Abstract book

SCIENTIFIC MEETING

Dutch Society for Clinical Pharmacology and Biopharmacy (NVKFB) &
Dutch Society for Pharmacology (NVF)

ABSTRACTS

PHOTOSWITCHABLE SMALL-MOLECULE LIGANDS TO OPTICALLY MODULATE CHEMOKINE RECEPTORS

Authors

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Background

Photopharmacology allows the optical modulation of protein activity with light-responsive molecules such as azobenzene derivatives. This technology can be used to investigate the biological function of G protein-coupled receptors (GPCRs). In this study we developed functionally light-responsive ligands to optically modulate chemokines receptors such as CXC chemokine receptor 3 (CXCR3) and atypical chemokine receptor 3 (ACKR3). Those GPCRs play crucial role in T-cell function and are associated with inflammatory diseases and cancer.

Methods

Design and synthesis of photoswitchable compounds were inspired by the CXCR3 antagonist VUF11211 and a patent of an ACKR3 agonist.
Phtoswitchable CXCR3 antagonist VUF16338 was characterized in radioligand binding assay.

Activation of CXCR3 by CXCL11 and inhibition of 10 nM CXCL11-induced CXCR3 activity by VUF16338, was measured by [^{35}S]GTPγs accumulation assay and NanoBit-based Gα_{i1} recruitment.
Photoswitchable ACKR3 agonis was characterized in NanoBRET binding assay using fluorescently labeled CXCL12-AF647. β-arrestin2 recruitment to the ACKR3 after stimulation with VUF25471 wad detected by NanoBit complementation.

Results

The CXCR3 photoswitchable ligand VUF16338 has been identified as a key compound from a library of eleven analogs. VUF16338 inhibits CXCL11-induced G protein activation by CXCR3 with a 10-fold inhibitory potency shift between dark and irradiated states. For ACKR3 VUF25471 has been selected as tool compound and has been found to recruit β-arrestin2 to ACKR3 with 10-fold potency shift between dark and irradiated states

Discussion/Conclusion

VUF25471 compound is the first photoswitchable ligand for ACKR3.VUF16338 and VUF25471 are a valuable tools to investigate the role of CXCR3 and ACKR3 in biological functions, respectively.

DESMOPRESSIN TO PREVENT AND TREAT BLEEDING IN PREGNANT WOMEN WITH INHERITED BLEEDING DISORDER: A SYSTEMATIC LITERATURE REVIEW

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Background
Although desmopressin (DDAVP) is an accessible and inexpensive hemostatic drug, its use in pregnancy is still debated due to safety uncertainties. We aim to review safety and effectiveness of DDAVP in women with an inherited bleeding disorder during pregnancy and delivery.

Methods
Databases were searched for articles up to July 25th 2022, reporting maternal and/or neonatal outcomes. PRISMA methodology was followed (PROSPERO CRD42022316490).

Results
Fifty-three studies were included, comprising 273 pregnancies. Regarding maternal outcomes, DDAVP was administered in 73 pregnancies during pregnancy and in 232 pregnancies during child delivery. In 2 to 32 pregnancies mild adverse events (AE) (headache and facial flushing) were reported and in two pregnancies two severe AE (hyponatremia with neurological symptoms) (21% pregnancies unknown outcome). DDAVP was used in 232 pregnancies as monotherapy (54% effective, 12% ineffective and 34% unknown outcome). Regarding neonatal outcomes, of the 73 pregnancies with DDAVP during pregnancy, 60 resulted in the birth of a child of which in 2 a severe AE was reported (preterm delivery n=1; fetal growth restriction n=1). In addition, one of these women was treated for a planned abortion and 12 were treated before undergoing a prenatal testing and for subsequent abortion. Of the 232 deliveries, 169 neonates were exposed to DDAVP during delivery. Two experienced a moderate AE (low Apgar score n=1; transient hyperbilirubinemia not associated with DDAVP n=1) (33% deliveries unknown outcome).

Discussion/Conclusion
DDAVP use during pregnancy and child delivery seems safe for the mother, with special attention to the occurrence of hyponatremia. However, due to poor design and limited documentation of outcomes, a well-designed prospective study is warranted.

THE QT_C INTERVAL IN FORMER VERY PRETERM INFANTS IN ADOLESCENCE AND YOUNG ADULTHOOD IS NOT DIFFERENT FROM TERM-BORN CONTROLS

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Background

Although relevant for precision pharmacovigilance, there are conflicting data on whether former preterm birth is associated with $QT_{c\text{-}Bazett}$ prolongation in later life.

Methods

To explore $QT_{c\text{-}Bazett}$ interval differences between former preterm and/or extreme low birth weight (ELBW) cases and term-born controls in adolescence and young adulthood, we analyzed pooled individual data after a structured search on published cohorts.

To test the absence of a $QT_{c\text{-}Bazett}$ difference, a non-inferiority approach was applied (one-sided, upper limit of the 95% confidence interval (CI) mean $QT_{c\text{-}Bazett}$ difference, 5 and 10 ms). We also investigated the impact of characteristics, either perinatal or at assessment on $QT_{c\text{-}Bazett}$ in the full dataset (cases and controls).

Results

The pooled dataset contained 164 preterms and/or ELBW (cases) and 140 controls from 3 studies. The median $QT_{c\text{-}Bazett}$ intervals were 409 (335-490) and 410 (318-480) ms in cases and controls. The mean $QT_{c\text{-}Bazett}$ difference was 1 ms, with an upper CI 95% of 6 ms ($p=0.1015$ and 0.0019 for 5 and 10 ms respectively). In the full dataset, females had a significantly longer $QT_{c\text{-}Bazett}$ than males (415 vs. 401 ms, $p<0.0001$), and there was a significant, but weak correlation (Spearman's 0.151, $p=0.0377$) between $QT_{c\text{-}Bazett}$ and the plasma phosphate level.

Conclusions

$QT_{c\text{-}Bazett}$ intervals are not significantly different between former preterm and/or ELBW cases and term-born controls, and we rejected a potential prolongation >10 ms in cases. When prescribing QTc prolonging drugs, pharmacovigilance practices in this subpopulation should be similar to the general public.

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO CONTROLLERD, FOUR-WAY CROSS-OVER STUDY TO INVESTIGATE THE ANALGESIC EFFECTS AND CNS EFFECTS ON MORPHINE AND PREGABALIN IN HEALTHY SUBJECTS

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Background and aims

Chronic pain is currently treated mostly with opioid monotherapy which may induce debilitating adverse effects. One solution may be adding a non-opioid analgesic to opioid treatment to lead to opioid-sparing effects. We aimed to investigate the potential of pregabalin and morphine as such a combination treatment.

Methods

We performed a double-blind placebo-controlled cross-over study. In four identical study days with 7 days wash-out in-between, 24 healthy volunteers (18-65years) received 300mg pregabalin, 3mg + 7mg morphine, a combination of these two and placebo in randomized order. A comprehensive nociceptive test battery, a neurocognitive test battery and pharmacokinetic blood sampling were performed pre-dose and up to 10h post-dose. Data were analysed with a repeated-measures ANOVA.

Results

Mean age was 39 ±16.4 years. Significant effects on pain tolerance thresholds (PTT) were found for cold pressor (figure 1), electrical burst (figure 2), electrical stair and pressure test. A difference on postural stability and eye-hand coordination (figure 3) are significant for morphine – morphine + pregabalin. Detailed results will be presented at the congress.

Discussion/Conclusion

Pregabalin and morphine combined induced superior analgesic - and limited additional cognitive effects compared to either monotherapy and placebo. Results suggest benefit of a combination therapy as opioid-sparing treatment.

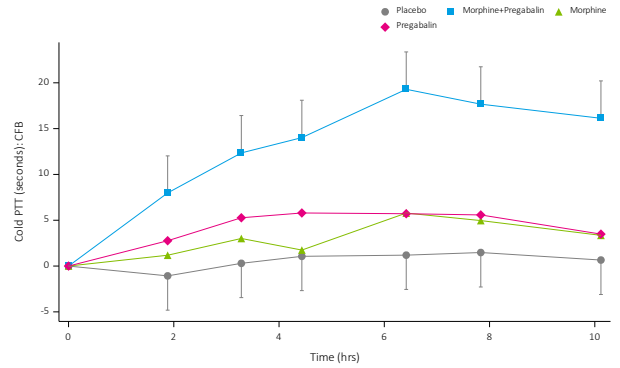

Figure 1 . Cold pressor pain tolerance, morphine – morphine + pregabalin ED – 11.23 sec, 95% CI -16.05 sec to -6.42 sec)

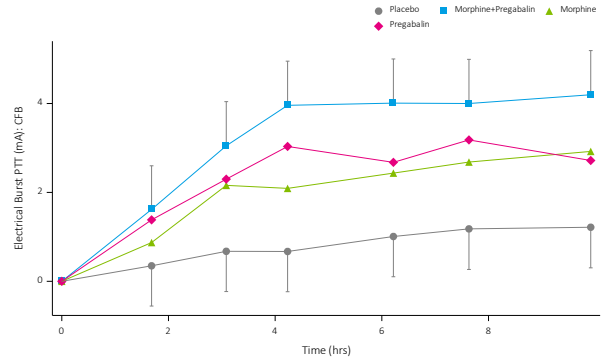

Figure 2. Electrical Burst pain tolerance, morphine – morphine + pregabalin ED – 1.28 mA, 95% CI -2.34 mA to -0.22 mA

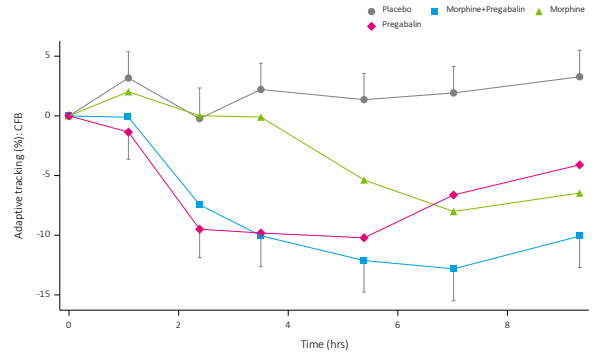

Figure 3 Eye-hand coordination, morphine – morphine + pregabalin ED 5.786%, 95% CI 3.499% to 8.072%

QUANTIFYING THE EFFECT OF METHOTREXATE ON THE ADALIMUMAB RESPONSE IN PSORIASIS BY PHARMACOKINETIC-PHARMACODYNAMIC MODELLING

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Background
The OPTIMAP trial showed that the combination of methotrexate (MTX) and adalimumab (ADL) treatment leads to less anti-drug antibodies (ADA) development. In this study, we quantify the pharmacokinetics (PK)/pharmacodynamics (PD) of ADL and evaluate the influence of MTX co-treatment.

Methods
A population PK-PD model was developed using a two-stage approach with prospective data from 59 psoriasis patients (baseline PASI score: 12.6) receiving ADL over 49 weeks. Typical PK and PD parameters and their corresponding inter-patient variability (IIV) were estimated. We performed a covariate analysis to assess whether IIV could be explained by addition of MTX and specific patient characteristics.

Results
In total, 330 PASI scores, 252 ADL serum concentrations and 247 ADA titers were available. A one-compartment model was used and resulted in an apparent volume of distribution (Vd/F) of 14.7 L/82 kg, an apparent clearance (CL/F) of 0.365 L/day/82 kg and an IIV on Cl of 31.8%. Presence of ADA (ADL group 46.7%, ADL+MTX group 38.7%; $p = 0.031$) increased CL/F ($p < 0.001$), e.g. an ADA level of 30 AU/ml increased CL/F with a factor of ~4.1. The relationship between ADL level and PASI was described with a turn-over inhibitory Emax model with an IC_{50} of 1.19 mg/L, a K_{out} of 0.0314 L/day and an IIV of 152.6%. In the PD model, a trend between a reduced IC_{50} and the concomitant use of MTX was detected ($p = 0.06$).

Discussion/Conclusion
Based on our PK-PD model, concomitant used MTX increases the clinical efficacy of ADL, through less ADA formation, a greater drug exposure and possibly via an additional clinical effect.

EUROPEAN CONDITIONAL MARKETING AUTHORIZATION IN A RAPIDLY EVOLVING TREATMENT LANDSCAPE: A COMPREHENSIVE STUDY OF ANTICANCER MEDICINAL PRODUCTS IN 2006-2020

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Background

Since 2006, the European conditional marketing authorization (CMA) aims to facilitate timely patient access to medicinal products for which there is an unmet medical need by accepting less comprehensive data than normally required. The granting of CMA requires a positive benefit-risk balance, unmet medical needs to be fulfilled, likely submission of comprehensive data postauthorization, and the benefit of immediate availability outweighs the risks of data noncomprehensiveness. Since its first use, more than half of all CMAs represent (hemato-)oncology indications. Therefore, we aimed to investigate how the concept of CMA has been applied and evolved for anticancer medicinal products, and how it shaped regulatory decision-making by the European Medicines Agency (EMA).

Methods

We retrospectively assessed the European public assessment reports of all anticancer medicinal products granted CMA in 2006-2020.

Results

In 2006-2020, 30 anticancer medicinal products were granted CMA (51% of all 59 CMAs). Comparison of 2006-2013 to 2014-2020 highlighted increased proportions of proactively requested CMAs (+40%), medicinal products that addressed unmet medical needs by providing a major therapeutic advantage over authorized treatments (+38%) and orphan designated indications (+32%). Alternatively, the proportion of medicinal products for which a Scientific Advisory Group was consulted (-55%) and phase 3 randomized controlled trial data were available decreased (-38%).

Discussion/Conclusion

Our study suggests that applicants and the EMA have learned how to use the CMA as regulatory tool through better planning and proactive interaction. However, the increasing number of granted CMAs complicates the establishment of unmet medical need and the (relative) benefit-risk balance, especially in crowded indications and when only phase 2 uncontrolled trials are available.

MODEL-INFORMED PRECISION DOSING OF ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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Background: Eculizumab is a lifesaving, yet expensive humanized monoclonal anti-complement C5 inhibitor which is approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Eculizumab is dosed as a fixed dose, but previous studies in patients with atypical hemolytic uremic syndrome showed a large inter- and intraindividual variability in pharmacokinetics of eculizumab. Adequate therapy with eculizumab is necessary to prevent breakthrough hemolysis in patients with PNH. In case of supratherapeutic concentrations, the dosing interval could be prolonged to reduce cost and to improve patient-friendliness. With this current study, we want to gather more insight in the pharmacokinetics of eculizumab in PHN to develop patient-friendly dosing strategies to improve treatment response at preferably reduced costs.

Methods: A prospective observational pharmacokinetic study (ClincialTrials.gov: NCT04079257) was conducted at the Radboud university medical center. Pharmacokinetic sampling was performed at 1-3 separate occasions and both peak and trough samples were collected. Data were used to enrich a dataset used for our previous pharmacokinetic analysis of eculizumab in aHUS patients[1]. Pharmacokinetic modelling was performed with non-linear mixed effects modelling. The final model was used to develop new dosing strategies with the use of Monte Carlo simulations in 1171 individuals.

Results: In total, 27 PNH patients were included in this study, with a total of 123 paired observations of time and free eculizumab serum concentrations. A two-compartment model with parallel linear and non-linear elimination best described the data. The addition of disease as a covariate on inter-occasion variability (IOV) resulted in a statically improved fit ($p<0.001$, difference in objective function: -86). The estimates of the model were clearance 0.163 L/day (RSE 6%), volume of distribution 1 4.3 L (RSE 6%), volume of distribution 2 2.6 L (RSE 5%), Q 0.62 L/day, maximum rate (Vmax) 25.6 mg/day (RSE 5%), plasma concentration for 50% of maximum rate (Km) 13.5 mg/L (RSE 38%).

A weight-based loading dose on day 1 of therapy followed by the maintenance dose on day 15 improved therapy. We predicted that 52.0% of the individuals reach effective complement blockade on day 7 of treatment with the standard loading dose, compared to 99.9% of the patients with the new loading dose. Drug costs are comparable for both strategies. A therapeutic drug monitoring based dosing strategy in the maintenance phase resulted in 16.2% dose reduction. Interval prolongation to three weeks and four weeks was possible in 47.9% and 2.7% of the patients, respectively. A dose increase form 900 mg to 1200mg was necessary in 3.2% of the patients.

Conclusion: An individualized, patient-friendly dosing strategy of eculizumab in PNH patients results in better treatment response at lower drug costs.

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DOSE OPTIMIZATION BY A CLINICAL DECISION SUPPORT SYSTEM OF VANCOMYCIN IN (MORBID) OBESE PATIENTS

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Background

Obese patients treated with vancomycin may need a higher dosing regimen to achieve therapeutic drug levels. In the Maasstad and Ikazia hospital the recommended starting dose in obese patients is 30 mg/kg/day. We developed a Clinical Decision Support System (CDSS) for (morbid) obese patient using vancomycin, to alert the pharmacist of incorrect dosing. The aim of this study was to determine if the use of CDSS of vancomycin would lead to attaining vancomycin target levels quicker.

Methods

During this retrospective pre- post intervention study a total of 100 patients were included. Patients were included when they were ≥ 18 years, received vancomycin IV and had a BMI ≥ 35 and/or TBW ≥ 100 kg. The Control (CTRL)-group were compared to the clinical rule (CR)-group. Primary outcome is time until therapeutic vancomycin target level. For primary outcome measure, Kaplan-Meier (K-M) and Cox proportional hazard models were used to assess difference in time to therapeutic vancomycin target level.

Results

In total 100 patients were included, 55 CTRL and 45 CR. In total 69 patients reached a therapeutic vancomycin target level, 32 (71%) in the CR and 38 (69%) in the CTRL-group. In the CR group, the median was 3 days for 50% of the patients to reach therapeutic target level and 3,5 days for the CTRL-group.

In the CR-group 24 times action was taken by the pharmacist. No action was taken in 12 cases (30%) when needed recording to the clinical rule. This resulted in incorrect dose at start of vancomycin therapy. Besides in 17 of 45 cases no correct starting dose of 30 mg/kg/day was given, nevertheless the standard dose of 2dd1000mg was prescribed. The median time to initial target level is higher in these incorrect dose group (2.6 days vs. 1.9 days).

Discussion/Conclusion

Implementing a CDSS for vancomycin in (morbid) obese patients did not have impact on the time until therapeutic vancomycin target levels were reached. We observed a lack of intervention by the pharmacist, caused by a “wait and see” attitude for the first blood vancomycin level was known. Besides the first dose of vancomycin was already given before the CDSS alerted the pharmacist to take action. The starting dose is not often corrected for obesity by physicians.

Therefore it is important to evaluate the use of a CDSS in order to optimize the system and to improve obese patients response on vancomycin therapy.

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INFLUENCE OF CANNABIDIOL (CBD) ON TAMOXIFEN PHARMACOKINETICS IN PATIENTS WITH PRIMARY BREAST CANCER AND TAMOXIFEN-RELATED SIDE EFFECTS

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Background

Tamoxifen is frequently used in the adjuvant treatment of hormone sensitive breast cancer. Unfortunately, tamoxifen can lead to bothersome side effects resulting in non-adherence in 40% of patients [1]. Patients searching for relief from these side effects are increasingly turning to cannabinoids such as CBD [2]. However, since tamoxifen is mainly metabolised by CYP2D6, and CBD is suggested to be an inhibitor of CYP2D6, the use of CBD might affect tamoxifen pharmacokinetics (PK) [3]. Since the effect of CBD on both tamoxifen PK as tamoxifen-related side effects has never been investigated, the aims of this study were to determine the pharmacokinetic interaction between CBD and tamoxifen, and to subsequently investigate whether there is a beneficial influence of CBD on tamoxifen-related side effects.

Methods

Patients had to be treated with tamoxifen for at least 3 months, have steady-state endoxifen levels $\geq$16 nM (conservative threshold) and experience tamoxifen-related side effects. PK sampling was done at initiation of CBD-oil and 28 days thereafter. CBD-oil was used sublingually in the highest over the counter dose (CBD 10% 5 drops t.i.d., i.e. 50 mg). Bio-equivalence could be concluded according FDA guidelines if the 90% confidence interval (CI) for the difference in endoxifen area under the curve (AUC) fell within the [-20%; +25%] interval (n = 15, two-sided α 0.05, β 0.20). The effect of CBD on side effects was evaluated with the FACT-ES questionnaire (n = 25, two-sided α 0.05, β 0.20). An improvement of more than 0.5 times standard deviation (SD) of baseline scores was considered clinically relevant.

Results

In this study 15 patients were included for PK analysis and 26 patients for side effect analysis. There was no difference in tamoxifen AUC with or without CBD. Endoxifen AUC decreased after CBD by 12.6% (90% CI -18.7%, -6,1%) but remained within bio-equivalence boundaries. The endocrine sub-scale of the FACT-ES improved clinically relevant with 6.7 points (n=26, p<0.001) and health-related quality of life improved with 4.7 points after using CBD (95% CI +1.8, +7.6).

Discussion/Conclusion

As endoxifen levels with or without CBD remained within bio-equivalence boundaries and CBD-oil might have a positive effect on tamoxifen-related side effects, it does not have be discouraged in patient using it for tamoxifen-related side effects.

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RE-EVALUATING THE NEED FOR CHRONIC TOXICITY STUDIES WITH THERAPEUTIC MONOCLONAL ANTIBODIES, USING A WEIGHT-OF-EVIDENCE APPROACH

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Background

To support registration of monoclonal antibodies (mAbs) for chronic indications, 6-month toxicity studies have historically been conducted as per ICH S6(R1) guidance. Experience with mAb development has shown a relatively benign and well-understood safety profile for this class, with most toxicity findings anticipated based on pharmacology. A consortium of 14 pharmaceutical companies, the Medicines Evaluation Board (MEB) and the NC3Rs conducted an European Partnership for Alternative Approaches to Animal Testing (EPAA)-funded study to evaluate whether a 6-month toxicity study is still necessary to assess the long-term safety of mAbs.

Methods

Companies submitted anonymized data by survey, including product information, species selection and pharmacological relevance, study details and information on findings in FIH-enabling (short-term) and chronic studies. The incidence of new toxicities identified in chronic studies, along with impact on mAb development or clinical trial design, was reviewed from data shared by industry participants.

Results

Data on First-in-Human (FIH)-enabling and chronic toxicity studies were shared for 142 mAbs submitted by 11 companies. Opportunities to further optimize study designs to reduce animal usage were identified. For 71% of mAbs, no toxicities or no new toxicities were noted in chronic studies compared to FIH-enabling study findings. New toxicities related to exaggerated pharmacology or ADA-mediated (not considered of human concern) were identified in 15.3% of cases. New toxicities of potential concern for human safety or that changed trial design were identified in 13.5% of cases, with 7% being considered critical and 2% leading to program termination. A longer dosing duration in the FIH-enabling study, e.g., 3 months vs. 1 month, resulted in fewer new toxicities in the chronic studies.

Discussion/Conclusion

In retrospect, only a small proportion of chronic studies provided additional safety findings relevant for clinical dosing. An iterative, weight-of-evidence model which considers factors that influence the overall risk for a mAb to cause toxicity was developed, to drive selection of the optimal duration of toxicity study without defaulting to a study of 6 months duration. This model enables an evidence-based justification, suggesting when 3-month toxicity studies are likely sufficient to support late-stage clinical development and registration for some mAbs.

PHARMACOKINETIC-PHARMACODYNAMIC MODELLING IN HEMOPHILIA A: RELATING THROMBIN AND PLASMIN GENERATION TO FACTOR VIII ACTIVITY AFTER ADMINISTRATION OF VWF/ FVIII

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Background Hemophilia A (HA) is characterized by a deficiency of coagulation factor (F) VIII leading to recurrent spontaneous and trauma-induced bleeding**.** HA patients are treated with FVIII prophylactically to prevent bleeding. Dosage and frequency are adjusted in case of bleeding and increasingly on pharmacokinetic (PK) measurements. An alternative approach is to adjust dosage and frequency based on an effect outcome measurement; the thrombin generation assay (TGA). The effect of FVIII suppletion is reflected by the TGA.
Methods In this study we validated a previously developed pharmacokinetic/pharmacodynamics (PK-PD) model [1] for standard half-life recombinant and plasma-derived (pd)FVIII, relating FVIII dose and FVIII activity levels to thrombin and plasmin generation.
Results PK and PD measurements were obtained from 29 severe hemophilia A patients treated with pd von Willebrand factor (VWF)/FVIII concentrate (Haemate P®). The predictive performance of the previously developed PK-PD model was evaluated. When predictions of FVIII activity or TGA parameters were inadequate (median prediction error (MPE) >20%), new PK-PD models were developed. The published PK-model generally underestimated clearance and was refined based on a two-compartment model with additional data. The PD model adequately predicted the observed normalized thrombin peak height and normalized thrombin potential (MPE of 6.4% and 2.2%, respectively). EC50 and Emax values of these parameters were relatively comparable between the published model and the validated model. Prediction of normalized plasmin peak height was inaccurate (MPE 56.5%).
Discussion/Conclusion Previously developed PK-PD models were validated and the PK model overestimated the prediction of pdVWF/FVIII concentrate. While the PD models showed acceptable predictive performance, indicating the PD models may be used for multiple factor concentrates. A prospective crossover study is foreseen in which PK-PD based multiple FVIII concentrates dosing will be correlated with bleeding outcome to establish impact on bleeding reduction.

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CHARACTERISTICS OF POLYPSYCHOPHARMACY PATIENTS IN PRIMARY CARE

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Background
Concurrent use of multiple psychopharmaca (polypsychopharmacy) has increased in recent years and concerns have been raised about the effectiveness and safety of this practice.[1] Recent literature shows an increase in polypsychopharmacy in specialist care, but data from a general population is lacking. This study aims to investigate which patient characteristics are associated with psychopolypharmacy in a Dutch general population in the Nijmegen region.

Methods
Basic patient characteristics, medication use, and disease episodes of ~450.000 patients in were obtained from the Raboudumc Health Technology Primary Care database. Inclusion criteria were age > 18, and data availability for at least 1 year. Polypsychopharmacy was defined as the use of two or more psychopharmaca from different classes (ATC4 level) simultaneously for at least 3 months on 1-7-2021. A multivariate analysis was performed to investigate the influence of age, sex, non-psychiatric comorbidities (asthma/copd, cancer, cardiovascular, diabetes, epilepsy, neuropathy and rheumatic disease), analgesic use, and number of doctor appointments per year on polypsychopharmacy. The analysis was adjusted for several psychiatric diagnoses, and having a psychiatric referral in the patient history.

Results
In total 311.029 patients were included. Polypsychopharmacy was present in 3921 (1.26%) of all patients. All variables were significantly associated with polypharmacy, except for diabetes, neuropathy, and less than 6 doctor appointments per year. Having more than 13 appointments per year (OR 2,84 CI 2.52-3.19), age 65+ (OR 1.72 CI 1.55-1.91), and use of analgesics (OR 1.98 CI 1.83-2.15) had the highest odds ratios. The comorbidities most strongly associated were epilepsy (OR 1.49 CI 1.21-1.84), and asthma/COPD (OR 1.22 CI 1.11-1.34).

Discussion/Conclusion
Polypsychopharmacy in primary care increases with age, and is primarily associated analgesic use and frequent visits to the general practitioner. Future research should focus on the consequences of polypsychopharmacy, the drivers for psychotropic drug prescribing in these patients, guideline adherence, and what measures can be taken to deprescribe and prevent unnecessary polypsychopharmacy.

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FREQUENCY AND ASSOCIATION OF *NUDT15*3* GENETIC POLYMORPHISM WITH THIOPURINE-INDUCED MYELOSUPPRESSION IN A DUTCH PATIENT POPULATION WITH INFLAMMATORY BOWEL DISEASE

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Background
Thiopurine drugs are the cornerstone for treatment of inflammatory bowel disease (IBD). Nonetheless, up to 15-28% of patients experience adverse drug reactions causing them to withdraw from using thiopurines. One severe adverse drug reaction is thiopurine-induced myelosuppression (TIM). The enzyme nudrixhydrolase 15 (NUDT15) is the primary inactivation route for the active and toxic thiopurine triphosphates 6-TGTP and 6-TdGTP. The polymorphism *NUDT15*3* reduces NUDT15 enzyme activity, and thus thiopurine inactivation capacity, increasing the risk for TIM. The worldwide prevalence of *NUDT15*3* ranges from 0.3% in Caucasians to 11.6% in Asians, however, the frequency and association with TIM in a Dutch patient population has not yet been determined. The aim of this study was to determine the frequency and association of *NUDT15*3* with thiopurine-induced myelosuppression in a Dutch IBD patient population.

Methods
In this multicentre retrospective genetic association study, DNA from all patients previously genotyped for *TPMT* between 2018-2022 were genotyped for *NUDT15*3*. Patient and treatment characteristics were obtained from the electronic patient files. Subsequently, all patients with IBD were selected and association tests with TIM were conducted. TIM was defined as WBC $\leq 3.0 \times 10^9$/L or ANC $\leq 1.5 \times 10^9$/L, and related to thiopurine treatment, and occurring within a 2-year timeframe after start of treatment.

Results
A total of 990 patients were included, of which 13 (1.3%) were heterozygous for the *NUDT15*3* variant. Of these 990 patients, 604 patients had IBD and were actually treated with a thiopurine drug. Of these patients, 8 (1.3%) were heterozygous polymorphic for *NUDT15*3* of which 50.0% developed TIM compared to 2.3% in the wild type patients ($p<0.001$).

Discussion/Conclusion
This is the first study to determine the frequency and association of *NUDT15*3* with thiopurine-induced myelosuppression in a Dutch patient population. Patients polymorphic for *NUDT15*3* developed TIM more often than patients wild type for *NUDT15*. Furthermore, the study results suggest that the *NUDT15*3* polymorphism in this Dutch patient population is slightly higher compared the frequency in Caucasians, and that pretherapeutic genotyping for *NUDT15*3* could be beneficial to reduce the risk for TIM. The frequency of *NUDT15*3* in this Dutch patient population is considered sufficiently high to warrant pretherapeutic screening.

THE EUROPEAN PRESCRIBING EXAM: A QUALITY ANALISYS OF THE FIRST CROSS-BORDER ESTABLSHED PHARMACOTHERAPY ASSESSMENT FOR FINAL YEAR MEDICAL STUDENTS

Authors

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Organisations

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Background

This study describes the development and quality analysis of the first two pilot exams of The European Prescribing Exam (EuroPE$^+$), a standardized cross-border final exam on safe and rational prescribing for medical students in Europe.

Methods

Based on pre-defined learning objectives established by European consensus studies and the Dutch National Pharmacotherapy Assessment [1,2], two pilot exams with peer-reviewed questions were created. Each exam contained 36 multiple choice/answers questions (knowledge) and 11 prescription questions (skills). Both exams were piloted formatively during two academic years (2020/2021 and 2021/2022) in 11 European universities. The reliability was examined through psychometrical analysis (R_{ir}-value, Cronbach's alpha, difficulty index (DI)). The content validity was determined by an independent expert panel (content validity ratio (CVR)). Questions with low quality (negative Rir-value or CVR, or DI<0.44) were identified. Moreover, all median (IQR) exam scores were described and the differences in scores between universities and curricula were evaluated.

Results

A total of 1.883 unique students were included in the analysis. The questions were predominantly of high quality; 18/94 (19.1%) were potentially of lower quality (14 low DI, 7 negative CVR) and were selected for second hand evaluation. Median scores on the knowledge parts were 78.8% (19.2) and 70.6% (13.6), and on the skills parts 36.4% (27.3) and 35% (25.5), respectively for each exam. Having a problem-based learning curriculum as well as having a national prescribing exam within the medical curriculum led to significant ($p<0.001$) higher exam results.

Discussion/Conclusion

This study demonstrates the feasibility of developing a validated and reliable standardized European Prescribing Exam in a transnational manner, as the quality of both pilot exams appears to be favourable. However, the exam was conducted as a formative test, and the median scores were found to be wide-raging and significantly lower than desired. This highlights the need for further improvement and harmonisation of clinical pharmacology and therapeutics education across Europe, where the implementation of the EuroPE$^+$, along with a problem-based learning curriculum and other new initiatives, could prove to be a valuable contribution.

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THE IMPACT OF A SUMMATIVE NATIONAL PRESCRIBING ASSESSMENT AND CURRICULUM TYPE ON THE DEVELOPMENT OF THE PRESCRIBING COMPETENCE OF JUNIOR DOCTORS

Authors

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Organisations

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Background

The primary aim of this study was to investigate the effect of a national prescribing safety assessment during the medical curriculum on the level and development of prescribing knowledge and skills of junior doctors. The secondary aim was to evaluate the relationship between the curriculum type and the prescribing competence of junior doctors.

Methods

We re-analysed the data of a longitudinal study involving recently graduated junior doctors from 11 medical schools across the Netherlands and Belgium [1]. Participants completed three assessments during the first year after graduation (around graduation, and 6 months and 1 year after graduation), each of which contained 35 multiple choice questions (MCQs) and three clinical case scenarios. Only one medical school implemented the Dutch National Pharmacotherapy Assessment (DNPA) during its medical curriculum while the others used conventional assessments. Five medical schools were classified as having only theoretical education, whereas the six others were classified as having both theoretical and practical education.

Results

326 participants completed the MCQs and 325 completed the skills questions of all three assessments. Junior doctors with the DNPA in their curriculum had better knowledge scores than junior doctors without the DNPA (76.7% [SD 12.5] vs. 67.8% [SD 12.6], 81.8% [SD 11.1] vs. 76.1% [SD 11.1], 77.0% [12.1] vs. 70.6% [SD 14.0], $p<0.05$ for all three assessments, respectively), but there was no difference in skills scores at the moment of graduation ($p=0.110$). Junior doctors educated with a mixed curriculum showed significantly higher scores for both knowledge and skills compared to the theoretical curriculum($p<0.05$ in all assessment).

Discussion/Conclusion

Although only one medical school implemented the DNPA, our study shows that the implementation of a national prescribing safety assessment in the medical curriculum might improve the prescribing knowledge of junior doctors but has little to no effect on their prescribing skills. Additionally, a curriculum with both theoretical and practical education seems to improve both prescribing knowledge and skills.

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A RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE ON ORAL CHOLERA VACCINATION WITH INTRANASAL RECHALLENGE AS ADAPTIVE IMMUNE CHALLENGE MODEL

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Background
The mucosal immune system is a new and promising pharmacological target. It consists of mucosa-associated lymphoid tissues (MALT), containing a specialized immune system protecting against in invasion of pathogens, and is located in all mucous membranes. Specific characteristics of the mucosal immune system are secretion of IgA-antibodies and compartmentalization, with a segmentalized antibody production per vaccination route. To measure the effect of novel immunomodulatory drugs targeting the gut mucosal immune system, an adaptive immune challenge model is warranted. In this study, the use of an oral cholera vaccination (Dukoral®) as adaptive challenge model is investigated. To this end, the IgA and IgG serum responses after initial oral cholera vaccination and a 2-week booster will be followed over time. To evaluate the use of this adaptive immune challenge model for drugs targeting the upper respiratory tract, antibody production in nose fluid and saliva after intranasal rechallenge will be measured. As benchmark drug, mycophenolate mofetil (MMF) will be used. To further characterize the systemic response to mucosal immunization, the following additional endpoints will be explored: *ex vivo* T- and B-cell response upon cholera rechallenge, local and circulating cytokines after oral cholera vaccination and changes in the microbiome after oral cholera vaccination.

Methods
This study will be a randomized, placebo controlled, single blind, single centre study including 16 male and female subjects (MMF : placebo is 1:1) Subjects will receive an oral cholera vaccination (3 mL Dukoral suspension containing $1.25x10^{11}$ inactivated cholera bacteria and 1 mg recombinant cholera toxin subunit B) at Day 1 and Day 14, with intranasal rechallenge (0.750 mL containing 250 μg recombinant cholera toxin subunit B) at Day 18. MMF or placebo treatment will take place between Day -2 until Day 4, with a dosing of 2g per day. Blood samples for measuring antibody levels will be taken at Day 1, 14, 18, 20, 25 and 28. Nasal fluid will be collected by nasosorption, at Day 18, 19, 20, 25 and 28. Saliva will be collected at Day 1, 14, 20 and 28. For exploratory endpoints, faecal samples and blood samples for peripheral blood mononuclear cells (PBMCs) will be collected.

Results

This study will be conducted in the spring of 2023.

Discussion/Conclusion

The mucosal immune system is a promising new target for drugs with immunomodulatory properties. In this study, the use of an oral vaccination with intranasal rechallenge will be explored as new adaptive immune challenge for measuring drug effects on the gut and intranasal mucosal immune system.

ORAL AND INTRAVENOUS AMOXICILLIN DOSING RECOMMENDATIONS IN NEONATES AT RISK FOR POSSIBLE SEVERE BACTERIAL INFECTIONS: A POOLED POPULATION PHARMACOKINETIC STUDY

Authors

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Background

Oral amoxicillin use is limited in neonates due to lack of evidence on its pharmacokinetics. The bactericidal activity of amoxicillin depends on the time during which the free drug concentration exceeds the minimal inhibitory concentration (fT>MIC). In neonates, a fT>MIC of ≥50% is recommended. Our aim was to describe amoxicillin disposition following oral and intravenous administration and to provide dosing recommendations for (pre-) term neonates treated for possible severe bacterial infection.

Methods

We performed a pooled population pharmacokinetic study using three different datasets from the Netherlands and Pakistan. This resulted in a cohort of 261 (79 oral, 182 intravenous) neonates with a median (range) gestational age (GA) of 35·8 (24·9-42·4) weeks, postnatal age (PNA) of 6·8 (0-55) days and bodyweight of 2·6 (0·5-5) kg. A total of 938 blood samples were available for population pharmacokinetic modeling using NONMEM 7.4. A target of 50% fT>MIC with an MIC of 8 mg/L (to cover Gram-negative bacteria such as *E. coli*) was used during simulation analysis to review existing dosing recommendations.

Results

A one-compartment model with first-order absorption best described amoxicillin pharmacokinetics. An additional non-linear influence of GA and PNA on amoxicillin clearance was identified. Clearance (L/hour/kg) was 2·6-fold and 4·7-fold higher in neonates with a GA of 34 and 40 weeks, respectively, compared to 30 weeks. Oral bioavailability was 87%. A twice daily regimen of 50 mg/kg/day is superior to a three- or four times daily schedule in the first week of life, for both oral and intravenous administration. Dose adjustments are needed beyond the first week of life.

Discussion/Conclusion

This is the first combined population pharmacokinetic description of intravenous and oral amoxicillin in neonates, resulting in age-specific dosing recommendations. We conclude that neonates treated with oral amoxicillin reach adequate amoxicillin levels following a twice daily dosing regimen. Oral amoxicillin therapy could therefore be an adequate and more patient friendly alternative for neonates worldwide.

PHARMACOLOGICAL CHARACTERIZATION OF PHOTOCAGED HISTAMINE H_3 AND H_4 RECEPTOR AGONISTS

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Background

The photocage strategy enables precise, one-way spatio-temporal control of ligand bioactivity by removing a protective group using light to allow subsequent ligand interaction with the target of interest. The histamine H_3 and H_4 receptors are G protein-coupled receptors that are involved in cognitive-related processes and inflammatory responses, respectively. The purpose of this study is to characterize the newly developed photocaged compounds regarding pharmacological properties on H_3 and H_4 receptors.

Methods

The radioligand binding assay determined the binding affinity of ligands. Briefly, cell membranes expressing hH3R or hH4R were incubated with radioactive ligands in combination with a serial dilution of ligands for 2 hours before scintillation counting. A FRET-based cAMP biosensor was used to detect functional activity by transient transfection on intact cells.

Results

We have developed photocaged agonists for the H_3R and H_4R by protecting immepip and 4-methylhistamine, respectively, with a photo-responsive BODIPY group, resulting in a more than 10-fold decrease in receptor binding affinity. Illumination of BODIPY-caged immepip (VUF25657) compounds at 560 nm resulted in rapid uncaging within minutes as detected by LC-MS and restored binding affinity and efficacy in radioligand binding and a FRET-based cAMP biosensor. Light-induced uncaging of BODIPY-caged 4-methylhistamine (VUF25678) was confirmed by LC-MS analysis. However, low solubility in assay buffer prevented accurate assessment of the pharmacological parameters for VUF25678 and also prevents its application.

Discussion/Conclusion

In conclusion, BODIPY-based photocaging of histaminerigic agonists has proven to be an effective strategy to obtain a photocaged H_3 receptor agonist, that will serve as a new photosensitive GPCR tool for the spatio-temporal control of the H_3 receptor.

THE EFFECT OF NASAL CONGESTION ON THE BIOAVAILABILITY OF INTRANASALLY ADMINISTERED EPINEPHRINE IN HEALTHY ADULT SUBJECTS WITH SEASONAL ALLERGIES

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Background
Intramuscular (IM) administration of epinephrine is a first-line treatment of anaphylaxis. Intranasal (IN) epinephrine may offer a faster route of administration avoiding reluctance to IM injection and application error, yet nasal congestion may affect IN absorption.

Methods
In an open-label, 4-period study, 51 subjects with seasonal allergy received a single IN dose of 13.2 mg epinephrine (given in 2 consecutive sprays), with and without nasal congestion, as well as a single IM epinephrine injection by 2 modalities (0.3 mg by EpiPen® and 0.5 mg by manual syringe). IN sprays were administered in opposite nostrils. A nasal allergen challenge was performed to establish nasal congestion prior to IN dosing. Washout between IN epinephrine dosings was ≥ 14 days. Blood samples were collected and blood pressure and heart rate were measured out to 360 minutes postdose. Pharmacokinetic parameters included $AUC_{0\text{-}360}$, C_{max}, T_{max}.

Results
Geometric means for baseline-adjusted epinephrine $AUC_{0\text{-}360}$ and C_{max} for 13.2 mg IN were 34200 pg•min/mL and 458.0 pg/mL (with congestion) and 29680 pg•min/mL and 270.1 pg/mL (without congestion); the 70% increase in Cmax was significant. Following 0.5 mg and 0.3 mg IM doses, $AUC_{0\text{-}360}$ were 32400 and 16710 pg•min/mL, and C_{max} were 364.2 and 279.0 pg/mL, respectively. Median T_{max} were 15.1, 25.2, 45.0 and 21.5 minutes after IN dosing with and without congestion and after 0.5 mg and 0.3 mg IM dosing, respectively. Cardiovascular effects mirrored epinephrine levels. There were no serious or unexpected adverse effects.

Discussion/Conclusion

Nasal congestion enhances peak levels of IN epinephrine. Exposure after 13.2 mg IN epinephrine (with and without nasal congestion), however, was similar to that after 0.5 mg IM epinephrine by manual syringe, but greater than for the 0.3 mg IM dose (EpiPen®).

UNDERSTANDING THERAPEUTIC REASONING: INSIGHTS FROM COGNITIVE PSYCHOLOGY

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Background: Despite efforts to improve undergraduate clinical pharmacology & therapeutics (CPT) education, residents regularly make prescribing mistakes. To improve CPT education and daily prescribing, it is important to understand how therapeutic reasoning works. Some research on this topic has been done yet, but there are also new insights, for instance whether therapeutic reasoning and diagnostic reasoning are comparable? The aim of this study is to gain insight into the therapeutic reasoning process in order to improve CPT education and to optimize the prescribing process in practice.

Methods: The literature on therapeutic reasoning was reviewed.

Results: On the basis of literature on cognitive psychology and diagnostic and therapeutic reasoning, it can be assumed that when a patient is diagnosed, a primary, automatic response arises based on pattern recognition via therapy scripts (type 1 thinking). At some stage, this response is evaluated by the reflective mind (using metacognition) and, if incorrect or incomplete, an alternative response has to be formed through a slower, more analytical and deliberative process, namely, type 2 thinking (figure 1). After the correct therapy is chosen, new therapy scripts are developed through metacognition. Experienced physicians have more and richer therapy scripts, mostly based on experience and appreciation of the relevance of enabling conditions, such as patient characteristics, and therefore their type 1 response is more often correct.

Discussion/Conclusion: Metacognition (“thinking about thinking”) plays an important role in the entire therapeutic reasoning process and this should be recognized in CPT education. Both trainees and teachers should be aware of the possibility to monitor and influence these cognitive processes. More needs to be learned about therapeutic reasoning and how to encourage it.

OPTIMIZING PRE-NATAL BETAMETHASONE DOSING TO PREVENT FOETAL RESPIRATORY DISTRESS SYNDROME: A COMBINED PLACENTA PERFUSION AND PREGNANCY PBPK MODELLING APPROACH

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Introduction
Betamethasone (BETA) is standard care for women at risk of preterm delivery to prevent foetal respiratory distress syndrome. Maintaining a foetal plasma concentration higher than 1 ng/ml for 48 hours (h) is considered sufficient for lung maturation, whereas high foetal plasma levels are undesirable due to potential foetal toxicity, without added therapeutic benefit. The current dosing regimen of 2 intramuscular (IM) doses of 11.4 mg (2 ampuls) 24h apart, results in such excessive foetal concentrations. We aimed to optimize maternal BETA dosing using a pregnancy physiologically-based pharmacokinetic (p-PBPK) modelling approach.

Methods
p-PBPK modelling for alternative BETA regimens was performed in Simcyp. We predicted the dose-foetal exposure relationship for virtual subjects of 26-30, 31-35 and 36-40 weeks of gestation (n=100 per gestational group). Performance of the model was first verified in non-pregnant subjects. Subsequently the model was adapted to include physiological and anatomical changes in pregnancy and extended with placental transfer parameters. *Ex vivo* placenta perfusion experiments (n=3) were performed to derive placental transfer clearances. p-PBPK model predictions for maternal and foetal exposure were then verified against clinical data for the standard dose, after which alternative dosing regimens were explored in order to optimize the dosing regimen.

Results
The model adequately predicted plasma exposure in non-pregnant individuals with 72.5% of predicted-to-observed (p/o) PK ratios within 2-fold, 68.6% within 1.5-fold and 47.1% within 1.25-fold range. In placenta perfusion studies, BETA intrinsic unbound clearance values for maternal placenta uptake and efflux were 14.7 and 5.7 mL/min, and foetal placenta uptake and efflux values were 8.0 and 1.7 mL/min, respectively. After incorporation of these parameters in the pregnancy model, maternal and foetal plasma concentrations for the standard dosing regimen were adequately predicted with 76.3% of maternal p/o PK ratios within 2-fold range, 63.2% within 1.5-fold, and 44.7% within 1.25-fold range. Exploration of alternative dosing regimens indicated that 4 IM doses of 1.425 mg (1/4 ampul) BETA administered every 12h, will maintain 95% of simulated individuals for 48h above the minimal exposure target, while lowering foetal peak concentrations from 20.63 ng/ml (12.46 - 35.19, 5th and 95th percentile) to 4.16 ng/ml (2.40 - 7.05 5th and 95th percentile).

Conclusion
We provided model-based directions for improved BETA dosing during pregnancy. Next steps should focus on exploring the proposed dose in a clinical setting.

DIFFERENTIAL CYP3A ACTIVITY IN PATIENTS WITH METASTATIC PROSTATE CANCER AND OTHER SOLID TUMOURS: AN *IN VIVO* PHENOTYPING STUDY WITH MIDAZOLAM

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Background Patients with metastatic prostate cancer have a higher docetaxel clearance (Cl) compared to patients with other solid tumours, resulting in an 1.8-fold lower exposure for intravenous (IV) docetaxel and 2.8-fold oral docetaxel. Furthermore, patients with metastatic prostate cancer experience less neutropenia, suggesting that the difference in Cl might be clinically relevant. Docetaxel is predominantly metabolized by Cytochrome P450 3A (CYP3A). A difference in CYP3A activity between the two patient populations might explain the observed differences in docetaxel exposure.

Aims The aim of the study was to quantify CYP3A activity in patients with metastatic prostate cancer and patients with other solid tumours, by *in vivo* phenotyping using midazolam as a probe for CYP3A activity. CYP3A activity was defined as midazolam Cl.

Methods A prospective, interventional, pharmacokinetic study was conducted at the Netherlands Cancer Institute (NCT05518799). Patients could be included independently of their hormone-sensitivity status or disease-state as long as their World Health Organisation (WHO) performance score was ≤1. Patients with prostate cancer had to have castration levels of testosterone (<50 ng/mL). The use of drugs and herbs influencing CYP3A activity and smoking were prohibited 14 days before or within 5 half-lives before the start of the study. Patients received 2 mg oral midazolam and 1 mg IV midazolam on two consecutive days. Pharmacokinetic samples were collected predose, 15 min, 30 min, 1, 2, 4, and 8 h after administration. Midazolam Cl as well as the metabolic ratio of 1'-hydroxy midazolam to midazolam were determined.

Results A total of 9 patients were included in each group. The other solid tumour group consisted of colorectal carcinoma (n=4), melanoma (n=4), and small cell lung cancer (n=1). All patients were Caucasian. Oral midazolam Cl was 16% higher in patients with metastatic prostate cancer (mean ± SD; 87.22 ± 22.50 L/h) compared to patients with other solid tumours (75.00 ± 26.24 L/h; p=0.14). IV midazolam Cl was not significantly different between the two patients groups: 38.95 ± 8.89 L/h vs. 41.79 ± 13.71 L/h, respectively (p=0.73). The metabolic ratio of 1'-hydroxy midazolam to midazolam was also not significantly different between the two subgroups for oral administration (0.24 ± 0.08 vs 0.19 ± 0.16; p=0.73) and IV administration (0.12 ± 0.03 vs 0.09 ± 0.17; p=0.34). However, a difference in variability was observed.

Discussion/Conclusion Midazolam Cl was not significantly different in metastatic prostate cancer patients and patients with other solid tumours. Although, oral Cl was 16% higher in metastatic prostate cancer patients compared to patients with other solid tumours, this difference in midazolam Cl could not explain the observed 1.8 to 2.8-fold difference in docetaxel exposure. Future studies will be focused on alternative hypotheses regarding the clinical relevant difference in docetaxel exposure, such as differences in activity of liver transporters.

THERAPEUTIC DRUG MONITORING OF ANTIPSYCHOTIC DRUGS IN CHILDREN AND ADOLESCENTS: THE INTERNATIONAL MULTICENTRE SPACE 2: STAR RANDOMISED CONTROLLED TRIAL PROTOCOL

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Background
Antipsychotic drugs are an important part of the treatment of irritability and aggression in children with an autism spectrum disorder (ASD). However, antipsychotic use in children is associated with serious side effects, like significant weight gain and metabolic disturbances. In the SPACe study, we showed positive correlations between both risperidone[1] and aripiprazole[2] plasma trough concentrations and weight gain over a 6-month period. In the follow-up trial SPACe 2: STAR, we aim to research whether therapeutic drug monitoring (TDM) in clinical practice can prevent severe weight gain, while retaining clinical effectiveness.

Methods
SPACe 2: STAR is an international, multicentre, randomised controlled trial (RCT). 140 children aged 6 to 18 who are about to start risperidone or aripiprazole treatment for ASD related behavioural problems will be randomised into a TDM group or a care as usual (CAU) group. Participants will be assessed at baseline and 4, 10, 24, and 52 weeks follow-up. In the TDM group, physicians will receive dosing advice based on plasma levels of risperidone and aripiprazole and their metabolites at 4 and 10 weeks. Plasma levels will be measured in dried blood spots. The primary outcome will be BMI z-score at 24 weeks follow-up. Among the secondary outcomes are effectiveness, metabolic and endocrine laboratory measurements, extrapyramidal side effects, and quality of life.

Discussion/Conclusion
This will be the first RCT evaluating the effect of TDM of antipsychotic drugs in children and adolescents. Thus, our findings will be of great value in optimising treatment in this vulnerable population.

1. Kloosterboer SM, de Winter BCM, Reichart CG, Kouijzer MEJ, de Kroon MMJ, van Daalen E, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *Br J Clin Pharmacol*. 2021;87(3):1069-81.

2. Hermans RA, Sassen SDT, Kloosterboer SM, Reichart CG, Kouijzer MEJ, de Kroon MMJ, et al. Precision dosing of aripiprazole in children and adolescents: linking blood levels to weight gain and effectiveness. Submitted 2022.

OPTIMISING RISPERIDONE TREATMENT IN CHILDREN WITH AUTISM SPECTRUM DISORDER: A THERAPEUTIC DRUG MONITORING SIMULATION STUDY

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Background
Risperidone is often prescribed to children and adolescents with autism spectrum disorder (ASD) and comorbid irritability and aggression. In the SPACe study, we showed that sum trough concentrations of risperidone and its metabolite (9-hydroxyrisperidone) are positively correlated to weight gain and effectiveness. In the current study, we aim to determine a target range for risperidone sum trough concentrations that balances weight gain with effectiveness. In addition we will simulate the effect of therapeutic drug monitoring (TDM) to optimise treatment.

Methods
In a retrospective cohort (n=24 patients) from the SPACe study[1], the target window for risperidone leading to the smallest increase in body mass index z-scores (BMIz) while still retaining effectiveness as measured by the irritability subscale of the Aberrant Behavior Checklist (ABC-I) was determined. This target range was used to simulate the effect of TDM using a population PK model implemented in the software InsightRX. Dosing advice was based on blood concentration levels and administered dose at 12 weeks, to simulate if more patients would be on target at 24 weeks after start of treatment.

Results
We found that a risperidone sum trough target range of 3.5-7 µg/L would minimise increase in BMIz and optimise effectiveness. Dosing advice using TDM and a population PK model would lead to a larger proportion of patients achieving a concentration within the target range (62.5% vs 16.7%).

Discussion/Conclusion
Based on this simulation study, TDM could be a useful tool in optimising risperidone treatment for children and adolescents with ASD.

1. Kloosterboer SM, de Winter BCM, Reichart CG, Kouijzer MEJ, de Kroon MMJ, van Daalen E, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *Br J Clin Pharmacol*. 2021;87(3):1069-81.

DO INFANTS NEED A TWO TIMES HIGHER GENTAMICIN DOSE THAN NEONATES? A PBPK DOSE-FINDING STUDY

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Background: Gentamicin is a frequently used antimicrobial in paediatric patients. The Dutch Paediatric Formulary (DPF) recommends almost doubling its dose when a neonate becomes 29 days old (from 4 mg/kg/day to 7 mg/kg/day). Doubling the dose overnight is irrational, even when taking into account the higher plasma target levels that have been proposed for these ages. We used a physiologically-based pharmacokinetic (PBPK) modelling approach to propose rational dosing recommendations, based on predictions of target plasma exposure levels.

Methods: A PBPK model was used to predict gentamicin PK. Model performance was verified in adults, children and term neonates, based on visual predictive checks and predicted-to-observed PK parameter ratios. Ratios within 2-fold were considered acceptable. After verification of the model, we simulated the current DPF dosages as well as several other dosing scenarios and assessed the predicted peak and trough levels. Model-informed dosages were established for term neonates and infants, taking into account the recommended peak (8-12 mg/L for neonates and 15-20 mg/L for infants) and trough (<1 mg/L) levels.

Results: The PBPK model was able to capture gentamicin PK, as 82% and 91% of the predicted PK parameter values in the adult and paediatric population, respectively, were within two-fold of the observed values from literature. Simulations of current DPF dosages showed that peak levels in neonates and infants exceeded 12 and 20 mg/L, respectively. Trough levels were predicted to be below 1 mg/L in infants, but this was not the case in neonates younger than 21 days. For the most optimal dosing scenario, the dosing interval for term neonates should be extended from 24 to 48h, and the dose should be reduced from 4 to 3.5 mg/kg. For infants <1 year, a dose of 5 mg/kg every 24h is predicted to reach desired peak levels.

Discussion/Conclusion: PBPK modelling is a relevant tool for predicting drug PK. In this study, we successfully used the model to inform gentamicin dosing in term neonates and infants. The next step is to inform the editorial board of the DPF. They will assess the impact and consequences of implementing the model-informed dose, as well as its safety, efficacy and practicality.

ASSESSING THE PLACENTAL TRANSFER OF SOTALOL VIA *EX VIVO* HUMAN PLACENTA PERFUSIONS: A STEP-UP TOWARDS MODEL-INDFORMED DRUG DOSING IN PREGNANCY

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Background
Sotalol, a betablocker with antiarrhythmic effects, is used as a first-line transplacental treatment of foetal supraventricular tachycardia during pregnancy. The rate of placental transfer is an important determinant of foetal exposure and thus the efficacy of sotalol in the unborn child. The kinetics of placental sotalol transfer are difficult to study in a clinical setting. Physiology-based pharmacokinetic (PBPK) modelling allows to predict foetal exposure after maternal dosing based on human anatomical and physiological data in combination with *ex vivo* pharmacokinetic data.

Methods
To further characterize the placental handling of sotalol *ex vivo*, we performed dual-side perfused isolated human cotyledon experiments with term placentas, in closed-closed setting. The tissue was perfused for 3 hours with 1000 µg/mL sotalol in Krebs-Henseleit buffer. From this data transfer values were extrapolated to incorporate in a pregnancy PBPK model to allow maternal and foetal exposure predictions during sotalol treatment.

Results
After 3 hours of perfusion, maternal perfusate concentration had decreased from 1123 to 289 µg/mL and concentrations in the foetal buffer increased from 0 to 76 µg/mL. Hence, foetal concentrations only reached 7% of maternal levels at the end of the perfusion period. Transfer clearances derived from the *ex vivo* data were incorporated in Simcyp's pregnancy PBPK modelling platform and dosing of a single oral dose of 80mg sotalol was modelled to estimate maternal and foetal exposure. Maternal exposure was within 2-fold of reported literature plasma concentrations, but foetal exposure was underestimated.

Discussion/Conclusion
Sotalol displayed only limited transport across the placental barrier, over the time period investigated. Maternal model performance was accurate, however in vitro-to-in vivo extrapolation of sotalol needs further optimization to be able to predict accurate foetal exposure as well.

PRESCRIPTIONS OF NEWER GLUCOSE REGULATING AGENTS IN OLDER HOSPITALIZED PATIENTS WITH TYPE 2 DIABETES

Authors
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Background

GLP-1-analogues, DPP4-inhibitors, and SGLT2-inhibitors have become available to treat type 2 diabetes. Little is known about the extent to which these glucose regulating agents (GRA) are prescribed to older patients. We describe the prescription prevalence of these GRA in a clinical population of older patients with type 2 diabetes.

Methods

We performed a retrospective observational cohort study. All clinical admissions of patients who had one or more prescriptions for non-insulin GRA between 2017 and 2021 were selected. We analyzed prescription trends over the years and differences in prescription prevalence for frail and non-frail older patients, as well as for older (≥70 years) versus younger patients.

Results

A total of 7,659 admissions met eligibility criteria. In 11.5% of these admissions, one or more newer GRA were prescribed; GLP-1-analogues 1.6%, DPP4-inhibitors 7.3% and SGLT2-inhibitors 2.3%. Total prescription prevalence increased from 8.4% to 16.3% between 2017 and 2021 ($p<0.001$). GRA prescription prevalence was 11.1% (N=129) in admissions of frail patients versus 14.6% (N=344) in admissions of non-frail patients ($p=0.005$). The difference in prescription prevalence was highest for the SGLT2-inhibitors (4.2% versus 1.9%, $p=0.001$). GRA prescription prevalence was 15.0% in admissions of younger patients versus, 11.5% in admissions of older patients ($p<0.001$).

Discussion/Conclusion

The prescription prevalence of newer GRA in clinical admissions of older patients (≥70 years) increased from 2017 to 2021. The prevalence was lower in admissions of frail patients and older patients. These patients are possibly undertreated as a result of the lack of clear recommendations for older patients in guidelines and underrepresentation of these patients in clinical trials.

SMALLER NADROPARIN DOSE REDUCTIONS REQUIRED FOR PATIENTS WITH RENAL IMPAIRMENT: A MULTICENTER STUDY

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***** Both authors have contributed equally to this work**.**

Background

Guidelines vary in dosage recommendation for nadroparin in patients with renal impairment. Dutch guidelines advise 50 and 25% dose reduction of the registered dose (86 IE/kg twice-daily) in eGFR 15-29 and 30-60 mL/min respectively. Peak anti-Xa levels 0.5-1.0 IU/mL are suggested for twice-daily dosing. However, it is unclear which dosage results in anti-Xa levels of 0.5-1.0 IU/mL or in anti-Xa levels that are comparable to those of patients with eGFR >60 mL/min. We aimed to develop a prediction model to simulate dose ranges that result in similar anti-Xa levels compared to patients without renal impairment.

Methods

A retrospective observational cohort study was conducted in five hospitals. Patients ≥18 years of age, with an eGFR ≥15 mL/min were included. The first correct sample (i.e. 3-5h after ≥ 3rd nadroparin administration) per patient was included. Prediction models were developed using multiple linear regression. The Medical Research Ethics Committees United provided a waiver for informed consent (W20.055).

Results

770 patients were included. eGFR and mainly hospital affected the association between dose and anti-Xa level. Of the therapeutically dosed patients 41.6% of the anti-Xa levels were subtherapeutic. In patients with an eGFR 15-29 and 30-60 mL/min, dosages of 69.7% and 84.9% respectively, were needed to achieve anti-Xa levels similar to patients with an eGFR >60 mL/min (Table 1).

Table 1 Simulated nadroparin dosages according to hospital and eGFR

Hospital	N	eGFR	% of dose i.c.w. eGFR >60 ml/min
A (n=148)	24	15-29	84.8%
	50	30-60	85.3%
	74	>60	NA
B (n=64)	18	15-29	44.7%
	23	30-60	213.4%*
	23	>60	NA
C (n=155)	50	15-29	58.0%
	44	30-60	103.5%
	61	>60	NA
D (n=361)	50	15-29	80.8%
	66	30-60	99.5%
	245	>60	NA
E (n=42)	11	15-29	80.9%
	15	30-60	95.5%
	16	>60	NA
Weighted average (n=770)	153	15-29	69.7%
	198	30-60	84.9%
	419	>60	NA

eGFR estimated Glomerular Filtration Rate, i.c.w. In Comparison With, NA Not Applicable.
* Data from hospital B in patients with eGFR 30-60 ml/min were excluded from the weighted average as the simulated dosages were impossibly high.

Discussion/Conclusion

Anti-Xa targets were often not met in patients with eGFR >60 mL/min, and levels differed substantially between hospitals. This hampers the usefulness of anti-Xa based dosing for renally impaired patients. A better approach might be to target levels similar to patients with eGFR >60 mL/min. This is achieved by smaller dose reductions than currently advised.

SYSTEMIC EXPOSURE TO CISPLATIN AND PACLITAXEL AFTER INTRAPERITONEAL CHEMOTHERAPY IN OVARIAN CANCER

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Background

Treatment for advanced-stage epithelial ovarian cancer involves primary debulking surgery followed by adjuvant platinum-based chemotherapy. A major controversy concerns the route of administration which can be intravenous or intraperitoneal. Although chemotherapy is delivered directly into the abdominal cavity, intraperitoneal administration is associated with high incidence of systemic adverse events.

Method

This is a prospective pharmacokinetic study in patients with newly diagnosed advanced ovarian cancer who were treated with intraperitoneal administered cisplatin 100mg/m^2 and paclitaxel 60mg/m^2. Plasma and peritoneal fluid samples were obtained during the first treatment cycle. The systemic exposure to cisplatin and paclitaxel was determined and compared to previously published exposure data after intravenous administration. An exploratory analysis was performed to investigate the relation between systemic exposure to cisplatin and the occurrence of adverse events.

Results

Eleven patients were enrolled in the study. Pharmacokinetics of ultrafiltered cisplatin were studied in eleven evaluable patients. The geometric mean [range] peak plasma concentration (C_{max}) and area under the plasma-concentration time curve ($AUC_{0\text{-}24h}$) for cisplatin was 2.2 [1.8 - 2.7] mg/L and 10.1 [9.0 – 12.6] mg*h/L, with a coefficient of variation (CV%) of 14 and 13.0%, respectively. Pharmacokinetics of paclitaxel were available from six patients. The geometric mean [range] observed plasma concentration of paclitaxel was 0.06 [0.04 - 0.08] mg/L. Due to limited short-term sampling it was not possible to calculate a reliable AUC for paclitaxel in the plasma compartment. No correlation was found between systemic exposure to ultrafiltered cisplatin and adverse events.

Discussion/Conclusion

Systemic exposure to ultrafiltered cisplatin after intraperitoneal administration is high. Systemic uptake from the peritoneal cavity is highly drug dependent. In contrast to cisplatin, paclitaxel is very slowly absorbed from the peritoneal compartment. This study provides an explanation for the high incidence of systemic adverse events associated with high-dose cisplatin-based intraperitoneal therapy. However, in addition to a local treatment effect, the systemic ultrafiltered cisplatin exposure might also contribute to the survival benefit seen with intraperitoneal cisplatin-based chemotherapy in ovarian cancer.

NOVEL INSIGHTS INTO THE INTERACTION BETWEEN BCRP AND ANTIBIOTICS IN DIFFERENT SPECIES

Authors
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Background
Breast Cancer Resistance Protein (BCRP/ABCG2) is an ATP-binding cassette (ABC) efflux transmembrane transporter located on a variety of cells, playing a key role in maintaining the barrier function of organs. In the mammary gland it is upregulated during lactation and the most abundant efflux transporter known to be present in the blood-milk-barrier. BCRP is thought to be an important element in the oral availability, tissue distribution and elimination of different drugs and other xenobiotics. Its role in the excretion of xenobiotics into the milk of mothers and dairy animals is not yet fully known. In this research we look at the interaction of oxytetracycline, marbofloxacin, spiramycin and amoxicillin with human, bovine, caprine, and ovine BCRP and assess if interspecies differences exist. Knowledge of species differences are essential to investigate to allow for appropriate risk assessment in individual species.

Methods
Vesicular and Cellular transport assays
Transport activity was measured using Estrone-3-Sulfate in species-specific BCRP transfected vesicles (n>3). D-luciferin, oxytetracycline, marbofloxacin, spiramycin and amoxicillin accumulation was measured in stable transfected Human Embryonic Kidney (HEK)293 cells expressing human, bovine, ovine or caprine BCRP, or Enhanced Yellow Fluorescent Protein (EYFP) as control.

Results
We characterized human, bovine, caprine and ovine BCRP showing Km values of Estrone-3-Sulfate of 6,1 (95% CI 4,5-8,2); 10(7,1-15); 5,4(3,7-7,9); 7,9(5,8-11) uM, respectively. In addition we showed that we were able to measure transport activity by performing the cellular transport assay with D-Luciferin. We had significant transport in all species: Human 54%, Bovine 37%, Ovine 37%, Caprine 52% (p=0,0384; p=0,0002; p=0,0003; p=0;0256). Coming experiments we expect to present the transport of the different antibiotics by BCRP.

Discussion/Conclusion
Our results form the basis for future pharmacokinetic studies for species-specific transport of xenobiotics into milk. This information could be useful in risk assessment and guide new policies for antibiotic use in lactating woman and dairy animals.

PHARMACOLOGICAL CHARACTERIZATION OF H_1R AND H_3R SMALL MOLECULE PHOTOLIGANDS – REACHING BEYOND THE UV SPECTRUM

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Background Photopharmacological modulation of G protein-coupled receptors (GPCRs) offers new exciting ways to modify ligand on-target activity in a spatio-temporal way. One way to do this is introducing a photosensitive moiety to a pharmacologically active compound, hereby hindering its activity (photocaging). The active compound can then be irreversibly uncaged with light. On the other hand, having a photosensitive moiety (e.g. azobenzene), that can reversibly be modified with light, allows controlled toggling between an on- and off-state of a given molecule (photoswitching). However, most researched photoligands rely on UV light for photo-modulatory effects, which can be harmful for living cells. In addition, despite being lower in energy, longer wavelengths provide better tissue penetration, hereby opening doors for more efficient real-time photo-modulation of ligand activity.

Methods Radioligand binding, dynamic uncaging via confocal imaging, non-dynamic H_1R reportergene assays, (non) dynamic H_3R nBit-PKA complementation assays

Results

Compound	Receptor	pK_i ±SEM non-irradiated	pK_i ± SEM irradiated	ΔpK_i (irradiated – non-irradiated)
Deslo-caged	H_1R	6,8 ± 0,1	8,5 ± 0,1	1,7
VUF25946	H_3R	6,7 ± 0,0	7,4 ± 0,2	0,7
VUF25947	H_3R	9,3 ± 0,2	9,1 ± 0,2	-0,2
VUF26010	H_3R	9,1 ± 0,1	8,2 ± 0,1	-0,9
VUF26025	H_3R	7,7 ± 0,2	6,6 ± 0,1	-1,1
VUF26026	H_3R	8,6 ± 0,1	7,3 ± 0,1	-1,3

Table 1. Affinity values of photoligands obtained via radioligand binding experiments on either H_1R or H_3R-expressing membranes.

Discussion/Conclusion An in-house synthetized, red-shifted H_1R photocaged antagonist is shown to have more than 50-fold lower affinity than its uncaged counterpart, and can be uncaged in live-cell confocal imaging assays. In addition, we present a series of H_3R photoswitches, with photosensitive moieties ranging from UV to visible red light spectrum, and assess how these moieties influence their H_3R binding affinity. Our research shows not only that small histamine photoligand activity can be modulated by light, but also offers the potential of real-time on-target activity modulation of both H_1- and H_3R by light in living cells.

SUL138 SUPPORT OF MITOCHONDRIAL FUNCTION PRECLUDES VASCULAR AND KIDNEY DYSFUNCTION IN A MOUSE MODEL OF ENDOTHELIAL-SPECIFIC AGING

Authors
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Background
Vascular aging is marked by decreased nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signalling. This is partly caused by increased reactive oxygen species levels in endothelial cells (EC), believed to be produced by mitochondria. Here, we investigated the effect of chronic treatment with SUL138, an inhibitor of reverse mitochondrial electron transfer which reduces free electron spill-over, in a model of EC-specific aging. EC-specific deletion of DNA repair endonuclease *Ercc1* in mice (EC-KO) led to accelerated vascular aging features, marked by reduced endothelium-dependent (ED) NO-cGMP relaxation at 22 weeks of age.

Methods
EC-KO mice and corresponding littermates (LM) received SUL138 treated (30 mg/kg/day) (N=6 vs. N=6) or vehicle treated (0,0015 % ethanol) (N=11 vs. N=12) chow for 8 weeks (14-22 weeks of age). At the age of 21 weeks, animals were put in metabolic cages and 24 h urine was collected. At the age of 22 weeks, mice were euthanized. Thoracic aorta was used for wire myograph experiments to assess vascular function. Albumin/ creatinine levels were measured in 24h urine. Proteins (in RIPA buffer) and mRNA (in TRIzol) were isolated from kidney and abdominal aorta for Western Blot and qPCR.

Results
ED relaxation was decreased by 25 % (Emax) in EC-KO vehicles compared to LM vehicle mice (2-way ANOVA, $p<0,01$). Chronic treatment with SUL138 restored ED relaxation to LM vehicle treated level, driven by increased endothelium derived hyperpolarization (GLM, $p<0,01$). Protein expression of senescence marker p21 and oxidative stress marker 4-HNE was significantly increased (409 %; 266 % of LM) in EC-KO vehicle aorta compared to LM vehicle treated aorta and reduced after SUL138 treatment (51%; 82% of LM) (Kruskal Wallis test, $p<0,05$).

Vehicle treated EC-KO mice displayed polydipsia (5,1 vs. 3,1 ml in LM vehicles), polyuria (2,1 vs. 0,5 ml) and albuminuria (70,4 vs. 16,0 mg/g) which was normalized by treatment in EC-KO (3ml/day; 0,8 ml; 58 mg/g respectively). mRNA expression of inflammatory and senescence markers was 2-4-fold increased in EC-KO vehicle kidneys compared to LM vehicle treated kidneys. mRNA expression of inflammatory and senescence markers in SUL138 treated EC-KO mice was reduced to LM vehicle level (all: 2-way ANOVA, $p<0,05$).

Discussion/Conclusion
Chronic treatment with SUL138 from 14 to 22 weeks of age restored vasodilator function and precludes kidney dysfunction. Therefore, maintaining mitochondrial electron transfer might represent an effective treatment of vascular aging and accompanied kidney dysfunction.

PERIPHERAL AND CENTRAL VASCULAR FUNCTION ALTERATIONS CAUSED BY UNILATERAL ADRENALECTOMY IN RATS AND EFFECTS OF BPC 157 PENTADECAPEPTIDE

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Background
Small blood vessels and the endothelium seem to have an essential role in maintaining homeostasis. Unilateral adrenalectomy (uADX) is a procedure used in experimental and human contexts. Pentadecapeptide BPC 157 (BPC157) has been shown to have potent cytoprotective effects by modulating minor blood vessels. We described the effects of BPC157 on acute phases of uADX and explain the role of small blood vessels in compensatory mechanisms.

Methods
Deeply anesthetized male Wistar rats (200-250g) were submitted to left uADX. Acute effects in 15 min, 5h and 24h after surgery and pretreatment with 1 mL saline (control animals) or 1 mL of BPC-157 pentadecapeptide (BPC157) solution (1ng/L or 1ug /L) applied intraperitoneally were described with ECG, pathoanatomical, pathohistological, invasive blood pressure measurement, thrombosis in major blood vessels.

Results

As time passed, more prominent signs of vascular failure-related phenomena were evident. Major veins, brain and heart became more congested. Venous pressure rose while aortic pressure fell. ECG showed progression of disturbances as prolonged QTc interval. PHD assessment showed progressed signs of hemorrhage, congestion, and/or thrombosis centrally (brain) and peripherally (viscera, heart, lungs). Macroscopically and histologically, the adrenal gland was pronouncedly hyperemic with BPC157 treatment, while control group had an initial physiological hyperemia that converted into congestion. Cytoprotection by BPC157 showed a beneficial effect on these changes counteracting the above-mentioned pathologies.

Discussion/Conclusion

uADX causes a vascular failure-induced peripheral and central syndrome similarly to other noxious procedures. Cytoprotection by BPC157 had a curative role on the syndrome. These findings have meaningful clinical implications for acute uADX as thrombosis, hematoma, and hemorrhages present the main complications of this procedure in humans which could be antagonized with agents such as BPC157. Also, acute compensation phases of the reminent adrenal gland have been modified with BPC157, which further elaborates this elusive physiological response which is vascular in nature. Gene expression analysis of selected genes (aVEGF, bFGF, PDGF, iNOS and eNOS), NO and oxidative radical levels in reminent adrenal gland, brain, and stomach will further elaborate these findings.

INVESTIGATING THE ROLE OF CLASSES OF ANTIHYPERTENSICE DRUGS ON BLOOD PRESSURE VARIABILITY

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Background

Blood pressure variability (BPV) can be an important determinant in the complex relation between cardiovascular disease and Alzheimer's disease. Recently, multiple studies have shown the prognostic value of BPV as a risk factor for cognitive impairment or dementia. It has been suggested that different types of antihypertensive drugs can have varying effects on BPV. This study investigates the association between different antihypertensive drug classes (AHD) and BPV in memory-clinic patients.

Methods

This is a cross-sectional study that includes patients with cognitive complaints, ranging from subjective memory complaints to (Alzheimer's) dementia. All patients visited the memory clinic of the Radboud Alzheimer Centre and performed home blood pressure measurements. The main study parameter is day-to-day blood pressure variability, defined by the within-subject SD of all measurements performed by a subject in a period of 7 days. Four AHD classes were defined: calcium antagonists, diuretics, beta blockers and ACE or ARB. The association between BPV and AHD class was assessed using a linear regression model.

Preliminary Results

The study includes 200 patients who visited the memory clinic and performed home blood pressure measurements. Of those patients, 112 were treated with an antihypertensive drug. Baseline characteristics show an average age of 74 (SD 8.6) and 66% was female. Statistical analyses concerning the association between AHD and BPV is in progress and will be final before the conference.

Discussion/Conclusion

Blood pressure variability (BPV) is a risk factor for cognitive impairment or dementia. Assessing the influence of blood-pressure treatment on BPV is therefore highly relevant. This is the first study investigating the association between BPV and antihypertensive drug classes. The study as at its final stage with results ready before the conference.

QUALITY OF REGISTRATION OF THE CONTRAINDICATIONS MORBID OBESITY AND BARIATRIC SURGERY AND THE EFFECT ON THE NUMBER OF DRUG RELATED PROBLEMS

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Background
As a result of pharmacokinetic changes, individuals with morbid obesity and/or with a history of bariatric surgery may require dose adjustments and additional monitoring while other drugs should be avoided. To enable medication surveillance, correct registration of these patient characteristics in the Hospital Information System (HIS) is essential, as inadequate registration might lead to undetected Drug Related Problems (DRPs). The primary objective is to determine the quality of registration of the contraindications morbid obesity and bariatric surgery, defined as the percentage of correct registrations, in the HIS. The secondary objective is to determine the percentage of patients with a DRP in the group with a missing *versus* correct registration. Also, the type of DRPs and the medication involved are determined.

Methods
A prospective cohort study was performed. In patients admitted to the hospital that were identified as morbidly obese and/or with bariatric surgery using a validated algorithm, registration of the contraindications was evaluated. Subsequently, patients records were reviewed for DRPs using the automatic medication surveillance in the HIS followed by manual review. The identified DRPs were categorized and intervened drugs were registered.

Results
In total 206 patients were included (113 morbid obesity, 72 bariatric surgery and 21 both). Overall, in 23.8%, the contraindications were correctly registered. A DRP occurred in 15.3% *versus* 2.0 % of patients without and with registration of the contraindications, respectively. The most common DRP in morbid obesity was underdosing (e.g. antibiotics) versus prescription of a contra-indicated drug (e.g. NSAID) in bariatric surgery patients.

Conclusion
The quality of registration of bariatric surgery and/or morbid obesity as contraindication in the HIS is low, which is associated with a higher risk of DRPs.

A PROSPECTIVE STUDY ON THERAPEUTIC DRUG MONITORING OF ORAL TARGETED THERAPIES IN ONCOLOGY − UPDATED RESULTS

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Background Although oral targeted therapies in oncology show high interpatient variability in pharmacokinetics, resulting in overdosing (>15%) and underdosing (30%) of patients, the one-size-fits-all approach is still currently used. Considering the established exposure-response and exposure-toxicity relationships for many of these drugs, this could potentially lead to increased toxicity and decreased efficacy. Therapeutic drug monitoring (TDM) is a form of personalised medicine, with individual dose adjustments based on measured drug-levels, and could be a way of addressing these issues.

Methods This ongoing[1] dynamic prospective study (NL6695) focusses on the feasibility, efficacy and tolerability of TDM of multiple oral targeted therapies in oncology. Pharmacokinetic (PK)-levels are measured at 4-8-12 weeks after starting treatment and every 12 weeks thereafter. Recommendations are given based on established efficacy targets and, if not available, the average mean C_{min} of the approved dose is used. Recommended interventions include dose adjustment, intake with food, splitting intake moments, emphasizing compliance and adjusting interacting medication. Intervention is defined as successful if there is no dose limiting toxicity within one month and a PK-level above target after the intervention.

Results As per 1 January 2023, 1006 patients have been included from 14 hospitals using 1 of 24 different oral targeted therapies. Largest cohorts are abiraterone (n = 189), imatinib (n = 165), sunitinib (n = 112) and pazopanib (n = 106). From 902 evaluable patients, 41.6% (n = 375) had all PK-levels above target and 58.4% (n = 527) had a PK-level below target. A PK-guided intervention was possible in 55.9% (n = 295) of this group, and was successful 68.8% of the time. Of all patients with a PK-level below target, intervention was successful in 38.5%. This resulted in a 23% gain in patients with PK-levels above target, with a total of 64.6% (n = 578). Interventions were not successful due to persisting low PK-levels (n = 51), toxicity after intervention causing decrease of dose (n = 27) or no measurement after intervention (n = 14).

Discussion/Conclusion This study shows that TDM is feasible for oral targeted therapies in oncology. PK-guided intervention was successful in 38.5% of all patients with a PK-level below target. This resulted in a 23% gain in patients with PK-levels above target. However, the efficacy of TDM for these oral targeted therapies still needs to be evaluated, and for the biggest cohorts this evaluation will follow in future reports.

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LINKING PHARMACOKINETICS OF IBOGAINE AND ITS METABOLITES WITH CARDIAC AND CEREBELLAR SIDE EFFECTS AND EFFECTS ON WTIHDRAWAL IN DETOXIFYING OPIOID USE DISORDER PATIENTS

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Background
Ibogaine is a hallucinogenic drug that may be used to treat opioid use disorder (OUD). The relationships between ibogaine (and its metabolites) pharmacokinetics and opioid withdrawal severity and side effect are unknown. We aimed to study this relationship in patients with OUD undergoing detoxification supported by ibogaine, and explored alternative dosing regimens *in silico*.

Methods
The study was performed in 14 subjects with OUD. They received a single dose of 10mg/kg ibogaine-HCl. Plasma concentrations of ibogaine, noribogaine and noribogaineglucuronide were measured during 24 hours after administration. CYP2D6 genotyping was performed to obtain a CYP2D6 activity score. Clinical outcome measures were QTc prolongation, cerebellar ataxia and opioid withdrawal. Pharmacokinetic analysis was performed by means of non-linear mixed effects modelling. The relationship between individual pharmacokinetics and effects was explored.

Results

The biotransformation of ibogaine to noribogaine was related to CYP2D6 genotype ($p<0.001$) The basic clearance (at an activity score of 0) of ibogaine was 0.82 L/h. This increased with 30.7L/h for every point of activity score. The relation between ibogaine plasma concentrations and QTc was best described by a sigmoid E_{max} model. Spearman correlations were significant ($p<0.03$) for ibogaine but not noribogaine to QTcF ($p=0.109$) and cerebellar effects ($p=0.668$); neither correlated with the severity of opioid withdrawal symptoms. *In silico* modelling predicted 0.1 mg/kg as a potentially safe dose with minimal QTc prolongation.

Discussion/Conclusion

The clearance of ibogaine is strongly related to CYPD2D6 genotype. Ibogaine cerebellar effects and side effects (QTc time) depend on systemic exposure. Lower ibogaine doses might be safer and need further investigation.

RISPERIDONE-INDUCED WEIGHT GAIN AND ALTERATIONS IN APPETITE HORMONES IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER

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Background
Risperidone, while efficacious in reducing irritability and hyperactivity in children with autism spectrum disorder (ASD), is associated with significant weight gain. Although weight gain is multifactorial, metabolic and endocrine changes may play an essential role in this process. This study explores the association between appetite hormones and weight gain over time in relation to risperidone exposure.

Methods
In the prospective SPACe study, we collected blood samples in risperidone-treated children with ASD. In addition to the risperidone and 9-OH-risperidone levels (sum C_{trough}), we determined the appetite hormones leptin, bioleptin, neuropeptide-Y (NPY), gastric inhibitory peptide (GIP), insulin, and glucose levels at the fasting state, before the start, and at 12 and 24 weeks of treatment. We used Wilcoxon's two-tailed signed-rank test to evaluate the differences in the parameters between distinctive time points.

Results
Sixteen patients (68.75% boys, mean age 11.4 yr, and mean body weight 42.8 kg) were included. Significantly elevated levels of bioleptin and insulin, and homeostasis model assessment insulin resistance (HOMA-IR) index ($p<0.05$) were found in the first 12 weeks, followed by a trend toward a plateau at 24 weeks. The levels of leptin ($p=0.06$) and NPY ($p>0.1$) increased between baseline and 12 weeks. GIP levels showed a downward trend ($p>0.1$) in the first 12 weeks followed by a normalization at 24 weeks. A concomitant increase in the risperidone sum C_{trough}, and BMI z-score was observed ($p<0.05$).

Discussion/Conclusion
In risperidone-treated children and adolescents, we have observed alterations in certain appetite hormones, despite a relatively small sample size.

THIOSULFATE SULFURTRANSFERASE DEFICIENCY PROMOTES CEREBRAL CORTICAL OXIDATIVE DISTRESS RESULTING IN ANTIOXIDANT SYSTEM DYSFUNCTION

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Background
Dementia affects 55 million people around the world. Oxidative stress is a contributor to neurodegeneration along with the accumulation of amyloid and tau proteins. Thiosulfate sulfurtransferase (TST, EC 2.8.1.1) is a mitochondrial rhodanese that uses thiosulfate as a substrate to detoxify cyanide. Its advantageous properties are linked to sulfide metabolism, antioxidant response, and mitochondrial respiration, all of which are vital biological safeguards under oxidative stress. The function of TST during oxidative stress remains unknown.

Methods
Control C57BL/6J (wild type; WT) and Tst-/- mice's brains were extracted, and the cortex of each animal's brain was examined for antioxidant enzymes and OXPHOS protein by immunoblotting, anti-oxidant activity levels by biochemical assay, and mitochondrial function by high-resolution respirometry. Reactive oxygen and reactive sulfur species were measured using fluorescent probes. A luminous assay was used to determine the total ATP level. Nrf2-keap1 signalling pathway were detected via qRT-PCR.

Results

When compared to C57BL/6J mice, Tst-/- mice showed significant increased thiosulfate levels in the plasma and urine. The cortex of Tst-/- animals showed lower amounts of H2S, higher levels of polysulfides (H_2S_n), and a dysregulated pathway downstream of H_2S as shown by a markedly lower GSH/GSSG ratio. In tandem with decreased OXPHOS complex I and IV protein and enhanced Complex IV respiratory capability, total ATP levels rose in the cortex of Tst-/- mice. As OXPHOS products, H_2O_2 and O_2 levels were higher in the cortex of Tst-/- mice than in C57BL/6J animals. Comparing Tst-/- animals to C57BL/6J mice, SOD activity was lower in the cortex of the Tst-/- mice. Compared to Tst-/- animals, catalase activity was 10% higher in the cortex of Tst-/- mice. Lastly, the Nrf2-keap1 signalling pathway also showed dysregulation in the Tst-/- mice.

Discussion/Conclusion

Overall, our study revealed that TST deficiency promoted dysregulation of the reactive species interactome through both ROS and RSS polysulfides overgeneration coupled with mitochondrial OXPHOS remodelling and antioxidant elements dysregulation.

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE PHARMACODYNAMICS AND PHARMACOKINETICS OF ORAL AND INTRAVENOUS S-KETAMINE IN HEALTHY VOLUNTEERS

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Background
Intravenous Ketamine (KetIV) demonstrates rapid antidepressant efficacy after single administration, which is not sustained, in patients with Treatment Resistant Major Depressive Disorder (TR-MDD)[1]. This makes maintenance therapy necessary, whilst repeated IV administration is burdensome. Alternatively, oral ketamine (KetPO) is under investigation in patients with TR-MDD[2]. Little is known about the pharmacokinetic(PK)-profile of KetPO, even though extensive first-pass metabolism is expected to alter the ratio of ketamine (Ket) versus norketamine (Nor) significantly for KetPO[3], compared to KetIV, raising questions on KetPO's pharmacological profile in terms of safety and efficacy. The aim of this study was to characterize the PK, safety and pharmacodynamic (PD) profile of KetPO and KetIV.

Methods
A randomized, double blind, double dummy, placebo-controlled, 4-way cross-over study was conducted with esketamine. KetPO 0.2mg/kg and 0.45mg/kg, and a 40 minute KetIV 0.4mg/kg infusion were administered to 16 healthy male and female volunteers. PK and adverse events (AE) were collected, and PD characterized with a CNS test battery (Neurocart), quantitative electroencephalography (qEEG) and Mystical Experiences Questionnaire (MEQ30). PD measurements were analysed up to 6 hours post dose with a mixed model analysis of covariance with treatment and period as fixed factors and subject as random factor.

Results
The mean Cmax (ng/ml) plasma concentrations for Ket and Nor were 9.8 and 62.0 (KetPO, 0.2 mg/kg), 22.7 and 127.3 (KetPO, 0.45 mg/kg), and 145.5 and 55.2 (KetIV), respectively. Dissociation, euphoria and nausea/vomiting occurred in up to 75% of subjects receiving KetIV, while euphoria was reported in 12.5% and 31.3% for 0.2 mg/kg and 0.45 mg/kg KetPO, respectively, and nausea/vomiting was absent with KetPO. Compared with placebo, KetIV significantly reduced saccadic peak velocity, smooth pursuit eye movements, adaptive tracking, Digit Symbol Substitution Test (DSST) total number of correct responses, visual analogue scale (VAS) alertness, EEG alpha, beta and delta power, and increased body sway, DSST average response time, VAS feeling high, mood and psychomimetic effects, and MEQ30. KetPO 0.45 mg/kg significantly decreased smooth pursuit eye movements, EEG alpha, beta and delta power, and increased VAS feeling high, while 0.2 mg/kg lacked PD effects.

Discussion/Conclusion
At similar Nor plasma levels for KetIV and KetPO 0.2 mg/kg (62.0~55.2 ng/mL), the former demonstrated 14.5 times higher Ket plasma levels compared with the latter. Moreover, KetIV was associated with a distinct PD profile and was less well tolerated than either KetPO 0.2 mg/kg or 0.45 mg/kg, indicating that Ket and not Nor mediates psychomimetic effects and unwanted side-effects associated with ketamine. Although KetPO demonstrates superior safety and tolerability, its antidepressant efficacy, however, remains to be established. Our data support safety of KetPO up to 0.45 mg/kg to further investigate its efficacy in patients with TR-MDD.

A HIGHER RED BLOOD CELL METHOTREXATE POLYGLUTAMATE 3 CONCENTRATION IS ASSOCIATED WITH AN INCREASED METHOTREXATE DRUG-SURVIVAL IN PATIENTS WITH CROHN'S DISEASE

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Background

There is an unmet need to predict and monitor methotrexate (MTX) response in patients with Crohn's disease (CD). MTX-polyglutamates (MTX-PGs) in red blood cells (RBC) are potential markers for response and a therapeutic drug monitoring (TDM) tool. Our objectives were to investigate the relationship between MTX-PGs and efficacy and identifying predictors of response in CD patients treated with MTX monotherapy.

Methods

In a multicenter prospective cohort study, CD patients starting subcutaneous (s.c.) MTX without biologics were included and followed up for 12 months. Potential predictors of response were measured at baseline. Primary outcome was either MTX s.c. discontinuation or initiation of step-up therapy. Secondary outcomes included fecal calprotectin (FCP) and Harvey Bradshaw Index (HBI). At week 8,12,24,52 or at discontinuation RBC MTX-PGs, FCP and HBI were measured.

Results

Eighty CD patients were included (mean age 55±13y, 35% male) with a median FCP of 268µg/g (IQR 73-480). After 12 months, 21 patients were still on MTX s.c. monotherapy, 21 patients stopped because of disease activity, 29 because of toxicity, 4 because of both (5 patients censored).
MTX-PG_3 was the most abundant subspecies (median 51 nmol/L (IQR 37-62) at week 12) and associated with a higher MTX survival rate (HR 0.98, 95% CI 0.971-0.999). For every 10 nmol/L increase in MTX-PG_3, the rate of MTX discontinuation decreased with 14%. A higher MTX-PG_3 was associated with a lower FCP (1 nmol/L increase gives 3 µg/g (SD: 1) decrease in FCP) as well as biochemical response (FCP ≤ 250 µg/g: OR 1.1, p=0.03). There was no association between MTX-PG and HBI.
A higher HBI at baseline was associated with MTX discontinuation (HR 1.08, 95% CI 1.02-1.16). Predictors of discontinuation because of active disease were male sex (3.83, 1.62-9.05), higher eGFR (1.06, 1.02-1.09), higher HBI (1.12, 1.02-1.23) and lower plasma folate (0.94, 0.88-0.99). Sex and plasma folate were not correlated with HBI. No cause specific hazards for stopping MTX because of toxicity were identified.

Discussion/Conclusion

TDM using RBC MTX-PG_3 concentrations could be feasible since MTX-PG_3 is related to better MTX drug survival and decreased FCP levels in patients with CD.

PHOTOSWITCHABLE ANALOGUES OF THE PDE5 INHIBITOR SILDENAFIL

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Background

Photoswitches are molecules that undergo a reversible conformational change upon exposure to light of a certain wavelength. Coupling this conformational change to a large functional change presents the possibility of focusing drug action with temporal and spatial precision [1].

Sildenafil (Viagra) is a potent and selective inhibitor of PDE5, a phosphodiesterase that plays an important role in the regulation of blood flow in the penis [2].

Here we describe an in vitro functional analysis of Sildenafil analogues in which 4-methylpiperazin-sulfonamide is replaced by an azobenzene photoswitch at either the ortho-, meta-, or para- position.

Methods

Inhibition of the PDE5A enzyme was measured using a fluorescence polarisation based PDE5A1 Assay Kit (BPS Bioscience, art. 60351). The assay was performed following the standard protocol [3]. Compounds were illuminated using a Sutter Instruments Lambda LS with a 360 nm filter and light intensity of 0.93 mW/mm^2. Fluorescent polarisation was measured in a PHERAstar FS plate reader (BMG LABTECH) using the FP 485 520 520 optic module.

Results

The Sildenafil analogue VUF25334 with an azobenzene photoswitch in the para- position was able to inhibit PDE5 with the same potency as Sildenafil (pK_i=8.2) when in the *cis*-form (illuminated). In the *trans*-form (dark), the pK_i was reduced to 7.2 (Table 1). For analogues with the azobenzene photoswitch in either the ortho- or meta- position (VUF25333 and VUF25334 respectively) potency was lost for both *cis*- and *trans*- forms with pK_i values less than 6 (Table 1).

Compound	Dark	Illuminated	Δ pKi
Sildenafil	8.0 ± 0.3	8.2 ± 0.2	+0.2
VUF14663^{scaffold}	7.4 ± 0.2	7.2 ± 0.1	-0.2
VUF25333^{ortho}	5.4 ± 0.3	4.9 ± 0.2	-0.6
VUF25385^{meta}	5.6 ± 0.4	5.5 ± 0.1	-0.1
VUF25334^{para}	7.2 ± 0.1	8.2 ± 0.2	+1.1

Table 1: pKi ± SEM (n≥3) at human PDE5A1 measured using a fluorescent polarization based PDE5A1 assay.

Discussion/Conclusion

We have generated VUF25334, a functionally photoswitchable Sidenafil analogue and pharmacological tool useful for future studies into the photo-regulation of drug action in vivo.

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DIGIFAB® AND FREE DIGOXIN ELIMINATION IN A PATIENT WITH A COMBINED DIGOXIN/METFORMIN INTOXICATION ON CVVHD

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Background/case
Digoxin immune antigen-binding fragments (DigiFab®) are recommended in the treatment of severe digoxin intoxication, but haemodialysis is not recommended [1,2]. Thus, little is known about dosing and pharmacokinetics of DigiFab® during continuous venovenous hemodialysis (CVVHD). We admitted a 70 year old male with nausea and bradycardia (29 bpm) as a sign of severe digoxin intoxication (total digoxin concentration 4,9 µg/L) and a metformin induced lactic acidosis (lactate 14mmol /L, pH 7.24) Both intoxications were thought to be the result of acute kidney injury (serum creatinine 500 µmol/L). DigiFab® (80mg) was administered to counteract toxic digoxin effects, while CVVHD was started to mitigate the severe metabolic acidosis.

Methods
We measured free and total concentrations on T=7 h; T=26 h; T=50 h and T=74 h after DigiFab® administration. Total concentrations included both free and DigiFab® bound digoxin. Concentrations were measured with an Abbott immunoassay. Free concentrations were determined by filtration.

Results
Free digoxin concentrations were 0.1; 0.9; 1.16 and 0.84 µg/L at T=7, T=26, T=50 and T=74 hours after DigiFab® administration. The total digoxin concentrations were 10.5; 6.2; 2.4 and 2.2 µg/L at the same times respectively.

Discussion/Conclusion
DigiFab® is excreted in urine with a half-life of 20-30 hours (bound to digoxin) [3], rising to 100 hours or more in AKI [2]. Extracorporeal elimination of DigiFab® by CVVHD is unlikely due to the molecular weight of 50kDa, which is too big to permeate through the 30kDa filter membranes [4,5,6]. After an initial increase in total digoxin concentration, a fast decrease was observed in the first 43 hours. This could reflect clearance of DigiFab® by a (partially) preserved intrinsic renal function or clogging of DigiFab® in the CVVHD filter. Free concentration of digoxin increased, suggesting redistribution of digoxin not bound to Fab antibodies from tissues into the circulation. This rebound effect, that occurs in chronic intoxication, can cause re-intoxication. This effect is expected within 24 hours in normal renal function, but in renal insufficiency could occur after >130 hours [2]. We observed a rebound effect up until 50 hours after administration of DigiFab®. Current guidelines do not recommend haemodialysis in treatment of digoxin intoxication, although free digoxin could be eliminated via CVVHD [6,7]. Our observed increase in free digoxin concentration did not result into toxic concentrations. Hypothetically, CVVHD could have blunted the redistribution effect. In our patient on CVVHD treated with DigiFab®, total digoxin concentrations dropped faster than expected. However, either remaining DigiFab® or elimination of free digoxin by CVVHD or preserved renal function were adequate to prevent re-intoxication by rebound effect.

References available on request

LABEL-FREE DETECTION OF PROSTAGLANDIN TRANSPORTER (SLCO2A1) ACTIVITY USING A TRACT ASSAY

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Background

The prostaglandin transporter (PGT, SLCO2A1) mediates transport of prostanoids (a.o. prostaglandin E2 (PGE_2)) into the cells to promote their degradation. Overexpression of PGT leads to low extracellular PGE_2 levels and has been linked to impaired wound healing of diabetic foot ulcers[1]. Inhibition of PGT would be beneficial, however, there are currently no high-through screening assays for this transporter. Here we developed a label-free impedance-based assay for PGT that measures transport activity through receptor activation (TRACT).

Methods

Label-free impedance-based TRACT measurements were recorded on intact cells using the xCELLigence real-time cell analyzer. Here, activation of prostanoid receptors EP3 or EP4 with PGE_2 leads to changes in cell morphology. Uptake of PGE_2 by PGT will reduce extracellular PGE_2 levels and thereby attenuated the response of co-expressed EP3 or EP4 receptor. Thus, PGT activity is detected as a change in receptor activity. To this end, HEK293-JumpIn-SLCO2A1 cells with doxycycline (dox)-inducible SLCO2A1 expression were transfected to express prostanoid receptors EP3 or EP4 and induced or non-induced cells were pretreated with inhibitor or vehicle prior to stimulation.

Results

Induction of PGT expression on EP3 or EP4 expressing HEK293-JumpIN-SLCO2A1 cells results in over 10-fold reduction in potency of PGE_2 (Figure 1). Potency was recovered upon inhibition of the PGT-mediated PGE_2 uptake with PGT inhibitor olmesartan. The results confirm that prostanoid receptor activity can be used as a measure of PGT activity. In addition, we were able to study PGT activity in Huh-7 cells endogenously expressing SLCO2A1 and EP4R.

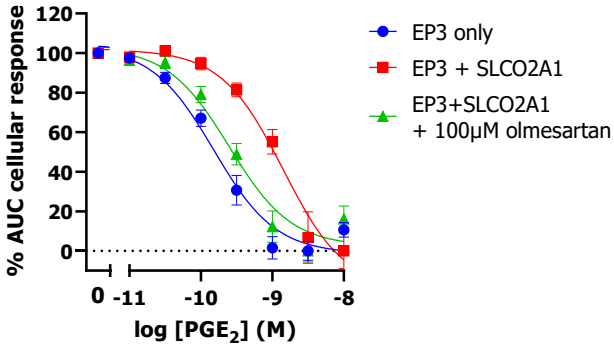

Figure 1. Concentration response curves of the influence of PGT co-expression on EP3 receptor activity as measured by xCELLigence. Induced and non-induced HEK293-JumpIn-SLCO2A1 cells expressing EP3 receptor were pretreated with vehicle or PGT inhibitor olmesartan for 1 hr prior to stimulation with PGE_2.

Discussion/Conclusion

An impedance-based TRACT assay was established that measures prostaglandin transporter (SLCO2A1) activity through prostanoid receptor signaling. This will enable a novel way to better study the wound healing capacity of SLCO2A1 inhibition on a cellular level.

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EXPOSURE-RESPONSE ANALYSES OF OLAPARIB IN REAL-LIFE PATIENTS WITH OVARIAN AND BREAST CANCER.

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Background

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor; this enzyme plays a role in the base excision repair of DNA single-strand breaks. Inhibition of this enzyme leads to accumulation of DNA single-strand breaks, what ultimately leads to tumour cell death. Olaparib is given in a fixed dose of twice-daily 300 mg in patients who are diagnosed with ovarian, breast, prostate or pancreatic cancer and has a high interpatient variability in pharmacokinetic exposure.

The objective of this study was to investigate whether pharmacokinetic exposure of olaparib is related to efficacy and safety in a real-life patient cohort.

Methods

A longitudinal observational study was conducted with all participating patients who were treated with olaparib. Exposure-efficacy analyses were conducted in patients receiving olaparib maintenance therapy for platinum-sensitive recurrent ovarian cancer and did not participate in a clinical trial. Patients with other indications were excluded in this analyses, because of difference in treatment setting ((neo)adjuvant vs maintenance).

A reverse Kaplan-Meier curve analyses was used to explore the relationship between olaparib exposure, measured as (calculated) minimum plasma concentrations (C_{min}) and efficacy, measured as progression free survival (PFS). Univariate and multivariate cox-regression analyses were performed.

Exposure-toxicity analyses were conducted in all patients (ovarian- and breast cancer patients) treated with olaparib. The median C_{min} of patients who experienced toxicity was compared with patients who did not experience any toxicity.

Results

Thirty-five patients were included in the exposure-efficacy analyses, with a median olaparib C_{min} of 1514 ng/mL. There was no statistical significant difference in PFS of patients below and above the median C_{min} concentration of olaparib (median PFS 10.0 months and 14.1 months, respectively), with a hazard ratio of 1.06 (95% confidence interval: 0.46 – 2.45, p=0.9)).

In total, 58 patients were included in the toxicity analyses of which 25 patients experience dose limiting toxicity. For seven patients pharmacokinetic samples of olaparib were available at the time the toxicity occurred, and these patients had a higher median C_{min} of olaparib in comparison with patients who had not experienced any toxicity (median C_{min} of 2118 ng/mL n=7 and median C_{min} of 1292 ng/mL n=33, respectively), but it was not statistically significant (p=0.069).

Discussion/Conclusion

This study shows that exposure of olaparib is not related to PFS, and the relationship between exposure and toxicity could not be confirmed, possibly due to small patient numbers. This highly suggests that the approved dose of olaparib yields sufficient target inhibition in the majority of patients. Therefore, monitoring C_{min} levels of olaparib to identify patients who have a low exposure, may not lead to better treatment effect, but monitoring C_{min} levels of olaparib can identify those patients who are overdosed and could be at risk of an adverse event.

KILLING ME UNSOFTLY: COLCHICINE A POTENTIAL SAVIOR OF ARTERIAL STIFFNESS

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Background
Vascular aging is an important determinant of cardio/cerebrovascular diseases. Several factors have been considered causal to vascular aging, among which chronic low-grade inflammation. However, there is a paucity of data on the potential effectiveness of anti-inflammatory therapies in prevention of cardiovascular aging. We hypothesized that long-term therapy with colchicine, a well-known anti-inflammatory agent, inhibits persistent vascular inflammation, improves endothelium function, and hence decelerates vascular ageing.

Methods
We performed experiments in vascular age-accelerated mouse models based on smooth muscle-selective Ercc1 DNA repair gene excision (SMC-Ercc1KO), treated with colchicine (0.1mg/kg/day) or vehicle at the age of 10 weeks and for 3 months. In-vivo/In-vitro vascular, cardiac and endothelial function were assessed. To shed light on clinical translation of our findings, incident colchicine users from the population-based Rotterdam Study cohort were frequency-matched (1:2) to non-users based on age, sex, and prevalent cardiovascular diseases.

We used a linear regression model adjusted for hypertension, diabetes, co-medications and baseline lipid profile markers to assess the effectiveness of colchicine on longitudinal changes of carotid intima-media thickness (cIMT).

Results
In the mouse study, aging of SMC increased arterial stiffness, as witnessed by increased pulse wave velocity (PWV) in SMC-Ercc1KO than in wild-type littermates (WT) at the age of 22 weeks ($p<0.01$). Colchicine therapy for 12 weeks resulted in decreased PWV levels compared to the placebo group ($p<0.01$) and normalized it to the WT levels. Nitric oxide-mediated endothelium-dependent vasodilation was decreased in SMC-Ercc1KO ($p<0.01$), which was restored by chronic colchicine treatment. SMC-Ercc1KO mice showed diminished reactive hyperemia compared to WT ($p<0.01$) while no effect of the treatment was observed ($p=0.65$). In our longitudinal analysis of 333 participants (mean ±SD age= 61.1±5.51, males= 72.4%) and during a median follow-up of 9.97 years, incident colchicine users had decreased cIMT, a marker of vascular aging compared to non-users, although the difference was not statistically significant (B= -0.027, $p=0.09$). Sex-stratified analysis (P-interaction <0.001), however, revealed that the association was exclusively strong among females (B= -0.097, $p=0.01$).

Discussion/Conclusion
Our mouse studies identify smooth muscle cell aging as a cause of increased vascular stiffness and decreased nitric oxide-mediated endothelium-dependent vasodilation . Inhibition of inflammation with colchicine prevents this development. Our human observational findings indicate that colchicine prevents cIMT, an important vascular aging marker, particularly in women. Further inspection of this sex-specific effect is needed. Thus, this translational research approach provides a rationale for anti-inflammatory treatment in vascular aging.

ADMETTRE MTX-STUDY: ADHERENCE TO LOW-DOSE METHOTREXATE IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS USING A SENSITIVE METHOTREXATE ASSAY

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Background
Low-dose weekly methotrexate (MTX) is the mainstay of treatment in patients with juvenile idiopathic arthritis (JIA). Unfortunately, a substantial part of patients has insufficient efficacy of MTX. Next to pathophysiological and genotypical factors, one potential cause of inadequate response is suboptimal drug adherence. For JIA patients, reported MTX adherence percentages are 76-92%. However, adherence numbers from literature could be overestimated with the commonly used subjective methods, such as questionnaires and diaries. The aim of this study was to assess MTX adherence in JIA patients through objective analysis of MTX concentrations in plasma. In addition, we wanted to establish whether there was an association between non-adherence to MTX and the use of concomitant biological treatment.

Methods
This was a retrospective, observational study using plasma samples from JIA patients stored in the Pharmachild biobank of the Wilhelmina Children's Hospital, Utrecht. We developed an ultrasensitive Liquid Chromatography Tandem-Mass Spectrometry (LC-MS/MS) method for quantification of MTX and its metabolite 7-hydroxy-MTX (7-OH-MTX) in plasma. The assay was validated in accordance with the EMA guidelines and had a lower limit of quantification of 0.02 nM for MTX and 0.16 nM for 7-OH-MTX. The determined MTX plasma concentrations of the patients were compared with previously published adherence limits, [1] corresponding with a certain MTX dose and time between administration and blood sampling. Patients were labelled accordingly as either adherent or possibly non-adherent to MTX therapy.

Results
Plasma samples of 43 JIA patients were analysed. Adherence to MTX in our population of JIA patients was 88% shortly after initiation of MTX therapy and decreased to 77% after one year of therapy. Undetectable MTX and 7-OH-MTX concentrations were found in one patient. The use of concomitant therapy with biologics was not associated with adherence to MTX therapy (P=0.27, Fisher's Exact).

Conclusion
The developed ultrasensitive LC-MS/MS method for MTX and its metabolite seems to be a suitable and objective method to assess (potential non-)adherence in patients using low-dose weekly MTX. The use of this method in clinical practice could be helpful for physicians to refute or support suspicion of non-adherence to MTX therapy.

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INACTIVATION OF THE ACKR3 BY A SMALL-MOLECULE INVERSE AGONIST

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Background
The atypical chemokine receptor type 3 (ACKR3) is frequently explored as a drug target for the treatment of various diseases, like cancer and cardiovascular disease. Until recently, all characterized small-molecule-ligands that bind the ACKR3 were agonists and it was shown that the ACKR3 had a high propensity for activation when compared to other chemokine receptors.

Methods
NanoBRET and radiolabelled ligand-based assays were utilised to study ligand binding at ACKR3. NanoBRET and NanoBiT based luminescence assays were utilised to measure receptor activation as a function of receptor-intracellular effect interactions. Molecular modelling techniques were used to predict small-molecule-ACKR3 interactions.

Results
The antagonist (VUF16840) was synthesized and its effect on the ACKR3 was characterized. VUF16840 is confirmed to antagonize chemokine induced receptor activation. It is additionally shown that this ligand stabilizes the inactive conformation of the ACKR3, as is evident from a dose-dependent inhibition of constitutive receptor signalling. Despite the distinct intrinsic activity of VUF16840 at the ACKR3, site-directed mutagenesis studies show a partial overlap in receptor binding interactions between VUF16840 and a small-molecule agonist. It is finally shown that VUF16840 has selectivity for the ACKR3 over all other human chemokine receptors. Some off-target activity was observed for the CCR3, which is the only other chemokine receptor that is modulated by VUF16840 at a concentration of 1 mM.

Discussion/Conclusion
We therefore suggest that VUF16840 constitutes a valuable tool compound for probing the utility of ACKR3 as a drug-target. Moreover, the pharmacological characterization of ACKR3 binding site might facilitate further design of new agonists and antagonists.

LIMITED PHARMACEUTICAL LITERACY IN PATIENTS ON HEMODIALYSIS IN THE NETHERLANDS AS ASSESSED WITH THE RALPH INTERVIEW GUIDE

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Background
No data are available on the prevalence of limited pharmaceutical literacy in patients with CKD or on hemodialysis. Recently, the RALPH (Recognizing and Addressing Limited Pharmaceutical Literacy) interview guide was developed in the Netherlands to assess pharmaceutical literacy skills in the functional, communicative, and critical domains. The objective of this study was to provide data on the prevalence of limited pharmaceutical literacy, associated problems, and the domains in which these problems occur, in hemodialysis patients using phosphate-binding drugs in the Netherlands.

Methods
This study was part of a prospective observational study in a teaching hospital in Rotterdam, investigating a complex adherence-improving intervention in hemodialysis patients using phosphate-binding drugs. One of the aims of the original study was to explore pharmaceutical literacy at baseline, using the RALPH interview guide. Limited pharmaceutical literacy was defined as the presence of at least one problem in one or more of the domains of the RALPH. The primary outcome was the prevalence of limited pharmaceutical literacy. Secondary outcomes was the prevalence of one or more problems in the three domains. Data were analyzed using descriptive statistics (SPSS version 28.0).

Results
A total of 63 patients were included in the study. Mean age was 66 years, 65% of the patients were male. The prevalence of limited pharmaceutical literacy was 79%. Fifty-two percent of the patients had at least one problem in the communicative domain, 46% in the functional domain, and 78% in the critical domain. Around 90% of patients could correctly reproduce the user instructions for phosphate-binding drugs. The most prevalent problems were a lack of knowledge about the indication (40%) in the functional domain and finding understandable information (51%) in the communicative domain. In the critical domain, the most frequently encountered problems were a lack of adequate judgment of both the reliability and applicability of information (62% and 65%, respectively). Almost half of the patients did not search for information. Furthermore, 32% of patients did not engage in shared-decision making or found this difficult to do.

Conclusion
Limited pharmaceutical literacy is frequent in patients on hemodialysis. The results of this study are generally in line with earlier findings studying pharmaceutical literacy in Dutch community pharmacies in the Netherlands. Recent data show that limited health literacy in general negatively affects certain aspects of self-management, such as adherence, communication, and knowledge. This is also apparent in our study. These data together underline the need for dialysis healthcare providers to individualize their communication and support to meet their patients' needs.

ALGORITHM-MANAGED DOSING AND PHARMACIST-MANAGED DOSING OF ERYTHROPOIETIN STIMULATING AGENTS IN RENAL ANEMIA: A SYSTEMATIC REVIEW

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Background
In clinical practice, the treatment of renal anemia is challenging. The attainment of target levels for hemoglobin is often low, due to the high incidence of infections, hyporesponsiveness to erythropoietin stimulating agents (ESA), and suboptimal prescribing of ESA and iron. Several interventions to improve the treatment of renal anemia have been developed, two of them being algorithm-managed dosing and pharmacist-managed dosing of ESA. We performed a systematic review to identify and summarize these two types of interventions and to determine their effectiveness in improving the treatment of renal anemia.

Methods
We followed the PRISMA guidelines for systematic reviews. Studies that explored the effect of algorithm-managed and pharmacist-managed dosing of ESA in adult patients with renal anemia were evaluated for inclusion. No restrictions were set on outcome parameters. All observational and interventional studies published as full-text articles with a control group and a follow-up of at least six months were eligible for inclusion. PubMed, Embase, Web of Science, and the Cochrane Library were searched from their inception through July 2022. All studies were evaluated by two independent reviewers. The quality of studies was assessed by the Newcastle Ottawa Scale and the risk of bias was assessed by the ROBINS-I and RoB1 tools. Data were summarized and tabulated. Studies were grouped according to intervention type, study design, and risk of bias. The protocol of this study was registered in PROSPERO (International Prospective Register of Systematic Reviews, ID CRD42021243678). This study was funded by the Franciscus Gasthuis and Vlietland hospital.

Results
After screening 20 articles, 16 articles could be included with a total of 3777 patients. Available evidence was scarce and generally of low to moderate quality; only two RCTs could be identified. Thirteen studies were observational in nature. The risk of bias was serious in fifteen studies. In six studies, ESA dosing was pharmacist-managed, in one study it was algorithm-managed, and in nine studies both strategies were combined. The quality of the intervention description was low to moderate, interventions generally were not reproducible. Four types of outcome parameters could be qualitatively assessed: hemoglobin/hematocrit, ESA dose and expenditure, iron status, and iron dose. Limited low-quality evidence suggests that pharmacist-managed ESA dosing may improve ESA dose and expenditure and iron status. However, quantitative data synthesis was not possible due to the substantial heterogeneity in outcome parameters and the high risk of bias.

Discussion/Conclusion
Available evidence was scarce with a high risk of bias, and quantitative data synthesis was not possible. Therefore, no definite conclusions could be drawn on the effectiveness of algorithm-managed and pharmacist-managed dosing of ESA in renal anemia. Consequently, recommendations on the implementation of either of the two interventions could not be made.

PROGNOSTIC VALUE OF NIVOLUMAB CLEARANCE IN NON-SMALL CELL LUNG CANCER PATIENTS TO ASSESS NON-RESPONSE EARLY IN TREATMENT

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Background
Immune checkpoint inhibitors have greatly improved survival of advanced stage non-small cell lung cancer patients, but the overall response rate remains low. A biomarker that identifies non-responders is vital to prevent unnecessary treatment. Clearance of immune checkpoint inhibitors has shown to be related to treatment response, but the prognostic value early in treatment remains unknown. Our aim was to assess the prognostic value of nivolumab clearance to identify non-response within the first 12 weeks of treatment.

Methods
Individual estimates of nivolumab clearances at first dose, 6 and 12 weeks after treatment initiation were obtained via nonlinear mixed effects modelling using a previously validated population pharmacokinetic model[1]. The predictive value of nivolumab clearance was estimated using univariate Cox proportional hazards regression models at first dose and for the ratios between 6 and 12-weeks-to-first-dose. The cut-offs for nivolumab clearance at first dose and the 6 and 12-weeks-to-first-dose ratios were estimated using maximally rank statistics. For sensitivity and specificity calculations, a patient was considered a non-responder when they died within 6 months after start of nivolumab treatment.

Results
In total, 69 patients were included and the majority (86%) died during follow-up of 75 months. Patients with a nivolumab clearance ≥7.3 mL/h at first dose were more likely to die compared to patients with a nivolumab clearance <7.3 mL/h at first dose (HR=3.55, 95% CI=1.75-7.20). The HRs of dose nivolumab clearance ratios showed similar results with a HR of 3.93 (95% CI=1.66-9.32) for 6-weeks-to-first-dose clearance ratio at a 0.953 cut-off and a HR of 2.96 (95% CI=1.32-6.64) for 12-weeks-to-first-dose clearance ratio at a cut-ff of 0.814. For nivolumab clearance at first dose, the 6-weeks-to-first-dose clearance ratio and the 12-weeks-to-first-dose clearance ratio, sensitivity was high (≥0.95) but specificity was low (0.29, 0.19, 0.11, resp.).

Discussion/Conclusion
Nivolumab clearance distinguishes non-response within the first 12 weeks of nivolumab treatment. Our results encourage to prospectively evaluate the prognostic potential of immunotherapy clearance monitoring to guide treatment.

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THE EFFECT OF A REDUCED DOSE OF ENZALUTAMIDE ON FATIGUE AND COGNITION

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Background

Enzalutamide (ENZA) is a highly effective treatment for patients (pts) with metastatic prostate cancer, but central nervous system (CNS)-associated side effects occur frequently. These side effects can potentially be prevented by starting at a reduced dose, since androgen receptor saturation is already observed at dose levels above 60 mg once daily (OD) and ENZA plasma concentrations > 5 mg/L.[1] We hypothesized that a lower starting dose of ENZA can reduce the risk of CNS side effects in frail pts while preserving efficacy.

Methods

This randomized multi-center trial compared the ENZA standard dose of 160 mg OD to the reduced dose of 120 mg OD in 51 frail prostate cancer pts. At baseline and 6, 12, and 24 weeks after start, fatigue and cognitive side effects were measured by the FACIT-F and FACT-Cog questionnaires. Linear mixed effects models were used to study within and between-group differences in fatigue and cognitive side effects over time.

Results

A total of 51 pts were included (25 reduced dose, 26 standard dose). Completion rates for the questionnaires were high throughout the study (>90%). Pts treated at the reduced dose showed increasingly better FACIT-F and FACT-Cog scores compared to pts treated at the standard dose, which became clinically relevant and statistically significant after 24 weeks, as shown in table 1. All pts had therapeutic ENZA concentrations (>5 mg/L) throughout the study. PSA response did not differ between both groups (87% for 120mg OD vs 80% for 160mg OD, p=0.796).

Discussion/Conclusion

By starting with a reduced dose of ENZA of 120mg OD CNS side effects can be reduced in frail prostate cancer pts, without any indication of interference with efficacy endpoints.

Table 1: Difference in change from baseline between the reduced vs standard dose at 24 weeks (95% CI). *Significant

	6 weeks	**12 weeks**	**24 weeks**
FACIT-F	2.0 (-2.8, 6.8)	3.0 (-2.0, 8.0)	6.4 (1.1, 12)*
FACT-Cog	3.8 (-5.6, 13)	1.1 (-8.7, 11)	11 (0.24, 22)*

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CXCR4 OLIGOMERIZATION: DETECTION, MODULATION AND FUNCTIONAL CONSEQUENCES

Authors

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Background

G protein-coupled receptors (GPCRs), crucial therapeutic targets, play an important role in cancer by enhancing various cancer hallmarks. GPCRs can oligomerize, potentially affecting downstream signaling. CXCR4, a chemokine receptor overexpressed in numerous cancer types, oligomerizes upon increased expression and binding of its endogenous ligand CXCL12[1]. However, the molecular mechanisms underlying CXCR4 oligomerization and the functional consequences are poorly understood.

Our aim is to determine the presence and functional consequence of CXCR4 oligomerization in solid cancer.

Methods

U87 glioma cell lines expressing CXCR4 WT or mutants were studied via BRET (Bioluminescence Resonance Energy Transfer) and CXCR4 oligomers could be specifically detected with either tagged receptors or nanobodies by BRET. Western Blots, JAK2 target genes (qPCR), 2D and 3D spheroid growth techniques were employed to study differences between CXCR4 oligomerization with WT or dimer-deficient CXCR4.

Results

CXCR4 oligomerization was modulated by mutating CXCR4 transmembrane residues or by a panel of nanobodies with different pharmacological profiles and allowed us to monitor functional consequences of CXCR4. Some nanobodies reduced CXCR4 dimerization, whereas bivalent Fc-linked nanobodies $(Nb\text{-}Fc)^2$ induced oligomerization. Western Blots, JAK2 target genes (qPCR), 2D and 3D spheroid growth showed that Nb-Fc also induced signaling at WT but not mutant CXCR4. CXCR4 showed increased oncogenic signaling and tumor growth, as compared to the dimer-deficient CXCR4 mutant.

Discussion/Conclusion

Our results provide insights in endogenous CXCR4 oligomerization and demonstrate its importance for signaling in cancer.

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HCMV-ENCODED VIRAL GPCR US28 SIGNALS TO THE HIPPO PATHWAY VIA Gq/11

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Background

Up to 80-100% of the adult European population carry the human cytomegalovirus (HCMV)(1), a common herpesvirus. In healthy individuals, HCMV infection usually induces little to no symptoms. However, recent findings indicate that HCMV might contribute to a variety of diseases, including heart disease and cancer(1), two of the leading causes of death in Europe. HCMV affects these diseases by encoding proteins that upon expression in the host cell hijack its signaling network(1). Previously, we have shown that the HCMV-encoded G protein-coupled receptor (GPCR) US28(1) constitutively activates oncogenic signaling pathways. In this study we show that it also interferes with the Hippo signaling pathway, a regulator of cell proliferation(2). Dysregulation of this Hippo pathway has been linked to cancer(2).
In order to develop effective treatments, it is essential to understand the molecular mechanisms that drive HCMV-mediated oncomodulation. We hypothesize that one such mechanism involves modulation of the Hippo pathway by the virus-encoded GPCR US28. Thus, we aimed to investigate how US28 modulates the Hippo pathway, and examine the functional consequences.

Methods

We used a TEAD reporter gene assay to detect Hippo pathway activity, combined with pharmacological inhibitors to determine the transducers affecting it. We also used qPCR to quantify the changes in expression of proliferative Hippo target genes.

Results

We found that expression of US28 in HEK293 cells interferes with the Hippo pathway and leads to an increase in TEAD reporter transcription. This increase is entirely dependent on Gq/11 activation. Finally, we demonstrated that US28 signaling increases the expression of Hippo-dependent YAP/TEAD target genes Cyr61 and CTGF.

Discussion/Conclusion

These results demonstrate that HCMV-encoded US28 hijacks the Hippo pathway upon expression in a mammalian cell, and thereby provides a new perspective of how US28 could contribute to HCMV-mediated oncomodulation.

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DOSING OF CONVALESCENT PLASMA AND HYPERIMMUNE ANTI-SARS-COV-2 IMMUNOGLOBULINES: A PHASE I/II DOSE FINDING STUDY

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Background
During the COVID-19 pandemic, multiple trials on convalescent plasma (ConvP) have been performed without preceding dose-finding studies. This study aimed to assess potentially protective dosing regimens by constructing a population pharmacokinetic (popPK) model describing ConvP and hyperimmune globulin (COVIg) levels.

Methods
Immunocompromised patients, testing negative for anti-SARS-CoV-2 spike antibodies despite vaccination, and without COVID-19 received a predetermined dose of anti-SARS-CoV-2 antibodies given as a COVIg or ConvP infusion. Antibody titers were obtained until anti-SARS-CoV-2 antibodies became negative. A popPK model was constructed using NONMEM v7.4 and Monte Carlo simulations were performed to assess COVIg and ConvP dosing regimens for prevention of COVID-19.

Results|
44 patients were enrolled, whereas data from 42 patients were used for constructing the popPK model. Antibody elimination was best described by a two-compartment model with mixed residual error and IIV (%CV) on CL (44.3%), V1 (27.3%), and V2 (29.2%). Lean body weight and type of treatment (ConvP/COVIg) were associated to V1 and V2, respectively. Median elimination half-life was 20 days (interquartile-range, 17–25 days). The 90% probability target attainment (PTA) for the 300 $BAUmL^{-1}$ titer threshold could not be achieved using 600mL ConvP every 8 weeks. For a target of 100 $BAUmL^{-1}$, the 90% PTA was achieved with longer dosing intervals as long as ConvP or COVIg with high $BAUmL^{-1}$ can be administrated (e.g. every 8 weeks with 32,000 $BAUmL^{-1}$ or higher).

Discussion/Conclusion
Administered dosing regimens did not allow to achieve the predetermined 90% PTA titer thresholds. However, dosing regimens with higher antibody concentrations are possible. Future intervention studies on the prophylactic and therapeutic application of antiviral antibodies in the form of ConvP or COVIg may be informed by the constructed popPK model.

EXPOSURE ESTIMATION IN A NEXT GENERATION RISK ASSESSMENT CONTEXT: USING BEWO B30 CELLS TO STUDY TRANSPLACENTAL PASSAGE OF DRUGS AND CHEMICALS

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Background
Next generation risk assessment (NGRA) uses an exposure-led, hypothesis-driven approach to toxicology by combining different *in silico* and *in vitro* methods. In such an approach, *in vitro* studies are used to determine concentrations associated with adverse effects (points of departure) which are then combined with exposure estimates (physiologically-based kinetic [PBK] modelling), to derive safety margins. We now explore whether an NGRA approach for developmental and reproductive toxicity (DART) is feasible. As part of this, we aimed to set-up a BeWo b30 transwell assay as a high throughput alternative to the *ex vivo* human placenta perfusion approach for deriving parameters for PBK modelling.

Methods
BeWo b30 cells, a human trophoblast cell line, were seeded on human placental collagen coated inserts (24-well plates) at a density of 100.000 cells/cm^2. Plates were incubated at 37 °C, 5% CO_2. Culture medium was changed daily. To study trophoblast monolayer formation, we characterized cells time via microscopic inspection and transepithelial electrical resistance (TEER) measurements using a volt-ohmmeter. As a functional measure of monolayer integrity, transport of sodium-fluorescein, a paracellular transport marker, was also studied. In short, 5 µM of sodium-fluorescein wad added to the apical side of an insert on day 5, 7 and 11 after seeding. After 3 h of incubation, culture medium from the basolateral side was collected and fluorescence was measured at 485 nm excitation and 520 nm emission.

Results

TEER values were monitored over 12 consecutive days after seeding, showing an increasing pattern over time with highest TEER values, 106.1 ± 3.9 Ω*cm^2, observed at day 11. However, at day 7 day post-seeding, a confluent monolayer already appeared to be present based on visual microscopic inspection of the BeWo b30 cells within the inserts. This was confirmed by the sodium-fluorescein data. The concentration of fluorescein found in the basolateral chamber, decreased from 64.5 ± 10.1 nM at day 5 post-seeding to 46.5 ± 1.5 nM at day 7 day post-seeding and finally stabilizing at day 11 post-seeding at 42.1 ± 2.9 nM.

Discussion/Conclusion

We demonstrate that an adequate monolayer of BeWo cells is likely formed over a period of 7 to 10 days post-seeding. Future steps include studying the transfer of a number of model drugs and chemicals in order to derive apparent permeability (Papp) values to be used in pregnancy PBK models.

THE ROLE OF ELECTRONIC PRESCRIBING SYSTEMS IN THE MANAGEMENT OF ADVERSE DRUG REACTIONS TO BIOLOGICALS

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Background

Biologicals are proteins that are produced in a way to make them as similar to human proteins as possible. Because of their more direct and focused effect biologicals are superior to immunosuppressive and cytotoxic drugs, which use is often limited by severe generalized unwanted side effects. Nevertheless, biologicals can also cause adverse drug reactions. [1] In this literature study we examined what side effects occur, what actions are needed and what precautions are needed for the next administration.

Methods

We identified studies about adverse drug reactions in biologicals. We extracted data concerning the reported adverse reactions, actions needed, and suggested precautions.

Results

Adverse drug reactions to biologicals can be divided in ‘target related’ and ‘agent related’ side effects. Agent related side effects are either directly linked to the mechanism of action (type α), or to a hypersensitivity reaction (type β).

Re-exposure is possible with premedication and a reduced infusion rate, unless the reaction is severe. Only severe reactions should be registered in the system.
Target related side effects are specific for biologicals (type δ, ε or γ). They are the consequence of direct interference with the immune system, what makes the patient vulnerable for undesirable effects even though the biological itself is relatively safe. Target related side effects can present with a new condition caused by a biological used in the past. Future exposure to the biological has to be avoided. [2]

Cross-reactivity can only occur if binding epitopes on the protein are similar. Since most biologicals have a unique protein structure, they are generally not expected to cross-react. [3]

Discussion/Conclusion

Biologicals can cause agent and target related side effects. With agent related side effects, re-exposure is often possible. In case of severe reactions, re-exposure has to be avoided. Target related side effects are unique to biologicals and also acquire avoidance of the biological. Lastly, due to the uniqueness of the protein structure, cross-reactivity testing has no place in adverse reaction protocols for biologicals.

Literature

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PREECLAMPSIA INCREASES MATERNAL EXPOSURE TO BETAMETHASONE IN PREGNANCY: A POPULATION PHARMACOKINETIC STUDY

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Background
Maternal dosing of antenatal corticosteroids (ACS) to improve fetal lung development in case of imminent preterm birth has remained the same "one dose fits all" for years, although dosing is not optimal based on side effects and variable efficacy. The first step to improve ACS dosing is to understand factors that may influence maternal exposure.
Therefore, we aim to improve maternal dosing of corticosteroids, by establishing a population pharmacokinetic model of betamethasone in pregnant women including analyses of clinically relevant covariates.

Methods
Prospective single center pharmacokinetic study in women admitted for imminent preterm birth (23+5 - 33+6 weeks of gestation) treated with intramuscular betamethasone (2 doses, 12 mg once daily) were included. Betamethasone serum concentrations were determined in serial venous blood samples. Population pharmacokinetic modelling was performed using Non-linear mixed effects models (NONMEM).

Results
194 blood samples from 28 patients were collected and analyzed. The model was best described using a two-compartment model. The population mean estimate for absorption constants, central volume distribution, peripheral distribution volume, clearance and half-life for an average patient were 1.7 h-1 (IIV 27%), 46.1L, 109L, 14.4 L/h and 7.4h, respectively. Betamethasone clearance in preeclamptic women was 40% lower compared to non-preeclampsia women (9.35 versus 15.78 L/h) resulting in a 40% median increase in betamethasone exposure (1567 versus 1114 ng.h/ml).

Discussion/Conclusion
Our population PK model showed that maternal betamethasone exposure in women with preeclampsia is significantly increased. The study suggests that a significant dose reduction of betamethasone may be needed to reach similar maternal exposure in preeclampsia.

A FRAMEWORK FOR CLINICAL PHARMACEUTICAL REASONING

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Background
Nowadays, hospital pharmacists (in training) are often involved in direct patient care as the medication specialists. Pharmacists are generally risk avoiding and search for certainty. However, hospitalized patients do often have complex medication issues in which hospital pharmacists have to deal with uncertainties. Clinical pharmaceutical reasoning is required for these complex cases and is learned on the job. However, a systematic framework to teach or support this skill is lacking, which also compromises competence evaluation of entrustable professional activities of residents in hospital pharmacy.

Methods
A practical, schematic framework including all aspects relevant in clinical pharmaceutical reasoning was developed. A systematic stepwise approach evolved next to it. Two hospital pharmacists analysed clinical reasoning in patient cases presented at daily meetings of the hospital pharmacy and while supervising residents. Furthermore, they reflected on their own approach on solving medication problems on the wards, and their own clinical reasoning on complex patient cases in multidisciplinary meetings. Hospital pharmacists (in training) were given an introduction on the framework and were asked to use the framework in daily practice and give feedback.

Results
A practical framework for clinical pharmaceutical reasoning was developed and implemented in daily practice of an academic hospital pharmacy. No adjustments on the framework were required after implementation. The scheme consists of three main pillars: drug, patient and diagnosis/indication and relevant aspects are categorized and linked to these pillars.
The framework has been used in both simple and complex medication issues, patient- as well as pharmacy-based cases. The framework was applicable in multidisciplinary meetings, outpatient counselling and entrustment-based discussions with residents.

Discussion/Conclusion
The framework was developed bottom-up from daily practice. After implementation of the framework a scoping review on this topic became available, defining clinical reasoning as a context-dependent stage of the pharmacists' clinical decision-making process whereby pharmacists apply and integrate knowledge and clinical experience to interpret all available clinical data. This review lacked a schematic framework or stepwise approach. The developed, practical framework appears to be useful in daily practice to support clinical pharmaceutical reasoning by hospital pharmacists (in training) and can also be used in entrustment-based discussions for competency statements in residency.

Mertens JF et al. Clinical reasoning by pharmacists: a scoping review. Curr Pharm Teach Learn 2022(14):1326-36

VARIABILITY IN WHOLE BLOOD TACROLIMUS CONCENTRATIONS AFTER ORAL AND CONTINUOUS INTRAVENOUS ADMINISTRATION EARLY POST-LUNG TRANSPLANTATION

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Background
High tacrolimus variability after lung transplantation (LTx) is related to an increased risk for rejection or nephrotoxicity [1]. There is no consensus on the optimal administration route. The aim was to investigate the effect of continuous intravenous (CI) versus oral (OR) administration on tacrolimus variability, measured as intrapatient variability (IPV) and time within therapeutic range (TTR), in early post-lung transplantation.

Methods
Patients who had undergone LTx in the UMCU or UMCG between January 2010 and January 2020 were eligible for inclusion. Patients were excluded if <3 tacrolimus concentrations were available early post-LTx. TTR was calculated using linear interpolation (Figure 1) [2].
In this retrospective study, 224 patients received oral tacrolimus and 298 continuous intravenous administration with a switch to oral administration once the patient stabilized. IPV and TTR were calculated using daily tacrolimus whole blood concentrations from the first 14 days after LTx. Linear regression was used to investigate the effect of the administration route on variability.
Ethical approval was waived by NEDMEC.

Results
The mean IPV in the CI group, weighted for the number of samples available per patient, was 29.2% ± 10.9 compared to 31.7% ± 10.5 in the OR group ($p<0.001$). After adjustment for effect modifiers, the mean IPV in the CI group was 20.2% and 7.8% higher in the OR group (95%-CI 5.3-10.4; $p<0.001$). Median TTR was 30.7% (18.7-41.1) and 22.1% (13.0-30.8) in the CI and OR group, respectively ($p<0.001$). After adjustment, the mean TTR in the CI group was 27.7% and 14.4% lower in the OR group (95%-CI -22.1 - -6.8; $p<0.001$). Median hospital admission was 35 (25-54) days for patients in the CI group and 28 (21-44) days in the OR group ($p<0.001$).

Discussion/Conclusion
The variability in tacrolimus concentrations, measured as IPV and TTR, is higher when tacrolimus is administered orally in the first 14 days after LTx in comparison to continuous intravenous infusion.

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THERAPEUTIC DRUG MONITORING OF VEDOLIZUMAB IN INFLAMMATORY BOWEL DISEASE PATIENTS DURING MAINTENANCE TREATMENT – TUMMY STUDY

Authors

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Background

There is limited data on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD) patients treated with vedolizumab (VDZ), precluding determination of its position in clinical practice. Although an exposure-response relation has been demonstrated in de post-induction phase, this relationship is even more uncertain in the maintenance phase of treatment. The aim of our study was to determine whether there is an association between VDZ trough concentration and disease activity in the maintenance phase.

Methods

A prospective, observational multicentre study has been performed in IBD patients on VDZ in the maintenance treatment(≥14 weeks). Patient demographics, biomarkers and VDZ serum trough concentrations were collected. Clinical disease activity was scored by Harvey Bradshaw Index for Crohn's disease (CD) and Simple Clinical Colitis Activity Index for ulcerative colitis (UC). Clinical remission was determined as HBI<5 and SCCAI<3. Biochemical remission was defined as fecal calprotectin <250 mg/kg and serum CRP <5 mg/L.

Results

A total of 159 patients (59 CD, 100 UC) was included. Vedolizumab concentrations varied from 0.1 to 74.4 mg/L. Median VDZ level in patients in remission was 16.3 mg/L in CD patients and 16.6 mg/L in UC patients. In neither group of patients, a statistically significant correlation between trough VDZ concentration and clinical remission could be observed. Patients in biochemical remission had significantly higher VDZ trough concentrations (p=0.019).

Conclusion

Large interindividual variability in VDZ trough concentrations was observed by TDM. In this population, higher trough VDZ concentrations were associated with biochemical remission, but no association was found in VDZ trough concentrations and clinical remission.

SUSTAINABILITY INITIATIVE: DOSE BANDING OF PACLITAXEL TO MINIMZE DRUG WASTE

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Background

The aim of this project was to reduce paclitaxel waste caused by cancellation of administrations. In the light of rising health care costs and increased environmental awareness increasing focus is aimed at reducing drug waste. Standardized dose-bands make interchangeability of already reconstituted paclitaxel bags easier, as more patients use the same dose. This could potentially save drug- and material waste and costs as well as manpower. Therefore Paclitaxel fixed dose-bands were created for patients treated with a weekly dose of 80mg/m^2.

Methods

In consultation with prescribers dose bands for paclitaxel where created (see table 1). The maximal deviation for dose-rounding rules for paclitaxel in our hospital is set at 10% of the prescribed dose. Doses ≤72mg or >200mg were rounded as normal.
These doses were implemented as dose-rounding rules in the drug preparation software (Hix 6.2, ChipSoft BV) on 01-04-2022. Paclitaxel 80mg/m^2 waste and reuse was compared between 01-05-2022 until 31-12-2022 and the same period in 2021.

Table 1: paclitaxel dose-bands

Prescribed dose (mg)	Dose-band (mg)	m2 (dose 80 mg/m^2
>72≤88	78	1.0
>88≤102	96	1.2
>102≤116	114	1.4
>116≤136	126	1.6
>136≤152	144	1.8
>152 ≤168	162	2.0
>168≤184	174	2.2
>184≤200	192	2.4

Results

In 2022 a total of 1589 infusions were prepared, consisting of 16 different doses. Compared to 1829 infusions in 2021, consisting of 30 different doses. Interchangeability was improved as, top 3 of dosages prepared by the pharmacy were: 144mg (33%), 162mg (22%), and 126mg (22%) compared with 144mg (16%), 162mg (11%), and 138mg (10%) in 2021. In 2021 we discarded 67 prepared doses of paclitaxel of which 12 infusions (18%) could be reused. Using dose-banding, 27 of 41 (66%) discarded infusions were reused in 2022. Resulting in a 3.7-fold increase of reuse paclitaxel infusions.

Discussion/Conclusion

With this intervention we increased interchangeability of infusion and we reduced waste. We are aiming to expand this strategy to other classic chemotherapeutic drugs.

EXPOSURE OF IMATINIB USING DIEFFERENT FORMULATIONS FOR THE TREATMENT OF GASTROINTESTINAL STROMAL TUMOR

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Background
A 65-year old male presents with an obstructive ileus due to a giant unresectable gastrointestinal stromal tumor (GIST). Treatment with imatinib is indicated however the patient has no oral intake (stomach drainage tube) and no gastrointestinal passage. Currently, only tablets are available. In 2007 van Erp et al reported a case in which ±40% bioavailability (F) of imatinib after rectal administration of imatinib tablets was achieved in a patient. Our aim was to effectively treat our patient with an alternative formulation of imatinib, using blood concentrations for monitoring.

Methods
The recommended dose of imatinib is 400mg/day for adult patients with unresectable and/or metastatic malignant GIST. Dosages can be increased to 600-800mg depending on mutation status and response. Reference values for imatinib trough concentrations >1100µg/L. Imatinib trough levels were measured using an in-house validated LC-MS assay and dosages were adapted based on plasma concentrations. Based on the results of van Erp et al the start dosage was 400mg BID, administered as a suspension via a duodenum tube.

Results
On day 4 of treatment, the first imatinib plasma concentration was 750µg/L. The dosage was increased to 400mg TID on day 5. On day 6 patient started vomiting after each administration of the imatinib suspension trough the tube. The tube was replaced and despite vomiting exposure at day 7 was adequate (1500µg/L). At day 8 the tube was removed because of persistent vomiting. Imatinib tablets were administered rectally in a dose of 400mg QID. Exposure was too low on day 11 (290µg/L). As by that time the ileus started to resolve and oral intake was possible again, it was decided on day 12 to treat patient with an oral suspension (400mg BID). The resolution of the ileus was considered an early sign of response to treatment. On day 16 exposure was 3200 µg/L and on day 25 4000µg/L, therefore the dosage was decreased to 400mg QD after which imatinib levels dropped to 1900µg/L. Unfortunately, by treatment day 40 patient had disease progression complicated by bleeding and an emergency resection was performed. The patient continued on a dose of 400mg QD suspension.

Discussion/Conclusion
No licensed drug formulations of imatinib other than tablets are available and thus no treatment was possible for our patient. Due to creation of alternative dosages forms and therapeutic drug monitoring, the patient received effective treatment. Imatinib had decreased absorption and non-linear PK with the suspension after administration through the tube and ‘normal’ absorption and linear PK after oral administration.

STATINS INTERFERE WITH CARDIOMYOCYTE MITOCHONDRIAL FUNCTION AND INTRACELLULAR ACIDIFICATION

Authors
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Background
Cholesterol-lowering statins have proven to significantly reduce major cardiovascular events and are used by 180 million patients worldwide. Musculoskeletal complaints are experienced by 7–29% of all users and associated with decreased mitochondrial function. Cardiomyopathy has not been described for statins, probably due to a much higher mitochondrial content compared to skeletal muscle. However, statins are usually taken lifelong and as mitochondrial function reduces with age, cardiac tissue may also become susceptible to side effects in the elderly. We aimed to investigate the metabolic effects of statins on induced pluripotent stem cell (iPSC)-derived cardiomyocytes (CMs).

Methods
CM viability, intracellular pH, mitochondrial morphology and membrane potential were determined using high-throughput microscopy after 48h exposure to 0.3-100 µM of the acid and lactone form of various commonly used statins. Next, oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were determined using the Seahorse XF-96 Flux Analyzer.

Results
Lipophilic statins decreased cell viability dose-dependently, most prominently by simvastatin lactone (42 ± 8%, mean±SEM, $p<0.0001$ at 100 µM; IC50: 95 µM, 95% CI: 17-169). OCR was decreased by lipophilic statins, again most strongly by simvastatin lactone, which declined basal and maximal respiration by 46 and 68%, respectively (IC50: 3 and 9 µM, 95% CI: 1-9 µM and 2-77 µM, respectively, $p<0.001$). Additionally, simvastatin lactone reduced ECAR up to 73% ($p<0.05$) of control. This could be correlated with a dose-dependent reduction of intracellular pH with the strongest reduction of BCECF intensity ratio again by simvastatin lactone to 50% ($n=1$, $p<0.05$, 100µM; IC50: 0.6 µM, 95% CI: 0.1-21). Finally, statins reduced mitochondrial membrane potential by 20±1% (simvastatin acid, 100µM, $p<0.0001$; IC50: 50 µM, 95% CI: 35-73) without affecting mitochondrial morphology.

Discussion/Conclusion
Lipophilic statins decrease cardiomyocyte viability, cellular respiration, and mitochondrial membrane potential, whilst increasing intracellular acidification. We thus provide a novel mechanism that could explain the recently observed adverse cardiac effects after chronic statin treatment in mice. These results may have clinical implications for patients with a decreased cardiac mitochondrial capacity, in whom chronic use of statins could be harmful. Future studies should investigate whether this could contribute to a more personalized statin treatment to prevent future cardiac discomfort by using more hydrophilic statins for example.

TAMOXIFEN PHARMACOKINETICS AND PHARMACODYNAMICS IN OLDER PATIENTS WITH NON-METASTATIC BREAST CANCER

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Background
We aimed to study the pharmacokinetics and -dynamics of tamoxifen in older women with non-metastatic breast cancer.

Methods
Data for this analysis were derived from the CYPTAM study (NTR1509) database.
Patients were stratified by age (age groups < 65 and 65 and older). Steady-state
trough concentrations were measured of tamoxifen, NDM-tamoxifen, 4-hydroxytamoxifen, and endoxifen. CYP2D6 and CYP3A4 phenotype were assessed for all
patients by genotyping. Multiple linear regression models were used to analyze
tamoxifen and endoxifen variability. Outcome data included Recurrence Free Survival
at time of tamoxifen discontinuation (RFSt) and overall survival (OS).

Results
667 patients were included, 141 (21%) were 65 and older. Demografics and treatment duration were similar across age groups. Older patients had significantly higher concentrations of tamoxifen 129.4 ng/ml (SD 53.7) versus 112.2 ng/ml (SD 42.0) and endoxifen 12.1 ng/ml (SD 6.6) versus 10.7 ng/ml (SD 5.7) (p all < 0.05), independently of CYP2D6 and CYP3A4 gene polymorphisms. Age independently explained 5% of the variability of tamoxifen (b=0.95, p< 0.001, R2=0.051) and 0.1% of the variability in endoxifen concentrations (b=0.45, p=0.12, R2= 0.007). Older patients worse RFSt (5.8 versus 7.3 years, p=0.01) and worse OS (7.8 years versus 8.7 years, p=0.01). This was not related to differences in endoxifen concentration (HR 1.0, 95% CI 0.96-1.04, p=0.84) or CYP polymorphisms.

Discussion/Conclusion
Serum concentrations of tamoxifen and its demethylated metabolites are higher in older patients, independent of CYP2D6 or CYP3A4 gene polymorphisms. A higher bioavailability of tamoxifen in older patients may explain the observed differences. However, clinical relevance of these findings is limited and should not lead to a different tamoxifen dose in older patients.

NOVEL EXPLANTED HUMAN LIVER MODEL TO ASSESS HEPATIC EXTRACTION, BILIARY EXCRETION AND TRANSPORTER FUNCTION

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Background

Realistic models predicting hepatobiliary processes in health and disease are lacking. We therefore aimed to develop a physiologically relevant human liver model consisting of normothermic machine perfusion (NMP) of explanted diseased human livers that can assess hepatic extraction, clearance, biliary excretion and drug-drug interaction.

Methods

Eleven livers were included in the study, seven with a cirrhotic and four with a non-cirrhotic disease background. After explantation of the diseased liver, NMP was initiated. After 120 minutes of perfusion, a drug cocktail (rosuvastatin, digoxin, metformin and furosemide; OATP1B1/1B3, Pgp, BCRP and OCT1 model compounds) was administered to the portal vein and 120 minutes later, a second bolus of the drug cocktail was co-administered with perpetrator drugs to study relevant drug-drug interactions.

Results

The explanted livers showed good viability and functionality during 360 minutes of NMP. Hepatic extraction ratios close to *in vivo* reported values were measured. Hepatic clearance of rosuvastatin and digoxin showed to be the most affected by cirrhosis with an increase in Cmax of 11.50 and 2.89 times, respectively, compared to non-cirrhotic livers. No major differences were observed for metformin and furosemide. Interaction of rosuvastatin or digoxin with perpetrator drugs were more pronounced in non-cirrhotic livers compared to cirrhotic livers.

Discussion/Conclusion

Our results demonstrated that NMP of human diseased explanted livers is an excellent model to assess hepatic extraction, clearance, biliary excretion and drug-drug interaction. Gaining insight into pharmacokinetic profiles of OATP1B1/1B3, Pgp, BCRP and OCT1 model compounds is a first step towards studying transporter functions in diseased liver.

INTESTINAL TISSUE ORGANOIDS TO STUDY DRUG TRANSPORT AND METABOLISM IN VARIOUS AGE GROUPS

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Background
For development of drugs with good oral bioavailability, it is important to understand intestinal absorption, potential regional differences, and age-related effects. Preclinical models are lacking and this study aims to explore the use of intestinal organoids derived from adults and children to assess drug metabolism and transport and the potential impact of age.

Methods
Organoids from adult human jejunum and pediatric and adult ileum tissues were established. Intestinal organoids were grown as a monolayer on a membrane. Drug transport by MDR1 and BCRP, and drug metabolism by CYP3A4, were determined in bidirectional transport assays.

Results
We established adult (jejunum n=4, ileum n=3) and pediatric ileum (n=5, age range: 5-52weeks) organoids, showing active transport by MDR1 and BCRP. In adult organoids, efflux was higher in the ileum then jejunum region. Organoid monolayers from adults and children also showed CYP3A4 metabolism. No age-related differences in transport and metabolism have been observed so far.

Discussion/Conclusion
Findings show the potential of tissue-derived intestinal organoids to study drug transport and metabolism. More samples spanning a larger age range are needed to study age-related effects.

SERUM IVABRADINE ASSOCIATES WITH HEART RATE REDUCTION BUT ENTERAL EXPOSURE IS UNPREDICTABLE IN POST-SURGICAL JET

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Background
Ivabradine is a heart rate lowering drug, approved for the treatment of heart failure, but is increasingly used as an off-label drug for post-surgical junctional ectopic tachycardia (JET) in children. In contrast to most antiarrhythmic drugs, ivabradine has no negative inotropic or vasoactive effects, which makes it an attractive anti-arrhythmic agent in patients with low cardiac output state following cardiac surgery.

However, there is no rationale for ivabradine dosing regimens in pediatric arrhythmias. Current dosing is based on extrapolation of adult data and studies in pediatric heart failure patients. Ivabradine is available as an oral substrate only. It is absorbed enterally and primarily metabolized by CyP3A4. Both enteral dysfunction as well as decreased CyP3A4 metabolism due to younger age and critical illness will likely alter the pharmacokinetics of ivabradine.

We describe serum levels of ivabradine in post-surgical JET patients in relation to the administered dose and effect on heart rate.

Methods
Eight children treated with ivabradine for post-surgical JET received therapeutic drug monitoring i.e. determination of serum levels of ivabradine and its equipotent n-desmethyl metabolite using LC/MS as standard of care.

Pharmacokinectics: Using non-compartmental pharmacokinetic analysis the time to maximum concentration (Tmax), maximum concentration reached (Cmax) and area under the curve (AUC) are described.

Pharmacodynamics: To investigate the association between serum levels of ivabradine and its metabolite and heart rate a linear mixed model analysis was used.

Results
The serum concentration after enterally administered ivabradine is unpredictable in post-surgical JET patients. Some patients reached high serum levels within 2 hours whereas others never gained measurable serum levels after receiving a double dose.

The combined ivabradine and metabolite concentration showed a significant negative association with heart rate ($p=0.009$), after correction for body temperature, use of clonidine and amiodarone.

Conclusion
Oral administration of ivabradine results in unpredictable serum levels, yet the association of higher serum levels with lower heart rates infers that ivabradine can treat JET. An intravenous dose finding trial for ivabradine in JET may be the best step forward.

CABOZANTINIB POPULATION PHARMACOKINETICS IN METASTATIC RENAL CELL CARCINOMA PATIENTS: TOWARDS DRUG EXPENSE SAVING REGIMENS

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Background

Cabozantinib is the preferred treatment option in latest metastatic renal cell carcinoma (mRCC) guidelines [1,2]. However, a considerable gap between the real-world tolerability and clinical trial results has been observed. Most patients cannot tolerate the daily dose of 60 mg[3,4]. Moreover, a previous study[3] showed that higher exposure was not correlated with improved response. Furthermore, the high cost of cabozantinib can be a barrier for its use. High-fat diet resulted in an increase of cabozantinib exposure of 57% on average[5], which seems of relevance given flat pricing strategy for the 20, 40 and 60 mg tablets.
In this study, the pharmacokinetics (PK) of cabozantinib was evaluated using real-world patient therapeutic drug monitoring (TDM) data. Using the results, we explored drug expenses saving regimens with comparable exposures to that of the conventional daily dose in fasted state.

Methods

Retrospective data from mRCC patients including cabozantinib TDM concentrations were obtained. A previously published PK model for cabozantinib reported in the FDA registration documents[6] (cabozantinib PK model) was used as a basis for the PK analysis after an external evaluation.
This cabozantinib PK model consists of a two-compartment disposition model with a dual (fast and slow) lagged first-order absorption process. Subsequently, a model with better fit to our data was developed on the basis of cabozantinib PK model by estimating CL.
Simulations were performed to propose drug expense saving regimens by decreasing the dosing frequency and exploiting the drug-food interaction after the internal model evaluation of the final PK model.

Results

In total, 75 TDM observations (48% trough samples) from 27 patients were included. Patients were treated for a median 75 (IQR, 42-280) days with a median dose of 40 (IQR, 40-60) mg. Demographics of the included patients were similar to those of the patients included in the registration study in which the cabozantinib PK model was developed. Data analysis showed that the cabozantinib TDM concentrations were adequately predicted by the cabozantinib PK model in which only CL was estimated and proved to be 2.84 L/h which is slightly higher than the reported value (2.23 L/h). Model-based simulations indicated that taking 60 mg of cabozantinib under fasted conditions for 2 days and then skipping for one day results in comparable exposure when compared to taking cabozantinib 40 mg QD under fasted conditions, while 33% of the total drug expenses could be saved. The effect of a high-fat meal on exposure was also considered showing that a regimen of 40 mg q72h fed versus 20 mg QD fasted resulted in comparable exposures while potentially saving 66% of drug expenses.

Discussion/Conclusion

In this study, a cabozantinib PK model was developed using real world cabozantinib TDM data showing slight differences in CL between the clinical trial and real world population. Alternative dosing regimens including those administered together with high-fat meal are proposed with comparable exposure, but with the potential to save 33%-66% of drug expenses.

References are available on request.

MITOCHONDRIAL TRANSPLANTATION RESCUES NEURONAL CELLS FROM FERROPTOSIS

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Background

Ferroptosis is a form of oxidative cell death that involves mitochondrial damage and that has been frequently linked to neuronal cell death in neurodegenerative diseases. Previous studies demonstrated that preventing mitochondrial dysfunction can rescue cells from ferroptotic cell death. However, the complexity of mitochondrial dysfunction and the timing of therapeutic interventions make it difficult to develop an effective treatment strategy against ferroptosis in neurodegeneration conditions.

Methods

In the present study, we employed mitochondrial transplantation to neuronal cells as a novel therapeutic approach to prevent ferroptotic cell death induced by glutamate, erastin, or RSL3. We checked cell metabolic activity by MTT assays. The incorporation of mitochondria was observed by live imaging. Cell death and cellular oxidative stress level were assessed via specific dyes followed by flow cytometry. The oxygen consumption rate was determined through seahorse analysis. In addition, we employed microfluidic devices which enable us to separate the neurites of primary neurons from their cell bodies. The neurite area after different treatment was measured by immunofluorescence and quantified by ImageJ-Plug-In NeuronJ.

Results

Our data indicate that isolated exogenous mitochondria are incorporated into both healthy and ferroptotic immortalized hippocampal HT-22 cells and primary neurons. The mitochondrial incorporation into ferroptotic cells was accompanied by increased metabolic activity and cell survival through attenuating lipid peroxidation and mitochondrial superoxide production. Further, the function of mitochondrial complexes I, III and V of mitochondria in ferroptotic host cells have been supported by the transplanted mitochondria. Similarly, we have also captured the internalization of exogenous mitochondria in host mouse primary neurons; these internalized mitochondria are found to effectively preserve the neuronal networks when challenged with RSL3. The administration of exogenous mitochondria into the axonal compartment of a two-compartment microfluidic device induced mitochondrial transportation to the cell body, which repaired the fragmented neuronal network in ferroptotic primary neurons.

Discussion/Conclusion

Our findings propose mitochondria transplantation as a promising therapeutic approach for protecting neuronal cells from ferroptotic cell death.

IDENTIFYING REQUIREMENTS OF DUTCH PRIMARY CARE PHARMACISTS AND GENERAL PRACTICIONERS FOR THE DEVELOPMENT OF TELEPHARMACOLOGY

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Background

Patients are becoming increasingly pharmacologically complex as a result of an increase in life expectancy, multimorbidity and polypharmacy. These complex patients are overseen by primary healthcare providers. Telepharmacology might support primary healthcare providers in their role. Telepharmacology is a telecommunication tool for consulting secondary care specialists on pharmacology-based topics. The aim of this study is to identify the need and requirements of telepharmacology.

Methods

A survey was developed, based on previously conducted focus groups and sent to GPs and pharmacists. Questions regarding requirements were designed as Likert scales. Analyses were performed using descriptive statistics, t-tests and chi-square tests.

Results

27 pharmacists and 51 GPs met the inclusion criteria. The mean age for pharmacists was 42 and for GPs it was 49. 66 % of pharmacists and 55 % of GPS were female. 62%(N=32) of GPs and 70%(N=19) of pharmacists were in favour of the implementation of telepharmacology. 45%(N=12) of pharmacists compared to 22%(N=11) of GPs declared that they would use the service at least monthly ($p<0.04$). In Table 1 the preferences for the medium are shown. Primary healthcare providers require using existing channels and an answering time of 2 to 3 days. Telepharmacology should be a cost effective, non-bureaucratic and non-time-consuming service.

Table 1: Desired contact medium for telepharmacology

	GP (N=47)	*Pharmacist (N=26)*
Zorgdomein*	4.2 (± 1.2)	2.7 (±1.6)
Telephone	3.0 (±1.4)	3.4 (±1.2)
E-mail*	2.3 (±1.3)	3.9 (±1.1)
Siilo*	2.7 (±1.4)	3.9 (±1.1)
New application	1.5 (±1.1)	2.0 (±1.1)

Likert Scale from 1: least wanted to 5: most wanted -mean (SD)
**Statistical significance between occupation*

Discussion/Conclusion

Most GPs and pharmacists are in favour of telepharmacology. Pharmacists want to use telepharmacology more frequently than GPs. Telepharmacology can be a helpful tool to contact secondary care health care providers. Existing channels should be used for telepharmacology. The results of the research justify starting a pilot which satisfies the identified requirements.

PRECLINICAL DEVELOPMENT AND CLINICAL PHARMACOLOGY OF ^{89}ZR-PEMBROLIZUMAB

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Background
Immune checkpoint inhibitors, such as programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) targeting antibodies, show impressive antitumor effects. However, not all patients respond, and serious toxicity can occur. Strategies for early treatment choices are required. Molecular imaging with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) using radiolabeled molecules might be such a strategy. We developed different radiopharmaceuticals for this purpose. Here, we describe the preclinical development of the (^{89}Zr) labeled PD-1 targeting monoclonal antibody pembrolizumab, including preclinical and clinical imaging studies.

Methods
Preclinical development consisted of optimizing radiolabeling and *in vitro* testing. To gain more insight into the *in vivo* behavior, a preclinical imaging study has been performed in human A375M melanoma-bearing humanized NOG mice (huNOG) [1]. We developed a good manufacturing practices (GMP) compliant production process for clinical studies. Lastly, we performed a PET imaging study in patients with melanoma or NSCLC before PD-1 antibody treatment to study pharmacology and tumor targeting [2].

Results
^{89}Zr-pembrolizumab was produced with a specific activity of 500 MBq/mg and radiochemical purity of >95%. PET imaging studies in mice showed high ^{89}Zr-pembrolizumab uptake in the spleen, lymph nodes, and bone marrow. In huNOG mice, ^{89}Zr-pembrolizumab tumor uptake was lower than uptake in lymphoid tissues but higher than in other organs. An imaging study performed in 18 patients (n=11 melanoma; n=7 NSCLC) showed no difference in tumor uptake between melanoma and NSCLC (SUVmax 4.9 and 6.5, P = 0.49). Tumor ^{89}Zr-pembrolizumab uptake correlated with tumor response (P trend = 0.014) and progression-free (P = 0.0025) and overall survival (P = 0.026). ^{89}Zr-pembrolizumab uptake was highest in the spleen, but there was also uptake in Waldeyer's ring, normal lymph nodes, and sites of inflammation.

Discussion/Conclusion
We developed ^{89}Zr-pembrolizumab for preclinical and clinical imaging studies. In mice ^{89}Zr-pembrolizumab biodistribution showed high PD-1-mediated uptake in lymphoid tissues, and modest tumor uptake. In human ^{89}Zr-pembrolizumab, uptake in tumor lesions correlated with treatment response and patient survival. ^{89}Zr-pembrolizumab also showed uptake in lymphoid tissues and at sites of inflammation. This approach might lead to better patient selection and therapy evaluation before cancer immunotherapy treatment.

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THE ROLE OF ABC TRANSPORTERS IN TYROSINE KINASE INHIBITOR TREATMENT OF CHRONIC MYELOID LEUKEMIA PATIENTS

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Background

Chronic myelogenous leukemia (CML) is caused by a reciprocal chromosomal translocation resulting in the expression of the constitutively active tyrosine kinase BCR-ABL1. Tyrosine kinase inhibitors (TKIs) have turned CML from a once-fatal blood cancer to a manageable disease. However, life-long TKI treatment of CML patients is associated with adverse effects and the risk to acquire drug resistance, resulting in disease relapse. Therefore, novel therapeutic strategies are warranted to specifically re-sensitize TKI treatment-resistant CML stem cell (SC) populations to prevent relapse. ATP-binding cassette (ABC) transporters could play a pivotal role in rendering the cells resistant to TKIs as they are expected to decrease intracellular drug concentrations by mediating TKI efflux across the plasma membrane. ABC transporters are also abundantly expressed in the lysosomal membrane, which could contribute to subcellular TKI sequestration and further lowering of cytosolic TKI levels.

This project aims to elucidate the contribution of ABC transporters to TKI resistance of CML SCs to enable their eradication. A deeper understanding of the role of these transporters might help in finding new therapeutic options and thus optimized treatment of CML patients.

Methods

A bone marrow on chip (BMoC) model in which CML SCs can be studied at the single-cell level will be developed and validated. After the deposition of bone marrow extracellular matrix in the BMoC the ABC transporter-mediated TKI distribution in CML SCs will be studied using fluorescence microscopy. A distinction will be made between TKI-resistant and TKI-sensitive CML SCs by using a CRISPR-Cas9 based gene painting approach.
In addition, transporters of interest will be overexpressed in HEK293 cells using a mammalian baculoviral expression system. These cells will be used to study the TKI uptake characteristics per transporter. Absolute intracellular TKI concentrations will be quantified using LC-MS/MS. Hereafter the potential of pharmacological and genetic inhibition of the transporters of interest will be evaluated. Also, cytotoxicity will be determined as a measure of re-sensitization to TKI treatment.

Results/Discussion

Preliminary data show that ABC transporter expression is specifically enhanced in CML SCs as compared to normal hematopoietic stem cells, with differential lysosomal expression of ABCA1, ABCA5 and ABCD1, when comparing newly diagnosed patients versus patients that have been treated with TKIs for 5 years.

The intended outcomes of this study are a thorough understanding of the contribution of ABC transporters to TKI resistance of CML SCs at the single-cell level.

THE CLINICAL IMPACT OF THE DRUG-DRUG INTERACTION BETWEEN CYCLOSPORINE AND LETERMOVIR IN ALLOGENENIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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Background
Cytomegalovirus (CMV) reactivation/infection is a severe complication in allogenic hematopoietic cell transplantation (HCT) recipients. In this setting, letermovir is routinely used as CMV prophylaxis. A significant, reciprocal drug-drug interaction exists between letermovir and cyclosporine (CsA). The FDA recommends standard dose reductions in letermovir when concomitantly used with cyclosporine. However, data on the effect of letermovir on cyclosporine levels is very limited. Therefore, the aim of this study is to examine the impact of the drug-drug interaction between letermovir and cyclosporine in HCT recipients on cyclosporine trough levels.

Methods
In this retrospective, single center study data from HCT recipients whom were transplanted between June 2019 and March 2021 and concomitantly used letermovir and cyclosporine were analyzed. Steady state PK samples for cyclosporine levels were taken before and after the start of letermovir and were analyzed separately for the cohort that was on intravenous *versus* oral cyclosporine.

Results

In patients who received cyclosporine intravenously (n=19), CsA trough levels showed a significant rise (pre 74.2 µg/L *versus* post: 112.1 µg/L, $p<0.0001$) after the start of letermovir. When administered orally (n=10), a similar increase in trough levels was observed (pre: 245.7 µg/L versus post: 371.1 µg/L, $p< 0.0001$). 93% of the patients demonstrated signs of CsA toxicity.

Discussion/Conclusion

Co-administration of letermovir causes a ~30% rise in cyclosporine trough levels in HCT recipients which resulted in a high incidence of cyclosporine toxicity. This suggests the need for prospective data to examine this interaction which could ultimately lead to recommendations on dosage adjustments of cyclosporine.

DETERMINING THE ABSOLUTE BIOVAILABILITY OF OXALIPLATIN FOLLOWING INTRAPERITONEAL ADMINISTRATION BY PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY

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Background
Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is a new technic for treatment of local peritoneal metastases in which chemotherapy is intraperitoneally administered as an aerosol, and is considered local therapy. However, absolute bioavailability and hence relative systemic drug exposure remains unknown. One of the aims of the CRC-PIPAC-II trial was to determine the absolute bioavailability (Fabs) of oxaliplatin following administration by PIPAC.

Methods
Patients enrolled in the CRC-PIPAC-II trial underwent three cycles of bidirectional therapy, each consisting of six weeks of systemic therapy (CAPOX-bevacizumab [130 mg/m2 oxaliplatin in 3-weekly cycles] or FOLFOX-bevacizumab [85 mg/m2 oxaliplatin] in 2-weekly cycles) followed by PIPAC-OX (92 mg/m2). For each patient, whole blood samples were collected at standardized time-points during and after the first ePIPAC-OX and the first cycle of systemic therapy.Total oxaliplatin concentrations were determined using atomic absorption spectrometry; Areas under the curve (AUCs) of oxaliplatin were calculated using Nonlinear Mixed Effect Modelling (NONMEM). Fabs was calculated as the fraction of the AUC of the systemic oxaliplatin exposure following intraperitoneal administration over the AUC following intravenous administration, corrected for the dose: Fabs= 100% x AUCintraperitoneal x doseintravenous / (AUCintravenous x doseintraperitoneal).

Results
Eighteen patients were included in the pharmacokinetic analyses, providing a total of 195 blood samples. The mean Fabs for total oxaliplatin following administration by PIPAC was 100%.

Discussion/Conclusion
The total bioavailability of oxaliplatin after administration by PIPAC was 100%, thus indicating full systemic drug absorption. Thereby, PIPAC cannot be seen as solely local therapy, but may contribute to cumulative systemic toxicity. This finding questions the position of PIPAC as solely local therapy as well as its hypothesized benefits of low systemic exposure and accompanying side-effects.

CLINICALLY RELEVANT PHARMACOKINETIC INTERACTION OF CLOZAPINE AND TOPIRAMATE THROUGH CYP3A4 INDUCTION

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Background For patients not adequately responding to clozapine, several augmentation strategies exist with varying degrees of effect and level of evidence. The Dutch Clozapine Plus Working Group offers topiramate as an augmentation strategy beneficial for decreasing positive symptoms.

Case Description A 61-year old male, with long-standing treatment-resistant schizophrenia and a high risk of violence in case of disease relapse, was treated with clozapine 450 mg/day, reaching the target plasma concentration of 700-800 mcg/L. Clozapine treatment had previously been augmented with electroconvulsive therapy. Augmentation with both risperidone and aripiprazole was current in stable dosages. Due to continuing psychotic symptoms, additional augmentation with topiramate was initiated, titrated up to a dose of 500 mg/day over a course of eight months. At a topiramate dose-level of 425 mg/day, clozapine plasma levels suddenly started to decrease to 500 mcg/L, in spite of clozapine dose increases from 450 mg to ultimately 950 mg/day. Treatment compliance and changes in smoking habits were ruled out as a cause. After 13 months of treatment, topiramate was tapered down over a course of 11 weeks due to ineffectiveness, and simultaneously clozapine plasma levels started to increase to target levels again. Subsequently, clozapine dose could be decreased to baseline within a few months.

Discussion Clozapine is a substrate for CYP1A2 (major pathway), but also for CYP2C19 and CYP3A4. The SmPC reports potentially clinically relevant interactions with strong CYP3A4 inducers such as carbamazepine and rifampicin, but not with topiramate. Systematic literature search revealed only one described clinically relevant interaction via CYP3A4 induction by topiramate, i.e. reduced levels of hormonal contraceptives [1].
Migliardi *et al* investigated the effect of topiramate on steady-state plasma levels of clozapine, olanzapine, quetiapine and risperidone. None of the plasma concentrations of the studied drugs were significantly affected up to a dose of 200 mg/day of topiramate addition after 8 weeks [2].
Nallani *et al* investigated *in vitro* the extent to which topiramate induces CYP3A4 in human hepatocytes, and showed a clear concentration-dependent effect. The authors alert for potential CYP3A4 drug-drug interactions for topiromate doses ≥400 mg/day [3]. This fully corresponds with the observed decrease in clozapine plasma levels in our patient, which were only observed at a topiramate dose > 400mg/day.

Conclusion Based on the mechanistic rationale, the clearly observed temporal relationship, and the *in vitro* evidence, a clinically relevant pharmacokinetic interaction between clozapine and topiramate through CYP3A4 induction could be demonstrated at topiramate doses of > 400 mg/day.

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DURATION OF IMMUNO-ASSAY INTERFERENCE IN METHOTREXATE-LEVELS AFTER GLUCARPIDASE ADMINISTRATION FOLLOWING HIGH-DOSE METHOTREXATE THERAPY

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Background
Glucarpidase has demonstrated to be an highly effective antidotum for methotrexate (MTX) intoxications caused by high dose (HD)-MTX therapy. Glucarpidase is an enzyme that hydrolyses MTX into its inactive metabolites 4-deoxy-4-amino-N10- methylpteroïnezuur (DAMPA) and glutamate [1]. However, the nontoxic metabolite DAMPA cross-reacts with MTX in standard immuno-assays (IA), resulting in artificially elevated MTX-levels. Different sources state that IA analysis is unreliable during 48 hours after glucarpidase administration due to DAMPA's half-life of 10 hours [2-4].

Methods
We present two patients treated with glucarpidase:
Patient 1 (male, age 71, 77 kg, BSA 2,06 m2, creatinine 80 umol/L, eGFR 85 ml/min/1,73m2) was treated with a second cycle of R-MP with a MTX dose of 3 gram/m2 in 4 hours. Creatinine was 233 and 264 umol/L and MTX 98,97 and 29,36 umol/L at t=24hr and t=48hr respectively. He was given 3850 IE glucarpidase at t=58,5hr.
Patient 2 (male, age 18, 86 kg, BSA 2,06 m2, creatinine 56 umol/L, >90 ml/min/1,73m2) was treated with ALL consolidation B with a MTX dose of 5 gram/m2 in 24 hours. Creatinine was 140 umol/L at t=24hr and MTX 24,33 umol/L at t=36hr; at t=48hr creatine was 196 umol/L and MTX 18,08 umol/L. He was given 1000 IE glucarpidase at t=56,5hr and 3000 IE at t=80hr.

Results
After glucarpidase administration we measured MTX-levels with both IA and LC-MS/MS-analysis (table 1):

Table 1:

	Patient 1			*Patient 2*		
*Time (hr)**	*MTX IA#*	*MTX LC-MS/MS#*	*Ratio*	*MTX IA#*	*MTX LC-MS/MS#*	*Ratio*
36	0,96	0,01	96,00	2,84	0,03	94,67
60	0,87	0,19	4,58	2,01	0,52	3,87
84	0,72	0,34	2,12	0,78	0,38	2,05
108	0,42	0,27	1,56	0,39	0,26	1,50
132	0,52	0,38	1,37	0,25	0,2	1,25

* *time after full glucarpidase administration* # MTX in umol/L

We observed similar ratio's for MTX measured with IA and LC-MS/MS in both patients. MTX measured with IA showed unreliable results > 48hr after glucarpidase administration.

Discussion/Conclusion
We showed that even after much longer than 48hr MTX measured with IA is still elevated compared to LC-MS/MS-analysis. Most likely the duration of interference is dependent on the patients renal function (to eliminate DAMPA). DAMPA half live might be much longer in patients with severely impaired renal function. Further, clinicians might benefit from using ratio's to estimate LC-MS/MS MTX-levels, especially in hospitals where only ARK measurement is available.

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LOWER EXPOSURE TO BICTEGRAVIR IN THIRD TRIMESTER IN PREGNANT WOMEN LIVING WITH HIV

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Background
Antiretroviral treatment in pregnant women living with HIV serves to reduce the risk of mother to child transmission of the virus, but also to guarantee maternal health. Due to physiological changes during pregnancy, drug concentrations may be altered, whereby drug efficacy might be hampered. The aim of this study was to compare the pharmacokinetic profile of bictegravir – an integrase inhibitor which is increasingly being used in the treatment of HIV - during the third trimester of pregnancy and in a non-pregnant state.

Methods
In this multicentre, open-label, non-randomized trial pregnant women living with HIV and using a bictegravir containing regimen were included. Pharmacokinetic sampling (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours) was performed in the third trimester and 4-6 weeks postpartum. If possible, cord blood and maternal plasma at the delivery date were also collected. Plasma concentrations were determined with the use of LC-MSMS. Pharmacokinetic parameters were determined with noncompartmental analysis. To evaluate the influence of pregnancy on the pharmacokinetics of bictegravir, a linear mixed-model (with pregnancy as fixed-effect and random effect for participant) was used on the log transformed pharmacokinetic parameters to calculate the geometric mean ratios and 90% confidence interval (CI).

Bictegravir trough levels were compared to the protein-adjusted IC_{95} (PA-IC_{95}) value of 0.162 mg/L. In addition, clinical efficacy and safety outcomes were collected.

Results
6 women were included, from who 6 third trimester and 5 postpartum curves were obtained. The geometric mean (CV%) in third trimester for AUC_{0-24}, $C_{max,}$ C_{min} and $T_{1/2}$ was 51,0 (21) h*mg/l, 4.3 (21) mg/l, 1.0 (34) mg/L and 11,0 (22) (h) respectively. The geometric mean ratio third trimester versus postpartum (%, 90% CI) of these parameters were 0.56 (0.41-0.77), 0.68 (0.50-0.92), 0.38 (0.29-0.49) and 0.56 (0.45-0.71) respectively. None of the bictegravir trough levels were below the PA-IC_{95}. No virologic failure or mother to child transmission occurred in this cohort. Three cord blood concentrations were obtained, the cord blood : maternal plasma ratios were: 0.65, 1.42 and 1.49 respectively. No congenital abnormalities were reported.

Discussion/Conclusion
The lower exposure to bictegravir in third trimester compared to postpartum might be attributed to increased hepatic clearance trough CYP3A4 and UGT1A1. Despite the decrease, bictegravir trough levels remained above the PA-IC95 and no virological failure or mother-to-child transmission occurred. More data are needed to confirm our findings.

THE USE OF SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS OR GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS VERSUS SULFONYLUREAS AND THE RISK OF LOWER LIMB AMPUTATIONS

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Background
Numerous studies have investigated the potential association of sodium-glucose co-transporter-2 inhibitors (SGLT2-Is) with an increased risk of lower limb amputations (LLAs), but have produced conflicting results. Particularly studies comparing SGLT2-Is to glucagon-like peptide-1 receptor agonists (GLP1-RAs) seem to find a higher LLA risk with SGLT2-I use. This raises the question whether the results are driven by a protective GLP1-RA-effect rather than a harmful SGLT2-I-effect. GLP1-RAs could promote wound healing and therefore reduce the risk of LLAs, but the associations between both drug classes and LLA remain uncertain. Therefore, the aim of the current study was to investigate the risk of LLA and diabetic foot ulcer (DFU) with SGLT2-I use and GLP1-RA use versus sulfonylurea use.

Methods
A retrospective population-based cohort study was conducted using data from the Danish National Health Service (2013-2018). The study population (N = 74,475) consisted of type 2 diabetes patients aged 18+ who received a first ever prescription of an SGLT2-I, GLP1-RA or sulfonylurea. The date of the first prescription defined the start of follow-up. Time-varying Cox proportional hazards models were used to estimate the hazard ratios (HRs) of LLA and DFU with current SGLT2-I use and GLP1-RA use versus current SU use. The models were adjusted for age, sex, socio-economic variables, comorbidities and concomitant drug use. Sensitivity analyses included changing the reference group to current dipeptidyl peptidase-4 inhibitors, and excluding individuals a history of LLA.

Results
Current SGLT2-I use was not associated with a higher risk of LLA versus sulfonylureas (adjusted HR 1.10 [95% confidence interval (CI) 0.71-1.70]). This finding remained consistent after stratification by sex, age, and continuous duration of use. Current GLP1-RA use, on the other hand, was associated with a lower risk of LLA (adjusted HR 0.57 [95%CI 0.39-0.84]) compared to sulfonylureas. Several sensitivity analyses supported the robustness of the findings. The risk of DFU with SGLT2-I use and GLP1-RA use was similar to that with sulfonylurea use.

Conclusion
SGLT2-I use was not associated with a higher risk of LLA, but GLP1-RAs with a lower risk of LLA. Previous studies reporting a higher risk of LLA with SGLT2-I use compared to GLP1-RA use might have been looking at a protective GLP1-RA effect, rather than a harmful SGLT2-I effect.

DEVELOPMENT OF AN ELEARNING TO IMPLEMENT THE NEW ADDENDUM IN THE GUIDELINE POLYPHARMACY IN ELDERLY

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Background

Medication related admissions occur frequently in the Netherlands . The HARM study in 2006 concluded that 5.6% of all acute admissions where medication related, 68% of these admissions were in the elderly (65 years or older) and almost half of the admissions were considered to be preventable[1]. In 2018 an addendum to the Polypharmacy Guideline considering in hospital use of medication was published to improve patient safety. during the hospital admission [2]. The guideline advised an implementation plan to develop subject specific education for those using the guideline. eLearning effectively increases knowledge, however there is still limited evidence that eLearning improves skills or professional practise [3]. In medical practise residents in training and residents not in training often work in a hospital ward for a limited period of time. Most hospitals have general education and introduction programmes important for all physicians independent of their specialty

Methods

We developed an eLearning that covered all aspects of the addendum to the guideline. Whilst developing the eLearning, classical didactical teaching was in place to transfer knowledge on the new addendum meanwhile. The programme Rise was used. This is a secure, cloud based commercial training system. The system uses basic modules that can be personalised, for example multiple choice questions, text with a question but also audio fragments and video is optional. This system can be easily integrated in the hospitals learning portal. The AVL academy provided support in the development of the eLearning, content was determined by expert physicians, based on the addendum to the guideline and adapted to local needs.

Results

We developed an eLearning that can be used by al new residents, physicians and physician assistants, but also the currently working physicians can do the eLearning. A combination of background knowledge and test questions was used, so the participants do not need background knowledge or preparation before the eLearning. Links to the addendum were incorporated in the eLearning, as well as to hospital specific knowledge on medication related problems that occur in the hospitals specific patient category, i.e. oncology patients. In the eLearning participants are not formally tested on their knowledge, however they are asked to perform test questions for educational purposes. The eLearning is being implemented in the introduction programme and the discipline transcending educational programme, starting with the residents and with the ambition to further to all physicians and physician assistants in the AVL. Classical didactical teaching still supports the implementation of the eLearning.

Discussion/Conclusion

Implementing a guideline can be challenging in the hospital environment with often changing personnel. An eLearning is a method that creates an easily accessible and adaptable programme that can be offered to many students. There is little evidence that eLearning is effective in changing professional practise, so further research is necessary to evaluate the benefit of this eLearning on the long term [3]. We aim to evaluate the impact of our eLearning as part of a blended learning course on professional practise concerning medication related problems in the hospital in the near future. An eLearning can be an educational tool to implement guidelines in the hospital setting, how this can impact professional practise and hopefully improve patient safety needs to be further evaluated.

References are available on request.

AIR POLLUTION PARTICLES ACCELERATE RSL-3-INDUCED FERROPTOSIS IN HT22 CELLS VIA CAMP-EPAC1 PATHWAY

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Background

Air pollution exposure is one of the important threats to human health. Diesel combustion produces diesel exhaust particles (**DEP**) which seem to contribute to the onset of different neurological diseases due to the induction of oxidative stress, inflammation and neuronal degeneration[1]. Underlying molecular mechanisms are ill defined. **RSL-3**-induced neurotoxicity has been linked to the newly identified iron-dependent form of cell death **ferroptosis**[2]. Cyclic adenosine monophosphate (**cAMP**) seems to be linked to ferroptosis type of cell death in processes involving **Epac** (exchange protein directly activated by cAMP[3].

Methods

Hippocampal neuronal (HT22) cells were treated with increasing concentrations of NIST DEP (24h) or RSL-3 (17h) alone and with different concentrations of NIST DEP and RSL-3 (17h) in combination. Cell viability was measured by MTT assay. To further determine the basis of NIST DEP and RSL-3-mediated cell death, pan-caspase inhibitor QVD (10 μM) and ferroptosis inhibitor ferrostatin-1 (5 μM) were used, and fluorescence microscopy was used to capture the photographs (Hoechst 33342/PI double staining assay). To elucidate the role of cAMP/Epac1 signaling in regulating the response to the combined effect, the expression of Epac1 was analyzed by western blotting, and Epac1 inhibitor CE3F4 (30 μM) and Epac2 inhibitor ESI-05 (30 μM) were used.

Results

NIST DEP alone does not significantly change HT22 cell viability. Importantly, co-treatment with NIST DEP (100 μg/mL) further increased RSL-3-induced (75 nM) cell death by MTT assay. Ferrostatin-1 restored cell viability and reduced the number of PI-positive cells after treatment of RSL-3 and NIST DEP. Epac1 expression is detectable in HT22 cells. CE3F4 but not ESI-05 prevented cell death after NIST DEP and RSL-3 cotreatment.

Discussion/Conclusion

Our current work demonstrates that co-treatment of HT22 cells with RSL-3 and NIST DEP caused a significant increase in cell death compared with RSL-3 treatment alone. Accelerated cell death of HT22 cells seems to involve ferroptosis, in a process dependent on Epac1. Currently, studies are focused on the effect of NIST DEP on microglia.

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MODEL-BASED DOSING RECOMMENDATIONS FOR VANCOMYCIN IN HOSPITALIZED PATIENTS WITH VARYING DEGREES OF OBESITY AND RENAL (DYS)FUNCTION

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Background
The variable pharmacokinetics (PK) and relatively narrow therapeutic window of vancomycin make it challenging to dose patients with obesity, renal insufficiency, critical illness, or a combination of these characteristics. We developed a population PK model in a large and representative population with varying degrees of obesity and renal function admitted to the hospital ward or ICU, and provide model-derived dosing recommendations.

Methods
Vancomycin concentrations from TDM sampling (n=1188) from 215 patients (25% from ICU) with varying degrees of obesity (BMI> 25 kg/m^2) and renal function (without renal replacement therapy), receiving continuous or intermittent intravenous infusion, were pooled with published prospective data (n=207) from 20 (morbidly) obese subjects undergoing bariatric surgery. A population model was developed using non-linear mixed effect modeling. Stochastic simulations were performed to design dosing guidelines targeting an AUC_{24h} between 400–650 mg·h/L.

Results
In a three-compartment model, we quantified how vancomycin CL increases with renal function (CKD-EPI 75 [6-155] ml/min/1.73m^2) and total bodyweight (TBW 92 [59 – 235] kg). Compared to non-ICU subjects, CL proved 15.5% lower in ICU patients. Dosing guidelines for continuous infusion with a loading dose derived from the final model were proposed. AUC_{24h} and concentration-time profiles obtained with the proposed guidelines show that in obese patients, concentrations at the end of the first days of treatment are below the reported target of 20–25 mg/L, even though the target AUC_{24h} exposure is achieved. In steady-state, these dosages however do lead to both AUC_{24h} and concentration within target. Besides, time to steady-state proved longer than 7 days for groups with compromised renal function. Our results indicate that attention should be paid when increasing the dose based on sub-therapeutic concentrations in the first days of treatment and that TDM may still be required in later days of treatment, particularly upon renal dysfunction.

Discussion/Conclusion
We quantified how ICU admission, TBW, and renal function should be used to individualize dosing of vancomycin to get safe and effective vancomycin exposure. It should be noted that time to steady-state is prolonged in the obese patient population.

ACTIVATION OF SK CHANNELS FACILITATES HUMAN NEURONAL DIFFERENTIATION

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Background
Small-conductance Ca^{2+} activated K^{+} (SK) channels are involved in afterhyperpolarization, firing rate regulation and neuroprotection. Activation of SK channels was shown to regulate cardiac stem cells differentiation and murine neuronal progenitor cell (NPC) development. However, their role in human neuronal differentiation is not well characterised. SK channels include four subtypes that share similar structural composition and functional activities. 1-EBIO and CyPPA are well studied SK channel openers with different selectivity: 1-EBIO activates all SK channel isoforms, while CyPPA targets mainly SK2 and SK3 channel isoforms. In our lab, we generated human mature neurons from iPSC and investigated how SK channel activation can affect neuronal differentiation during NPCs stages and early differentiation period.

Methods
We differentiated mature neuronal networks from iPSC cells and characterised various stages during differentiation from NPC to mature functional neurons. Activation of SK channels was performed with 1- EBIO and CyPPA at various stages of differentiation for 16, 23 and 30 days of differentiation. We collected samples for RNA-seq and performed immunofluorescence to quantify the ratio between stem cell and neuronal cell markers (i.e. βIII tubulin). Cell differentiation was assessed by calcein staining.

Results
Activation of SK channels in NPCs, during the differentiation process resulted in alterations in cell morphology, with more elongated structures compared to solvent-treated control cells. While 1-EBIO exerted a significant impact on the morphology of cells and facilitated neuronal differentiation, CyPPA displayed a comparatively modest effect on cell morphology.

Analysis of the RNAseq showed that several genes responsible for cytoskeleton development were upregulated, while extracellular matrix (ECM)-related genes including COL1A2, COL3A1, FGFR1 were found downregulated following treatment with 1-EBIO for 30 days. Enrichment pathway analysis showed that EBIO mediated a dysregulated ECM assembly, and upregulated neurogenesis, neuron differentiation and skeletal system development.

Discussion/Conclusion
SK channels activation increases neuronal development in NPCs by regulation of genes related to neurogenesis. Downregulated ECM-related genes are in agreement with the calcein measurements for the neuronal outgrowth. Interestingly, both 1-EBIO and CyPPA promote neuronal development during early differentiation stages of NPCs.

In conclusion, modulation of SK channels plays an important role during early neuronal differentiation.