLA-DRB1*03* negative patients (tag SNP rs2040410 GG genotype) showed a significantly higher reduction in sIL-2R compared to *HLA-DRB1*03* positive patients (tag SNP rs2040410 GA+AA, 3996 vs 2283 pg/mL, p=0.03).

Conclusions: We found that the *TNFRSF1A* rs1800693 AA genotype, *TNFRSF1B* 196T and absence of *HLA-DRB1*03* associate with a better response according to clinical and inflammatory parameters after treatment with infliximab in patients with severe sarcoidosis. Future studies are needed to evaluate the role of pharmacogenetics in predicting response to anti-TNF agents in severe sarcoidosis.

ARE JUNIOR DOCTORS GOOD PRESCRIBERS: AN INTERNATIONAL 1-YEAR PROSPECTIVE FOLLOW-UP STUDY

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A ZonMw study on behalf of the Education subcommittee, Working Group Landelijke Eindtoets Farmacotherapie of the NVKF&B

Background: Poor prescribing adversely affects patient safety and healthcare costs. Studies have shown that medical students in Europe lack adequate prescribing skills at graduation (Brinkman et al., 2017, Brinkman et al., 2018), probably due to inadequate training in clinical pharmacology and therapeutics (CP&T) during undergraduate education (Brinkman et al., 2017). Although this has never been studied, it is assumed that prescribing skills increase by learning in practice once the student becomes a junior doctor.
Objectives: The aim of this study was to investigate how the prescribing skills of junior doctors in the Netherlands and Flanders (Belgium) develop during the first year after graduation.
Methods: In this multicentre (n= 11), longitudinal study in the Netherlands and Flanders 1.506 medical students graduating between July 2017 and March 2018 were invited to participate. They were asked to complete an online assessment at three different time points: T0= around graduation, T1= six months after graduation, T2= one year after graduation. Each assessment contained 3 polypharmacy case scenarios covering 3 subjects (reduced kidney function, pain management and anticoagulants). All cases were scored (inappropriate, suboptimal or appropriate) independently by two investigators (ED and DB) on non-pharmacological and pharmacological policy and on the proposed control management.
Preliminary results: In total, 556 (36.9%) junior doctors agreed to participate, 317 (57.0%) of whom completed all three assessments. The first results show that 41% of the therapies for patients with polypharmacy and reduced kidney function were inappropriate in assessment 1, 70% in assessment 2 and 62% in assessment 3.With a mean of 72% inappropriate prescriptions, the pharmacological policy was formulated the worst. The most common errors were 'preventing/protecting medication omitted' (81%), 'adjustment omitted' (70%), and 'unneeded stopped/changed medication' (30%). In total, 5.6% of all therapies were scored as potentially harmful, and 0.3% as harmful.
Conclusion: The first results show that we cannot automatically presume that prescribing skills of junior doctors improve by working in practice. Moreover, this study even shows that their prescribing skills decrease the first year after graduation. Therefore we suggest the following: (1) training in CP&T in the undergraduate phase should be intensified in order to enhance the prescribing skills level when graduated; (2) new educational programmes on prescribing skills should be introduced for all junior doctors.
The complete results will be presented at the scientific spring meeting.

References:

- Brinkman DB et al. Br J Clin Pharmacol 2018;84(4):615-635
- Brinkman DB et al. Clin Pharmacol ther 2017;101(2):281-289
- Brinkman DB et al. Clin Pharmacol ther 2017;102(5):815-822

COMPARISON BETWEEN FVIII QUANTIFIED WITH ONE-STAGE CLOTTING ASSAY AND MASS SPECTROMETRY IN HAEMOPHILIA A: PROOF OF PRINCIPLE

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Introduction: Haemophilia A is a hereditary bleeding disorder characterized by a factor VIII (FVIII) deficiency. As biomarker, FVIII activity is used to classify disease severity and to monitor the treatment of exogenous FVIII products (Srivastava *et al*., 2013). The one-stage clotting assay (OSA) is performed to measure this FVIII activity, but OSA's limitations may result in misclassification of disease severity or suboptimal monitoring of treatment, as stated by Peyvandi *et al*. (2016). Measurement of FVIII plasma concentration with a novel liquid chromatography tandem-mass spectrometry (LC-MS/MS) method might overcome these challenges and could eventually be used for telemonitoring with dried blood spot, facilitating blood sampling from home. The objective is to investigate the association between FVIII activity and plasma concentration, and to investigate determinants for discrepancies.

Methods: In this cross-sectional study, patients with haemophilia A receiving standard-of-care treatment were eligible for inclusion. Within the activity categories of <1%, 1–5%, >5–40%, >40–150%, and >150–600% we selected 15–20 plasma samples, and compared FVIII plasma concentration (LC-MS/MS) to FVIII activity (OSA) with Bland-Altman analysis. The association of potential determinants and discrepancies between OSA and LC-MS/MS were analysed with linear regression analysis.

Results: A total of 87 samples were included. Bland-Altman analysis demonstrated an overall mean difference of -1% with an SD of 64% between the two methods. The discrepancies between the two methods were significantly associated with the presence of anti-FVIII antibodies (133% [95% CI 81, 185] n=5) and use of exogenous FVIII products (-37% [95% CI -65,-9] n=58), e.g. plasma-derived and B-domain modified FVIII products.

Conclusions: Despite almost no discrepancy overall, the variability between FVIII activity and FVIII plasma concentration was large. Anti-FVIII antibodies or use of exogenous FVIII products might result in differences of potential clinical impact. We suggest that the new LC-MS/MS method could eventually lead to a change in clinical practice therefore more research is needed to determine the value of FVIII plasma concentration in addition to FVIII activity.

References: El Amrani et al. J Pharm Biomed Anal. 2019;175:112781
Peyvandi et al. J Thromb Haemost. 2016;14:248-61
Srivastava et al. Haemophilia 2013;19:e1-47

COMPARISON OF INTRATUMORAL DOCETAXEL EXPOSURE IN CANCER PATIENTS BETWEEN NANOPARTICLE ENTRAPPED DOCETAXEL (CPC634) AND CONVENTIONAL DOCETAXEL: THE CRITAX STUDY

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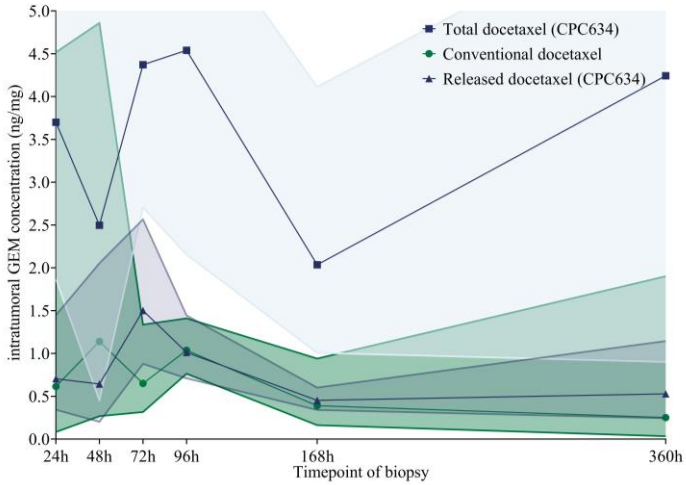
Background: Ineffective chemotherapy may partly be caused by subtherapeutic intratumoral drug levels. Nanomedicines are developed to improve the therapeutic index, by increasing intratumoral drug exposure and preserving healthy tissue. We hypothesized that CPC634, a new nanoparticle entrapping docetaxel, increases intratumoral docetaxel level and overall duration of exposure.

Methods: In this randomized cross-over study we assessed both plasma and intratumoral pharmacokinetics (PK) of docetaxel after administration of 75 mg/m^2 conventional docetaxel (Cd) and CPC634. We aimed to identify a 25% increase of intratumoral docetaxel exposure after CPC634 infusion compared to Cd. Patients were randomized to receive Cd in cycle 1 and CPC634 in cycle 2 or *vice versa*. Tumor biopsies were taken 24, 48, 72, 96, 168 or 336 hours after infusion during both cycles. Total docetaxel concentration (TDC) was determined for both drugs and released docetaxel for CPC634 in tumor tissue and plasma. PK data were analysed using mixed modelling.

Results: We included 24 evaluable patients. In plasma, the area under the curve (AUC_{inf}) of released docetaxel was higher (+27%, 95% CI: 12 to 44%, P=0.001) while peak plasma concentration (C_{max}) (-91%, 95% CI: -92 to -89%, P<0.001) decreased during CPC634 administration versus Cd. Intratumoral TDC was 461% higher (95% CI: 243 to 816%, P<0.001) after CPC634 administration, while released docetaxel was comparable to Cd (+17.3%, 95% CI: -22 to +69%, P=0.43) **(Figure 1)**



Conclusions: The plasma PK profile of CPC634 is favourable compared to Cd since a lower Cmax and prolonged higher systemic exposure is seen. Higher intratumoral TDC levels were reached with CPC634, while released docetaxel levels were comparable to Cd. The almost 5-fold increased tumor accumulation for prolonged period of time of TDC supports the expectation that CPC634 will exhibit beneficial efficacy/safety balance. Additional studies assessing the intratumoral exposure to CPC634 (NCT0371243) and a phase II efficacy study in platinum resistant ovarian cancer patients (NCT03742713) are currently ongoing.

CHARACTERIZING THE NEURO-VASCULAR UNIT IN DIFFUSE INTRINSIC PONTINE GLIOMA

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Introduction: Diffuse intrinsic pontine glioma (DIPG) is a rare childhood brainstem tumor with a median overall survival of eleven months. Lack of chemotherapy efficacy is hypothesized to be related to an intact blood-brain-barrier (BBB), restricting drugs from reaching the tumor. In this study we aim to compare the neuro-vascular unit (NVU), containing the vascularity and BBB, of DIPG to healthy pons tissue.

Methods: End-stage DIPG autopsy samples (n=5) and age-matched healthy pons samples (n=22), obtained from the NIH NeuroBioBank, were immunohistochemically stained for tight-junction proteins claudin-5 and zonula occludens-1 (ZO-1), basement membrane component laminin, and pericyte marker PDGFRβ. Claudin-5 stains were also used to determine vascular density and diameters.

Results: In DIPG, expression of claudin-5 and ZO-1 was reduced, and claudin-5 was dislocated to the abluminal side of endothelial cells. Laminin expression at the glia limitans was reduced in both pre-existent vessels and neovascular proliferation. In contrast to healthy pons, no PDGFRβ expression was detected.

The number of blood vessels in DIPG was significantly reduced compared to healthy pons, 13.9±11.8/mm^2 versus 26.3±14.2/mm^2, respectively (P<0.01). Especially the number of smaller blood vessels (<10µm) was significantly lower (P<0.01). Distribution of larger blood vessels (≥10µm) did not differ between groups (P=0.223). Mean vascular diameter was 9.3±9.9µm for DIPG versus 7.7±9.0µm in healthy pons (P=0.016).

Conclusions: Our study demonstrates evidence of structural changes in the NVU in end-stage DIPG. Chemotherapeutic inefficacy could be the result of reduced vascular density, limiting the systemic transport of drugs to the tumor. However, further research is needed to determine meaning and extent of these changes and to determine whether these observations are caused by the tumor or the result of treatment.

PREDICTION OF DRUG EXPOSURE IN CRITICALLY ILL ENCEPHALOPATHIC NEONATES TREATED WITH THERAPEUTIC HYPOTHERMIA BASED ON A POOLED POPULATION PHARMACOKINETIC ANALYSIS OF SEVEN DRUGS AND FIVE METABOLITES

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Introduction: Drug dosing in encephalopathic neonates treated with therapeutic hypothermia is challenging; exposure is dependent on body size and maturation but can also be influenced by factors related to disease and treatment. A better understanding of underlying pharmacokinetic principles is essential to guide drug dosing in this population.

Methods: The prospective multicenter cohort study PharmaCool was designed to investigate the pharmacokinetics of commonly used drugs in neonatal encephalopathy. In the present study, data from seven drugs obtained in the PharmaCool study were combined to study the structural system specific effects of body size, maturation, recovery of organ function and temperature on drug clearance using nonlinear mixed effects modelling.

Results: Data from 192 term and near-term encephalopathic neonates treated with therapeutic hypothermia were included. An integrated population pharmacokinetic model of seven drugs (morphine, midazolam, lidocaine, phenobarbital, amoxicillin, gentamicin, benzylpenicillin) and five metabolites (morphine-3-glucuronide, morphine-6-glucuronide, 1-hydroxymidazolam, hydroxymidazolam glucuronide, monoethylglycylxylidide) was successfully developed based on previously developed models for the individual drugs. For all compounds, body size was related to clearance using allometric relationships and maturation was described with gestational age in a fixed sigmoidal Hill equation. Organ recovery after birth was incorporated using postnatal age. Clearance increased by 1.23%/h (95% CI 1.03 - 1.43) and by 0.54%/h (95% CI 0.371 - 0.750) for high and intermediate clearance compounds, respectively. Therapeutic hypothermia reduced clearance of intermediate clearance compounds only, by 6.83%/˚C (95% CI 5.16%/˚C - 8.34%/˚C).

Conclusion: Data from seven drugs and five metabolites were successfully combined in an integrated population pharmacokinetic model. This integrated model can be used to facilitate drug dosing and future pharmacokinetic studies in this vulnerable population.

DOSE ADJUSTMENTS IN OBESE PATIENTS IN CLINICAL PRACTICE

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Introduction: In 2017, an alarming 13% of the Dutch population older than 20 was obese (BMI>30 kg/m2), 2% of the population had a BMI over 35 kg/m2 and even 1% was considered morbidly obese with a BMI over 40 kg/m2. Since obesity is associated with the development of a large number of health disorders, it is likely that the incidence of obesity in the hospital population is even larger. Obesity may effect affect the both pharmacokinetics and pharmacodynamics in several ways and therefore. Because of this dose adjustments may be necessary, especially for drugs with a small therapeutic window and for which the dose is not guided by clinical presentation. Currently there is no clinical decision support alerting prescribers nor is it monitored by the hospital pharmacy. We therefore conducted a study in a real life setting to evaluate the amount of pharmacist interventions in response to obesity.

Methods: During a 30-day period, we actively reviewed the prescriptions of all in house patients with a BMI over 35 kg/m^2. Pregnant woman were excluded. The dose of antibiotics, antimycotics and anticoagulants were checked with the current guidelines and literature and if necessary dose adjustments were advised. If the patient had a BMI over 40, morbid obesity was recorded in the hospital information system to facilitate dose monitoring in the future.

Results: The prescriptions of in total 402 patients were reviewed. On average there were 28 patients per day with a BMI over 35 kg/m^2, this is 5% of all admitted patients. Of the patients 64% was female, the average weight was 116 kg (83-240), the average BMI was 40,6 (35,1-81,1) and the average amount of prescriptions was 13 (0-36). A total of 91 possible interventions were recorded. This comes down to an average of 3 (0-9) interventions per day. On average, there was one patient per day for which the BMI over 35 kg/m^2 was unjust.

Conclusion: This study showed that 5% of the admitted patients in our general hospital ad a BMI over 35 kg/m^2. Since an average of 3,1 interventions were proposed each day it seems worth the effort to actively evaluate the medication of these patients. During our study, the complete set of prescriptions was reviewed by the hospital pharmacist, which took up a considerable amount of time. This could be greatly reduced by developing a clinical rule that combines the information on BMI with the specific use of antibiotics, antimycotics and anticoagulants. Currently there are some nation-wide dose recommendations being developed for implementation in a clinical decision support system that can trigger an alert upon prescribing. Unfortunately, this is depended of the registration of morbid obesity as a disorder and is therefore not a real time evaluation of the patients BMI. Therefore, we advise hospital pharmacist to evaluate the use of antibiotics, antimycotics and anticoagulants in obese patients based on their current BMI on a daily basis.

POPULATION PHARMACOKINETIC MODEL AND LIMITED SAMPLING STRATEGY FOR CLOZAPINE USING PLASMA AND DBS SAMPLES

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Introduction: To improve efficacy and avoid toxic adverse effects, therapeutic drug monitoring is highly recommended for clozapine therapy. Trough level monitoring is regularly used for this purpose but the $AUC_{0\text{-}24h}$ is generally considered to be a better marker of drug exposure in time. Calculating AUC generally needs a population pharmacokinetic model and a limited sampling scheme with the highest predictive performance to measure AUC. Multiple venapunctions are a burden for the patient, so collecting clozapine blood samples by means of dried blood spot sampling instead of the regular venous blood sampling method not only facilitates AUC monitoring but also makes regular TDM of clozapine easier and more patient friendly in daily practice.

Objective: Development of a population pharmacokinetic model and limited sampling strategy for estimating the $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}24h}$ of clozapine, using both the regular blood sampling method and DBS sampling.

Method: From 15 schizophrenic patients (18- 55 years) treated with clozapine who participated in a clinical trial, plasma and dried blood spot samples were obtained at the same time point before administration and 2, 4, 6 and 8 hours after clozapine intake. MWPharm was used to parameterize population pharmacokinetic models and limited sampling strategies.

Results: A total of 49 plasma and 72 DBS samples were collected. Three population pharmacokinetic models were developed (DBS, Plasma and Total population) A three time point sampling strategy at 2, 6 and 8 hours after clozapine intake gave the best estimation of the clozapine $AUC_{0\text{-}12h}$ and a three time point sampling strategy at 4, 10 and 11 hours for the $AUC_{0\text{-}24h}$

Conclusion: A PopPK model and related limited sampling strategy was successfully developed using clozapine plasma and DBS sampling.

THERAPEUTIC DRUG MONITORING OF ORAL ANTICANCER DRUGS – PRELIMINARY RESULTS OF A PROSPECTIVE STUDY

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Background. Oral anticancer drugs show a high interpatient variability in pharmacokinetics (PK). While exposure has been linked to efficacy and toxicity for many of these drugs, they are still dosed using a one-size-fits-all approach. Consequently, individual patients (pts) have a high probability to be either underdosed or overdosed, potentially leading to decreased antitumor efficacy or increased toxicity. Therapeutic drug monitoring (TDM), which is personalised dosing based on measured drug levels, could be used to address these problems and eventually optimize treatment outcomes.

Methods. This prospective clinical study (www.trialregister.nl, NL6695) evaluates the feasibility, tolerability and efficacy of TDM of oral anticancer drugs. In total, 600 patients will be included using 23 different drugs. Patients are eligible for inclusion if they start regular treatment with one of these drugs at the registered dose. PK sampling is performed 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter. Drug concentrations are measured and trough concentrations (C_{min}) are derived. In case of an estimated C_{min} below the predefined target and acceptable toxicity, a PK-guided intervention is recommended. This may include improvement of compliance, adaptations in concomitant medication (due to drug-drug interactions), concomitant intake with food, splitting intake moments or dose increments.

Results. As per 13 January 2020, 482 patients were included (imatinib (n=79), abiraterone (n=74), trametinib (n=68), enzalutamide (n=43), sunitinib (n=39), pazopanib (n=34), other (n=145)), of whom 432 patients had available PK data. 197 patients (46%) were underdosed and had at least 1 PK sample below the predefined target. In 105 of 432 patients (24%) a PK-guided intervention was performed, which was successful (i.e. target attainment without additional toxicities) in 79 patients (75%). In 92 patients, a PK-guided intervention could not be performed, due to intolerable toxicity (54 patients), treatment discontinuation (11 patients) or lack of physician adherence (8 patients).

Conclusion. This prospective study shows that PK-guided dose optimization of oral anticancer drugs is feasible in daily clinical practice. A PK-guided intervention was recommended in 24% of the patients which resulted in target attainment without additional toxicities in 75% of these patients.

GANCICLOVIR AND THE DEVELOPEMENT OF ACUTE KIDNEY INJURY IN THE INTENSIVE CARE UNIT

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Introduction: Ganciclovir therapy is the standard of care for Cytomegalovirus (CMV) infected patients. Side effects of ganciclovir treatment are nephrotoxicity and pancytopenia. Therapeutic drug monitoring (TDM) may limit ganciclovir toxicity. However, a retrospective study (n=82) on the effect of TDM of ganciclovir revealed that 54% of patients using ganciclovir developed nephrotoxicity (Ritchie *et al*.,2019). Thus far, ganciclovir-induced nephrotoxicity hasn't been previously studied in intensive care unit (ICU) patients. Most hospitals in the Netherlands choose to do TDM on ICU patients receiving ganciclovir treatment. Ganciclovir exposure could possibly have an effect on the development of nephrotoxicity in patients receiving treatment (Ritchie *et al.*, 2019;Slater *et al*., 2017). Aim: This study will investigate the relation between ganciclovir exposure and the development of AKI in ICU patients.
Methods: This study was a retrospective single centre observational cohort study. The patients were divided into one group above the median and one group under the median cumulative dosage. The patients included into this study are adult ICU patients with an active CMV infection that have been treated with ganciclovir and that have a minimum of one ganciclovir through blood level. All patients were admitted to the ICU between 2008 and 2018. Exclusion criteria included patients receiving treatment for less than two days. The data were extracted from the ICU database in the OLVG east hospital in Amsterdam. The primary endpoint was the difference in kidney function between the two groups. Renal impairment was determined by using the difference in Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE), renal Sequential Organ Failure Assessment (SOFA) score and the creatinine clearance between the first and last day of treatment (Slater *et al*., 2017). Secondary endpoints were development of neutropenia, thrombocytopenia, leukopenia and anaemia.
Results: A total of 125 patients was included. The observed median cumulative ganciclovir dose received of 30 mg/kg was selected as the cut-off for defining the two cumulative ganciclovir dose groups for this analysis. The average differences (±SD) between the first and last day of treatment were determined for the kidney function parameters. The group with the high cumulative dosage had an average difference in creatinine clearance of -9.22(± 67.88) vs the lower group -9.26 (±68.68). The average difference in RIFLE scores was 0.30(±1.51) for the group receiving a high cumulative dosage and 0.03(±2.28) for the group with a low cumulative dosage. The average difference in renal SOFA score was respectively 0.06(± 0.95) and 0.016 (± 1.56). There were no statistically significant differences between the average difference in creatinine clearance (p=0.864), RIFLE score (p=0.550) and renal SOFA score (p=0.924) between the two groups. The analysis of the secondary endpoints revealed no statistically significant difference.
Conclusion: The present data show that a higher TDM-guided ganciclovir exposure does not result in decreased kidney function, and pancytopenia in ICU patients. Thus, TDM-guided dosing of ganciclovir in ICU patients may reduce ganciclovir toxicity in these vulnerable patients.

References:
[1] Ritchie *et al*. Antimicrob Agents Chemother. 2019 Jan; 10(1128):01855-18.
[2] Slater *et al*. Pediatric Drugs. 2017 Feb; 19(1): 59–67.

SEX DIFFERENCES IN HOSPITAL ADMISSIONS RELATED TO ADVERSE DRUG REACTIONS

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Introduction: Adverse drug reactions (ADRs) are a major health concern and are responsible for approximately 5% of all acute hospital admissions. Women are 1.5-1.7 times more likely to develop ADRs than men. Differences in ADR-related admissions between women and men have been described before in studies on spontaneous ADR reports and in an earlier study where adjusting for potential confounders was not possible due to its ecological design. The objective of this study was to investigate whether there are sex differences in ADR-related hospital admissions and examine whether women or men are more prone to develop particular drug-ADR combinations.

Methods: Patients were selected from the PHARMO Database Network, consisting of over four million residents of the Netherlands with an average follow-up of ten years. ADR-related hospital admissions between 2005 and 2017 were identified using hospital discharge codes indicating an ADR of a drug group used at a therapeutic dose, conform the ICD 9 and 10 coding system. Patients aged ≥ 16 years who had a dispensing of the relevant drug within three months before the hospital admission were included. Drug-ADR combinations with at least 50 hospital admissions for women or men were examined, excluding sex-specific ADRs. Age-adjusted odds ratios (OR) with 95% CIs for drug-ADR combinations for women versus men were calculated with respect to the number of female and male users.

Results: There were a total of 18,469 hospital admissions involving women (0.35% of the total number of admissions) and 14,678 admissions involving men (0.35% of the total number of admissions) due to an ADR. ORs were calculated for 48 drug-ADR combinations. There were 10 combinations with a statistically significantly higher risk in women versus men and 8 in men versus women. The most substantial differences were seen in ADRs due to anticoagulants and diuretics. Anticoagulants showed a lower risk of hospital admissions with persistent haematuria (OR 0.31; 95% CI 0.21, 0.45) haemoptysis (OR 0.47, 95% CI 0.30, 0.74) or subdural haemorrhage (OR 0.61; 95% CI 0.42, 0.88) in women than in men and a higher risk of rectal bleeding in women (OR 1.48; 95% CI 1.04, 2.11) than in men. Also, there was a higher risk of hospital admission in women using thiazide diuretics causing hypokalaemia (OR 3.03; 95% CI 1.58, 5.79) and hyponatraemia (OR 3.33, 95% CI 2.31, 4.81) than in men.

Conclusions: Sex differences exist for ADR-related hospital admissions due to anticoagulants and diuretics. Further research into the mechanisms of and potential confounders for these observed differences can contribute to the development of sex-specific guidelines.

EFFECT OF METFORMIN ON CLINICAL GOUT OUTCOMES IN GOUT PATIENTS WITH DIABETES MELLITUS

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Background:

Gout and diabetes mellitus type 2 (DM) are frequently co-existing. Metformin is the first choice of treatment for patients with DM type 2, and might – based on previous studies - have beneficial clinical effects on gout through a putative anti-inflammatory as well as serum uric acid (SUA) lowering effect.[1,2,3]

Objectives:

To investigate the anti-inflammatory and SUA lowering effect of metformin in patients with gout starting uric acid lowering treatment (ULT).

Methods:

Patients with clinical diagnosis of gout, a first outpatient visit between January 2010 and March 2018 and a follow-up of at least 6 months were included in a retrospective cohort study, conducted in two rheumatology centers in the Netherlands. From this cohort patients with DM starting ULT were selected. Patients with metformin use were compared to patients using other or no antidiabetic medication (control group). Metformin use was defined as use ≥80% of the time during the first six months after initiation of ULT.

To evaluate the anti-inflammatory effect, the differences in incidence density (ID) of gout flares in the first six months after starting ULT was measured and analyzed using Poisson regression. To evaluate the SUA lowering effect, the difference in baseline SUA, proportion of patients reaching target serum uric acid (SUA < 0.36 mmol/l) at six months follow up, and ULT dosage at time of reaching this target were analyzed. All analyses included correction for confounding.

Results:

Of 2108 gout patients, 309 patients who started ULT also had DM, with 155 in the metformin group and 154 in the control group. ID of flares was 2.8 and 3.3 per patient year in the control and metformin group respectively, resulting in an incidence rate ratio of 0.93 (95% CI 0.75 – 1.15). SUA levels at baseline were similar, between the two groups. At six months 46.1% and 57.4% reached target SUA in the control and metformin group respectively, odds ratio of 1.30 (95%CI 0.80 – 2.08). No difference was found in allopurinol dose at time of reaching target SUA between the groups (difference 1.14 mg, 95% CI -38.89 – 41.19).

Conclusion:

In contrast to a previous report[1], in this study in patients with DM and gout and starting ULT, metformin does not have a clinically relevant added anti-inflammatory or urate lowering effect.

1. Vazirpanah N et al. Ann Rheum Dis. 2019;78(5):663-71.
2. Simao AN et al. Expert Opin Ther Targets. 2012;16(12):1175-87.
3. Barskova VG et al. Klin Med (Mosk). 2009;87(7):41-6.

INFLUENCE OF ALLOPURINOL ON THIOPURINE ASSOCIATED TOXICITY: A RETROSPECTIVE POPULATION-BASED COHORT STUDY

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Introduction: Thiopurines are important for treating inflammatory bowel disease, but are often discontinued due to adverse effects. Concomitant use of allopurinol might lower the risk of these unwanted effects, but large studies in the general population are lacking. Aims of this study were to evaluate rates of hepatotoxicity, myelotoxicity, pancreas toxicity, and therapy persistence in adult thiopurine users with or without allopurinol.

Design: A retrospective population-based cohort study was conducted within current thiopurine users (Clinical Practice Research Datalink). Among these patients, co-use of allopurinol was compared to non-use. Hazard ratios (HRs) for hepatotoxicity, myelotoxicity and pancreatitis were derived using time-dependent Cox proportional hazards models, and were adjusted for potential confounders. Persistence of thiopurine use was evaluated using Log-rank statistics.

Results: Patients using thiopurines (N=37,360) were identified of which 1,077 were concomitantly taking allopurinol. A 58% decreased risk of hepatotoxicity was observed in those concomitantly taking allopurinol (HR 0.42; 95%CI; 0.30–0.60; NNT 46). Rate of myelotoxicity (HR 0.96; 95%CI, 0.89–1.03) was not influenced. Risk of pancreatitis was increased (HR 3.00; 95%CI, 1.01–8.93; NNH 337), but was only seen in those with active gout (suggesting confounding by indication). Finally, allopurinol co-users were able to maintain thiopurine therapy over twice as long as those not on allopurinol (3.9 years versus 1.8 years, P<0.0001).

Conclusion: In thiopurine users, allopurinol is associated with a 58% reduced risk of hepatotoxicity. In addition, thiopurine persistence was prolonged by 2.1 years in allopurinol users. These data support the use of allopurinol in individuals requiring thiopurine therapy.

DIFFERENCES IN USE OF ADJUVANT TREATMENT OF STAGE III COLON CANCER PATIENTS BETWEEN DUTCH HOSPITALS

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Introduction: The external validity of randomized controlled trials (RCTs) are limited, leading to a gap in the knowledge of the real-world use and effectiveness in clinical practice of expensive drugs treatments. The aim of our study is to describe differences in adjuvant treatment of stage III colorectal cancer patients between hospitals, by using multiple real-world data sources and compare this to study data.

Methods: Administrative data on the use of expensive drugs in colorectal cancer, from hospital pharmacies were linked to clinical data from national (cancer) quality registries. These clinical data include information on patient- and tumor characteristics as well as clinical outcomes. Data were visualized in dashboards. As an example, we investigated the adjuvant treatment of stage III colorectal cancer patients with capecitabin and oxaliplatin.

Results: Linkage of the data sources led to the visualization of 1383 colorectal cancer patients. Fourteen hospitals were included in this study. After surgery of stage III colorectal patients (n=688), 141 (20.5%) were treated with capecitabine monotherapy and 486 (70.6%) with combination therapy of capecitabine and oxaliplatin. No large differences between hospitals were observed in the number of cycles of capecitabine plus oxaliplatin (median = 4). These results are in contrast with a large RCT where patients received a median of 8 cycles[1].

Conclusion: Linkage of the data sources led to insights in the use of expensive drugs in colon cancer patients. Patients subgroups and treatment patterns were visualized in dashboards.

References:

[1] Haller, D. G., Tabernero, J., Maroun, J., De Braud, F., Price, T., Van Cutsem, Schmoll, H. J. (2011). Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol, 29(11), 1465-71.

ASSOCIATION BETWEEN SERUM BIOMARKERS CEA AND LDH AND RESPONSE IN ADVANCED (NON-) SMALL CELL LUNG CANCER PATIENTS TREATED WITH PLATINUM-BASED CHEMOTHERAPY

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Background. Biomarkers can be useful in evaluating therapy response in addition to radiological evaluation, supporting clinical decision making. The objective of this study was to investigate carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) as biomarkers for early assessment of response in patients with advanced (non-) small cell lung cancer ((N)SCLC) treated with platinum-based chemotherapy.

Methods. CEA and LDH levels were examined from 2012-2017 in a retrospective follow-up study among 593 consecutive patients with advanced (N)SCLC treated with first-line platinum-based chemotherapy (q3w) in a large teaching hospital. Prior to treatment and at week 3, 6, 9 and 12 after treatment initiation CEA and LDH levels were measured. Pretreatment biomarker levels and changes were studied for association with radiologic response (RECIST 1.1, PR or CR at week 6 and 12) and overall survival (OS) using multivariate logistic regression respectively COX proportional hazard modelling. Patient and disease characteristics such as age and disease stage were taken into account as potential confounding factors.

Results. Pretreatment high (≥247 U/L) LDH and high (non-smokers ≥5.0 ng/ml, smokers ≥10 ng/ml) CEA were not associated with radiological response. Significant associations were found between CEA decrease (≥20%) at week 3 (OR_{adj} 2.27 95%CI 1.28-4.03) and LDH decrease (≥20%) at week 3 (OR_{adj} 1.72 95%CI 1.02-2.88) and response at week 6. Also CEA decrease (≥20%) at week 3 (ORadj 2.09, 95% CI 1.14-3.83) was associated with response at week 12.
Pretreatment high LDH (HR_{adj} 1.42 95%CI 1.15-1.76) was associated with inferior OS. Increased CEA (≥20%) at week 3 (HR_{adj} 1.70 95%CI 1.27-2.27) as well as LDH increase (≥20%) at week 3 (HR_{adj} 1.62 95%CI 1.18-2.22) were negatively associated with OS.

Conclusions. Our results support determination of CEA and LDH levels for earlier assessment of response to platinum–based chemotherapy in patients with advanced (N)SCLC. Hence, routine determination and evaluation of CEA and LDH levels, prior to each cycle of platinum–based chemotherapy in advanced (N)SCLC, should be considered as part of daily clinical practice.

FEASIBILITY AND FIRST RESULTS OF THE USSING CHAMBER TECHNIQUE TO STUDY AGE-RELATED CHANGES IN DRUG TRANSPORT

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Introduction: Most drugs are given to children orally. However, insufficient information about the activity of intestinal transporters in this specific population hampers pharmacotherapy.

Objectives: To assess the feasibility of the Ussing chamber technique to study passive and active transport across the intestine in adults and children and explore age-related differences.

Methods: Leftover adult and pediatric ileal tissues from surgeries were collected and mounted in the *ex vivo* Ussing chamber. Electrophysiological parameters (potential difference, short circuit current and transepithelial resistance) were determined. A cocktail of compounds was used to survey the major intestinal passive (para- and transcellular transport) and active efflux transport routes (BCRP, P-gp). Apparent permeability values were determined by sampling of the donor and receiver compartments at defined time points and drug concentration measurement by LC-MS/MS. Mann-Whitney U test was performed to compare pediatric and adult datasets.

Results: Samples from five children (age range: 39 weeks to 17 years) and seven adults were analysed. Based on the electrophysiological parameters the Ussing chamber method has been successfully applied for both adult and pediatric ileal tissue (Sjöberg *et al.*, 2013). The efflux ratios (ER; range) were 1,23 (0,87-1,96) for the passive paracellular substance and 0,86 (0,81-2,73) for the transcellular marker compound in pediatric tissues. The substrate for P-gp showed an ER of 2,93 (1,26-4,82), while 1,85 (1,32-2,16) was calculated for the BCRP transported drug. The rate of transport was comparable with the adult ER data: paracellular drug: 0,87 (0,59-1,41); transcellular substance: 0,91 (0,78-1,02); P-gp substrate: 2,39 (1,19-6,30); BCRP substrate: 2,07 (0,97-3,22).

Conclusion: The Ussing technique represents a feasible approach to study intestinal drug transport in both adults and children. Our first data show no difference in transport activity in the studied age range, but tissue collection continues to further investigate age-related differences in intestinal drug disposition.

Reference: Sjöberg *et al.*, Eur J Pharm Sci. 2013. Jan 23;48(1-2):166-80.

SAFETY OF IBOGAINE ADMINISTRATION IN OPIOID DEPENDENT INDIVIDUALS: AN OPEN LABEL TRIAL

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Aims: The aim of this study was to evaluate the cardiac, cerebellar and psychomimetic toxicity of ibogaine-HCl in patients with opioid use disorder (OUD). Ibogaine use has been linked to several deaths, mostly due to cardiac events called torsades des pointes (tdp) preceded by QTc prolongation. It is used outside of standard care as a possible treatment for addiction.

Methods: An open-label observational study was performed among 14 patients on opioid maintenance treatment with a lasting wish for abstinence, who failed on standard care. After conversion to morphine-sulphate, ibogaine-HCl 10mg/kg was administered and patients were clinically monitored for at least 24 hours. Electrocardiograms were performed every half hour during the first 12 hours to assess QTc prolongation. Blood pressure and heart rate were measured. The Scale for the Assessment and Rating of Ataxia was used to assess cerebellar toxicity. The delirium observation scale and clinical observations were used to assess psychomimetic effects.

Results: The maximum QTc prolongation was on average 100ms (range 40-168ms). Half of subjects reached a QTc of over 500ms during the observation period. In 6 out 14 subjects prolongation above 450ms lasted beyond 24 hours after ingestion of ibogaine. Transient severe ataxia, with inability to walk without support, occurred in all patients. Psychomimmetic effects resulted in little, if any, behavioral effects and were tolerable and manageable. Based on these findings and current lack of efficacy data concerning ibogaine treatment, the use of ibogaine-HCl outside a clinical experimental setting with intense clinical monitoring should be strongly dissuaded.

STATINS AFTER ISCHAEMIC STROKE IN THE OLDEST: A COHORT STUDY USING THE CLINICAL PRACTICE RESEARCH DATALINK DATABASE

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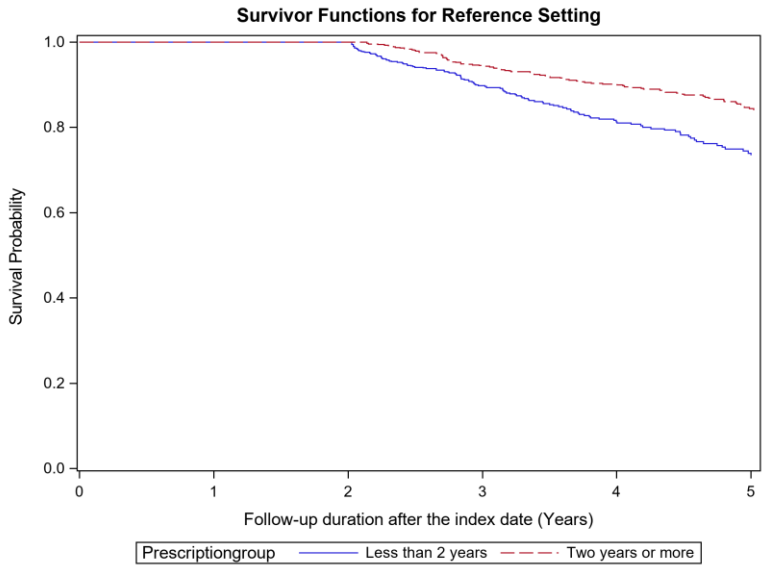
Introduction: In patients aged 80 years and above, 50-80% use statins after an ischaemic stroke. However, evidence to support initiation and use of statins in this population is limited to patients below the age of 80 years. Therefore, our aim was to investigate effects of cumulative statin prescription after a first ischaemic stroke in patients aged 80 years and older on recurrence of stroke, myocardial infarction or cardiovascular mortality, and on overall mortality

Methods: A cohort study in the Clinical Practice Research Datalink was conducted. Between January 1st , 1999 and February 26, 2016 3,157 patients aged 80 years and above, hospitalised for a first ischaemic stroke, surviving 30 days after discharge, without statin treatment one year before hospitalisation, were included. Time varying Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of statin treatment on the primary composite outcome (either recurrent stroke, myocardial infarction or cardiovascular mortality) and on overall mortality, adjusted for potential confounders including frailty. HRs were converted into numbers needed to treat (NNTs) and adjusted for two year mortality.



Results: Two years of statin prescription in patients aged 80 years and older resulted in a lower risk of the primary composite outcome (adjusted HR 0.80; 95% confidence interval 0.62 to 1.02) and overall mortality (adjusted HR 0.67; 95% CI 0.57 to 0.80). After a median follow-up of 3.9 years, the NNT for prevention of the primary outcome was 49 and for overall mortality 15. After correction for the mortality of 24% of the patients in the first two years, the NNT was 64 for the primary outcome and 19 for all-cause mortality.

Conclusion: Our data support statin initiation after an ischaemic stroke in patients aged 80 years and older.

EFFECTS OF DIETARY RESTRICTION IN CANCER PATIENTS RECEIVING IRINOTECAN CHEMOTHERAPY

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Introduction:

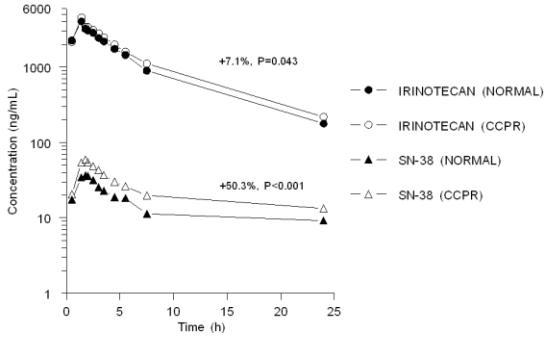
Irinotecan is widely used in the field of oncology, but is also known for its severe toxicity. Based on preclinical data, combined caloric and protein restriction (CCPR) might improve irinotecan tolerability without impairing antitumor effects. Therefore, we studied the influence of CCPR on irinotecan pharmacokinetics and toxicity.

Methods:

In this cross-over trial, patients with liver metastases of solid tumors were randomized to treatment with irinotecan preceded by 5 days of CCPR during the 1st cycle and a 2nd cycle preceded by a normal diet (ND) or *vice versa*. During both cycles, 24-hours plasma pharmacokinetics was performed and biopsies of healthy liver (HL) and liver metastasis (LM) were taken. Primary endpoint was the relative difference in geometric means for the active metabolite SN-38 in HL as analyzed by a linear mixed model. Secondary endpoints included irinotecan and SN-38 LM concentrations, plasma area under the curve ($AUC_{0\text{-}24h}$), and toxicity.

Results:

Interpatient variability (n=19) in tissue concentrations was high, showing no significant differences in irinotecan concentrations (+16.8%, 95%-CI: -9.7 to 51.1%, P = 0.227) and SN-38 concentrations (+9.8%, 95%-CI: -16.4 to 44.2%, P = 0.48) between CCPR and ND in HL, as well as in LM (irinotecan: -38.8%, 90%-CI: -59.3 to -7.9%, P = 0.05 and SN-38: -13.8%, 90%-CI: -40.7 to 25.4%, P = 0.50). CCPR increased irinotecan plasma $AUC_{0\text{-}24h}$ with 7.1% (95%-CI: 0.3 to 14.5%, P = 0.04), while the SN-38 plasma $AUC_{0\text{-}24h}$ increased with 50.3% (95%-CI: 34.6 to 67.9%, P < 0.001). Grade ≥3 toxicity was not increased during CCPR (P = 0.69). Also, no difference was seen in neutropenia grade ≥3, diarrhea grade ≥3, febrile neutropenia and hospitalization during CCPR (P > 0.10).



Conclusions:

CCPR resulted in a dramatically increased plasma SN-38 exposure, while toxicity did not change. CCPR did not result in altered irinotecan and SN-38 exposure in healthy liver and liver metastasis, though interpatient variability was high. Therefore, in the future, CCPR could potentially improve the therapeutic window in patients treated with irinotecan.

POPULATION PHARMACOKINETICS OF MELTDOSE TACROLIMUS (ENVARSUS®) IN STABLE ADULT LIVER TRANSPLANT RECIPIENTS

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Introduction: Meltdose tacrolimus (Envarsus®) is marketed as a tacrolimus formulation with a more consistent exposure. Due to the narrow therapeutic window, therapeutic drug monitoring is essential to maintain adequate exposure and the area under the concentration-time-curve over 24 hours (AUC) is the best link between exposure and response. The primary objective was to develop a population pharmacokinetic (PK) model of Envarsus® and construct a limited sampling strategy (LSS). The secondary objective of this study was to find potential covariates suitable for initial dose individualization.

Methods: adult liver transplant patients were converted from prolonged release tacrolimus (Advagraf®) to Envarsus® and AUC analysis (8 time points) was performed. Demographic factors, recipient and donor CYP3A4, and -5, IL-6,-10 and-18 genotype were tested as covariates. Nonlinear-mixed-effects-modelling and R statistics were used for analyses.

Results: 55 patients were converted to Envarsus® (median dose 2mg; range: 0.75-6mg) of which 53 (total 748 concentrations) could be included for PK analysis. The PK was best described by a two compartmental model with delayed absorption described with 1.6 transit compartments with mean transit time of 3.4h for absorption. The PK parameters along with their % interindividual variability (IIV) were as follows: clearance (CL): 3,27 L/h (34%); intercompartmental clearance (Q): 9,6 L/h (24%), volume of distribution of compartment (V) 1: 95 L (141%); V2: 500 L.
Hematocrit and CYP3A5-genotype of the recipient were significantly correlated to CL in univariate analyses and reduced unexplained IIV of CL from 34% to 27%. Transplant recipients with a functional CYP3A5 enzyme had on average 43% higher CL than non-expressors. Hematocrit was negatively correlated with CL, i.e. a lower hematocrit led to higher CL. However, in a multi-variate analysis, these correlations failed to be statistically significant and were therefore not included in the PK model.
The 4-point LSS of t=0,3,6,8 resulted in adequate AUC prediction with a median(range) bias of 0,6% (-8,9 – 7,2). The best 3-point LSS was t=0,4,8 with a median bias of 1,8% (-12,5 – 12,5). The correlation coefficient (Pearson, r^2) was 0,89 between trough concentrations and AUC.

Conclusion: The PK of Envarsus® in stable adult liver transplant patients was adequately described by a 2-compartmental model with delayed absorption described with transit compartments. Variability in CYP3A4 and CYP3A5 status was of much less impact on CL of Envarsus® and could not reduce IIV of CL in a clinically significant way, as opposed to what is known for other tacrolimus-formulations. A 3-point LSS predicted the AUC with maximal 12,5% bias. A 4-point LSS led to even lower bias. This LSS can be used in routine clinical care to adequately predict AUC with a reduced burden for both patients and the clinic.

DOPPLER ULTRASOUND OF THE SUPERIOR MESENTERIC ARTERY AS A BIOMARKER FOR SPLANCHNIC VASOACTIVE COMPOUNDS IN EARLY CLINICAL DRUG DEVELOPMENT

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Introduction: To prevent decompensated cirrhosis, long-term treatment with non-selective beta-blockers is currently standard of care. However, there are some safety concerns associated with these drugs in this fragile patient population, awakening interest in the development of new splanchnic vasoactive compounds that reduce portal pressure and prevent decompensation (Kockerling *et al.*, 2019). The efficacy of portal pressure-lowering medication can be evaluated by measuring the hepato-venous pressure gradient (Abraldes *et al.*, 2019). Unfortunately, this method is too invasive to use in healthy volunteers participating in phase I clinical trials. Therefore we assessed the reproducibility of flow measurements in the superior mesenteric artery using Doppler ultrasound to evaluate the reliability of this non-invasive method as a biomarker for the evaluation of splanchnic vasoactive compounds in early clinical drug development.

Methods: Fifteen healthy male volunteers (aged 18-50 years) with a body mass index of 18-27 kg/m² were included. A total of 8 flow measurements per subject was performed in the superior mesenteric artery using Doppler ultrasound: two observers each performed two measurements in each subject in an alternating manner during two study periods separated by a minimum of 5 days. Flow measurements included the following parameters: Peak Systolic Velocity (PSV, cm/s), End Diastolic Velocity (EDV, cm/s), Pulsatility Index (PI), Volume Flow (VF, ml/min) and diameter (cm). Reliability was assessed by the intraclass correlation coefficient (ICC).

Results: Due to a persistent high blood pressure, one subject was excluded for statistical analysis. Intra-period flow measurements recorded by the same observer correlated excellently with ICC > 0.80 for PSV, EDV, PI and VF during period 1 (0.888, 0.910, 0.844 and 0.916, respectively) and period 2 (0.925, 0.942, 0.883 and 0.915, respectively). Similarly inter-period flow measurements taken by the same observer correlated well for PSV (0.756) and excellently for EDV, PI and VF (0.836, 0.807 and 0.839, respectively). Measurements performed by different observers during the same study period correlated well or excellently for PSV, EDV and VF during period 1 (0.813, 0.884 and 0.786, respectively) and period 2 (0.779, 0.861, 0.810, respectively). Diameter measurements only correlated well within the same period and when taken by the same observer: 0.812 and 0.761 during periods 1 and 2, respectively.

Conclusion: Doppler ultrasound is a reproducible method for flow measurements in the superior mesenteric artery in a standardized group of healthy volunteers. A subsequent trial in which the effect of portal pressure-lowering medication on the splanchnic blood flow is assessed, will further evaluate the potential of this technique as a biomarker in early clinical drug development.

References:

Abraldes, *et al*. Hepatology 69, 1287–1299 (2019).
Kockerling, *et al*. World J. Gastroenterol. 25, 888–908 (2019).

FALL INCIDENTS IN NURSING HOME PATIENTS: DEVELOPMENT OF A PREDICTIVE CLINICAL RULE (FINDER)

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Introduction: Fall incidents are common among nursing home patients. Different tools have been developed to prevent fall incidents, but with unsatisfactory results.
Here we aimed to develop (part I) and validate (part II) a clinical rule (CR) that can predict a fall risk in nursing home patients.

Methods: An observational retrospective database study was conducted in two parts. For the identification of fall-risk variables in part I, logistic regression analysis was performed. With the identified fall-risk variables, a CR was developed, where the overall prediction quality was assessed using the *Area Under the Receiver Operating Characteristics* (AUROC), and a cut-off value was determined for the predicted risk ensuring a sensitivity ≥ 0.85. This CR and cut-off value were validated in part II.

Results: A total of 1668 (824 in part I, 844 in part II) nursing home patients from Zuyderland Medical Centre, The Netherlands were included in the study. 11 fall risk-variables were identified in part I. The validated AUROC of the CR, obtained in part II, was 0.603 (95%CI 0.565-0.641) with a sensitivity of 83.41% (95% CI 79.44%-86.76%) and a specificity of 27.25%(95% CI 23.11%-31.81%).

Conclusion: Medication data and patient characteristics only are not sufficient enough to develop a successful CR with a high sensitivity and specificity to predict fall risk. However, the developed CR could serve as a basis for future research.

Adverse events related to biologicals used for patients with multiple sclerosis: a comparison between information originating from regulators and from the scientific community

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Background: Clinical decision making is facilitated by health care professionals' and patients' adequate knowledge of the adverse events. This is especially important for biologicals used for treating multiple sclerosis (MS). So far, little is known about whether different information sources report adverse events consistently.

Methods: We included biologicals authorised by the European Medicines Agency for the treatment of MS in this study. We compared information on adverse events, derived from the phase three clinical trials, from European public assessment reports (EPARs) and scientific publications.

Results: In the study, we included eight biologicals used for the treatment of MS for which the EPAR and/or scientific publication reported a total of 707 adverse events. Approximately one-third of the adverse events was reported in both the EPAR and scientific publication, one-third was only reported in the EPAR and one-third only in the scientific publication. Serious adverse events and adverse events that regulators classified as "important identified risk" were significantly more often reported in both sources as compared to adverse events not classified as such (respectively, 38% vs 30% and 49% vs 30%). Adverse events only reported in the EPAR or scientific publication were, in general, not described in the benefit-risk section or abstract, which we considered to be the most important sections of both documents.

Conclusions: This study showed that there is substantial discordance in the reporting of adverse events on the same phase three trials between EPARs and scientific publications. To support optimal clinical decision making, both documents should be considered.

WORSE CAPECITABINE TREATMENT OUTCOME IN PATIENTS WITH A LOW SKELETAL MUSCLE MASS IS NOT EXPLAINED BY ALTERED PHARMACOKINETICS

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Introduction:
The anti-cancer drug capecitabine is an oral prodrug of 5-fluorouracil (5-FU). Capecitabine and its metabolites are highly water-soluble and therefore more likely to distribute to lean tissues. In patients treated with capecitabine a low skeletal muscle mass (SMM) is associated with shorter survival and more treatment-related toxicity (Kurk *et al.*, 2019). The primary aim of our study was to examine whether this association between low skeletal muscle mass and worse treatment outcome could be explained by pharmacokinetic (PK) parameters, such as high exposure due to lower volume of distribution (V) or altered clearance (CL) of capecitabine and its metabolites.

Methods:
A previously published population pharmacokinetic model was extended with the potential covariate SMM to assess the association between SMM and capecitabine and metabolite PK (Jacobs *et al.*, 2019).

The SMM was measured on abdominal computed tomography scans using the Slice-o-matic software.

Results:
PK and SMM data were available from 151 patients with solid tumors.

No relevant association was found between SMM and CL and V of capecitabine and the three major metabolites (Δ objective function value (OFV) between -1 and +13 and no improvement in goodness-of-fit plots). However, an association between SMM and V and CL of the inactive metabolite α-fluoro-β-alanine (FBAL) was found (ΔOFV -28).

Conclusion:
Results of the analyses demonstrated that PK of capecitabine and its metabolite 5-FU are not associated with SMM. SMM only correlated with PK of the inactive metabolite FBAL. Therefore, alterations in capecitabine and metabolite PK do not provide an explanation for increased toxicity and decreased survival in patients with a low SMM.

References:
1. Kurk S *et al.* J Cachexia Sarcopenia Muscle. 2019;10:803-813.
2. Jacobs *et al.* CPT Pharmacometrics Syst Pharmacol. 2019;8:940-950.

EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE: SURVEY TO MAP THE EXPERTISE OF THE EXCELLENCE OF DEVELOPMENTAL PHARMACOLOGY IN PAN-EUROPEAN COUNTRIES

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INTRODUCTION Currently, the European landscape related to the developmental pharmacology appears scattered and with low awareness of available services and facilities in this field. European Paediatric Translational Research Infrastructure (EPTRI) aims to design the framework of a paediatric Research Infrastructure (RI) intended to enhance technology-driven paediatric drug discovery. Within the project, 5 technical and scientific domains have been identified among which the developmental pharmacology platform aimed to enhance knowledge on developmental changes affecting drug disposition. We here present the developmental pharmacology platform.

METHODS Within EPTRI, a survey was launched among selected research centres in the field of developmental pharmacology to map the expertise within paediatric pharmacology in pan-European countries and identify the possible gaps in the available paediatric research services and facilities. Firstly, the survey was delivered to 74 recipients between April-June 2018. Later on, to have a wider map of the European research units and services, the survey was re-opened and distributed among 153 recipients between January-April 2019.

RESULTS 38 service providers answered the survey among which 8 came from UK, 7 from Italy, 6 from The Netherlands. The analysis allowed to define a map of services to be provided within the developmental pharmacology platform and represented in Figure 1. Relevant expertise has been identified such as analytical labs capable to set-up sensitive drug assays, paediatric omics facilities, pharmacometrics expertise, large databases adapted to paediatric pharmacoepidemiology, as well as placental platforms.

CONCLUSION This analysis allowed to map the research units and services that will be provided in the field of developmental pharmacology platform within EPTRI. Likewise, it provided a point of reflection for the scientific community on the strengths and weaknesses of this research areas and the relevance of EPTRI to fill these gaps.

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IS DEXAMETHASONE APPROPRIATELY DOSED AS ANTI-EMETIC DRUG IN COMBINATION WITH APREPITANT IN CHILDREN?

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Introduction: Nausea and vomiting are two of the most common side effects of pediatric oncology treatment. Both dexamethasone and aprepitant are cornerstone in controlling these side effects in patients treated with moderate to high emetogenic chemotherapy. However, children appear to have worse anti-emetic control compared to adults (i.e. 50% resp. 70-80%) using these drugs. A potential explanation for this could be suboptimal dosing of dexamethasone in children. A 50% dose-reduction of dexamethasone is applied when treatment is combined with aprepitant because of a potential interaction between aprepitant and dexamethasone. This interaction has only been studied in adults (Marbury et al. 2011; McCrea et al. 2003; Nakade et al. 2008; Takahashi et al. 2011). In this interim analysis, we describe the pharmacokinetics (PK) of dexamethasone in children and the influence of aprepitant on the PK of dexamethasone.

Methods: Children, aged 0-18 years, receiving anti-emetic therapy (dexamethasone +/- aprepitant) during chemotherapy as standard of care were eligible for inclusion in this study. Plasma concentrations of dexamethasone were determined in plasma samples drawn after administration of the antiemetic agents, using LC-MS. Pharmacokinetic analyses were performed using non-linear mixed effects modelling (NONMEM, version 7.3). Ethical approval was obtained.

Results: 28 patients (age 0.9-17.9 (median 9.9) years, 64.2% male), treated with dexamethasone, were included. Dexamethasone was administered intravenously in 93% of the patients. Aprepitant was co-administered in 20 patients (71.4%). 146 plasma samples were analysed. A one-compartment model, using weight based allometric scaling, was developed to describe the PK of dexamethasone. Clearance was estimated as 24.7 L/h (95% CI 18.8 - 32.3) and volume of distribution as 96.6 L (95% CI 83.9 - 113.5). In this population, the clearance of dexamethasone in patients with concomitant administration of aprepitant was reduced to 81.3% (95% CI 59.6% - 112.3%, $p > 0.05$).

Conclusion: Aprepitant appears to have little influence on the clearance of dexamethasone in this population. These results suggest that a 50% dose-reduction of dexamethasone might be inappropriate in children and this might explain the poor antiemetic control in children. Final analysis will be performed when the study is concluded and the effect of other covariates, such as age, will be explored in further analyses.

References: Marbury et al. 2011. *Journal of Clinical Pharmacology* 51(12): 1712–20; McCrea et al. 2003. *Clinical Pharmacology and Therapeutics* 74(1): 17–24; Nakade et al. 2008. *Cancer Chemotherapy and Pharmacology* 63(1): 75–83; Takahashi et al. 2011. *Cancer Chemotherapy and Pharmacology* 68(3): 653–59.

INVESTIGATING THE ENANTIOMER SPECIFIC PHARMACOKINETICS OF (R,S)-(NOR)KETAMINE: A POPULATION PHARMACOKINETIC MODELLING APPROACH

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Background: Ketamine's rapid onset antidepressant effects are of increasing interest for patients with major depressive disorder (MDD). However, it is unclear what the exact mechanism of action of these effects is and how the specific enantiomers and metabolites contribute. Still, most population pharmacokinetic (PK) models available in literature describe only (S)-(nor)ketamine. Therefore, the aim of this project was to validate existing PK-models of (S)-(nor)ketamine with in-house clinical trial data and to adapt and extend the most predictive model to quantify the PK of the (R)-enantiomer after racemic administration.

Methods: Data of three clinical trials performed at the Centre for Human Drug Research were available. Two studies (n=21/31) infused 10 mg or 0.4-0.9 mg/kg (S)-ketamine in healthy volunteers for 0.5 or 2h respectively and measured (S)-(nor)ketamine until 10 or 5.5h after administration. The third study (n=16) administered 0.5 mg/kg racemic ketamine in patients with MDD for 40 min and (nor)ketamine measurements were collected for 24h. The predictive capabilities of (S)-(nor)ketamine literature models were explored using visual predictive checks (VPC). The best model was further refined by structural modifications and re-estimation of inter-individual variability (IIV) if required. Development of the (R)-(nor)ketamine model was based on racemic concentrations with the assumption that (S)-ketamine clearance was inhibited by (R)-ketamine.

Results: The VPC of the model by *Fanta et al.*[8] showed the best agreement of predicted and observed data. However, the model structure of (S)-norketamine was adapted because the maximum concentrations were underpredicted. This resulted in a final model of three compartments for (S)-ketamine and two compartments for (S)-norketamine. Based on the racemic concentrations, two compartments for (R)-ketamine and for (R)-norketamine were identified. A higher IIV was quantified for the (R)-enantiomer model parameters compared to (S). The accuracy of all model parameters was high and the model showed an adequate description of the data over time, confirmed by VPCs.

Conclusion: On the basis of the model of Fanta et al.[8], a refined population PK model for enantiomer-specific (R,S)-(nor)ketamine was developed. This model was able to accurately predict the PK of (R,S)-(nor)ketamine after racemic or (S)-ketamine administration in healthy volunteers and MDD patients.

References:

Fanta, S. *et al.* Population pharmacokinetics of *S*-ketamine and norketamine in healthy volunteers after intravenous and oral dosing. *Eur. J. Pharmacol.* **71**, 441-447 (2015).

AN ACCIDENTAL REPETITIVE 10-FOLD OVERDOSE OF SILDENAFIL IN A NEWBORN WITH CONGENITAL DIAPHRAGMATIC HERNIA

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Background Sildenafil is a selective phosphodiesterase type 5 inhibitor that is increasingly used to treat pulmonary hypertension (PH) in neonates. Here we present a neonate with congenital diaphragmatic hernia (CDH) and PH who received an unintentional 10-fold overdose of oral sildenafil for 6 consecutive days. Clinical outcome as well as improvement measures to prevent overdosing in the future, are discussed.

Case description A newborn girl, born term with a birth weight of 3.0 kilo, was antenatally diagnosed with CDH. She developed PH and intravenous sildenafil treatment was started by a continuous infusion of 1.6 mg/kg/day. Subsequently intravenous administration was switched to an oral dose of 3.5 mg/kg/day in three doses. When she was discharged from the hospital, the oral administration of sildenafil was continued. Because of a difference in concentration between the sildenafil formulation used in the hospital and dispensed by the out clinic pharmacy (10 mg/ml vs 1 mg/ml, respectively), a 10-fold overdose of sildenafil was administered to the patient for 6 consecutive days. This overdose resulted in increased plasma concentrations of sildenafil (from 42 mcg/L 521 mcg/L) and desmethylsildenafil from 81 mcg/L to 393 mcg/L). Both concentrations were measured at trough levels.
Contrary to the expectations, the overdose only let to the development of diarrhea. After establishing the overdose, the patient was admitted to the hospital for monitoring the dose reduction and discharged without symptoms the next day. Thereafter, instructions about dosing sildenafil were repeated thoroughly and sildenafil was continued in the correct dose.

Conclusion Although a 10-fold overdose of sildenafil was administered to a newborn for 6 consecutive days, no life-threatening adverse events occurred. This case report adds knowledge to the lacking safety data of sildenafil use in neonates. Furthermore, it indicates that proper dose instructions and thereby communication, are crucial to prevent medication errors.

THE CLINICAL APPLICABILITY OF MONITORING ANTIHYPERTENSIVE DRUG LEVELS IN BLOOD

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Introduction: Non-adherence to antihypertensive drugs is one of the mean causes for patients with hypertension for not reaching blood pressure goals. Methods for identifying non-adherence are therefore needed to improve this. Dried blood spot (DBS) analysis is a novel analytical method for therapeutic drug monitoring (TDM) to identify non-adherence to antihypertensive drugs. The aim of the present study was to evaluate the clinical applicability of measuring drug concentrations of eight antihypertensive drugs, using DBS and venipuncture. Furthermore, this study investigated the variability of antihypertensive drug concentrations between patients and the influence of selected parameters on this variability.

Methods: False negative values from DBS compared to a venipuncture were determined to assess clinical applicability. A Generalized Estimating Equations (GEE) were used to estimate the model parameters, where after linear regression was applied to estimate the influence of the parameters including sex, dose, age, weight and the time interval between drug intake and sampling, on the C_{plasma} (drug concentration in plasma).

Results: No false negative values were found when measuring drug concentrations with DBS compared to venipuncture. A high variability in C_{plasma} between patients was observed, especially at peak concentrations with the lowest fold change of 2.3 for canrenone and the highest fold change of 35.2 for losartan. The time of intake was, for most antihypertensive drugs, related to the height of the C_{plasma}, but the influence of dose, weight, age and sex on drug levels differed largely between the measured drugs.

Conclusion: DBS is a reliable and convenient method to assess non-adherence to antihypertensive drugs in clinical practice. The C_{plasma} of the eight antihypertensive drugs in this study show a large inter-individual difference and therefore low plasma concentrations do not assume non-adherence. Non-adherence can only be confirmed if values are below the lower limit of detection.

THE JUNIOR-ADVERSE DRUG EVENT MANAGERS, A UNIQUE OPPORTUNITY FOR STUDENTS TO LEARN BASIC PHARMACOVIGILANCE WHILST INCREASING THE NUMBER OF REPORTED ADVERSE DRUG REACTIONS IN A HOSPITAL.

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Spontaneous reporting of adverse drug reactions (ADRs) is a cornerstone in pharmacovigilance which is highly dependent on the quantity and quality of reported ADRs. Most interventions to improve this problem in healthcare professionals have been unsuccessful. Adverse drug event managers have been successfully implemented in numerous hospitals in Denmark were they have shown to ease the pressure for clinicians and increase the number of Individual Case Safety Reports (ICSR). Since screening and reporting of these ICSR are of great value for educating our future doctors on pharmacovigilance we started a junior-adverse drug event mangers team (J-ADEMs). This study aims to investigate the feasibility of a J-ADEMs team and evaluate the clinical and educational value of this innovative intervention.

The J-ADEMS program was set up as a prospective longitudinal intervention study to detect and report possible ADRs on and during hospital admission. The J-ADEM team, consists of medical students, functioning as a passive and active service to manage and report medication related side effects. The J-ADEMs can be contacted by phone or email but they also actively screen the internal medicine ward for ADRs. When an ADR is detected the team report the ADR to the pharmacovigilance centre, answer all follow-up questions and update the electronic patient record. After the report, all patients evaluate the J-ADEM team and physicians were asked why they had not reported the serious ADR themselves.

From October 2017 to January 2018, 35 patients with 116 problem list symptoms were analyzed by the J-ADEMs team. Most patients (27) were actively screened by the J-ADEMs team while eight signals of possible ADRs were received by healthcare professionals. Of the 116 problem list symptoms, 25 ADRs were reported to the pharmacovigilance centre of which 20 were classified as serious ADRs. Compared to 2016 this showed a 300% increase in the number of ICSR by managing only one (of +/-20) ward. Most reports were on electrolyte disorders (n=11) or hematological disorders/bleeds (n=6) and were related to diuretics (6) and acetylsalicylic acid (4). Patient satisfaction was 7.9 (1-10, min-max) and 87% of patients found it (extremely) relevant that a ICSR was made when the ADR caused the hospital admission. All physicians agreed the symptoms were at least related to the medicine, however most frequently reported: indifference (14) and ignorance (7) as reasons they didn't' report the ADR themselves.

The J-ADEMs team is an highly innovative healthcare improvement for hospitals. Not only does this team fastly increase the number of ICSR, it also has the opportunity to increase pharmacovigilance awareness in current and future healthcare professionals. Further plans are to expand the service to other wards, evaluate the educational value for students and analyze the quality of the students ICSR.

OPTIMIZING THE COST-EFFECTIVENESS OF ACE-INHIBITORS: A REVIEW OF THE LITERATURE

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Introduction:
Hypertension is the most important risk factor for cardiovascular disease and mortality worldwide. Based on patient characteristics, treatment with a specific antihypertensive class is advised, of which 3-9 different pills are available per class. Guidelines do not recommend a specific pill *within a class*, but large differences in costs exist. We performed a literature review to examine whether differences in blood pressure lowering efficacy, side-effects or pharmacokinetic profile exist between the 9 available angiotensin-converting-enzyme (ACE) inhibitors and compared costs of daily defined doses (DDDs) to determine optimal cost-effective therapy within this drug class.

Methods:
We searched all relevant databases for literature describing efficacy of ACE-inhibitors. Hereafter, we determined the number of DDDs used in 2017 in the Netherlands (www.gipdatabank.nl) and compared costs for DDDs of all available ACE-inhibitors (www.farmacotherapeutischkompas.nl). Cost savings were based on monotherapy, using the number of DDDs in the suboptimal regimen and multiplying this by the difference in costs between the optimal and suboptimal regimen.

Results:
In total, 20 relevant articles on the blood pressure lowering efficacy of various ACE-inhibitors were included. Although some drugs have been studied more extensively than others and randomized controlled trials comparing various drugs head-to-head are scarce, no differences in blood pressure reduction at an equipotent dose were found. Furthermore, no differences in adverse events were found. In 2017, 438.966.660 DDDs of ACE inhibitor monotherapy were prescribed in 1.022.000 patients. The price per DDD differed between €0,02 and €0,25. Prescribing the cheapest drug (lisinopril) to all patients induces a cost-saving of approximately €6.5 million. Prescribing all patients one of the three cheapest drugs induces a cost-saving of approximately €4.3 million. As no differences in efficacy were found, no additional costs for hospitalization or treatment are expected.

Conclusion:
Among equipotent dosed ACE-inhibitors, there are no known differences in blood pressure lowering efficacy, but large differences in costs exist. More specific prescribing advices could induce a large cost-saving without compromising treatment efficacy.

PRESCRIPTION TRENDS OF SECOND-GENERATION ANTIPSYCHOTICS CHARACTERIZED AS P-GP SUBSTRATES IN THE NORTHERN DUTCH POPULATION

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Aims: The aim of this study was to investigate trends in the prescription frequency of antipsychotic drugs, known to be substrates of P-glycoprotein 1 (P-gp).

Introduction: Membrane transporters can be major determinants of the pharmacokinetic, safety and efficacy profiles of drugs. P-gp is an ATP-dependent efflux transporter protein that is expressed in various tissues with excretory functions such as the liver, kidney and intestine, but also on the capillary endothelial cells composing the blood-brain barrier. Lack of knowledge on the role of transporters, like P-gp, in the blood brain barrier is thought to be a major cause of treatment failure of CNS-acting drugs (Ghosh et al., 2011).This includes antipsychotic medications, prescribed for a variety of conditions such as schizophrenia, bipolar disorder, delirium and hallucinations associated with dementia and Parkinson's disease. Little is known about how frequent potential P-gp substrates within this class of medication are used in the community.

Methods: A search within the University of Groningen IADB.nl pharmacy prescription database was conducted towards four antipsychotic drugs identified as P-gp substrates (Boulton et al., 2002): clozapine, quetiapine, olanzapine and risperidone. The IADB database contains prescription data from 1994 onwards. Data is obtained from approximately 70 community pharmacies in the northern part of the Netherlands and covers an estimated population of 700,000 patients.

Results: The overall prevalence of patients that have been prescribed clozapine, quetiapine, olanzapine and risperidone combined increased from 359 [95% CI 341-378] patients per 100,000 patients of the underlying population in 2000 to 1026 [95% CI 1000-1052] per 100,000 patients in 2010 and 1524 per 100,000 [95% CI 1490-1559] in 2018. Quetiapine was the most frequently prescribed drug with a prevalence of 888 [95% CI 862-915] per 100,000 patients in 2018, compared to 16 [95% CI 12-20] per 100,000 patients in 2000 and 496 [95% CI 478-514] per 100,000 patients in 2010. The incidence rate of patients receiving clozapine, quetiapine, olanzapine and risperidone combined grew from 141 [95% CI 130-153] per 100,000 patients in 2000 to 294 [95% CI 279-307] in 2010, up to 397 [95% CI 380-415] per 100,000 patients in 2018.

Conclusion: All investigated P-gp substrates were atypical antipsychotics, approved for use in the 1990s. The prevalence and incidence rates of the selected antipsychotics significantly increased over the past 20 years in the Northern Dutch population. Whether any interaction with P-gp activity affected the treatment efficacy is subject of further research.

References:

Boulton et al.; Life Sci. 2002 May 31; 71(2): 163-9.
Ghosh et al.; Curr Drug Metab. 2011 October; 12(8): 742-749.

BRONCHIAL AIRWAY INDUCIBLE EQTL AND MEQTL MAPPING IDENTIFIES A SNP PREDICTING INHALED CORTICOSTEROIDS RESPONSE HETEROGENEITY IN CHILDHOOD ASTHMA

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Background: Approximately 35% of the asthma patients respond poorly to inhaled corticosteroids (ICS). It has been hypothesised that molecular mechanisms underlying poor response to ICS might be similar in asthma and chronic obstructive pulmonary disease (COPD). We aimed to identify genetic variants affecting gene expression and methylation changes in airway wall biopsies of COPD patients before and after ICS and investigate whether these are associated with poor response to ICS in children with asthma.

Methods: Candidate single nucleotide polymorphisms (SNPs) were selected based on steroid inducible expression and methylation. Quantitative Trait Locus (QTL) Mapping profiling of paired bronchial biopsies from 42 COPD patients, participating in the longitudinal GLUCOLD study, was performed prior to and 6 months post ICS use. The window size was 1Mb flanking the gene limits and the false discovery rate was used to adjust for multiple comparisons using the R package MatrixEQTL version 2.2. Association between SNPs and gene expression (eQTL) or gene methylation (meQTL) changes upon ICS use was evaluated. Subsequently, a candidate-gene study was conducted in asthma patients treated with ICS within the PiCA consortium to investigate whether these SNPs are associated with ICS response. Poor ICS response was defined as the presence of exacerbations despite ICS use in the last 6-12 months. Logistic regressions adjusted for age and gender were used to test the association with ICS response. Significance threshold was adjusted by means of Bonferroni correction.

Results: In the COPD study, 18 eQTL and 57 meQTL SNPs were identified to be associated with ICS response. When these SNPs were tested in asthma patients (3,722 children were included for eQTL SNPs and 1,166 children for the meQTL SNPs), the only significant variant was the meQTL SNP rs7220099, an intergenic variant at locus 17q12 with an allele frequency of 33%. The G allele increased the risk of exacerbations (pooled OR: 1.39 95%CI 1.19-1.63, p-value = 2.4×10^{-5}).

Conclusions: Our results show that gene expression and methylation profiling prior and post ICS use are quite different between asthma and COPD but still may help to find functional SNPs predicting ICS response. The G allele of rs7220099, a lung eQTL for *TBC1 domain family member 3D*, was associated with increased risk of exacerbations in children treated with ICS and higher methylation.

ROLE OF ORGANIC ANION TRANSPORTER 3 (OAT3) IN THE RENAL EXCRETION OF ENALAPRILAT

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Background: Enalapril has been extensively used in the treatment of hypertension, heart failure and chronic kidney disease. Clinical data suggest that the urinary excretion of enalaprilat (ENAT), the active metabolite of enalapril, is mediated by renal transporters. However, the membrane transporters involved have not yet been identified. We therefore aimed to identify ENAT specificity for renal proximal tubular uptake transporters.

Methods: Baculovirus-transduced HEK293 cells overexpressing proximal tubular influx transporters were used to study ENAT cellular uptake. Uptake into cells overexpressing the basolateral transporters OCT2, OAT1, OAT2, or OAT3, and apical transporters PEPT1, PEPT2, OCTN1 or OCTN2 was compared with mock-transduced control cells expressing an empty Enhanced Yellow Fluorescent Protein (EYFP) vector. Cellular ENAT concentrations were measured using LCMS-MS and the optimal incubation time as well as enzyme kinetics (K_m and V_{max}) were determined.

Results: Preliminary results showed that uptake of ENAT into cells expressing OAT3 was significantly higher compared to control cells, whereas no uptake was found for cells transduced with the other transporters. Transport of ENAT by OAT3 was linear up to 20 minutes. The enalaprilat affinity for OAT3 was 318 (95% CI: 149-487) µM and the maximum velocity of substrate transport was 14 (11-17) pmol/mg protein/min.

Conclusion: Uptake of ENAT is mediated by OAT3. Therefore, changes in activity of kidney OAT3 may alter the systemic exposure of ENAT and can therewith influence its therapeutic efficacy. Furthermore, as many cardiovascular drugs are known OAT3 substrates (i.e. furosemide, bumetanide and rosuvastatin), this finding could contribute to the understanding of the interaction of these drugs with enalapril.

EFFECTS OF INTERPROFESSIONAL PHARMACOTHERAPY EDUCATION: A SYSTEMATIC REVIEW

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Introduction

Medication management is becoming increasingly difficult because of the large group of prescribing healthcare professionals and the ageing multi-morbid patient with polypharmacy. Interprofessional collaboration could be a solution for this problem, however is not yet fully integrated in usual care and has many barriers. This is not surprising since healthcare professionals have been trained in mono-professional curricula. To achieve optimal interprofessional collaboration in the future, students need to be trained in interprofessional education (IPE), especially in the field of complex pharmacotherapy.

Therefore, the aim of this review is to explore the interprofessional educational interventions in pharmacotherapy and analyze which are effective in increasing IPE and pharmacotherapy competencies?

Methods

The PubMed, EMBASE, CINAHL, PsycINFO, and ERIC databases were searched using the terms “pharmacology”, “interprofessional”, “education” and “students”.

Results

Fifty-six intervention studies describing mostly pharmacy, medical and nursing students were included. The interprofessional interventions can be classified into four groups: digital communication, medical mission trips, clinical rotations and traditional education. Overall, students responded positively to the interprofessional and pharmacotherapy initiatives, developed a wider perception on each other’s roles and realized that working in an interprofessional setting improved quality of care. Students realized the importance of medication reconciliation and perceived it as their responsibility. After participating, students acted on medication-related safety problems and gaps in adherence to guidelines. To overcome logistical barriers, such as distance between universities, digital communication was frequently used. The articles regarding medical mission trips and clinical rotations that described clinical outcomes reported that students learned to make more appropriate medication decisions because of the interprofessional setting and that patients strongly agreed that the student-made recommendations would improve their health.

Conclusion

Interprofessional education is a new promising aspect within pharmacotherapy education. Innovative interventions such as digital communication and medical mission trips are new types of education that should be implemented in educational interventions and could reduce existing IPE barriers. Real challenges lie ahead in increasing students’ intrinsic motivation, analyzing IPE health outcomes and significantly improving research methodologies.

POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF USTEKINUMAB IN PSORIASIS PATIENTS

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Aims: To quantify interpatient variability in the relationship between dosage and serum concentration (pharmacokinetics (PK)) and Psoriasis Area and Severity Index (PASI score, pharmacodynamics (PD)).

Methods: A total of 205 ustekinumab serum samples and 222 PASI scores from 20 psoriasis patients with low baseline disease activity (PASI ≤5) and low quality of life score ≤5 (DLQI) at baseline were gathered over a period of 42 months. Population PKPD models were developed using nonlinear mixed-effects modelling (NONMEM). Furthermore, it was assessed how a PKPD model can help with controlled dose reduction and individualization of therapy.

Results: The PK of ustekinumab were described by a 1-compartment model. Typical values for volume of distribution and clearance were 9.0 L and 0.27 L/h, with inter-individual variability (IIV) of 18% for the latter. A positive correlation was found between clearance and both weight and alkaline phosphatase, explaining 1.4% and 2% of IIV. The relationship between serum ustekinumab concentrations and PASI scores was described by a turn-over model, in which ustekinumab inhibited the formation rate of psoriatic skin lesions (K_{in}). The value of IC_{50} was 0.11 µg/ml and K_{out} (the remission of lesions) was 0.0093 h^{-1}. The IIV for IC_{50} was large with a value of 133%, no covariates explained this IIV. Individual PKPD fits help to identify patients who are eligible for dose reduction.

Conclusion: We developed a PKPD model for ustekinumab in patients with psoriasis and low disease activity. In the future this model could be used for TDM of ustekinumab in patients with psoriasis.

INFLUENCE OF COW MILK AND ESOMEPRAZOLE ON THE ABSORPTION OF ERLOTINIB: A RANDOMIZED, CROSS-OVER PHARMACOKINETIC STUDY IN LUNG CANCER PATIENTS

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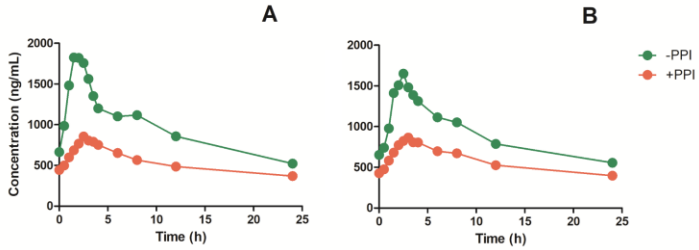
Introduction: Erlotinib is an oral EGFR tyrosine kinase inhibitor used in non-small cell lung cancer (NSCLC). Drug absorption largely depends on its solubility in the stomach and gastrointestinal tract. Potentially, erlotinib -as lipophilic drug- may dissolve better in a fatty drink such as cow milk compared to water. Gastric acid reducing agents like proton pump inhibitors (PPIs) decrease the solubility and thus the uptake of erlotinib. Hence, we hypothesized that administration of cow milk may be a feasible way to increase erlotinib uptake (both with or without PPI co-administration). We performed a two-period randomized cross-over study to investigate the influence of cow milk compared to water on the exposure of erlotinib with and without the PPI esomeprazole in NSCLC patients.

Methods: During 24 hours, pharmacokinetic sampling (PK) was performed at days 7 and 14. In the 7 days prior to PK, erlotinib was taken daily with either 250 mL water or cow milk with 3.9% fat. Patients were assigned whether to receive erlotinib with (arm A) or without esomeprazole (40mg qd; arm B) 3 hours prior to erlotinib intake starting 3 days prior to PK. Primary endpoint was change in geometric mean for the area under the curve ($AUC_{0\text{-}24h}$). A linear mixed model was used to analyse AUCs and maximal concentration (C_{max}).

Results: Erlotinib $AUC_{0\text{-}24h}$ did not significantly change when administered with milk compared to water in both non-PPI users (N=14; -3%; 95%CI: -12 to 8%; P=0.57) and in patients who did use esomeprazole (N=15; 0%; 95%CI: -15 to 17%; P=0.95). Esomeprazole decreased erlotinib $AUC_{0\text{-}24h}$ with 47% (N=9; 95%CI: -57 to -34%; P<0.001; see Figure below) and C_{max} with 56% (95%CI: -64 to -46%; P<0.001). No differences in toxicities were observed between milk and water.

Conclusion: Exposure to erlotinib did not change by erlotinib intake with milk compared to water, independent of PPI usage. The combination with milk instead of water is safe and well tolerated. Esomeprazole however strongly decreased both erlotinib $AUC_{0\text{-}24h}$ and C_{max}, and should be avoided if possible.



SUCCESFUL TREATMENT OF A LIFE-THREATENING DAPSONE INTOXICATION

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Background: Dapsone (DPS) is a sulfone antibacterial agent. The DPS adult dose is 50-400 mg daily. DPS undergoes enterohepatic circulation; the half-life in adults is 10-50 hours (average 28h); C_{max} is 4-8 hours; V_d is 1.5 L/kg and the protein binding is 70-90%. The DPS therapeutic serum concentration is 0.5-5.0 mg/L. The main limitation in clinical use is its hematologic toxicity, in particular methemoglobinemia (Met-Hb). In overdose, Met-Hb correlates well with the DPS concentration, resolving as the level declines to the therapeutic range.

Aim: Sharing experience to support others in decision making in the treatment of a life-threatening DPS intoxication.

Case history: A-middle-aged man intentionally ingested more than 200 tablets DPS 100 mg. He vomited spontaneously soon after this intake. He was found in a confused condition and showed central cyanosis. The measured oxygen saturation was 54%, for which oxygen was administered. Twelve hours after intake, he was hospitalized in an intensive care unit.

Treatment regimen: The hospitalization period is arbitrary divided in five periods, based on the timing of the DPS samples (see Figure 1). The elimination half-life was calculated for each period assuming linear pharmacokinetics.

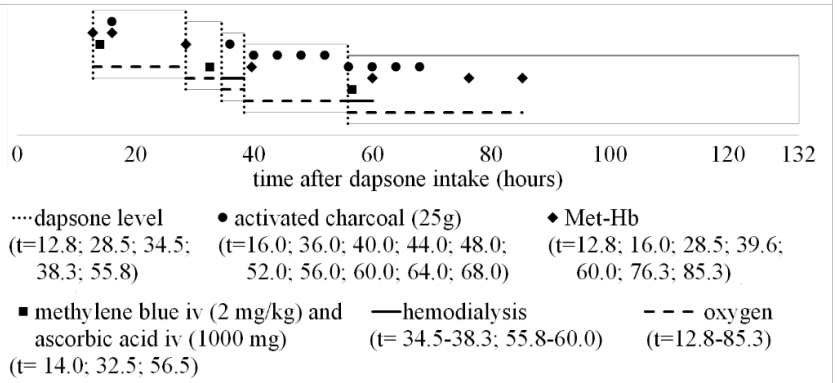

Figure 1: Treatment regimen DPS intoxication

Results: The measured DPS and Met-Hb levels are shown in Figure 2. The half-life was 33.0h with one double dose of activated charcoal 25g and laxatives (AC) (period 1), 23.2h without AC (period 2), 9.8h during hemodialysis and one dose of AC (period 3), and 14.8h during multiple doses of AC (period 4). The patient recovered completely and was discharged from hospital after 5 days.

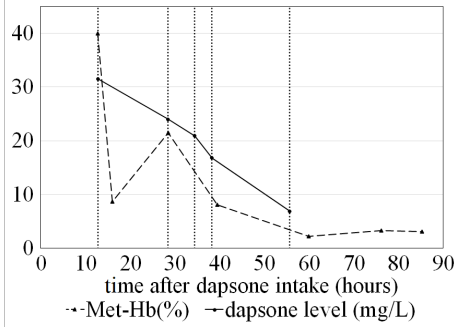

Figure 2: DPS and Met-Hb levels

Conclusions: In overdose the pharmacokinetics of DPS seems to be non-linear. The hemodialysis session seemed to accelerate the clearance of DPS. The use of AC seems to be effective in the treatment of the DPS overdose. The use of methylene blue and ascorbic acid was effective in the treatment of the Met-Hb.

THE EFFECT OF FEXINIDAZOLE ON *LEISHMANIA* BLOOD PARASITE KINETICS: A SEMI-MECHANISTIC MODEL

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Introduction: With the current treatment options for visceral leishmaniasis (VL), insufficient killing or recrudescence of the parasite is seen in a portion of patients. To improve treatment efficacy and to predict patient relapse in VL cases, understanding of the parasite dynamics is crucial. This study aimed to characterise the kinetics of circulating *Leishmania* parasites in blood, the activity of fexinidazole, and recrudescence of the parasite after treatment.

Methods: Data originated from a Phase II clinical trial (NCT01980199, report in preparation) in which Sudanese VL patients received a flat dosing of 1800 mg/day fexinidazole for 4 days, followed by 1200 mg/day for 6 days. From 14 adult patients, concentrations of fexinidazole and its active metabolites fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2) were available from dried blood spot samples. *Leishmania* kinetoplast DNA was quantified with real-time quantitative PCR (qPCR) in whole blood samples during and up to 6 months after treatment. An integrated PK-PD model was developed using NONMEM (v 7.3). PK parameters were fixed to their typical values based on a population PK model developed previously. A turn-over model and exponential growth model were evaluated to describe parasite proliferation. Fexinidazole dose, $AUC_{0\text{-}inf}$ of M2, and predicted PK concentrations of M1 and M2 were evaluated to induce drug-dependent killing of parasites (K_{KILL}). Both direct and delayed drug effects were evaluated.

Results: A decline in blood parasite load was observed in all patients, but only three out of 14 patients remained cured during the 6-month follow-up period. Parasite proliferation was best described by an exponential growth model, with an *in vivo* parasite doubling time of 7.4 days. Fexinidazole-dependent parasite killing was best described by a sigmoidal E_{max} model directly driven by the summed concentrations of M1 and M2. Between-subject variability was applied to baseline parasite load (158.4%) and IC_{50} (82.8%). To accommodate for successful cure of patients, parasite growth was completely suppressed if the predicted parasite load reached <1 parasite/mL.

Discussion: This semi-mechanistic PK-PD model could adequately describe the decline of *Leishmania* blood parasite loads in VL patients during treatment with fexinidazole, as well as recrudescence of the parasite in relapsing patients after the end of treatment. Suppression of parasite regrowth only accurately described 1/3 cured patients. Predictions for cured patients after the end of treatment might be improved in the future by incorporating haematological markers associated with immune reconstitution.

BLOOD PARASITE LOAD AS AN EARLY MARKER TO PREDICT TREATMENT RESPONSE IN VISCERAL LEISHMANIASIS

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Introduction: With the recent increase in the development of new treatment regimens for visceral leishmaniasis (VL), there is an urgent need for early markers to evaluate treatment response and predict long-term outcomes. These biomarkers would be particularly useful in clinical trials with new chemical entities, where the biomarker could serve as a surrogate endpoint for futility early after treatment.

Methods: Data from three clinical trials were combined in this study, where Eastern African VL patients were treated with various antileishmanial therapies. Kinetoplast DNA of the *Leishmania* parasite was quantified with real-time quantitative PCR (qPCR) in whole blood samples during and up to 6 months after treatment. The predictive performance of pharmacodynamic parameters for clinical relapse within 6 months of follow-up was evaluated using receiver-operating characteristic curves. Clinical trial simulations were performed to determine the power associated with the use of blood parasite load as a surrogate endpoint to predict final clinical outcome.

Results:
- The absolute parasite density on day 56 of follow-up was found to be a highly sensitive predictor of relapse within 6 months of follow-up with a cut-off of 20 parasites/mL (AUC 0.92, specificity 0.91, sensitivity 0.89).
- An approximately 2 log higher parasite load in qPCR spleen/bone marrow samples was found compared to whole blood, but concentrations were well correlated ($\rho = 0.80$). This indicates that whole blood is a good proxy compartment to monitor the parasite biomass in the infected tissues.
- Both blood and tissue qPCR showed a correlation with microscopy gradings from aspirate smears. qPCR analysis seems to be a more sensitive method, as parasites were detectable by qPCR in in 100% and 76.7% of tissue and blood samples, respectively, compared to 60.5% of tissue samples by microscopy. Noteworthy, detectable qPCR blood or tissue parasite loads during follow-up were observed in patients considered clinically cured. This could indicate that patients can still harbour *Leishmania* parasites at low levels, but nevertheless remain asymptomatic.
- Clinical trials achieved a >80% power to detect a difference in cure rate between treatment arms if this difference was high (>50%) and when minimally 30 patients were included per treatment arm.

Conclusion: Blood *Leishmania* parasite load determined by qPCR is a promising early biomarker to predict relapse in VL patients and might be useful in dose finding studies of new chemical entities.

AN INTERNATIONAL QUALITY CONTROL PILOT PROGRAM FOR THE MEASUREMENT OF ANTIMICROBIAL DRUGS

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Introduction: There is an increased interest in developing assays to determine plasma concentrations of antimicrobial drugs. Assays for antimicrobial drugs are used for pharmacokinetic research purposes as well as in clinical practice when performing therapeutic drug monitoring. Participation in an interlaboratory quality control (QC) program is an essential component of quality assurance. Whereas QC programs for aminoglycosides and glycopeptides have been in place for several years, there is no independent, international program for external QC of other antimicrobial drugs. Therefore, we developed an international QC program for the measurement of antimicrobial drugs.

Methods: Antimicrobial drugs involved in the first two rounds of this pilot program were ceftazidime, ciprofloxacin, flucloxacillin, piperacillin, tazobactam, sulfamethoxazole, n-acetyl sulfamethoxazole and trimethoprim. Two QC samples (one sample per round) were prepared by spiking drug-free plasma with all eight antimicrobial drugs in either low or high concentrations, all within the clinical exposure range. Participants were provided feedback anonymously on their performance. All weighed-in concentrations were considered true values. Acceptable accuracy was defined if measurements were within the 80-120% limits of the true weighed-in concentrations. A one-tailed unpaired *t*-test was performed on the absolute inaccuracies to determine a difference between the high versus low concentrations.

Results: A total of 143 laboratories were approached. Seventeen laboratories participated in the first round and 22 laboratories in the second round. A total of 129 analyses were performed in both rounds. A total of 81% of the measurements was determined accurately. The measurements of flucloxacillin showed the best performance; 100% (21 out of 21) of the samples was determined accurately. The measurements of ceftazidime showed the worst performance; 56% (14 out of 25) of the samples was determined accurately. The measurements of the higher antibiotic concentrations showed a trend towards better performance than of the lower concentrations (p=0.052).

Conclusion: The initial results of this pilot program showed a relatively good performance of the participating laboratories compared to previous program initiated by us (HIV, TB and fungal). Nevertheless, still one out of five (19%) measurements was inaccurate. By participating in the program these laboratories were alerted, which may help them to improve their methods. Our results emphasize the importance of an ongoing QC program. In future rounds we will consider incorporating other antimicrobial drugs as well as the possibility the report free concentrations.

USE OF SODIUM-GLUCOSE CO-TRANSPORTER-2-INHIBITORS AND RISK OF LOWER LIMB AMPUTATION

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Introduction: Sodium-glucose co-transporter-2-inhibitors (SGLT2-Is) have established favourable cardiac and renal outcomes in type 2 diabetes (T2DM). However, a trial indicated that patients using the SGLT2-I canagliflozin had a greater risk of lower limb amputations (LLAs) (Neal *et al.*, 2017). Since then, studies evaluating the association between SGLT2-I use and LLA have produced conflicting results. Furthermore, potential underlying mechanisms have not been studied. A proposed mechanism for the increased risk of LLA is based on the mechanism of action of SGLT2-Is. Increased renal glucose excretion leads to osmotic diuresis, which may cause reduced extravascular volume and decreased peripheral tissue perfusion. Reduced tissue perfusion may lead to necrosis, gangrene and subsequent LLA (Fadini *et al.*, 2017).

Aim: The aim of the current study was to investigate the association between the use of SGLT2-Is versus other anti-diabetic drugs and the risk of LLA. In addition, we explored the possibility of hypovolemia as an underlying mechanism.

Methods: A cohort study was conducted using data from the Clinical Practice Research Datalink (CPRD) GOLD. The study population (N=51,847) consisted of individuals over 18 years of age with T2DM and at least one prescription of a non-insulin anti-diabetic drug . Drug exposure was determined time-dependently using 30-day intervals and cumulative dose exposure was calculated at each current SGT2-I use interval. Concomitant diuretic use was determined to assess the role of hypovolemia. Cox proportional hazard models were used to estimate the hazard ratio (HR) for LLA, comparing current SGLT2-I use to current sulfonylurea derivative (SU) use. Analyses were adjusted for life-style variables, comorbidities and concomitant drug use.

Results: SGLT2-I use was not associated with an increased risk of LLA compared to SU use (adjusted HR 0.72 (95% confidence interval (CI) 0.38-1.34)). In addition, we did not find a dose-response relationship, as the risk of LLA did not increase with increasing cumulative dose exposure. The adjusted HR for the highest cumulative dose group (>145.8 g canagliflozin equivalents) was 0.96 (95%CI 0.33-2.77). Furthermore, concomitant diuretic use was not associated with an increased risk of LLA in current SGLT2-I use compared to current SU use.

Conclusion: The results of the current study indicate that SGLT2-I use is not associated with an increased risk of LLA compared to SU use. The findings suggest that hypovolemia might not be the underlying mechanism for the previously found increased risk of LLA.

References:

Fadini *et al.* Lancet Diabetes Endocrinol. 2017 Sep;5(9):680-681.
Neal *et al.* N Engl J Med. 2017;377(7):644-657.

INTERACTION BETWEEN TISSUE TRANSGLUTAMINASE AND AMYLOID-BETA: PROTEIN-PROTEIN BINDING VERSUS ENZYMATIC CROSSLINKING

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Introduction

Self-interaction, chaperone binding and posttranslational modification of amyloid-beta (Aβ) is essential in the initiation and propagation of Aβ aggregation. Aggregation results in insoluble Aβ deposits characteristic of Alzheimer's disease (AD) brain lesions, i.e. senile plaques and cerebral amyloid angiopathy. Tissue transglutaminase (tTG) is a calcium-dependent enzyme that catalyzes posttranslational modifications including the formation of covalent ε-(γ-glutamyl)lysine isopeptide bonds (molecular crosslinks), and colocalizes with Aβ deposits in AD. Two independent groups recently found that apart from the induction of Aβ oligomerization, the blood-derived transglutaminase member FXIIIa forms stable protein-protein complexes with Aβ independent of the transamidation reaction. However, whether tTG also forms protein-protein complexes with Aβ under these conditions has not been studied thus far.

Objectives

Here, we investigated whether also tTG forms rigid protein complexes with Aβ in the absence of catalytic activation.

Methods

Human neocortex tissue samples from three AD patients with CAA (age 77.7 ± 11.4 years; post-mortem interval 5.2 ± 2.8 h) were obtained from the Netherlands Brain Bank. The binding of tTG to $A\beta_{1-40}$ or $A\beta_{1-42}$ species was studied using surface plasmon resonance (SPR) performed with BIAcore 2000. Aliquots of $A\beta_{1-40}$ and $A\beta_{1-42}$, (25 μM or 50nM final concentration) were allowed to cross-link to either 6.25 mU/ml of Guinea pig tissue tTG, and, if indicated, in the presence of its pharmacological inhibitor Z006 (1uM) or EDTA (11mM). Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was performed. Samples were boiled and separated on Bis-Tris 4-12% NuPAGE 15-wells gels in MES-SDS running buffer (Invitrogen, Carlsbad, CA, USA). Blots were incubated overnight at 4°C with primary antibody, i.e. mouse anti-Aβ (clone 82E1) and rabbit anti-TG2 (D11A6)

Results

We found that both $A\beta_{1-40}$ and $A\beta_{1-42}$ are substrates for tTG-catalyzed crosslinking. In addition, in the absence of calcium or the presence of a peptidergic inhibitor of tTG, stable tTG-$A\beta_{1-40}$ complexes were found. Interestingly, the stable complexes between tTG and $A\beta_{1-40}$, were only found at 'physiological' concentrations of $A\beta_{1-40}$.

Conclusion

Together, our data suggest that depending on the Aβ species at hand, and on the concentration of Aβ, rigid protein-complexes are formed between tTG and $A\beta_{1-40}$ without the involvement of the crosslinking reaction.

NEPHROTOXICITY OF CONCOMITANT PIPERACILLIN-TAZOBACATAM AND TEICOPLANIN COMPARED TO MONOTHERAPY

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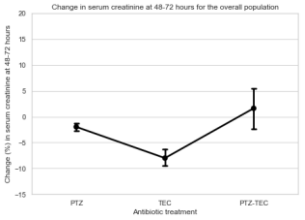
Introduction: Healthcare associated infections frequently require both *Pseudomonas spp*. and either methicillin-resistant *Staphylococcus Aureus* (MRSA), coagulase negative *Staphylococcus spp*. or *Enterococcus spp*. coverage. As such, a frequently used combination of antibiotics consists of piperacillin-tazobactam (PTZ) and vancomycin. There has been increasing evidence that this combination is associated with a decline in renal function compared to monotherapy. [1] Teicoplanin (TEC) is a glycopeptide with a similar profile to vancomycin. To date, no study has been performed to investigate whether the use of piperacillin-tazobactam combined with teicoplanin (PTZ-TEC) is associated with a decline in renal function. This is therefore the primary objective of this study.

Methods: We conducted a single center retrospective cohort analysis with data from our electronic health record over a 6 year period including all adult patients that received either PTZ, TEC or PTZ-TEC. Patients were excluded if they had chronic kidney disease, if no serum creatinine was known before commencing antibiotics or if they presented with AKI. To satisfy the assumption of underlying linearity, the log transformed data was considered regarding serum creatinine. An increase in serum creatinine at 48-72 hours compared to baseline was considered a decline in renal function. Data were analyzed with descriptive statistics and a multivariate linear regression model in which significant differences served as covariates.

Results: Out of 8326 patients, 4202 met the inclusion and exclusion criteria. Baseline characteristics are described in Table 1. A one way ANOVA between the change in serum creatinine at 48-72 hours compared to baseline and antibiotic treatment (PTZ, TEC or PTZ-TEC) showed a statistically significant correlation [$F = 27.07$, $p<0.001$]. Post hoc comparisons showed a mean difference between PTZ-TEC and TEC of 9.6% ($p = 0.001$) and between PTZ-TEC and PTZ of 3.6% ($p = 0.057$). Our multivariate linear regression analysis showed a significant correlation between the antibiotic treatment (PTZ, TEC, PTZ-TEC) and change in serum creatinine at 48-72 hours with a p-value of 0.0016.

		PTZ	TEC	PTZ-TEC	p-value	Total
Number of patients		3188	791	223		4202
Age, mean (SD)		63.4 (14.8)	56.5 (16.5)	60.7 (14.6)	<0.001	62.0 (15.4)
Sex, n (%)	M	1957 (61.4)	455 (57.5)	156 (70.0)	0.003	2568 (61.1)
	F	1231 (38.6)	336 (42.5)	67 (30.0)		1634 (38.9)
Length of stay, mean (SD)		17.3 (17.8)	22.5 (17.5)	29.6 (26.2)	<0.001	19.0 (18.5)
ICU admission, n (%)	N	2697 (84.6)	690 (87.2)	152 (68.2)	<0.001	3539 (84.2)
	Y	491 (15.4)	101 (12.8)	71 (31.8)		1634 (38.9)
Baseline GFR (ml/min), mean (SD)		89.3 (37.2)	92.2 (39.6)	83.2 (35.1)	0.006	89.6 (37.6)
Number of nephrotoxic drugs, mean (SD)		1.6 (1.6)	1.9 (1.7)	2.3 (1.8)	<0.001	1.7 (1.6)
Days on vasopressors, mean (SD)		3.9 (30.2)	3.1 (7.9)	3.4 (4.3)	0.890	3.7 (26.8)
Baseline GFR (ml/min), mean (SD)		89.3 (37.2)	92.2 (39.6)	83.2 (35.1)	0.006	89.6 (37.6)

Table 1: baseline characteristics



Conclusion: PTZ-TEC is associated with a decline in renal function, when compared to TEC monotherapy. This could very well be due to confounding, as ICU admission was used for severity of illness instead of a more specified marker. Considering these limitations, prospective studies are warranted to verify these results.

[1] Hammond DA, Smith MN, Li C, Hayes SM, Lusardi K, Bookstaver PB. *Systematic Review and Meta-Analysis of Acute Kidney Injury Associated with Concomitant Vancomycin and Piperacillin/tazobactam*. Clin Infect Dis **2017**; 64:666–674.