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CYSTATIN C AND CREATININE-BASED eGFR IN THE INPATIENT AND OUTPATIENT POPULATION

Authors: IA Janssen[1], N Abu Ezzat[1], RH Olde Engberink[1,2]

Organisations: Departments of Pharmacy[1] and Nephrology[2] Amsterdam UMC, the Netherlands.

Introduction

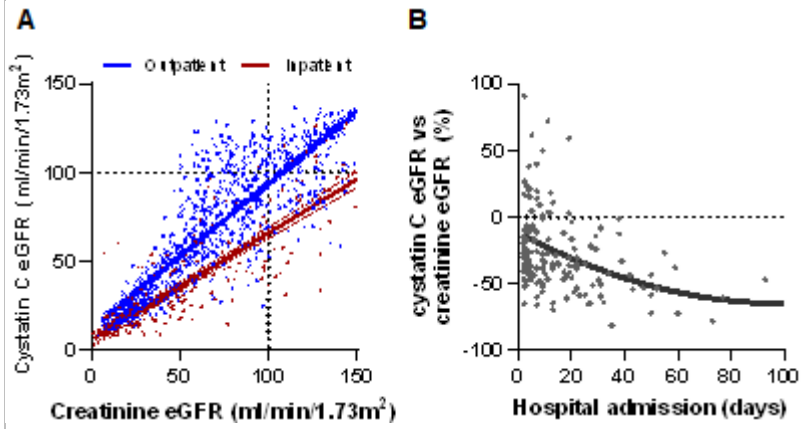
Measures for kidney function are used for clinical decision making and medication prescribing, therefore accurate and reliable markers for kidney function are crucial. Multiple non-renal factors influence creatinine concentration, the standard method of estimated glomerular filtration rate (eGFR) calculation. Cystatin C, a new marker, is influenced by other factors, which have been well-described in outpatients but have yet to be analysed in patients admitted to the hospital, in whom muscles are wasted because of bed rest. We hypothesized that the discrepancy between creatinine and cystatin C eGFR would be greater in the inpatient setting than the outpatient setting.

Methods

We performed a single-centre, retrospective, observational cohort study with 3 patient cohorts within Amsterdam UMC between 2022 and 2025. A cohort of admitted patients with additional cystatin C measurements upon the advice of the pharmacist, and two cohorts of outpatients and inpatients with simultaneous creatinine and cystatin C measurements. We excluded patients who used corticosteroids or had thyroid dysfunction We calculated the absolute and relative difference between eGFR values. In a multivariate analysis, corrected for age and sex, we assessed whether length of hospital stay and/or intensive care unit admission was associated with the discrepancy in creatinine and cystatin C eGFR.

Results

Within the pharmacy cohort cystatin C-eGFR was 42% lower (IQR: -54 to -20%; n=25) than creatinine-eGFR. In the inpatient cohort cystatin C-eGFR was 29% lower (IQR: -43 to -6%; n=200). In contrast, creatinine and cystatin C-eGFR were similar in the outpatient cohort (median difference 0%, IQR: -14 to 18; n=874; p<0.001 vs. the pharmacy and inpatient cohort; Fig A). Hospitalization duration was associated with the magnitude of difference between creatinine and cystatin C-eGFR in patients admitted to the hospital (p<0.001, Fig B)



Conclusions

The discrepancy between creatinine and cystatin C-eGFR is much greater in patients admitted to the hospital than in out-patients. The strong association with the length of hospital stay suggests that muscle mass loss explains this difference. Cystatin C-eGFR may be superior to creatinine-eGFR in subjects with prolonged hospital stay.

INCIDENCE AND PHARMACOKINETIC PREDICTORS OF ACUTE KIDNEY INJURY DURING VANCOMYCIN–PIPERACILLIN/TAZOBACTAM THERAPY

Authors
Sombogaard, F[1]; Manubulu, WP[1]; Berrier, S[1]; Zijlstra, HW[2]
Organisations
1) Clinical Pharmacy and Toxicology, 2) Intensive Care Unit, Martini Hospital Groningen, The Netherlands

Introduction
The combination of vancomycin and piperacillin/tazobactam (piptazo) (VPT) has consistently been associated with an increased incidence of acute kidney injury (AKI) compared with alternative vancomycin-based regimens. However, determinants of AKI and the potential role of vancomycin clearance as an early marker of renal dysfunction remain unclear. We aimed to determine the incidence, severity, and predictors of AKI during VPT therapy in routine clinical practice and to evaluate whether calculated vancomycin clearance differs prior to AKI onset.

Methods
We conducted a retrospective, observational study at Martini Hospital Groningen (The Netherlands) including adult patients treated with vancomycin combined with piptazo for ≥24 hours between January 2015 and March 2025. Inclusion required a baseline serum creatinine (SCr) measurement, ≥1 vancomycin TDM result, and SCr measurements during treatment. AKI was defined according to KDIGO criteria. Vancomycin clearance (CLvanco) was calculated using MWPharm++.

Results
A total of 187 patients were included; 33 patients (18%) developed AKI. AKI severity was stage 1 in 20/33 patients (61%), stage 2 in 9/33 (27%), and stage 3 in 4/33 (12%). Mean time to AKI onset was 2.0 days (range 0.1–12). Median CLvanco prior to AKI was 0.0400 (range 0.00905–0.0917) L/h/kg in AKI patients versus 0.0356 (0.00654–0.123) L/h/kg in non-AKI patients (p=0.393). However, stage-specific differences were observed: patients developing stage 1 AKI had higher CLvanco compared with non-AKI patients (0.0634 vs. 0.0356 L/h/kg, p=0.002), whereas stage 3 AKI was preceded by lower clearance (0.0109 vs. 0.0356 L/h/kg, p=0.017).
In multivariable logistic regression, CLvanco (OR 13.38 – >1,000 (95% CI); p=0.027) and BMI (OR 1.04–1.21 (95% CI); p=0.002) were independently associated with AKI. Other covariates, including age, diabetes mellitus, baseline eGFR, treatment duration, ward type, and concomitant nephrotoxins, were not independently associated.

Conclusions
In this observational cohort, VPT therapy was associated with an AKI incidence of 18%, with 39% of cases classified as stage 2 or 3. CLvanco and BMI were statistically associated with AKI occurrence; however, the wide confidence interval and stage-dependent directional differences limit the clinical applicability of clearance as a predictive marker. These findings support careful renal monitoring during VPT therapy but do not establish a reliable early predictor of AKI.

RISK OF ACUTE KIDNEY INJURY AFTER SHORT-TERM METAMIZOLE USE IN REAL-WORLD DATA

Authors
Charlott E Stein, MD[1,2], Lieke Mitrov-Winkelmolen, PharmD[1,3], Tessa Bosch, PharmD[1,4], Arjan van Alphen, MD, PhD[4,5], Namiko A Goto, MD, PhD[6], Rikje Ruiter, MD, PhD[4,5].

Organisations
1. Department of Hospital Pharmacy, Maasstad Hospital, Rotterdam, The Netherlands
2. Department of Geriatrics, Hospital Gelderse Vallei, Ede, The Netherlands
3. Department of hospital Pharmacy, Flevoziekenhuis, Almere, The Netherlands
4. Department of Clinical Pharmacology & Toxicology MaasstadLab, Maasstad Hospital, Rotterdam, The Netherlands
5. Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands
6. Department of Geriatrics, Jeroen Bosch Hospital ‘s-Hertogenbosch, The Netherlands

Introduction
Metamizole is a nonselective non steroid anti-inflammatory drug (NSAID). For long, its trading license for oral administration in the Netherlands was withdrawn because of a risk of agranulocytosis. In 2021 it has been re-approved for in-hospital use due to a supposed favorable side effect pattern compared to other NSAIDs. Since 2021, metamizole use has steadily increased. In this retrospective cohort study we evaluate the risk of acute kidney injury (AKI) after short-term metamizole use.

Methods
We included patients admitted to our hospital between January 2020 and December 2022, with at least four dosages of metamizole administered and a known renal function up to 7 days before and 24 to 72 hours after start of metamizole. Renal functions were compared before and after metamizole use.

Results
Renal function before and after metamizole use was available for 1,146 patients. Median cumulative metamizole dosage was 11.000 mg and median duration of use was 4.5 days. Mean age was 64 years, most patients (87%) had an eGFR > 60 ml/min/1.73m2 before start of metamizole and were admitted to a surgical ward (75%). Mean eGFR decreased after metamizole use (eGFR -0.7 ml/min/1.73m2, CI: -1.52-0.05, $p = 0.065$) albeit statistically non significant. However, in patients older than 70, a significant decline in kidney function was seen (n=527, difference in eGFR -3.2 ml/min/1.73m2, CI: -4.47-(-1.90), $p < 0.001$).

Conclusions
This study found no significant change in renal function after metamizole use. However, in patients over 70 years old, a significant decline in kidney function was observed, suggesting older patients may be at higher risk. No conclusions could be made on risk of AKI in patients with a poor renal function (eGFR < 30 ml/min/1.73m2) or about long-term metamizole use.

MODEL-INFORMED REPURPOSING OF ELIGLUSTAT FOR TREATMENT AND PROPHYLAXIS OF SHIGA TOXIN-PRODUCING ESCHERICHIA COLI HEMOLYTIC-UREMIC SYNDROME (STEC-HUS) IN CHILDREN

Authors
David F.G.J. Wolthuis, Jolien J.M. Freriksen, Mendy ter Avest, Reena V. Kartha, Saskia N. de Wildt, Kioa Wijnsma, Nicole C.A.J. van de Kar, Rob ter Heine

Organisations
Radboudumc (departments of Internal Medicine, Pharmacy, Pediatric Nephrology, Intensive Care) and University of Minnesota (Center for Orphan Drug Research)

Introduction
Shiga toxin-producing Escherichia coli hemolytic-uremic syndrome (STEC-HUS) is a severe illness predominantly affecting young children, with limited treatment options beyond supportive care. Eliglustat, approved for Gaucher disease, shows potential in reducing Shiga toxin binding to target glomerular endothelial cells in vitro, prompting interest as a treatment for STEC-HUS. However, it remains unknown what dose is likely to be effective and safe for treatment of STEC-HUS in the pediatric population. We hypothesize that effective and safe levels of can be reached in children.

Methods
We identified pharmacokinetic targets for efficacy for treatment and prophylaxis of STEC-HUS based on a preclinical model and human cardiac safety data. Then, we developed oral and intravenous dosing regimens using population pharmacokinetic (popPK) simulations based on an existing model enriched to allow extrapolation to a simulated virtualpediatric population.These dosing regimens were then confirmed using a verified physiologically-based pharmacokinetic (PBPK) model.

Results
We simulated, using popPK data, oral and intravenous dosing regimens resulting in adequate target exposure in >90% of all patients, with minimal expected risk for cardiotoxicity. Confirmation of these dosing regimens with PBPK modeling resulted in very similar exposure, with lower interindividual variability and minimal toxicity potential.

Conclusions
Based on pharmacokinetic modeling, we developed oral and intravenous eliglustat dosing regimens that are likely safe and effective for treatment of STEC-HUS and prophylaxis in case of outbreaks of STEC-infections. Clinical evaluation of these dosing regimens in children suspected of or diagnosed with STEC-HUS is required and should include assessment of pharmacokinetics, efficacy and safety (e.g. ECG monitoring).

SURVIVAL OUTCOMES AFTER *UGT1A1* GENOTYPE-GUIDED DOSING OF IRINOTECAN:

N. Heersche[1,2], S.L.J. Peeters[3,4], D. Böhm[3,4], S. Böhringer[4,5], R. Guiljam[1], E.C. Hulshof[3], F.M. de Man[1], M. de With[1], M. Joosse[3], G. Oomens[3], Q.-Y. Wu[4], A. Osman[3], S. Bins[1], I.E.G. van Hellemond[6], B.C.M. Haberkorn[7], A.J. Verschoor[8], M.L. Wumkes[9], R.H.N. van Schaik[2], A.M. Thijs[6], H. Gelderblom[10], H.J. Guchelaar[3], R.H.J. Mathijssen[1] and M.J. Deenen[3,4]

[1] Dept. of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Centre, Rotterdam; [2] Dept. of Clinical Chemistry, Erasmus University Medical Centre, Rotterdam; [3] Dept. of Clinical Pharmacy, Catharina Hospital, Eindhoven; [4] Dept. of Clinical Pharmacy and Toxicology, Leiden University Medical Centre, Leiden; [5] Dept. Of Biomedical Data Sciences, Leiden University Medical Center, Leiden. [6] Dept. of Medical Oncology, Catharina Hospital, Eindhoven [7] Dept. of Medical Oncology, Maasstad Hospital, Rotterdam; [8] Dept. of Medical Oncology, Reinier de Graaf Gasthuis Hospital, Delft; [9] Dept. of Medical Oncology, Jeroen Bosch Hospital, ‘s Hertogenbosch; [10] Dept. of Medical Oncology, Leiden University Medical Centre, Leiden;

Introduction
UGT1A1 genotype-guided dosing reduces severe toxicity in UGT1A1 poor metaboliser (PM) patients treated with irinotecan. However, the impact of a dose reduction on survival remains unknown. This study evaluated whether upfront 30% dose reductions of irinotecan in UGT1A1 PMs affect survival by comparing progression-free survival (PFS) and overall survival (OS) between 30% dose-reduced PMs and fully-dosed UGT1A1 intermediate and normal metaboliser (IM/NM) patients.

Methods
We conducted a retrospective, multicentre cohort study in patients with pancreatic cancer or colorectal cancer treated with *UGT1A1* genotype-guided irinotecan dosing at six Dutch. hospitals between August 2017-April 2024. Patients were included in the primary analysis if irinotecan was dosed according to *UGT1A1* genotype (i.e. an initial 100%±10% dose intensity for IM/NMs and an initial 70%±10% dose intensity for PMs) in at least cycle 1. Survival analyses for PFS and OS were performed using Kaplan-Meier estimates and univariable and multivariable Cox regressions, stratified by tumour type. Safety was also assessed.

Results
The primary analysis included 779 patients, 76 (9·8%) of whom were PMs. The median follow-up was 27·8 months (95% CI 15·2-31·6). No significant differences in PFS and OS rates were found between 30% dose-reduced PMs and fully-dosed IM/NMs (stratified log-rank test: PFS: P = 0·54; OS: P = 0·42). In stratified Cox regression analyses, the adjusted hazard ratio of PMs vs IM/NMs was 1.02 (95% CI 0·78-1·32; P = 0·90) for PFS and 1·10 (95% CI 0·82-1·48; P = 0·51) for OS, indicating no significant differences exist in PFS or OS between 30% dose-reduced PMs and fully-dosed IM/NMs. Severe toxicity rates were comparable between 30% dose-reduced PMs and fully-dosed IM/NMs (P = 0·59).

Conclusions
An upfront 30% dose reduction of irinotecan in UGT1A1 PMs does not lead to statistically significant differences in survival outcomes compared to fully-dosed IM/NMs. Therefore, *UGT1A1* genotype-guided dosing of irinotecan can be confidently performed to improve patient safety.

SEVERE TOXICITY RISK OF UGT1A1 INTERMEDIATE METABOLISER GENOTYPE AND OTHER RISK FACTORS IN PATIENTS TREATED WITH IRINOTECAN-CONTAINING CHEMOTHERAPY

S.L.J. Peeters[1,2], N. Heersche[3,4], D. Böhm[1,2], S. Böhringer[5], E.C. Hulshof[1], F.M. de Man[3], M. de With[3], S. Bins[3], I.E.G. van Hellemond[6], B.C.M. Haberkorn[7], A.J. Verschoor[8], M.L. Wumkes[9], R.H.N. van Schaik[4], A.M. Thijs[5], H. Gelderblom[10], H.J. Guchelaar[2], R.H.J. Mathijssen[3], M.J. Deenen[1,2].

[1] Dept. of Clinical Pharmacy, Catharina Hospital; [2] Dept. of Clinical Pharmacy and Toxicology, Leiden University Medical Centre; [3] Dept. of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Centre; [4]Dept. of Clinical Chemistry, Erasmus University Medical Centre; [5] Biomedical Data Sciences, Leiden University Medical Centre; [6] Dept. of Medical Oncology, Catharina Hospital; [7] Dept. of Medical Oncology, Maasstad Hospital; [8] Dept. of Medical Oncology, Reinier de Graaf Gasthuis Hospital; [9] Dept. of Medical Oncology, Jeroen Bosch Hospital; [10] Dept. of Medical Oncology, Leiden University Medical Centre.

Introduction:Approximately 1 out of 3 of irinotecan-treated patients who are UGT1A1 intermediate metaboliser (IM) or normal metaboliser (NM) experience severe toxicity. Several meta-analyses indicate that IMs are at increased risk of toxicity compared to NMs, while earlier dose-finding studies suggest that both groups can tolerate similar irinotecan doses [1]. We assessed treatment-related toxicities and irinotecan dose intensities in IMs *vs* NMs from a real-world patient cohort, and investigated baseline characteristics predictive of high severe toxicity risk.

Methods Patients who received treatment with systemic irinotecan and *UGT1A1* genotyping between 2017-2024 at six Dutch hospitals were eligible. IM and NM patients with a full irinotecan dose in at least cycle 1 were included in the primary analysis. The primary endpoint was overall, early-onset, severe toxicity (cycles 1-3, grade ≥3, CTCAE v5.0). Other endpoints included (febrile) neutropenia, diarrhoea and dose modifications.
Associations between baseline characteristics and endpoints were assessed with uni- and multivariable logistic regressions.
[1] Hulshof et al. Eur J Hum Genet. 2023 Sep;31(9):982-987.

Results
A total of 320 IMs and 350 NMs were included. Baseline characteristics were comparable between groups. Overall, early-onset, severe toxicity occurred in 39% of IMs *vs* 26% of NMs (adjusted Odds Ratio (aOR) 1.77 [95%CI 1.24-2.51]; *P* = 0.002), severe diarrhoea in 19% of IMs *vs* 13% of NMs (*P* = 0.03), and severe neutropenia in 20% of IMs *vs* 14% of NMs (*P* = 0.002). IMs were dose-reduced more often in subsequent cycles (51% *vs* 42%; *P* = 0.02). WHO performance score 2, type of treatment regimen, and abnormal alkaline phosphatase (ALP) were significantly associated with higher risk of overall, early-onset, severe toxicity, whereas G-CSF prophylaxis was significantly associated with a lower risk. Subgroup analyses revealed that higher overall, early-onset, severe toxicity rates in IMs *vs* NMs were only observed in those treated with standard FOLFIRINOX (51% *vs* 35%; aOR 1.95 [95%CI 1.12-3.41]; *P* = 0.02) or FOLFOXIRI (46% *vs* 22%; aOR 3.22 [95%CI 1.16-8.93]; *P* = 0.03), but not in those treated with mFOLFIRINOX, FOLFIRI or monotherapy. Overall, early-onset, severe toxicity occurred in 20% of IMs without risk factors (i.e., FOLFIRINOX or FOLFOXIRI, poor performance status, abnormal ALP), in 41% and 52% of IMs with 1 or ≥2 risk factors, and in 19%, 23% and 40% of NMs without, with 1, or with ≥2 risk factors.

Conclusions
UGT1A1 IMs overall are at increased risk of severe toxicity. IMs without risk factors seem to tolerate standard irinotecan doses, similar to NMs, whereas IMs with additional risk factors may benefit from additional monitoring, G-CSF prophylaxis, and/or initial dose reductions. Prospective studies combining genotype and clinical characteristics to guide irinotecan-treatment are warranted.

THE ROLE OF DEXAMETHASONE ROUTE OF ADMINISTRATION IN THE DEXAMETHASONE-APREPITANT DRUG-DRUG INTERACTION

Authors
S.W.J. Zielhuis[1], A. Embaby[1], A.L. Nijstad[2], B.A.W. Jacobs[1], E. de Vos-Kerkhof[2], M.M. Tibben[1], C.M. Zwaan[2], A.D.R. Huitema[1,2], N. Steeghs[1].

[1]The Netherlands Cancer Institute, Amsterdam.

[2] Princess Máxima Center for Pediatric Oncology, Utrecht.

Background
To prevent chemotherapy-induced nausea and vomiting, a triple prophylactic combination of antiemetic drugs could be indicated, consisting of a 5-HT3 receptor antagonist (f.e. granisetron), dexamethasone (DEX) and aprepitant (APR). APR is an moderate CYP3A4 inhibitor, while DEX is a CYP3A4 substrate. Adult studies[1,2] showed that APR use reduced DEX clearance (CL) by 50%. Therefore, the DEX dose in clinical practice is halved when used concomitantly with APR. Nijstad et al.[3] showed that APR use reduces DEX CL by only 30% in children, suggesting that halving of DEX dose might result in underdosing. However, nearly all (95%) DEX administrations were intravenously (i.v.) in this study. As CYP3A4 enzymes are also located in the gastrointestinal tract, DEX administration route might have an effect on the magnitude of the interaction. Therefore, we aimed to evaluate the effect of DEX route of administration on its interaction with APR in a prospective observational study.

Methods
Patients (≥18 years) were enrolled in two different groups: (1) patients treated with DEX (8 mg) without APR, and (2) patients treated with DEX (4 mg) and APR (125 mg oral) (both n = 10). Patients were sampled during two chemotherapy cycles, in cycle 1 DEX was given orally and in cycle 2 DEX was given i.v. In the samples, DEX and APR levels were measured using a validated LC-MS/MS method[4]. The population pharmacokinetic (popPK) model of Nijstad et al. was extended by describing the absorption phase of DEX, and estimating the effect of APR use on DEX bioavailability using NONMEM.

Results: 274 samples were drawn from 25 patients. DEX and APR concentrations were adequately described by the extended popPK model. DEX PK was described by a two-compartment model with absorption transit compartments, APR PK by a one-compartment model with absorption transit compartments. The DEX-APR drug-drug interaction was described by CYP3A4 activity representing compartments. Age was identified as a significant covariate on DEX CL in the study population. DEX absolute bioavailability was estimated as 87% (RSE 3.4%). An effect of aprepitant use on DEX bioavailability was not identified.

Discussion/Conclusion
A popPK model describing the PK and interaction of (oral and i.v.) DEX and APR was developed. APR use does not affect DEX bioavailability. Therefore, DEX route of administration does not play a relevant role in the DEX-APR drug-drug interaction. In children, DEX dose during concomitant APR use should be decreased by 30% instead of 50%, regardless of DEX route of administration.

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THE RELATIONSHIP BETWEEN LENVATINIB EXPOSURE AND DRUG LIMITING TOXICITIES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA AND RENAL CELL CARCINOMA

Authors: A.K. Bos[1], N. Steeghs[2,3], A.D.R. Huitema[1,4,5], H. Huisman-Siebinga[1]

[1]Department of Pharmacy & Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands [2]Department of Medical Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands [3]Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands [4]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands [5]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Introduction:
The multikinase inhibitor lenvatinib is poorly tolerated by differentiated thyroid cancer (DTC) and metastatic renal carcinoma (mRCC) patients in clinical practice, with 68.8% experiencing dose-limiting toxicities (DLTs) [1]. An initial exposure-toxicity relationship was explored in this population. However, a comprehensive analysis is desirable, since trough concentrations (C_{trough}) were log-linearly extrapolated and time-to-DLT was disregarded. Thus, we aimed to quantify the risk of any grade DLT in the first year of treatment as function of time-varying lenvatinib exposure in real-world DTC and mRCC patients using a repeated time-to-event (RTTE) model.

Methods:
Data from 35 DTC and 29 mRCC patients with 358 lenvatinib plasma concentrations were included [1]. First, a population pharmacokinetic (popPK) model was developed using the PRIOR subroutine in NONMEM. The reference model consisted of three compartments [2]. Individual daily C_{trough} and AUC_{0-24} were derived from the final model based on Maximum a Posteriori Bayesian estimation. Second, a RTTE model was developed to relate DLTs to time-varying lenvatinib exposure. Different baseline hazard parametrizations and a tumour type effect were explored. The effect of lenvatinib exposure (C_{trough} and AUC_{0-24}) on the hazard was tested with linear, exponential and (sigmoid) E_{max} relationships. The final RTTE model was selected based on scientific plausibility, objective function value (OFV), estimated parameter precision, kernel-based visual hazard comparisons (kbVHC) and Kaplan-Meier visual predictive checks (KM-VPC). Model development was performed in NONMEM (v7.5).

Results:
The parameters of the final popPK model were majorly informed by the prior model, except for clearance that was estimated at 6.35 L/h (RSE 3.88%). 36 patients experienced 60 DLTs and 22 patients discontinued treatment prematurely due to disease progression or other reasons. The final RTTE model included a Weibull function to describe the baseline hazard. The scale and shape parameter were estimated at 0.146 $year^{-1}$ (RSE 52.1%) and 1.01 (RSE 13.0%), respectively. Tumour type did not significantly affect the hazard (dOFV -1.05). The effect of lenvatinib exposure on the hazard was best described by C_{trough} using an exponential relationship, where a 10 ng/mL increase resulted in a 1.62-fold higher hazard. kbVHC and KM-VPC evaluations showed that the final RTTE model could predict DLTs based on lenvatinib C_{trough}, particularly for DTC patients.

Conclusions:
The final RTTE model adequately described the observed DLT data as a function of lenvatinib exposure. The model shows potential to be used in clinical practice to support lenvatinib dose decision making based on risk for DLTs.

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REDUCING LORLATINIB-RELATED TOXICITY BY ESTABLISHING THE OPTIMAL EXPOSURE-TOXICITY THRESHOLD IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

Authors
Daan A.C. Lanser,[a,b,c] G.D. Marijn Veerman,[b] Esther Oomen-de Hoop,[a] Peter de Bruijn,[a] Attila Icli,[a] Marthe S. Paats,[b] Ron H.N. van Schaik,[c] Anne-Marie C. Dingemans,[b] and Ron H.J. Mathijssen[a]

Organisations
[a] Dept. of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam;
[b] Dept. of Pulmonology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam;
[c] Dept. of Clinical Chemistry, Erasmus University Medical Center, Rotterdam.

Introduction
Lorlatinib demonstrates substantial efficacy in ALK+ NSCLC, but clinically significant toxicity (76% grade ≥3) frequently necessitates dose modification. Therapeutic drug monitoring (TDM) might guide individualized dosing and prevents severe toxicity, yet an exposure-toxicity threshold is lacking. We investigated the association between lorlatinib trough exposure (C_{trough}) and severe toxicity, evaluating an actionable C_{trough} threshold.

Methods
Patients treated with lorlatinib were included in the biomarker START-TKI study. Severe lorlatinib-related toxicity was defined as toxicity leading to dose reduction, interruption, hospitalization or CTCAE grade ≥3. Plasma samples were collected during outpatient visits (median 4 samples/patient, IQR 2 - 9); the first plasma sample was obtained at a median of 2.0 months on treatment. Exposure was dose-normalized to trough exposure for 100 mg QD. The association between median on-treatment C_{trough} (log-transformed) and time to first clinically significant toxicity was assessed using the Fine and Gray model with end of treatment or death prior to toxicity as competing risk. Threshold performance was evaluated using ROC analysis in patients with at least 3 months of treatment.

Results
Out of 56 patients treated with lorlatinib, 46 patients had an evaluable lorlatinib C_{trough}. Severe toxicity occurred in 43% of patients at a median of 2.2 months (IQR 1.1 - 4.5); most commonly peripheral edema (13%), cognitive impairment (13%) and peripheral neuropathy (9%). Higher lorlatinib exposure was associated with an increased risk of clinically significant toxicity (C_{trough} log-transformed: sHR 4.68 95% CI 1.76 - 12.4, p = 0.002; i.e. a 25% higher C_{trough} leads to a 42% higher hazard of toxicity). ROC analysis in 38 patients suggested an optimal C_{trough} threshold of 181 ng/mL (AUC 0.83 [95% CI: 0.69 – 0.96]; specificity 85%, sensitivity 61%). TDM would suggest an early dose reduction in 39% of patients with lorlatinib C_{trough} above the 181 ng/mL threshold.

Conclusions
Lorlatinib exposure correlates strongly with severe toxicity, supporting the clinical potential of TDM. A C_{trough} threshold of 181 ng/mL may identify patients at risk of toxicity and guide dose adjustment to improve tolerability.

THERAPY ACCELERATOR AT RADBOUDUMC: TEAMWORK TO ACCELERATE THERAPY DEVELOPMENT FOR RARE DISEASES

Authors Rob ter Heine, Karin Ruijtenbeek, Manoe Janssen, Gerty Schreibelt, Kevin Bos, Paul de Jonge, Najoua El Boujnouni, Marga Bosch-Bouma, Joanna in 't Hout, Anna de Goede, Dorien Hermkens, Margot Neefjes, Maaike Oosterveer, Rick Greupink, Sven van Laanen, Dirk Lefeber, Saskia de Wildt

Organisations Radboud University Medical Center

Introduction
Development of effective therapies for rare diseases faces significant scientific, regulatory, and economic challenges. The Therapy Accelerator for Rare Diseases at Radboud university medical center (Radboudumc) is a multidisciplinary team designed to overcome these barriers by fostering collaboration, innovation, and translational progress across the therapeutic development pipeline. This team aims to both accelerate the bench-to-bedside development of drugs for rare diseases from a societal perspective and to create a knowledge hub for rare disease treatment development.

Methods
The teams brings together expertise in clinical pharmacology and model-informed drug development, translational science, regulatory strategy, and patient-centered research. It acts as a bridge between academic research, clinical practice, patient organizations, and the pharmaceutical industry with focus on drug repurposing, cell- and gene-based therapies, support for early-stage therapeutic development, and the creation of sustainable access models for patients.

Results
The team has and is providing advice to variety of so-called use cases (yearly call for support) for acceleration of rare disease drug development and market access. In addition, it is involved in finding innovative approaches in this regard, i.e. translational and clinical pharmacometrics, innovative trial design, as well as community building and national networking.

The therapy accelerator team has started participating in RARE-NL, a national hub that supports integrated rare disease research and promotes socially responsible drug development. In addition, it represents Radboudumc within the Pharma Delta network, strengthening ties with biotech and pharma stakeholders in the Netherlands. Moreover, the team has set up training and education programs for researchers, clinicians and students aiming for better understanding of drug development and patient access.

Conclusions
The Radboudumc therapy accelerator teams is actively building capacity, a learning community and accelerating drug development for rare and orphan diseases and is sharing understanding among researchers and innovators involved in rare disease drug development. This abstract represents the mission, methodology, and impact of the Therapy Accelerator team, highlighting our role as a national frontrunner in the development and delivery of therapies for rare disease patients.

POPULATION PHARMACOKINETICS OF [177LU]LU-PSMA COMBINED WITH EBRT AND ADT IN TREATMENT NAÏVE PATIENTS: DIFFERENCES IN CLEARANCE AND CYCLE-DEPENDENT-EFFECTS

Authors: D. van Asten[1,2], B.J. de Wit-van der Veen[2], A.D.R. Huitema[1,3,4], H. Huisman-Siebinga[1,2]

Organisations:[1]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands. [2]Department of Nuclear Medicine, The Netherlands Cancer Institute, Amsterdam, The Netherlands. [3]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands. [4]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Introduction: [77]Lu]Lu-PSMA-617 is an approved radioligand therapy (RLT) that prolongs survival in metastatic castration-resistant prostate cancer. The PROQURE-I trial investigated its use in combination with radiotherapy as a curative regime for treatment-naïve patients with N1M0 prostate cancer, to improve recurrence rates [1]. In this trial, [^{177}Lu]Lu-PSMA-617 was added to standard-of-care whole-pelvis external beam radiotherapy (EBRT) and long-term androgen deprivation therapy (ADT) to evaluate safety and tolerability. In this population PK analysis, we evaluated if covariates previously identified in monotherapy, including cycle-dependent effects on tumour uptake and tumour-volume-related uptake, could account for the substantial variability observed [2,3].

Methods: The PROQURE-I trial was a multicentre phase I dose-escalation study (NCT05162573). Cohort A received single doses of 3, 6, or 9 GBq (n=7) [^{177}Lu]Lu-PSMA-617 two weeks after start EBRT. Cohort B received two 7.4 GBq cycles (n=5) (two-week interval) during EBRT. Pelvic SPECT/CT scans acquired at 4 h, 24 h, and 168 h post-RLT were analysed using MIM-software (v7.3.6). Plasma samples were collected up to 7 days. Consequently, activity concentrations (MBq/L) in plasma and tumour were available. A four-compartment PK model was developed using NONMEM (v7.5) representing plasma, tumour, PSMA-expressing organs, and non-target tissues. Effects of subsequent cycles and tumour volume on tumour uptake, as well as a potential maximum tumour-binding capacity (B_{MAX}), were explored to explain observed variability.

Results: The [^{177}Lu]Lu-PSMA-617 PK model showed good fit and acceptable precision despite limited data (RSE < 66%). k_{in} and k_{out} for non-target tissue were fixed to published values [3]. The clearance was estimated at 1.31 L/h (RSE k_{10}: 4.5% and V_1: 5.1%) compared to 2.04 L/h after monotherapy, likely reflecting different target-mediated drug disposition (TMDD) in the earlier treatment line. Cycle 2 tumour uptake decreased to 58% of cycle 1, a greater reduction than seen with monotherapy [2], potentially reflecting response to EBRT. Tumour uptake increased with 122% for patients with a twofold higher tumour volume compared to the median. B_{MAX} was not identifiable, because of the limited sample size at higher dose levels. Posthoc power-analysis indicated a requirement of at least 65 patients for identifying a relevant B_{MAX} (with a power of 80%).

Conclusions: The population PK model showed adequate fit and confirmed altered clearance of [^{177}Lu]Lu-PSMA-617 in multimodality treatment setting, likely due to TMDD. Variability was largely captured by expected covariates, including a strong cycle-two decrease in tumour uptake, likely caused by the combined therapies. Indications of nonlinear tumour uptake highlight the need to consider saturation in tumour uptake in future studies with larger sample sizes.

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TRASTUZUMAB IN PREGNANT WOMEN WITH BREAST CANCER: A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

Authors: L.J. Geschiere, M. Meijer, D.J. Touw, T.H. Oude Munnink, P.R.V. Malik, P. Mian

Organisations: Clinical Pharmacy and Pharmacology - UMCG

Introduction:
The hypothesis is that, for monoclonal antibodies, plasma concentrations in pregnant state are comparable as those observed in non-pregnant state, supporting the use of similar dosing regimens. However, there is still no original data supporting this hypothesis. Trastuzumab will be used to investigate this hypothesis, as it is the standard first-line treatment for HER2+ breast cancer in non-pregnant women, is highly effective and its dosing regimen during pregnancy remains unknown. Given limited clinical data, physiologically based pharmacokinetic (PBPK) modelling represents a valuable tool to provide insights into trastuzumab dosing strategies during pregnancy, supporting evidence base clinical decision-making in this population.

Methods:
First, a PBPK model for a non-pregnant population with HER2+ breast cancer is developed. Target-mediated drug disposition was implemented to simulate the non-linear PK. Thereafter, the model was optimized with PK data from HER2+ breast cancer patients receiving trastuzumab. Then it is scaled to pregnancy by implementing pregnancy physiological and enzymatic changes relevant to trastuzumab PK. This model is assessed by comparing predictions with PK data from pregnant women receiving trastuzumab. Simulations explored dosing regimens that would meet the criteria. Lastly, a systematic literature search is performed on trastuzumab use during pregnancy, focusing on fetal and pregnancy outcomes.

Results:
The PK of trastuzumab did not differ in the PBPK model for pregnant women compared with non-pregnant women. In addition, at the same dose, the concentration of trastuzumab in pregnant women were comparable to those in non-pregnant women. Finally, the systematic literature search showed that 19 out of 24 continued pregnancies resulted in viable births, frequently without reported fetal complications (n=9). When adverse outcomes such as oligohydramnios or transient renal dysfunction occurred, long-term child development appeared healthy (n=7). The two cases in which trastuzumab was continued throughout pregnancy under close monitoring resulted in children with healthy development. Overall, reported fetal effects were generally mild, transient and manageable, suggesting potential safety under strict clinical supervision

Conclusions:
The hypothesis that plasma concentrations of trastuzumab during pregnancy are comparable to those in the non-pregnant state, and that the same dosing regimen can be used during pregnancy, is supported. When there is an urgent need to use trastuzumab in pregnant women with HER2+ breast cancer the same dose can be given compared to non-pregnant patients. Only when the potential maternal survival benefit outweighs the risks, provided that close clinical monitoring is ensured.

EFFECT OF BARIATRIC SURGERY ON DIRECT ANTICOAGULANT (DOAC) DRUG LEVELS

Authors
A Keyany[1], E. Perkgöz [2] B Langenhoff [3], B Maat[1]

Organisations
[1]Department of Hospital Pharmacy, Elisabeth TweeSteden Hospital (ETZ), Tilburg, the Netherlands

[2]Department of Pharmaco-epidemiology and pharmacotherapy, Utrecht University, The Netherlands

[3]Department of Surgery, Elisabeth TweeSteden Hospital (ETZ), Tilburg, the Netherlands

Introduction
Bariatric surgeries, such as Roux-en-Y gastric bypass and sleeve gastrectomy, alter the gastrointestinal tract and may affect pharmacokinetics (e.g drug absorption). This study aimed to evaluate the impact of bariatric surgery on trough levels of direct oral anticoagulants (DOACs) in patients before and after surgery.

Methods
We conducted a retrospective cohort study at Elisabeth-Tweesteden Ziekenhuis, including bariatric patients with pre- and/or post-operative DOAC levels between 01/01/2019 and 01/10/2025. The primary outcome was the change in DOAC trough levels pre- and post-surgery over time (0–3, 3–6, 6–12 months, and annually up to 5 years. Secondary outcomes included comparison with reference ranges and adverse clinical outcomes and therapy adjustments. Descriptive statistics were used. To compare the pre- and post-bariatric trough drug levels a linear mixed model was used.

Results
No significant changes in DOAC trough levels were observed for apixaban (n = 7 patients, 33 levels; p = 0.843) or rivaroxaban (n = 11 patients, 45 levels; p = 0.674). For dabigatran analysis was not possible (1 patient). Most DOAC trough levels were within reference ranges (apixaban:, 92%; rivaroxaban: 93%), whereas three of six dabigatran levels (50%) were below the reference range. Adverse clinical outcomes occurred in 6/16 apixaban patients (37.5%) and 3/17 rivaroxaban patients (17.6%). Therapy adjustments were made in 1/3 dabigatran patients (33.3%), 0/16 apixaban patients, and 4/17 rivaroxaban patients (23.5%).

Conclusions
Apixaban and rivaroxaban drug levels were largely unchanged up to 5 years after bariatric surgery, and most levels remained within reference ranges. However, the small sample size limits statistical power. Adverse outcomes and therapy adjustments occurred in a subset of patients.

A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING APPROACH TO OPTIMIZE THERAPEUTIC NADROPARIN DOSE REGIMENS IN PAEDIATRIC PATIENTS

S.L. Teertstra[1], B. van Delden[1], D.J. Touw[1], P. Malik[2], P. Mian[1]

[1]Department of Clinical Pharmacy and Pharmacology, UMCG

[2]Ionis Pharmaceuticals, Carlsbad

Introduction

Nadroparin is a low-molecular weight heparin (LMWH) used to treat or prevent venous thromboembolism (VTE) in adults and children alike. Due to the lack of pharmacokinetic (PK) data in children, paediatric dose regimens are extrapolated from adult doses based on body weight. With these dose regimens however, children do not consistently meet the current therapeutic target range (TTR). They present with either sub- or supratherapeutic plasma levels, leading to un-treated thrombosis or excessive bleeding, respectively. Physiologically based pharmacokinetic (PBPK) modelling is a technique by which PK time profiles can be simulated based on physicochemical data of a drug of interest, and physiological data of a subject or population. This technique can provide a potentially vital role in developing novel, paediatric-specific dose regimens for nadroparin. The aim of this study was thus to develop a PBPK model for therapeutic nadroparin in paediatric patients, to develop new dose regimens for this population.

Methods

The PBPK models were developed in PK-sim version 12 (Open Systems Pharmacology). A PBPK model was first developed for healthy adults based on single dose (intravenous and subcutaneous administration) nadroparin PK studies and parameter optimisation, followed by verification by multiple-dose studies. The model was then scaled to children by accounting for physiological maturation by introducing ontogeny functions for GFR and antithrombin (ATIII). The model was validated by real-world measurements (n=1304) provided by the University Medical Centre Groningen (UMCG). The accuracy of the model was assessed by comparing predicted/observed plasma level ratios at t = 4h post-administration at steady state.

Results

Following parameter optimisation, a PBPK model visually describing healthy adult data was successfully developed. After scaling the PBPK model to children and comparing to the real-world data, the ratios of predicted/observed data for all examined cohorts (0-1 months, 0-2 months, 2-3 months, 2-6 months, 6-12 months, 1-2 years. 2-3 years, 6-12 years, 12-13 years and 12-18 years) fell within a 1.25-fold error (0.8-1.25) range (0.81, 1.06, 1.12, 1.07, 0.89, 0.98, 0.87, 0.84, 0.99 and 1.04, respectively), except for the cohort of 2-6 years (0.75), which fell within a 1.5-fold error (0.667-1.5) range.

Conclusions

A novel PBPK model of nadroparin in the paediatric population was developed, which can accurately predict nadroparin plasma levels after administration of therapeutic doses. Future research will focus on model-informed precision dosing within the TTR and scaling the model further to capture prophylactic doses and preterm neonates.

OPTIMAL DALTEPARIN DOSE IN OBESE PATIENTS – (THE ODOP STUDY)

Authors. L. Mitrov-Winkelmolen [1,2], S. de Wijse[2,3], T.M Kuijper[2], L. Brand[2,4], R. Ruiter[2], T.M. Bosch[2], L.L. Krens[2]

Organisations.1 Flevoziekenhuis, Almere. 2 Maasstad Ziekenhuis, Rotterdam. 3 Zaans Medisch Centrum. 4. LUMC

Introduction
Optimal dosing strategies for anticoagulants in the obese population are necessary, as the risk of thromboembolism and atrial fibrillation in this population is increased. Although the volume of distribution (Vd) of dalteparin increases propor-tionally with increasing total body weight (TBW), suggesting a need for higher dosing in obese patients, the manufacturer recommends dose capping on 18.000 IU daily in patients >90 kg. Limited information is available regarding higher doses of therapeutic dalteparin, especially in class III obesity, leading to inconsistent recommendations in different guidelines. In our hospitals, we follow the Royal Dutch Pharmacist Association (KNMP) advice to dose uncapped: 200 IU/kg based on TBW, with anti-Xa monitoring. Our study aimed to evaluate this current practice as to confirm or refute this recommendation.

Methods
In this observational, multicentre cohort study, 3 years of data were retrospectively collected in our affiliated hospitals. Patients weighing >99 kg with a dalteparin dose ≥7500 IU/day were included. We evaluated anti-Xa levels at 3-5 hours post injection in steady state and differentiated between anti-Xa levels below the upper threshold (BT) of <2.0 IU/ml for once daily dosing and <1.0 IU/ml for twice daily dosing and anti-Xa levels above this threshold (AT). Dalteparin dose was classified in dose categories: <170 IU/kg (<85%); 170-230. (100%) and >230 IU/kg (>115%). Furthermore, we identified thrombotic and bleeding events (classified as minor of major), age, sex, body weight, length, BMI, Covid status, ICU admittance, eGFR, dialysis status and comedication influen-cing anticoagulation. We used a repeated measures proportion-nal odds model to estimate the association between anti-Xa categories and dose categories. Additional analyses assessed the relationship between obesity classes and anti-Xa outcomes.

Results
326 anti-Xa measurements were taken in 219 patients with a mean weight of 115 kg (100-200 kg) and a mean BMI of 35.9 (24.5-76.3). 21 samples were from patients weighing >149kg, and 66 samples were from patients with class III obesity (BMI >40). 69% of patients received a 100% dalteparin dose, 28% received <85% and 3% received >115%. Of all anti-Xa mea-surements, 89% were BT. Off the AT anti-Xa levels, 38.9 % were obtained in patients with class III obesity. In the multiva-riate model, class III obesity showed a significant association with higher odds of AT anti-Xa levels: OR 3,45 [1.49-7.96]. 16 minor and 14 major bleeding events were reported, mostly in 100% dosed patients (88% and 79%, resp.) with BT anti-Xa levels (94% and 93%, resp.). 5 thrombotic events were reported, of which 3 (60%) in <85% dosed patients.

Conclusions
Uncapped TBW dalteparin dose in patients >99 kg resulted in few AT anti-Xa levels with no increase in bleeding or throm-botic events. An association with class III obesity and AT anti-Xa levels was observed, with uncertain clinical relevance. We recommend uncapped dosing of 200 IU/kg on TBW in all clas-ses of obese patients, without the need for anti-Xa monitoring.

CAROTID INTIMA THICKNESS AND CARDIOVASCULAR RISK ASSESSMENT IN PATIENTS TREATED FOR HEAD AND NECK CANCER

Tom J.J. Uyl[1,2,3], Amin Yusof[1,3], Sharissa Soerahi[1,3], Daan C.H. van Dorst[2,3], Ranisha Roopram[1], Daniëlle Legerstee[1], Esther van Meerten[2], Aniel Sewnaik[4], Paula M. Janssen[5], Esther Oomen- de Hoop[2], Margriet G. A. Sattler[6], A.H. Jan Danser[3], Ron H.J. Mathijssen[2], Harmke A. Polinder-Bos[7], Jorie Versmissen[1,3]

1 Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands
2 Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands
3 Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Cardiovascular Institute, Erasmus University Medical Center, Rotterdam, The Netherlands
4 Department of Ear, Nose and Throat Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
5 Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands
6 Department of Radiotherapy, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands
7 Division of Geriatric Medicine, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

Introduction
Cardiovascular disease (CVD) is the leading cause of non–cancer-related morbidity and mortality among patients treated for head and neck cancer (HNC). However, the extent to which these patients are screened for (CVD) remains unclear, and the long-term impact of different anticancer treatment modalities for HNC on the CVD risk is also not well established. A validated marker of subclinical atherosclerosis such as the carotid intima media thickness (cIMT) might be useful to predict CVD in these patients. The aim of this

Primary endpoint was the maximum cIMT, measured in μm on both sides by means of ultrasound. Secondary endpoints included associations of cIMT with low-density lipoprotein cholesterol, systolic blood pressure, use of lipid-lowering drugs, and use of antihypertensives via linear regression, as well as the proportion of patients who required modifications in medication for cardiovascular risk management. Differences between two independent groups were analysed using independent-samples t-tests, and comparisons among more than two groups were performed using one-way ANOVA.

Results
From December 2022 to December 2025, 112 patients were included with a median time after treatment completion of 32.5 months (IQR 26.0-46.2). Compared to their expected cIMT based on sex and age reference population, patients had a significantly higher cIMT (cIMT observed 927 μm, expected 679 μm; mean difference (MD) 248 μm; 95% CI: 213 to 282 μm; p<0.001). No significant differences in cIMT were found between the different HNC treatment modalities (p=0.453). After correction for age, sex, smoking, diabetes and alcohol use, both LDL-cholesterol (B= 32.8 μm per mmol/L; 95% CI: -7.53 to 73.2; p= 0.110) and systolic blood pressure (B: 1.68 μm per mmHg; 95% CI: -0.23 to 3.59; p= 0.097) tended to associate with cIMT. Patients treated with lipid-lowering drugs (MD: -44.3 μm; 95%CI: -108 to 19.1 μm; p=0.169) or antihypertensive medication (MD: -103 μm; 95%CI: 79.4 to 59.2 μm; p=0.773) did not have a lower cIMT than patients without these treatments. Lipid-lowering therapy was initiated in 41% of previously untreated patients and antihypertensive therapy in 14%.

Conclusions
Patients treated for head and neck cancer exhibited a substantially increased cIMT, suggesting elevated vascular risk. Preventive therapy

study is to assess cIMT and cardiovascular risk factors in patients treated for HNC more than two years after treatment completion. **Methods** This single-centre, cross-sectional observational study was conducted at the Erasmus University Medical Center in Rotterdam. Patients ≥18 years old who had completed treatment for HNC (surgery or radiotherapy, post-operative radio(chemo)therapy, or radio(chemo)therapy) at least two years prior underwent an outpatient cardiovascular risk assessment.		was frequently initiated, highlighting the importance for systematic cardiovascular risk assessment in these patients.

SERIOUS FUNGAL URINARY TRACT INFECTIONS WITH SGLT2-INHIBITORS – A CASE SERIES

Authors Jette van Lint[1], Linda Davidson[1], Eugène van Puijenbroek[1]

Organisations Netherlands Pharmacovigilance Centre Lareb

Introduction
While urinary tract infections and fungal infections are known adverse drug reactions (ADRs) of sodium-glucose cotransporter 2 (SGLT2) inhibitors, fungal urinary tract infections are potentially underrecognized ADRs and may have serious consequences for affected patients. Even though case reports on urinary tract infections caused by *Candida* species have been published [1-3], larger studies rarely mention the causative microorganism of the urinary tract infection. The aim of this case series is to describe the clinical features, time course, management, and outcomes of cases reported to Netherlands Pharmacovigilance Centre Lareb.

Methods
We selected cases of fungal urinary tract infections, including yeast infections, reported to the Netherlands Pharmacovigilance Centre Lareb concerning dapagliflozin, empagliflozin or canagliflozin.. The following preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA) were used: Bladder candidiasis, Candida urethritis, Urinary tract candidiasis, Fungal cystitis, Fungal urethritis, Pyelonephritis fungal, Urinary tract infection fungal, Urogenital infection fungal). Data collected included demographics, drug characteristics (e.g. indication and duration), clinical presentation, diagnostic findings, management, and outcomes. Data were analysed descriptively.

Results A total of 15 reports were received by Lareb until 14 January 2026. The median age of the patients was 78 years and 11 patients were male. The fungal urinary tract infections occurred after a median of 6 months (range 3 weeks to 3 years) after starting the drug. The SGLT2-inhibitor was prescribed for diabetes mellitus in 8 cases, for cardiac failure in 3 cases and for both in 1 case. Urine culture results were reported in six cases which showed *Candidalbicans* in two cases and *Candida glabrata* in fou r cases. A fungal ball had formed in bladder, ureter or renal pelvis in five patients, sometimes obstructing the urinary tract. Ten cases were serious and required hospital or intensive care admission and in four cases the reporter mentioned the reaction was life threatening with e.g. urosepsis and candidemia. All patients were treated with antimycotics and in addition, two patients were treated with amphotericin B bladder washout, one required transurethral resection to remove fungal balls and one a nephrostomy catheter. One patient died of myocardial infarction during hospitalization. Multiple reporters mentioned the risk of late diagnoses of fungal urinary tract infections as dipslide tests in the general practitioner’s office are not suitable to detect yeasts. In the hospital setting, yeasts in urine cultures are often considered non-pathogenic in the absence of predisposing risk factors for yeast infections.

Conclusions This case series demonstrates that fungal urinary tract infections are clinically relevant potential adverse drug reactions that are difficult to treat and can have severe consequences. As fungal urinary tract infections are rare in the general population and SLGT2-inhibitors are increasingly prescribed, awareness among healthcare professionals is warranted to prevent late diagnoses.

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PARACETAMOL HALF-LIFE DECLINES OVER TIME AFTER AN ACUTE OVERDOSE

Authors
Johannes A. Kroes1,2, Jeroen Poortvliet, Daan J. Touw1,3, Berdien E. Oortgiesen2, 4, Marieke G.G. Sturkenboom1.

Organisations
Frisius MC, UMCG. (full affiliations do not fit in this format)

Introduction
Paracetamol poisoning is one of the most common types of drug-induced poisoning worldwide and can cause severe hepatotoxicity. Acetylcysteine administration is the most effective intervention to prevent hepatotoxicity. Clinically, we observed multiple cases in which the initially prolonged paracetamol half-life decreased during acetylcysteine treatment. This study aimed to investigate the changes in the half-life of paracetamol in patients with paracetamol poisoning treated with acetylcysteine.

Methods
This was a retrospective observational study on patients with paracetamol poisoning who were treated with acetylcysteine. Patients with ≥3 paracetamol plasma concentrations during a single acute overdose were selected from 2 hospitals in the Netherlands. The half-lives of paracetamol in these patients were calculated using consecutive samples. A moderately prolonged paracetamol half-life was defined as a first half-life of >4.0 hours and a severely prolonged paracetamol half-life of >5.5 hours.

Results
Seventy-one paracetamol overdoses from 59 patients were included. The half-life of paracetamol changed from 4.6 (3.5-8.2) h for the first half-life to 2.9 (2.1-3.8) hours for the second half-life ($P < 0.001$). In 20 cases (28%), the initial half-life was moderately prolonged (4.0-5.5 hours), and in 26 cases (37%), it was severely prolonged (>5.5 hours). In all 3 subgroups, the half-life decreased significantly between the first and second half-lives ($P < 0.001$). The reported ingested dose, 4-hour paracetamol concentration, and time to acetylcysteine administration did not differ between the subgroups.

Conclusions
Our results suggest that the half-life of paracetamol decreases during acetylcysteine treatment. Health care professionals should consider repeated measurements of paracetamol concentrations and calculation of half-lives when using paracetamol half-life as a marker of hepatotoxicity, particularly when deciding whether to extend acetylcysteine treatment beyond the duration stated in the current guidelines.

THE EFFECT OF ECDSS-BASED PHARMACOTHERAPEUTIC RECOMMENDATIONS ON THE ANTICHOLINERGIC BURDEN OF HOSPITALIZED ELDERLY PATIENTS

ES Mense, T Leenders, MMPM Jansen, A Keyany, S Saini, T Van Asseldonk, D Arnoldussen, B Maat

Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands

Introduction

A high anticholinergic burden (ACB) is associated with an increased risk of impairment in physical and cognitive functioning, as well as an increased risk of dementia and falls in elderly. Medication reviews have been shown to reduce the ACB [1]. An electronic clinical decision support system (eCDSS) could facilitate this process. The aim of the present study was to investigate the effect of eCDSS-based pharmacotherapeutic recommendations on the ACB among hospitalized elderly patients.

Methods

In this pre-post intervention study an eCDSS was implemented to reduce the ACB. For hospitalized patients (aged ≥ 65 years) with an ACB score ≥ 8 or a strong anticholinergic medication in use, eCDSS-based recommendations were given to the physician to reduce the ACB. Primary endpoint was the change in ACB at hospital discharge compared to hospital admission before and after implementation of the eCDSS (analyzed with repeated measures ANOVA). Regression analysis was used to identify risk and protective factors for increase of ACB during hospitalization.

Results

A total of 1939 patients were included (969 in the pre-intervention cohort and 970 in the post-intervention cohort). For 514 patients in the post-intervention cohort the eCDSS alert was reviewed by a clinical pharmacist (eCDSS cohort). The ACB score increased by 0.15 points in the eCDSS cohort (95% CI -0.01;0.31) compared with 0.50 points in the pre-intervention cohort (95% CI 0.39-0.60). This difference was statistically significant ($F(2, 1261) = 54.72$, $p < 0.001$, $\eta 2\_partial = 0.042$). Higher ACB score at admission and higher age were protective factors for increase in ACB score during hospitalization, whereas hyperpolypharmacy, an admission duration > 96 hours and admission on an orthopedic or psychiatric ward were identified as risk factors. For 38% of the patients who received an eCDSS evaluation, one or more recommendations could be made. Most recommendations concerned discontinuing urological spasmolytics, opioids, antidepressants, and benzodiazepines.

Conclusions

The implementation of eCDSS-based pharmacotherapeutic recommendations led to a significantly smaller increase in ACB score in hospitalized elderly patients.

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SEX-SPECIFIC OUTCOMES IN METHOTREXATE THERAPY AMONG PATIENTS WITH PSORIATIC ARTHRITIS AND PSORIASIS

Michelle LM Mulder[1,2], Liana Barenbrug[3], Gonul Hazal Koc[4], Marisol E Otero[3], Emmerik FA Leijten[1,2], Sander I van Leuven[1], Irene E van der Horst-Bruinsma[1], Juul MPA van den Reek[3], Elke MGJ de Jong[3], Marc R Kok[5], Marijn Vis[4]

1 Department of Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands; 2 Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands; 3 Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands; 4 Department of Rheumatology, Erasmus Medical Center, Rotterdam, The Netherlands; 5 Department of Rheumatology and Clinical Immunology, Maasstad Hospital, Rotterdam, The Netherlands.

Introduction Prior studies have identified sex-differences in treatment response in patients with psoriasis (PsO) and psoriatic arthritis (PsA). Women generally show shorter drug survival for biological disease-modifying antirheumatic drugs (bDMARDs), both due to ineffectiveness and adverse events. However, sex-specific differences in methotrexate (MTX) treatment remain poorly understood, despite its widespread use as first-line systemic therapy for both PsA and PsO. Therefore, this study aimed to identify sex-specific patterns in MTX drug survival and related treatment outcomes among patients with PsA and PsO.

Methods Data from adult patients treated with MTX monotherapy included in the DEPAR (prospective rheumatology PsA cohort) or MTX-CAPTURE (prospective dermatology Pso cohort) registries were obtained. Kaplan-Meier survival curves stratified for sex were created to assess MTX drug survival (overall, and for discontinuation due to ineffectiveness and adverse events separately). Cox regression models corrected for precision variables were used to examine the association of sex with drug survival.

Results
A total of 525 (50.1% female) PsA patients and 217 (41.1% female) PsO patients were included. The age at MTX initiation was comparable between sexes in both the PsA cohort (M: 54.0 years vs F: 52.0 years) and the PsO cohort (M: 52.1 years vs F: 53.1 years). In the PsA cohort, unadjusted Kaplan-Meier analysis showed shorter drug survival in female compared to male patients, with a 3-year overall survival rate of 31.0% versus 55.7% ($p<0.001$) (Figure 1). In contrast, in the PsO cohort, females had longer 3-year overall survival than males (62.5% versus 45.3%, ns). These differences were confirmed in adjusted Cox regression analyses: in PsA, female sex was associated with shorter overall drug survival (HR=1.9, 95%CI 1.5–2.4, $p<0.001$), survival due to ineffectiveness (HR=2.1, 95%CI 1.2–3.6, $p=0.008$), and survival due to adverse events (HR=2.3, 95%CI 1.6–3.3, $p<0.001$). In PsO, female sex was associated with longer overall survival (HR=0.6, 95%CI 0.4–0.9, $p=0.008$) and survival due to ineffectiveness (HR=0.4, 95%CI 0.2–0.8, $p=0.009$), with a similar trend for adverse events (HR=0.6, 95%CI 0.4–1.0, $p=0.074$). Average MTX doses were comparable between sexes, though higher in PsA than PsO (18.2 vs 15.0 mg/week).

Conclusions
Drug survival and treatment response of MTX vary between PsA and PsO, with females with PsA but males with PsO having worse outcomes. These findings suggest that sex, disease phenotype and clinical setting can influence MTX treatment response and underscore the importance of considering both sex- and disease-specific patterns to optimize and individualize methotrexate therapy in PsA and PsO.

TOWARDS UNDERSTANDING THE PEDIATRIC PHARMACOKINETICS OF HYDROCHLOROTHIAZIDE VIA A PHYSIOLOGY-BASED PHARMACOKINETIC MODELING APPROACH

Authors Lianne P.M. van Bussel[1,2], Niki van Elst[1], Simon Koele[1], Tjitske M. van der Zanden[1,2,3], R. Greupink[1], Saskia N. de Wildt[1,2]

Organisations 1. Department of Pharmacy, Pharmacology, and Toxicology, Radboud Institute for Health Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands. 2. Dutch Knowledge Centre Pharmacotherapy for Children, The Hague, The Netherlands. 3.Department of Paediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands.

Introduction
Hydrochlorothiazide (HCTZ) is used to treat hypertension and edema in children, yet pediatric pharmacokinetic data to support age-appropriate dosing are scarce. PBPK modeling can provide support and optimize pediatric dosing in clinical practice. To this end, we explore a pragmatic PBPK modeling approach of HCTZ that incorporates renal OAT1/OAT3 transport. As a first step, we aimed to simulate HCTZ pharmacokinetics after single and multiple oral dosing in adults and verify the predictions against clinical data.

Methods
PBPK modelling was performed with Simcyp V24®. Parameters in the compound file, including renal OAT1 and OAT3 transporter activity, were retrieved from literature. The transporter data were applied within Simcyp's mechanistic kidney model to represent renal processes. Simulations were performed in healthy adults under oral single- and multiple-dose conditions, with 12.5 to 100 mg doses administered once- or twice-daily. Model performance was assessed using visual predictive checks and evaluation of observed/predicted AUC and C_{max} ratios (2-fold acceptance criterion).

Results
The model captured the typical biphasic elimination profile of HCTZ. In total, 13 single-dose and 6 multiple-dose scenarios were studied. For AUC predictions, all single-dose and multiple-dose predictions met the acceptance criterion (AUC ratios ranging from 0.51-1.13 and 0.63-1.22, respectively). For the observed/predicted C_{max} ratios, 8% of the single-dose predictions were within the 2-fold acceptance criterion (range 0.32-0.52), and 67% of the multiple-dose (range 0.35-0.76).

Conclusions
The PBPK model provides acceptable AUC prediction in adults, but systematic overprediction of C_{max}. Next steps include optimization of peak concentration prediction, and evaluation of model performance in pediatrics.

MULTI-OMICS ANALYSIS REVEALS SHARED MOLECULAR SIGNATURES ACROSS PSORIASIS TARGET LESIONS OF VARYING SEVERITY DURING GUSELKUMAB TREATMENT

Authors Nikita G. Koster[1,3,4], Robert Rissmann[1,3,4], Jannik Rousel[1], Menthe E. Bergmans[1], Catherine Mergen[3], Ingrid Tomljanovic[1], Marielle van der Peet[3], Thomas Hankemeier[3], Joke Bouwstra[3], Huma Shehwana[7], Johan Westerhuis[7], Tom Ederveen[5], Rob Vreeken[6], Eva Cuypers[6], Angiliki Birmpili[6], Martina Kutmon[6], Victor van der Valk[4], Boudewijn Lelieveldt[4], Marieke L. de Kam[1], Naomi B. Klarenbeek[1], Tessa Niemeyer-van der Kolk[1], Martijn B.A. van Doorn[2], The Next Generation ImmunoDermatology (NGID) consortium

Organisations [1] Centre for Human Drug Research, Leiden, the Netherlands, [2] Department of Dermatology, Erasmus Medical Centre, Rotterdam, the Netherlands, [3]Leiden Academic Center for Drug Research, Leiden University, [4]Leiden University Medical Center, [5]Radboud University Medical Center, [6]Maastricht Centre for Systems Biology and Bioinformatics (MaCSBio), Maastricht University, [7]University of Amsterdam

Introduction
Multi-omics profiling, including bulk transcriptomics, interstitial fluid (ISF) lipidomics, skin surface lipidomics, and spatial lipidomics, enables in-depth characterization of psoriasis pathobiology. Inter-individual differences in these profiles may influence treatment response.
To determine whether phenotypically similar plaques in mild and moderate-to-severe psoriasis differ molecularly, and to assess the effects of IL-23 blockade with guselkumab on transcriptomic and lipidomic profiles across disease severities.

Methods
Twenty patients with mild psoriasis (PASI ≤ 5) and six with moderate-to-severe disease (PASI ≥ 10) were enrolled, each with at least one target plaque on the extremities. Skin punch biopsies, tape strips, and peri-lesional suction blisters were collected before, during, and after 16 weeks of guselkumab therapy, alongside samples from ten healthy controls. Multi-omics analyses included RNA sequencing, LC-MS metabolomics, and mass spectrometry imaging.

Results
At baseline, plaques were comparable across groups in erythema, scaling, and induration. Transcriptomic profiling revealed similar molecular signatures in both severity groups versus healthy controls, with elevated Th17- and modestly increased Th2-related gene expression. Only twelve genes differed significantly, all with small fold changes ($log_2FC < 1$). Perilesional ISF metabolomics showed normalization of inflammatory lipid mediators (15-HETrE, S1P 18:2, S1P 16:1, 11-HETE) during treatment. Clinical, imaging, and molecular data indicated comparable therapeutic responses.

Conclusions
Despite the limited number of moderate-to-severe patients, these findings demonstrate that phenotypically similar plaques in mild and moderate-to-severe psoriasis share comparable molecular signatures. The results support the applicability of IL-23 blockade with guselkumab in patients with mild psoriasis. .

THE PREVALENCE AND IMPLICATIONS OF POLYPHARMACY IN INDIVIDUALS WITH TYPE 1 DIABETES

Authors
Namam Ali[1], Stephan van Erp[1], Cornelis Kramers[1,2], Cornelis J. Tack[1], Bastiaan E. de Galan[1, 3, 4]

Organisations
1 Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands

2 Department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands

3 Department of Internal Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands

4 CARIM School for Cardiovascular Disease, Maastricht University, Maastricht, the Netherlands

Introduction
Polypharmacy is increasingly recognized as a relevant issue in diabetes care, but its prevalence and clinical relevance in individuals with type 1 diabetes remain underexplored. This study aimed to determine the prevalence of polypharmacy and to identify associated clinical and psychological factors.

Methods
Participants were recruited from a tertiary diabetes outpatient clinic between February 2020 and April 2021. Polypharmacy was defined as the concurrent use of five or more medications, including insulin. Clinical, sensor-based, and psychosocial data were collected. Logistic regression was used to identify variables independently associated with polypharmacy.

Results
A total of 484 individuals with type 1 diabetes were included (mean age 51.3±15.9 years; 51.2% male; median diabetes duration 30 [IQR 16–40] years; mean HbA1c 60.3±11.6 mmol/mol). Polypharmacy was present in 175 (36.2%) participants. Individuals with polypharmacy were more often female, were older, and had longer diabetes duration, higher BMI, higher HbA1c, more complications and higher rates of hospital admission. They also were more likely to have impaired awareness of hypoglycaemia and reported higher levels of fear of hypoglycaemia with no differences in hyperglycaemia-related worry or behaviour or diabetes-related emotional distress.

Conclusions
Polypharmacy affects over one-third of individuals with type 1 diabetes and is associated with poorer health status and a greater hypoglycaemia related burden. Future studies should investigate whether targeted medication review and psychological interventions may alleviate some of the burden in this high-risk group.

FROM HOSPITAL TO HOME: PRIMARY CARE PHYSICIANS' EXPERIENCES WITH IMPLEMENTING HOSPITAL-INITIATED MEDICATION REVIEWS DURING TRANSITIONAL CARE OF OLDER ADULTS

Authors
Marijke H.M. van Bergeijk[1], Eline M.C. Engelen[2], Stephanie C.M. Wuyts[3], Marcel L. Bouvy[4] Michiel A. van Agtmael[2], Wilma Knol[1]

Organisations
1. Department of Geriatric Medicine University Medical Center Utrecht, Utrecht University
2. Department of Internal Medicine, Unit Pharmacotherapy, Amsterdam University Medical Center, Amsterdam, the Netherlands
3. Research Centre for Digital Medicine, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium
4. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Introduction Transitions between healthcare settings are associated with a high risk of medication errors, leading to adverse drug events and hospital admissions. The LIMONCELLO trial (NCT05899114) evaluates a transitional multidisciplinary pharmacotherapeutic care (TMPC) intervention to improve pharmacotherapy. As primary care physicians (PCPs) are crucial for implementing hospital-initiated recommendations, this study explored their experiences, perceptions, and perceived barriers and facilitators.

Methods A cross-sectional survey was conducted among Dutch PCPs treating patients who participated in the TMPC intervention of the LIMONCELLO trial. Eligible PCPs were invited electronically to complete closed- and open-ended questions on experiences with TMPC components, feasibility, barriers, and facilitators. Quantitative data were analysed descriptively; qualitative responses by thematic content analysis. Stratification was applied to compare PCPs who had contact with the intervention team compared to those who had not

Results
Of the 441 PCPs, 63 were excluded, resulting in 378 PCPs, of which 115 responded (response rate: 30%; 54% female; 84% ≥10 years of clinical experience). Contact with the pharmacotherapy team was reported by 50% (57/115), of whom 53% rated this contact as highly meaningful. The pharmacotherapeutic discharge letter was received by 54% (62/115) and rated positively (mean 7.6/10, SD 0.95). Complete implementation of TMPC recommendations was reported by 27% (31/115), partial implementation by 16% (18/115), and no implementation by 11% (13/115) of PCPs; 30% (35/115) could not recall receiving recommendations and 16% (18/115) reported none were applicable . Overall perceived value and feasibility were rated as neutral. Barriers included limited perceived added clinical value, misalignment with patient preferences, unclear professional responsibility, and time constraints. Facilitators were clear communication, well-substantiated recommendations, and structured discharge information. Stratified analyses showed that contact with the intervention team was associated with higher implementation rates and greater perceived value.

Conclusions
Implementation of hospital-initiated medication review recommendations in primary care was limited, mainly due to unclear roles and suboptimal presence of communication. Defining responsibilities, better integration in workflow and enhanced communication across care transitions is essential for effective medication reviews in older adults.

IMIPRAMINE: DO METABOLITE PLASMA LEVELS AFFECT TREATMENT RESPONSE?

R.Y.N. Kasanmonadi[a], dr. A.M. Kamperman[a], prof. Dr. B.C.P. Koch[b], dr. T.K. Birkenhager[a]

Organisations

[a]Department of Psychiatry, Doctor Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands

[b]Department of Hospital Pharmacy, Doctor Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands

Introduction

Although combined plasma levels of imipramine and its metabolite desipramine are routinely assessed during therapeutic drug monitoring (TDM) of imipramine treatment, individual plasma levels are often overlooked. Imipramine and desipramine differ in their pharmacokinetic properties. Previous research in patients with generalized anxiety disorder suggested that imipramine treatment efficacy might be negatively influenced by high desipramine levels. We thus explored the relationship between imipramine and desipramine levels and treatment response in depressed inpatients.

Methods

This exploratory retrospective study involved 70 inpatients with major depression disorder who had undergone five-week imipramine treatment. Weekly combined levels were measured, and adjustments made until adequate levels were reached. We assessed response rates on the 17-item Hamilton Rating Scale for Depression (HDRS17) and used Mann-Whitney U tests to compare imipramine and desipramine plasma levels between responders and non-responders.

Results

After five weeks of treatment, non-responders had significantly higher desipramine levels ($P = 0.015$) and combined plasma levels ($P = 0.020$) than responders. Imipramine levels did not differ significantly between groups. Plasma levels did not differ significantly between patients with and without concomitant CYP2D6- or CYP2C19-inhibiting medication.

Conclusions

By showing that desipramine plasma levels were higher in non-responders to imipramine treatment, our findings imply that desipramine negatively impacts imipramine's therapeutic effect. When performing TDM, it may be important to consider metabolite plasma levels as well as combined plasma levels.

A ‘SUSTAINABLE PRESCRIBING’ TRAINING PROGRAM TO REDUCE UNNECESSARY PROTON PUMP INHIBITION AND INTRAVENOUS PAIN KILLERS

Authors
Nadda N. Hamid, Michael O. Reumerman, Ron A.A. Mathôt, Michiel A. van Agtmael

Organisations
Amsterdam UMC

Introduction
Inappropriate (co-)prescribing of proton pump inhibitors (PPIs) (with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)) has increased recent years with potentially negative consequences for both patient and the environment [1]. Intravenous infusion and oral administration of 1000 mg paracetamol produces up to 628 g and 28 g CO2e respectively [2]. Furthermore with the oral tablet no plastic intravenous lines are wasted. Prescribing education can help to improve adequate prescription of PPIs and reduce carbon emissions from intravenous painkillers. The aim of this study was to reduce inappropriate co-prescribing of PPIs and intravenous painkillers.

Methods
A single center prospective cohort study at the Trauma surgery unit in Amsterdam UMC. Three consecutive 2-month periods (pre-intervention, intervention, post-intervention) were studied, implementing a multi-faceted nudge-based [3] education intervention for prescribers (consisting of a training, distribution of a protocol, daily medication reviews and case-related reminders). Prescribing of diclofenac (three times a day 50 mg orally) with (in)appropriate PPI (once daily 20 mg orally), metamizole and paracetamol administration four times a day 1000 mg (intravenously (in)appropriate) were compared using the non-parametric Mann- Whitney U test.
Patients older than 18 years old admitted during the three periods were included in the study. For confirming the adequate indication of co-prescribing of PPIs, guidelines of the Dutch physician society as well as local protocols were used.

Results
A total of 161 patients were included, 83 pre-intervention and 78 post-intervention. An absolute decrease of 47.5% in **inappropriate** PPI (co-)prescribing was found after the intervention (20 from 32 versus 3 from 20; $p<0.05$). An absolute decrease of 24.3% and 15.2% was found after the intervention in **inappropriate** intravenous metamizole (26 from 63 versus 8 from 47; $p<0.05$) and paracetamol (10 from 66 versus 0 from 66; $p<0.05$).

Conclusions
Multi-faceted nudge-based education improves the appropriate co-prescription of PPIs and reduces prescription at the Trauma surgery unit of intravenous painkillers significantly. This simple intervention contributes to sustainable prescribing and is clinically relevant.

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MEDICATION USE COMPLEXITY AND HEALTHCARE UTILIZATION IN OLDER ADULTS AFTER HOSPITAL DISCHARGE

Authors:
Hogewoning A.[1], Falke C.[2], Karapinar- Çarkit, F. [3], Bouvy M.[2], Emmelot. M.[1], Egberts T.[2,4], Knol W.[1]

Organisations
1 Department of Geriatric Medicine, University Medical Center Utrecht,
Utrecht University, Utrecht, the Netherlands
2 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht
Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, the Netherlands
3 Department of Clinical Pharmacy & Toxicology, Maastricht University
Medical Center, Maastricht, the Netherlands
4 Department of Clinical Pharmacy, University Medical Centre Utrecht, Utrecht,
the Netherlands.

Introduction Medication use complexity plays a significant role in the risk of medication-related problems among older adults, such as hospital readmissions and medication non-adherence. The aim of this study was to evaluate whether higher medication use complexity is associated with increased healthcare utilization following hospital discharge.

Methods In this prospective cohort study, patients aged ≥70 years with multimorbidity and polypharmacy were included from a cluster - RCT investigating the effect of pharmacotherapy optimization (OPERAM). Medication use complexity was measured at discharge, using the Medication Regimen Complexity Index (MRCI), which consists of dosage frequency, dosage form/route of administration, and administration instructions. Healthcare utilization was primarily defined as a composite endpoint of acute secondary care utilization (Emergency Department (ED) visits and hospital readmissions) at 2-, 6-, and 12-months post-discharge. Secondary endpoints included ED visits and hospital readmissions separately, as well as primary care utilization (GP visits), measured at the same time points. Data was analysed using descriptive statistics and multivariate Poisson regression, expressed as Incidence Rate Ratios (IRR) with 95% confidence intervals. The IRR reflects the relative difference in event rates between different MRCI scores.

Results
A total of 1923 patients were included (45% female, mean age 79 years). Acute secondary healthcare utilization at 2, 6 and 12 months was 431/1781 (26%), 711/1600 (44%) and 869/1482 (59%) respectively; for primary care visits these rates were 1215/1781 (73%), 1444/1600 (90%) and 1415/1482 (96%). Medication use complexity was not associated with secondary healthcare use at 2 months, IRR 1.005 (95% CI 0.998 – 1.012), but showed a significant association at 6 and 12 months: 1.015 (1.011 – 1.020) and 1.013 (1.009 – 1.017). Similar trends were observed for the secondary endpoints. For example, a 10-point higher MRCI score is associated with a 16% increase in the rate of the primary endpoint at 6 months ($IRR = 1.015^{10} = 1.16$).

Conclusions
A significant association between medication use complexity and healthcare use was found at 6 and 12 months for older adults with multimorbidity and polypharmacy after hospital discharge. These findings emphasize the need for further research to identify effective strategies to reduce medication use complexity and to evaluate their impact.

OLDER ADULTS' PERSPECTIVES ON TRANSITIONAL MULTIDISCIPLINARY PHARMACOTHERAPEUTIC CARE

Authors Eline M.C. Engelen[1], Kim Keukens[2], Marcel L. Bouvy[3] Michiel A. van Agtmael[1], Stephanie C.M. Wuyts[4], Wilma Knol[2]

Organisations 1. Department of Internal Medicine, Unit Pharmacotherapy, Amsterdam University Medical Center – location VUmc, Amsterdam, the Netherlands
2. Department of Geriatric Medicine University Medical Center Utrecht, Utrecht University
3. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
4. Research Centre for Digital Medicine, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium

Introduction Polypharmacy increases the risk of adverse drug events, particularly among frail older adults during care transitions. Transitional Multidisciplinary Pharmacotherapeutic Care (TMPC) is an in-hospital medication review intervention aimed at improving pharmacotherapy and supporting continuity of care for older patients with polypharmacy. Its effect on medication-related readmissions was evaluated in the LIMONCELLO-trial (NCT05899114).[1] The aim of this qualitative process evaluation was to explore patients' perspectives on the TMPC intervention.

Methods In this qualitative study, semi-structured interviews were conducted with a purposively selected sample of adults aged ≥70 years with polypharmacy who received the TMPC intervention. Interview topics included experiences with the intervention, acceptance of medication changes and perspectives on implementation. A thematic analysis using both inductive and eductive approaches was used to organize data into themes relevant to patients' experiences with TMPC.

Results Twenty patients were interviewed (median age 78 years (IQR 76-81); 45% female, median number of medications 13 (IQR 9-15), and medication-related recommendations 4 (IQR 2-5)). Patient perspectives varied widely, and three main themes were identified: (1) experiences with in-hospital medication-related discussion, (2) collaboration in medication-related decision-making across care settings, and (3) perceived impact of TMPC. Most participants were satisfied with the communication and information provided during in-hospital discussions, although some perceived the timing as suboptimal. Preferences regarding involvement in shared decision-making varied, and the role of primary care providers was highlighted. Despite TMPC aimed to strengthen communication with primary care, most participants were unaware of any such communication, either because they were not involved or because it did not occur. Responses to medication changes were mixed: some participants appreciated a reduced medication burden, while others were reluctant to discontinue long-term medications. Nearly all participants perceived TMPC as a valuable addition to standard care.

Conclusions TMPC was generally valued by patients. Tailoring the intervention to individual needs, particularly regarding timing, communication, involvement in decision-making and collaboration with primary care, may enhance patient engagement and experiences and support adherence.

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CHARACTERIZATION OF THE INTRADERMAL LIPOPLYSACCHARIDE CHALLENGE AS AN IN VIVO MODEL FOR CONTROLLED INDUCTION OF VASCULAR LEAKAGE IN HEALTHY VOLUNTEERS

Authors
Menno van Diemen1,2, Marella Cornelia Elizabeth van Ruissen1,2, Liza Botros1,2, Ingrid Tomljanovic3, Hind Achbo1, Dimitra Eleftheriou1,4, Paul Willem Schenk2, Naomi Bertine Klarenbeek1, Derek William Gilroy5, Manon Aleida Adriana Jansen1,2, Matthijs Moerland1,2

Organisations
1Centre for Human Drug Research, Leiden, The Netherlands; 2 Leiden University Medical Center, Leiden, The Netherlands; 3 Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands; 4 Division of Systems Pharmacology and Pharmacy, Leiden Academic Centre for Drug Research, Leiden, The Netherlands; 5 Department of Experimental & Translational Medicine, Division of Medicine, University College London, London, UK

Introduction:
Vascular leakage and its associated phenomena vasodilation and endothelial activation are pathophysiological features of various diseases. Multiple drug candidates targeting these phenomena are in development, necessitating translational models to demonstrate proof- of- pharmacology and proof- of mechanism in early-phase clinical trials. This single-center experimental study evaluated the intradermal lipopolysaccharide (id LPS) challenge model as a tool to induce and characterize vascular leakage in healthy participants.

Methods
Eight participants (male:female = 4:4) received id LPS in the volar forearms, followed by serial pharmacodynamic assessments, including imaging and suction blister induction up to 9 hours after injection.

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Results:
Id LPS administration resulted in significant increases in skin perfusion ($P < 0.0001$), erythema ($P = 0.0013$), and skin volume ($P = 0.0008$), indicating initial stages of inflammation and fluid extravasation. Blister fluid analysis revealed elevated extravascular concentrations of albumin ($P = 0.0011$), total protein ($P < 0.0001$), supporting the presence of vascular leakage. Moreover, the expression of endothelial activation markers VCAM-1 ($P = 0.0015$), ICAM-1 ($P = 0.0004$), ITGB1 ($P = 0.01$), and E- selectin ($P = 0.0218$) increased significantly. Disruption of endothelial cell–cell integrity was supported by increased expression of VE- cadherin ($P = 0.0002$) in blister fluid.

Conclusions:
These findings support the applicability of the id LPS model for the induction of vascular leakage in humans. This model holds potential as a translational tool for evaluating the pharmacodynamic responses of vascular leakage- targeting drugs in early clinical development.

BUDGET IMPACT ANALYSIS OF MEDICATION REVIEWS BY JUNIOR PHARMACISTS: A HOSPITAL PERSPECTIVE

Authors
Toon Hectors, Thirza Kooijman, Marit van Barreveld, Marianne Kuijvenhoven, Patty Teeuwisse, Rik Olde Engberink

Organisations
Amsterdam UMC location University of Amsterdam, Departments of Clinical Pharmacology and Pharmacy; Nephrology; Epidemiology and Data Science.

Introduction
Pharmacist-led medication reviews are increasingly recognised for their ability to generate significant cost savings within the hospital setting[1,2]. However, no cost-analysis has investigated the budget-impact of junior pharmacists conducting medication reviews under supervision of clinical pharmacists, nor included recommendations to start-, increase-, or monitor medications. We aimed to assess the budget impact of junior pharmacist-led medication reviews across hospital wards; explore budget impact differences between drug classes; and identify patient predictors that influence the net budget impact.

Methods
We developed a cost model over a one-year horizon, from the hospital perspective. Intervention costs were derived from labour time per medication review and salary of junior- and clinical pharmacists. Cost avoidance from preventable medication-related admissions were based on admission time, associated costs and proportion of preventable medication-related admissions (4.75%). Costs and savings from medication recommendations were aggregated using drug price per daily defined dose and its predicted days of therapy per year. Patient predictors of budget impact related to medication recommendations were assessed using multivariable linear regression, including age, gender, estimated glomerular filtration rate, medication count, and comorbidity index.

Results
Over 19 months, we collected 271 medication reviews, including 1,689 medication recommendations. Per-patient budget impact for labour, preventable medication related admissions, and medication recommendations were -€104; +€237; and +€46, respectively. Net estimated savings were €179 per patient, and €680,000 when upscaled hospital wide. Opioids, beta receptor agonists, corticosteroids, urological drugs, and muscarine receptor antagonists generated 43% of medication recommendation savings. Erytropoetic growth factors, SGLT2 inhibitors, Etanercept, Etravirin, and Calcium/vitamin D formulations generated 70% of medication recommendation costs. No significant associations were found between any of the included patient characteristics and budget impact related to medication recommendations

Conclusions
When comprehensively accounting for negative budget-impact from medication recommendations, junior pharmacist-led medication reviews still provide a cost-saving intervention from the hospital perspective, demonstrating savings across clinical populations with polypharmacy.

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APROPIATE CARE FOR PATIENTS WITH MULTIPLE MYELOMA: AN EXPLORATORY STUDY OF HOSPITAL CARE AT THE LAST 90 DAYS OF LIFE

Authors
E Hassan*, M Bakkal[#,] J Eijsink[@,] A Gerrits*, N.Khorsand*

Organisations:
*OLVG, [#]Utrecht University, [@]CWZ, Universiteit van Utrecht and OLVG

Introduction
Treatment decisions in the last months of life in patients with Multiple Myeloma (MM) may influence healthcare utilisation and place of death. Real-world data on anti-MM medication treatment in the last 90 days of life and associated outcomes are limited. The objective of this study was to determine which patients with MM receive treatment in the last 90 days of life and to evaluate its association with healthcare utilisation and in-hospital death, particularly in light of the high costs of these therapies.

Methods
This multicentre, retrospective, observational study was conducted in seven Santeon hospitals. Patients with MM who died between September 2024 and September 2025 were included (n = 100). Data on anti-MM treatment in the last 90 days before death, patient characteristics, advance care planning (ACP), healthcare utilisation, and place of death were collected from medical records. Descriptive statistics were used to summarise baseline characteristics and outcomes. Continuous variables are presented as medians. Categorical variables are presented as numbers and percentages. Differences between groups were analysed using chi-square or Fisher's exact tests where applicable. A p-value <0.05 was considered statistically significant.

Results
In the last 90 days before death, 55% of patients (55/100) received anti-MM treatment. Of these, 64% (35/55) received expensive medication until a median of 26 days before death. Treated patients were younger than untreated patients (median 73 vs 77 years, $p = 0.011$) and had a shorter time since diagnosis (28 vs 70 months, $p < 0.001$). Comorbidity score and number of previous treatment lines did not differ between groups. Patients who did not receive treatment in the last 90 days more frequently had ACP before this period (11/45 vs 4/55, $p = 0.024$). Treated patients had more emergency department visits and more hospital admissions in the last 90 days. In-hospital death occurred in 26/55 treated patients compared with 12/45 untreated patients ($p = 0.040$).

Conclusions
This study reflects daily clinical practice and shows that continuation of anti-MM treatment in the last 90 days of life is associated with higher healthcare utilisation and a higher proportion of in-hospital death. ACP were more frequent among patients who did not receive treatment in this phase. These findings underline the relevance of early ACP in treatment decision-making at the end of life and its potential role in facilitating care aligned with patient preferences, reducing hospital-based care, and improving the quality of end-of-life care for patients with Multiple Myeloma.

ALLOPURINOL AND RISK OF INCIDENT KNEE AND HIP OSTEOARTHRITIS: A POPULATION-BASED COHORT STUDY

Authors
J.P.A. Houwen[1,2], M. Hartog[3,4], M.W.J. Heijman[3,4], C.H.M. van den Ende[3,4], P.C. Souverein[1], A. Lalmohamed[1,2], C.D. Popa[4,5], B.J.F. van den Bemt[3,6,7]

Organisations:
Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, NL
Department of Clinical Pharmacy, UMC Utrecht, Utrecht, NL
Department of Research, Sint Maartenskliniek, Nijmegen, NL
Department of Rheumatology, Radboudumc, Nijmegen, NL
Department of Rheumatology, Sint Maartenskliniek, Nijmegen, NL
Department of Pharmacy, Sint Maartenskliniek, Nijmegen, NL
Department of Pharmacy, Radboudumc, Nijmegen, NL

Introduction:
Osteoarthritis (OA) is a highly prevalent disease with a substantial burden, and no disease-modifying pharmacological therapies are currently available. In-vitro evidence suggests that xanthine oxidase (XO) inhibition may influence early OA pathophysiology. This study aimed to examine whether allopurinol (a potent XO inhibitor) use is associated with a reduced risk of incident knee or hip OA in the general population.

Methods:
Using the UK Clinical Practice Research Datalink, adults aged ≥40 years initiating allopurinol were identified and matched 1:1 to non-users using propensity scores. Time-varying Cox proportional hazards models were used to estimate hazard ratios (HRs) for incident knee or hip OA, and secondary analyses assessed the associations with treatment duration, recency of use and medication adherence.

Results:
A total of 214 452 allopurinol users and 214 452 matched non-users were included. Over a mean follow-up of 7.6 and 7.4 years, respectively, 46 462 participants developed knee or hip OA. Allopurinol use was associated with a 19% lower hazard of OA compared with non-use; adjusted (adj) HR 0.81 (95% CI 0.74, 0.88). Joint-specific estimates were similar for hip OA (adj HR 0.82; 95% CI 0.69, 0.96) and knee OA (adj HR 0.80; 95% CI 0.73, 0.88). Longer cumulative use was associated with progressively lower OA rate, with the strongest association for >1 year of allopurinol therapy (adj HR 0.77; 95% CI 0.71, 0.84). High adherence (medication possession ratio >80%) showed the greatest reduction in risk (adj HR 0.18; 95% CI 0.16, 0.20).

Conclusions:
Allopurinol use was associated with a 19% lower rate of incident knee or hip OA, with stronger associations among long-term and adherent users. These findings suggest a protective association and support further research into XO inhibition in early OA.

REPERFUSION THERAPIES FOR EXTENSIVE SPLANCHNIC VEIN THROMBOSIS AND BUDD-CHIARI SYNDROME: A SYSTEMATIC REVIEW OF INTERNATIONAL GUIDELINES AND EXISTING EVIDENCE

Authors
Liselotte F.S. Langenhuijsen[1], Sophie N.M. ter Haar[1], Mark C. Burgmans[2], Maarten E. Tushuizen[3], Minneke J. Coenraad[3], Paul L. den Exter[1], Frederikus A. Klok[1], Ype de Jong[1,4]

Organisations
1. Internal Medicine, LUMC
2. Radiology, LUMC
3. Gastroenterology and Hepatology, LUMC
4. Clinical Pharmacology, LUMC

Introduction:
In patients with extensive symptomatic splanchnic vein thrombosis (SVT) and Budd-Chiari syndrome (BCS) where conventional anticoagulant therapy fails, reperfusion therapies (i.e., local and systemic thrombolysis or combined therapies of thrombolysis and/or thrombectomy with or without additional interventions) may be considered. Current guidelines lack clear consensus on their use and timing. This study aims to (1) review original studies evaluating the effectiveness and safety of reperfusion therapies in patients with extensive symptomatic SVT or BCS, (2) summarize international guideline recommendations published in the last decade regarding these therapies, and (3) assess their methodological quality and risk of bias (ROB).

Methods: We performed a systematic review of current guidelines and original studies including ≥5 patients studying reperfusion therapies for SVT or BCS. Data on thrombosis etiology, location and extent, clinical outcomes, recanalization rates, bleeding complications, reocclusion and mortality were extracted and summarized. ROB was assessed using the (ROBINS-I) tool.

Results:
We identified 40 studies. Five evaluated systemic thrombolysis (57 patients), reporting clinical improvement in 45.6%, complete recanalisation in 29.8% and bleeding complications in 8.8%. Twelve assessed local thrombolysis (184 patients), with 65.8% showing clinical improvement, 57.6% complete recanalisation and 27.2% bleeding complications. Twenty-seven described combined therapies (600 patients), reporting clinical improvement in 76.7%, complete recanalisation in 70.2% and bleeding complications in 8.0% (Figure 1). Five out of seven identified guidelines recommended considering reperfusion therapies in selected SVT or BCS patients. Evidence was largely based on case-reports or small case-series and only up to 28% of the identified studies were cited as evidence, despite the majority had been published prior to publication of these guidelines. All studies were at serious ROB, mostly because of concerns regarding confounding.

Conclusions:
Consistent with current clinical guidelines, our findings suggest that reperfusion therapies may be considered in selected patients with SVT or BCS. However, existing guideline recommendations are only based on a limited portion of the available evidence. All included studies were at serious ROB, precluding firm conclusions regarding the optimal patient selection criteria, reperfusion strategy, thrombolytic agent, dosing or treatment duration. High-quality, randomized controlled trials are needed to establish their comparative effectiveness and safety.

ASSOCIATION BETWEEN OBJECTIVE SKIN PIGMENTATION AND EPIDERMAL BARRIER FUNCTION IN HEALTHY ADULTS: A CROSS-SECTIONAL STUDY

Authors L.J. van den Oord, MD[1], T. Rutgers, BSc[1], R. Rissmann, PhD[2] W. Ten Voorde, PhD[2], D.M.W. Balak MD, PhD[1]

Organisations [1] Department of Dermatology, Leiden University Medical Center (LUMC), Leiden, The Netherlands [2] Centre for Human Drug Research, Leiden, The Netherlands

Introduction
Previous literature has reported associations between skin colour and epidermal barrier function, suggesting that structural and functional skin parameters may differ across pigmentation levels. However, existing evidence remains heterogeneous and inconclusive. Such differences could influence percutaneous penetration, topical treatment efficacy, and responses to environmental stressors such as low ambient humidity. The primary aim of this study is to examine the association between objectively measured skin pigmentation (melanin index) and epidermal barrier function (trans epidermal water loss (TEWL) and stratum corneum hydration (SCH)) in healthy adults.

Methods
A cross-sectional observational study was performed at the LUMC among healthy participants. Skin pigmentation was objectively quantified as melanin index using the DSM IV Colorimeter (Cortex Technology). Epidermal barrier outcomes were measured with the GPSkin Barrier Pro-1 (GPower), assessing TEWL and SCH. Measurements were obtained across 14 anatomical sites, which were subsequently grouped into four predefined regions: face, arm, leg and trunk.

Results
A total of 94 healthy participants were included. The median age was 30 (interquartile range (IQR) 16-44), and 70.2% were female. The mean melanin index was 36.77 ± 6.21 (range 28.16–78.16).

In unadjusted analyses, melanin index did not correlate to TEWL in any anatomical region. For SCH, weak inverse correlations were observed at the trunk ($r = -0.204$, $p = 0.049$) and leg ($r = -0.202$, $p = 0.051$), whereas correlations at the arm ($r = -0.169$, $p = 0.106$) and face ($r = -0.141$, $p = 0.174$) were not statistically significant. Adjustment for age and sex resulted in minimal changes in the regression coefficients, indicating no meaningful confounding.

Conclusions
In this cohort of healthy adults, melanin index was not found to be associated with TEWL or SCH. This suggests that there is no correlation between skin colour and epidermal barrier function. These findings help to provide a more nuanced understanding of functional skin parameters across different skin tones.

USE OF CIMETIDINE TO ENHANCE SYSTEMIC ACYCLOVIR CONCENTRATIONS IN PATIENTS WITH INEFFECTIVE SUPPRESSIVE THERAPY FOR RECURRING HERPES SIMPLEX VIRUS INFECTIONS: A NOVEL PURPOSE FOR AN OLD DRUG

Authors
D.G. Stuijt[1*], V.M. Cnossen[1*], A.F.Y.S.M. Osman[2], T. van Gelder[2], S.M. Arend[3]

Organisations
[*] These authors contributed equally.
[1] Centre for Human Drug Research (CHDR), Leiden, The Netherlands
[2] Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands
[3] Leiden University Centre for Infectious Diseases (LU-CID), Leiden University Medical Centre, The Netherlands

Introduction
Herpes simplex virus (HSV) is a common cause of oral or genital ulcerative infections, which may recur frequently. Valacyclovir may be used as suppressive therapy, but is insufficiently effective for some patients. To date, no guidelines are available for patients with ineffective suppression; we present a case series in which valacyclovir dose is guided by pharmacokinetic data, as well as the addition of cimetidine (a tubular transporter agonist competitive to acyclovir) to enhance systemic antiviral concentrations.

Methods
Four patients with frequently recurring HSV infections were included in this case series. Blood acyclovir concentrations were measured before, and 1 and 2 hours after valacyclovir administration. Prescribed valacyclovir doses were determined individually based on clinical effects and pharmacokinetic concentrations.

Results
All four patients were shown to have subtherapeutic levels of acyclovir with a regimen of either 500 or 1000 mg of valacyclovir. For three patients, addition of cimetidine to 1000 mg resulted in therapeutic levels; for one patient, valacyclovir dose was increased to 1500mg to achieve a sufficient concentration. All patients tolerated their therapy well over years of continuous use. A satisfactory clinical effect was achieved in all four patients.

Conclusions
Ineffective suppressive therapy of valacyclovir may reflect subtherapeutic systemic drug levels. Increase of valacyclovir dose or addition of cimetidine may result in sufficient concentrations and consequently achieve good clinical effects.

SEX DIFFERENCES IN ANTIDEPRESSANT SERUM LEVELS

Authors:
E.L. Bosch[a], F. de Beer[a], D.J. Touw[b,c], I.E. Sommer[a]

Organisations:
(a) UMCG, center for clinical neuroscience and cognition,
(b) UMCG, department of clinical pharmacy and pharmacology,
(c) GRIP, department of pharmaceutical analysis

Introduction:
Antidepressants are widely prescribed world-wide, and usage in women is more than double that in men. Sex influences antidepressant pharmacokinetics, potentially leading to sex differences in antidepressant tolerability, safety and therapeutic response, yet current prescription guidelines do not account for sex. This study aimed to examine whether sex is associated with differences in serum levels of 11 commonly prescribed antidepressants, including selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenalin reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs).

Methods:
Serum levels of amitriptyline, nortriptyline, citalopram, clomipramine, fluoxetine, fluvoxamine, imipramine, mirtazapine, paroxetine, sertraline, and venlafaxine, along with their active metabolites, were collected from the laboratory information system (GLIMS) database of the UMCG between January 2016 and October 2024. When metabolites exhibited comparable pharmaco-logical potency, parent and metabolite concentrations were summed. Linear mixed-effects models were applied with antidepressant serum level as the outcome measure. The dataset comprised 38,298 samples from 10,500 unique adult men and women. To assess whether dosing differences contributed to the sex differences in serum levels, subgroup analysis using dosing data from the MOnitoring psycho-PHARmacology (MOPHAR) program was performed.

Results:
Women exhibited significantly higher serum levels than men for citalopram (+38%, $p<0.001$), fluoxetine (+20%, $p=0.002$), fluvoxamine (+85%, $p<0.001$), paroxetine (+51%, $p<0.001$), sertraline (+13%, $p=0.048$), clomipramine (+10%, $p<0.001$), imipramine (+20%, $p=0.001$), nortriptyline (+9%, $p<0.001$), and venlafaxine (+25%, $p<0.001$). Trend level higher serum levels were observed in women for amitriptyline ($p=0.058$), and no sex differences were found for mirtazapine ($p=0.734$). Dosing did not significantly differ between sexes, except for higher doses in men than in women for clomipramine ($p=0.016$) and nortriptyline ($p<0.001$).

Conclusions:
Under current treatment guidelines, women are exposed to significantly higher antidepressant serum levels than men for all investigated SSRIs, three of the four TCAs, and the SNRI. Subgroup analyses confirmed that the observed sex differences are unlikely to result from dosing practices but instead reflect sex differences in underlying mechanisms such as pharmacokinetic variations. Whereas most antidepressants investigated are prescribed using standardized dosing regimens, dosing of TCAs is guided by therapeutic drug monitoring (TDM). The smaller, though persisting, sex differences observed for these antidepressants suggest that TDM partially mitigates but does not fully eliminate sex-related pharmacokinetic variability. These findings highlight the need to consider sex in antidepressant dosing strategies to improve treatment tolerability, and safety for women.

AGE AND SEX RELATED DIFFERENCES IN CYP450 MEDIATED METABOLISM RATE: A REVIEW OF THE CURRENT LITERATURE

Authors:
K. Kleine Schaars1,2,3, S. Bedi1, T.A.D. Pelgrim1
The PSY-PGx Consortium, R. van Westrhenen1,2,4,5

Organisations
1. Outpatient Clinic Pharmacogenetics, Parnassia Psychiatric Institute, Amsterdam, The Netherlands.2. Centre for Human Drug Research, Leiden, The Netherlands.3. Leiden University Medical Center, Leiden, The Netherlands.4. St. John's National Academy of Health Sciences, Bangalore, India
Institute of Psychiatry, Psychology & Neuroscience (IoPPN,)5. King's College London, London, United Kingdom

Introduction Variability in psychiatric drug response is common, with up to 50-70% of patients experiencing insufficient efficacy or adverse drug reactions[1]. Although genetic polymorphisms in cytochrome P450 (CYP) enzymes, a group of drug metabolising enzymes, account for part of this variability, other biological factors such as sex and age may also contribute to this interindividual heterogeneity. This systematic review summarizes evidence on sex- and age-related differences in the activity of five clinically relevant CYP isoforms in psychiatry (CYP1A2, CYP3A4, CYP2C9, CYP2C19, and CYP2D6).

Methods A systematic search of MEDLINE, PsycINFO, and Embase in 2024 identified studies assessing CYP activity using both genotyping and phenotyping approaches. It was conducted and reported in accordance with the PRISMA guidelines. In total, 21 studies were included, comprising 1901 participants. Study findings were synthesized narratively due to heterogeneity in study design, probe substrates, and genotyping panels. Risk of bias was assessed using the ROBINS-E tool.

Results
Given the heterogeneity in study designs, populations, probes, and outcome measures, a pooled statistical analysis was not feasible. CYP1A2 activity appeared higher in males, while oral contraceptive use was consistently associated with reduced activity in females. CYP3A4 activity generally tended to be higher in females, although endogenous markers suggested the opposite, and a consistent age-related decline was reported. Data on CYP2C9 were insufficient to draw conclusions. For CYP2C19, findings were mixed, but oral contraceptive use was associated with reduced activity, and an age-related decline was reported. CYP2D6 activity was generally slower in females, with activity stabilizing early in life.

Conclusions
Across enzymes, hormonal status and oral contraceptive use emerged as important modifiers of CYP activity, particularly for CYP1A2 and CYP2C19, yet were frequently unmeasured or unadjusted for. Smoking was a strong determinant of CYP1A2 activity but was not consistently accounted for. Differences in probe substrates, genotype methods and discrepancies between endogenous and exogenous markers, particularly for CYP3A4, further complicated interpretation. Despite these limitations, findings suggested sex and age specific effects for specific isoforms. Integrating CYP genotyping with data on sex and age differences in drug metabolism promises a more efficient guided pharmacological treatment, empowering clinicians to make informed decisions. This integration represents a significant step towards personalized medicine in psychiatry.

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HETEROZYGOUS VARIANT OF CYP2C8∗3 IS A PROTECTIVE FACTOR FOR DEVELOPING POST ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY PANCREATITIS

Authors Mike J.P. de Jong[1], Romy N. Kuipers[1], Joost P.H. Drenth[2], René H.M. te Morsche[1], Foke van Delft[1], Peter D. Siersema[3], Christina J. Sperna Weiland[1], Robert C. Verdonk[4] · Niels Venneman[5] · Muhammed Hadithi[6] · Tanya M. Bisseling[1] · Marco J. Bruno[3], Erwin-Jan M. van Geenen[1]

Organisations
1. Radboudumc, 2. Amsterdam UMC, 3. Erasmus MC, 4. Antonius ziekenhuis, 5. Medisch Spectrum Twente, 6. Maasstad ziekenhuis

Introduction
Acute pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP), with an incidence of 10.2%. Administration of diclofenac suppository prior to ERCP is recommended as prophylaxis for PEP, but PEP still occurs, potentially due to individual pharmacogenetic variations affecting diclofenac's pharmacokinetics.

Diclofenac is metabolized by cytochrome P450 (CYP) enzymes and UGT2B7. Single nucleotide polymorphisms (SNPs) of these enzymes result in interpersonal differences in pharmacodynamics and pharmacokinetics of diclofenac.

This study aims to gain more insight into pharmacogenetic variations related to diclofenac metabolization in patients with PEP, hypothesizing that identifying patient-specific SNPs could help to develop tailor-made PEP prophylactic management.

Methods
This is a multicenter cohort study that included patients over 18 years who underwent ERCP between 2012 and 2022 were screened for eligibility. Exclusion criteria included contraindications for non-steroidal anti-inflammatory drugs (NSAIDs), pancreatic cancer, acute or chronic pancreatitis, or biliodigestive anastomosis. Patients received an information letter, informed consent form, and buccal smear kit at home. Patients were included in either the PEP or non-PEP group. PEP was assessed according to the Cotton criteria.

Approval was obtained from the Radboudumc Medical Ethical Board (NL68494.091.18). This study was registered at ClinicalTrials.gov, NCT05267379.

Results
348 patients were included: 103 patients with PEP and 245 non-PEP patients. Baseline characteristics did not differ between both groups, except for age and body mass index (BMI). DNA amplification rate was 91.5%, with 81.6% of patients having DNA of sufficient quality to analyze all intended CYP and UGT enzymes. Presence of the heterozygous variant of *CYP2C8*∗3 differed significantly between patients with and without PEP (3% [3/103] vs 15% [32/245], respectively).

Conclusions
In conclusion, heterozygous variant of *CYP2C8*∗3 may reduce the prevalence of PEP, probably by a decreased diclofenac metabolization. A prospective cohort study with blood samples is needed to confirm the correlation between the heterozygous variant and diclofenac plasma levels for optimizing PEP prophylaxis.

IMPLEMENTING PHARMACOGENETIC TESTING IN PSYCHIATRY IN THE NETHERLANDS

Authors
Juriaan Muijsers, Carla van El, Martina Cornel, Loes Kreeftenberg, Pierre Bet, Roos van Westrhenen

Organisations
[1]*Outpatient Clinic Pharmacogenetics, Parnassia Psychiatric Institute, Overschiestraat 57, 1062HN Amsterdam, The Netherlands*
[2]*Amsterdam UMC location Vrije Universiteit Amsterdam, Section Community Genetics, Department of Human Genetics, Amsterdam Public Health Research Institute, De Boelelaan 1117, Amsterdam, the Netherlands*
[3]*Department of Clinical Pharmacology & Pharmacy, Amsterdam University Medical Center, Amsterdam, The Netherlands*
[4]*Personalized Medicine Programme, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands.*
[4]*Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience King's College London, UK*
[6]*St. John's National Academy of Health Sciences, Bangalore, India*
[7]*Centre for Human Drug Research, Leiden, The Netherlands*

Introduction
Pharmacogenetics (PGx) can link genetic variations to drug dosage, enabling more personalized prescribing. Evidence suggests persistent knowledge gaps, inconsistent confidence in utility, and organizational barriers to implementation. Although dosing recommendations have been and are being developed by the Dutch Pharmacogenetics Working Group (DPWG) qualitative data on perspectives of psychiatrists on how best to implement PGx in clinical settings are scarce. This study aims to explore how psychiatrists in three Dutch mental health services perceive the utility, barriers, facilitators, and future role of PGx testing in everyday practice.

Methods
Practicing psychiatrists from three different health care institutes (Parnassia Groep, Amsterdam UMC and OLVG) and working in different settings were interviewed. All 8 psychiatrist were

Results
According to psychiatrists, pharmacogenetics is an individualized and selective option that is typically utilized after a pattern of non-response or side effects. Process duration influenced uptake; integrated clinics allowed for earlier implementation, whereas acute wards' urgent stabilization requirements limit the use of PGx. Most of the barriers that psychiatrists anticipate are long turnaround times, their perceived complexity of placing an order, ambiguous instructions, worries about expenses, and insufficient training. Reported potential workflow-based facilitators were the Electronic Health Record integration of personalized dosing recommendations, clear patient communication, focused CYP enzyme testing, expedited local capacity, and clear working instructions . Some psychiatrists did not have any experience or almost no experience with pharmacogenetics themselves and therefore, their views are not based on practical experience or hands-on knowledge.

Conclusions
When pharmacogenomics was more integrated into routine care, with test results rapidly available, it was perceived as a valuable/potential tool for guiding individualized pharmacotherapeutic treatment. The psychiatrists recommended having a working infrastructure in place for efficient adoption, as is present at the Outpatient Clinic Pharmacogenetics at Parnassia Groep, where experts arrange everything, cover costs, and communicate to the patients as well as the referrers. At this outpatient clinic, test ordering is already indivualized and the results are part of a broader personalized advise, that also includes non-psychopharmacological suggestions and considerations, based on available guidelines.

Roelofsen, A. H. A., Kreeftenberg, L. L., van El, C. G., Henneman, L., Rigter, T., Sie, D., Bet, P. M., Cornel, M. C. (2025). Barriers and facilitators for implementing a pharmacogenetic passport: lessons learned from reusing sequencing data. Pharmacogenomics, 26(5–6), 143–156. https://doi.org/10.1080/14622416.2025.2504862

interviewed using structured interviews for a qualitative study. The interview guide has been revised from Roelofsen et al. (2024) with their consent. Between August 20 and October 10, 2025, interviews were performed. (v25.01), . These interviews were audio recorded, verbatim transcribed, and their accuracy verified. In Atlas.ti (v25.01), the analysis followed a hybrid inductive–deductive method aligned with Braun & Clarke's six-phase conceptual approach.		

BEYOND ONE-SIZE-FITS-ALL: EVALUATING DRUG-SPECIFIC DETERMINANTS OF CYTOCHROME P450 3A4 IN SPECIFIC POPULATIONS – ILLUSTRATED BY PREGNANCY AND HEPATIC IMPAIRMENT

Authors

Femke A. Elzinga[1,2], Paul R.V. Malik[3], Onno W. Akkerman[4], Jelmer R. Prins[5], Bart L. Rottier[6], Hester van der Vaart[4], Henkjan J. Verkade[7], Sanne J. Gordijn[5], Gerard H. Koppelman[6], Daan J. Touw[1,2,8], Paola Mian[1,2,9]

Organisations

1. Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, the Netherlands.
2. Pharmacometrics Expertise Center of the Northern Netherlands, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
3. Ionis Pharmaceuticals, Carlsbad, CA, USA.
4. Department of Pulmonary Diseases and Tuberculosis; University Medical Center Groningen, Groningen, the Netherlands.
5. Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
6. Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
7. Department of Pediatrics, Division of Pediatric Gastroenterology and Hepatology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Methods:

Drugs with a fraction eliminated by CYP3A4 ($F_{m,CYP3A4}$) ≥0.78 were identified from regulatory and literature sources. For each drug, exposure data in pregnancy and hepatic impairment were extracted relative to healthy control subjects. Physicochemical and ADME parameters, including unbound fraction (F_{ub}), apparent clearance (CL/F), bioavailability (F), and organic anion transporting polypeptide 1B1 (OATP1B1) substrate status, were incorporated into linear mixed-effects models. Pregnancy trimester and Child-Pugh class were included as covariates to evaluate determinants of exposure modulation.

Results:

23 drugs were identified, with exposure data available for six during pregnancy and twenty in hepatic impairment. In hepatic impairment, Child-Pugh class B and C were significant predictors of increased area under the curve (AUC) ($P = 0.012$ and $P < 0.001$, respectively) and peak concentration (C_{max}) ratios ($P = 0.047$ and $P = 0.016$, respectively), while F was inversely correlated with both AUC and C_{max} ($P < 0.01$, for both). Limited pregnancy data indicated decreasing AUC ratios with advancing gestation. During pregnancy, exposure data were limited and did not allow formal statistical modeling, however, a trend toward decreasing AUC ratios with advancing gestation was observed, with greater variability among OATP1B1 substrates.

Conclusin:

In hepatic impairment, exposure changes of CYP3A4 substrates were driven by disease severity, with F emerging as a key determinant. In pregnancy, limited exposure data suggested gestational variability in CYP3A4-mediated drug exposure. Together, these findings highlight the need for predictive approaches that move beyond empirical scaling to improve extrapolation to specific populations.

8. Department of Pharmaceutical Analysis, Groningen Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, the Netherlands.

9. Department of Pediatrics, Beatrix's Children's Hospital, University Medical Center Groningen, Groningen, the Netherlands.

Introduction:
Predicting pharmacokinetics (PK) of drugs in specific populations remains challenging. This is particularly relevant for drugs for which clearance is largely mediated by cytochrome P450 3A4 (CYP3A4), as this enzyme is responsible for the metabolism of 30-50% of drugs. Conditions such as pregnancy and hepatic impairment substantially modulate CYP3A4 activity/expression, yet current scaling approaches used to predict PK changes in these populations are largely empirical. Consequently, these approaches may insufficiently account for drug-specific physicochemical and absorption, distribution, metabolism, and elimination (ADME) characteristics, which may contribute to variability in exposure changes between CYP3A4 substrates.

This study aimed to identify physicochemical and ADME-related characteristics associated with variability in CYP3A4-mediated PK modulation in pregnancy and hepatic impairment.

ULTRA-LOW-DOSE CAPECITABINE IN A *DPYD**2A HOMOZYGOUS PATIENT WITH COMPLETE DPD DEFICIENCY: A CASE REPORT

Authors:
Michiel A. Damhof[1], PharmD; Lisanne N. van Merendonk[2], PharmD en Bart A.W. Jacobs[2], PharmD, PhD et al.

Organisations
[1]Department of Clinical Pharmacy and Pharmacology, Frisius Medical Center, Leeuwarden, The Netherlands.
[2]Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

Introduction:
Complete dihydropyrimidine dehydrogenase (DPD) deficiency caused by homozygous *DPYD**2A is a contraindication for fluoropyrimidines due to extreme risk of life-threatening toxicity, resulting in clinical dilemmas when alternative treatments are unavailable. Guidelines are lacking and evidence on safe and effective dosing is scarce [1]. We describe a case of a 36-year-old male with recurrent metastatic rectal adenocarcinoma and complete DPD deficiency successfully treated with an ultra-low-dose capecitabine and acceptable toxicity.

Methods:
The pharmacogenetic identified complete DPD deficiency was confirmed by absence of DPD activity in Peripheral Blood Mononuclear Cells. Capecitabine was initiated at 150 mg once every 5 days, omitting every third dose (0.76% of standard 1000 mg/m^2 BID), following a published low-dose algorithm for homozygous *DPYD* carriers [2]. Toxicity was graded using CTCAE v5.0. Pharmacokinetic sampling was performed during cycles 1 and 2.

Results:
Initial dose regimen (0.76%) caused grade 3 mucositis after the second dose, prompting reduction to 150 mg every 7 days, omitting every third dose (0.50%), which improved tolerability (Figure 1). Pharmacokinetic sampling showed markedly prolonged 5-FU exposure ($AUC_{0–\infty}$ 3.7–4.0 × 10^3 ng·h/mL) with undetectable FBAL, consistent with complete DPD deficiency [3] (Figure 3; Table 1). Despite minimal dosing, PET-CT after four cycles demonstrated a near-complete metabolic response in liver and lung metastases and strong reduction of rectal uptake, enabling surgical resection (Figure 2).

Conclusions:
Ultra-low-dose capecitabine, guided by PK and toxicity monitoring, can result in effective and well-tolerated treatment in selected complete DPD deficient patients.

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WHEN A HERBAL SUPPLEMENT TURNS DANGEROUS: A METOPROLOL–BERBERINE INTERACTION

Authors:
L.E.J. Peeters[1,3], V.G.E.T.M. Janssens[1], J.F. Ooms[2], J. Versmissen[3], S.W.E. van de Poll[2], E.C. Vasbinder[1]

Organisations
[1] Department of Hospital Pharmacy, Franciscus Gasthuis & Vlietland, Rotterdam

[2] Department of Cardiology, Franciscus Gasthuis & Vlietland, Rotterdam
[3] Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam

Case description

This case report describes a clinically relevant and potentially dangerous herb-drug interaction between the herb berberine and metoprolol.

A 61-year-old woman presented to the emergency department with symptomatic bradycardia (30 beats/min) due to a third-degree atrioventricular (AV) block. Bradycardia persisted despite treatment with multiple doses of atropine and continuous intravenous isoprenaline, resulting in a temporary pacemaker implantation. She had a history of diabetes mellitus type 2 treated with gliclazide and abasaglar and hypertension, treated with metoprolol and hydrochlorothiazide. The cause of the sudden bradycardia remained unclear until family members reported the use of herbal supplements, including berberine. Berberine, used for regulation of blood sugar and lowering cholesterol, is a potent CYP2D6 inhibitor that leads to a herb–drug interaction with metoprolol, decreasing its metabolism and consequently increasing plasma metoprolol concentrations. To confirm this suspected interaction, the plasma concentration of metoprolol was measured in a blood sample drawn directly after hospital admission**.**

Results & discussion

A concentration of 188 mcg/L was measured ~20 h after intake, which was within the therapeutic range (20-340 mcg/L) according to several Dutch sources on toxicology.[1] This range was derived from the highest and lowest mean steady-state plasma concentrations in 16 patients treated with metoprolol tartrate 100 mg three times daily and is therefore not representative of our case.[2] A review of additional literature indicated that median plasma concentrations of metoprolol succinate are often below 150 mcg/L, and levels above 150 mcg/L in women have been associated with an increased risk of bradycardia.[3] The CYP2D6 phenotype was not determined.

Conclusion

The metoprolol concentration measured in this patient could have led to the severity of her symptoms and is most likely caused by CYP2D6 inhibition by berberine.

This case highlights the clinical relevance of drug level measurements for diagnostic purposes and emphasizes the importance of thorough medication reconciliation, including over-the-counter products, as well as awareness of herb–drug interactions.

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SUCCESFUL USE OF RASBURICASE IN THE MANAGEMENT OF REFRACTORY GOUT WITH CHRONIC KIDNEY DISEASE: A CASE REPORT

Authors:
Britt W.M. van de Burgt [1], Albert-Jan L. H. J. Aarnoudse[2], Catharina H. M. Kerskes[1]

Organisations
1.Department of Clinical Pharmacy, Catharina Hospital, 5623 EJ Eindhoven, The Netherlands
2.Department of Nephrology and Dialysis, Catharina Hospital, 5623 EJ Eindhoven, The Netherlands

Introduction
Gout is a common inflammatory arthritis exacerbated by hyperuricemia, but its treatment is complicated in patients with chronic kidney disease (CKD). Reduced renal function affects the pharmacokinetics of urate-lowering therapies, necessitating careful management. The use of conventional medications like allopurinol and colchicine need to be adjusted in dosage to avoid toxicity and are therefore known to fail in severe cases of gout. In such cases, alternative therapies are crucial for effective management.

Methods
An 85-year-old woman with a history of gout and a CKD G5 (CKD-EPI<15) presented with worsening symptoms despite previous management. In September 2024, she developed an open wound on her foot due to tophic gout and a Methicillin-resistant Staphylococcus aureus (MRSA) infection. See figure 1A. She had been treated with allopurinol, colchicine and advised to begin benzbromaron as a long-term therapy, but her symptoms persisted. Laboratory results confirmed elevated serum uric acid levels despite ongoing colchicine therapy (up to 0,71 mmol/L). Given her intolerance to febuxostat due to an severe allergy for coloring agents and the urgency of the situation, the treatment regimen was adjusted to rasburicase in March 2025. Although hemodialysis was considered as an option to reduce uric acid levels, it was not initiated due to sufficient kidney function and the existing bacteremia. The decision to use rasburicase, besides an antibiotic treatment with vancomycin, was based on its effectiveness in rapidly reducing serum uric acid and resolving tophi in refractory cases.

Results
The patient was initiated on rasburicase treatment on 26 March 2025, with an initial dose of 15 mg on day 1, and with 7,5 mg on day 2 till 5. After this initial treatment, treatment was continued due to its positive effect, with monthly infusions of 0.2 mg/kg rasburicase as maintenance therapy. This treatment gave significant observed improvement within weeks. Serum uric acid levels dropped significantly (stored on ice, because rasburicase breaks down uric acid into allantoin in vitro), and the size of the tophi decreased. The open wound on her foot closed with no signs of infection. The patient tolerated the treatment well without any adverse reactions. Figure 1B shows the healed foot after two months of treatment with rasburicase. The wound remains closed till this day.

Conclusions
Rasburicase has demonstrated promising efficacy in managing refractory gout, especially in patients with renal insufficiency who do not respond to standard treatments. While it is approved for use in tumor lysis syndrome, its application in gout remains off-label. Given its potential, rasburicase should be considered in patients with large or disabling tophi, particularly those presenting with open wounds caused by gout and substantial urate crystal deposits.

OPTIMISING 5-FLUOROURACIL DOSING IN PATIENTS WITH PARTIAL DPD DEFICIENCY: A CASE SERIES INTEGRATING GENOTYPING, PHENOTYPING AND THERAPEUTIC DRUG MONITORING

Authors: S.L.J. Peeters[1,2], L. el Bouhali[3], J. Smits[3], N.K.M. Shehata[3], J.G. Maring[4], D.J.A.R. Moes[2], J.W. Wilmink[5], K.S. Versteeg[5], A.B.P. van Kuilenburg[6,7], M.J. Deenen[1,2], P.M. Bet[3,7].

Organisations: [1] Dept. of Clinical Pharmacy, Catharina Hospital Eindhoven; [2] Dept. of Clinical Pharmacy and Toxicology, Leiden University Medical Centre; [3] Dept. of Clinical Pharmacy and Pharmacology, Amsterdam University Medical Centre; [4] Dept. of Clinical Pharmacy, Isala Hospital Zwolle; [5] Dept. of Medical Oncology, Amsterdam University Medical Centre; [6] Dept. of Genetic Metabolic Diseases, Amsterdam University Medical Centre; [7] Cancer Centre Amsterdam

Introduction: *DPYD* genotype-guided dosing of 5-Fluorouracil (5-FU) is recommended to prevent severe toxicity in DPD-deficient patients [1]. Nonetheless, DPD activity and 5-FU clearance are also influenced by other factors, and 5-FU exposure and tolerability are found to be extremely variable even within heterozygous *DPYD* variant carriers [2,3]. DPD phenotyping and therapeutic drug monitoring (TDM) of 5-FU may complement *DPYD*-genotyping. Therefore, we present three patients with partial DPD deficiency in whom we combined genotyping, phenotyping, and TDM to optimise initial and subsequent 5-FU dosing.

Methods: Patients received pre-treatment *DPYD* testing for variants c.299-302del, c.1129-5923C>G, c.1679T>G, c.1905+1G>A, c.2846A>T and c.557A>G. DPD enzyme activity was measured in PBMCs using a radiochemical assay (reference normal DPD activity: 9.9[5.9-14.0] nmol/h/mg). In case of reduced DPD activity without presence of the six *DPYD* variants, additional *DPYD* gene sequencing was performed. Initial 5-FU dosing was determined according to the DPWG guideline [1]. One TDM sample at steady state (~24 hours after start of continuous 5-FU infusion) was taken each cycle, when feasible. Pharmacokinetic exposure, expressed as an area under the curve ($AUC_{0\text{-}46h}$) in mg.h/L, was calculated by multiplying measured steady state concentration by the total duration of continuous infusion. Dose adjustments of 5-FU after cycle 1 were made based on clinical tolerability and exposure until a 5-FU target $AUC_{0\text{-}46h}$ of 20-30 mg.h/L [4] was achieved, or until dose-limiting toxicity.

Results

Case 1 was heterozygous for c.496A>G and c.2194G>A (class 3 variants, unclear pathogenicity) and had a reduced DPD activity of 3.9 nmol/h/mg. FOLFIRINOX was initiated with a 50% dose of 5-FU, which was increased to 75% in cycle 2 based on clinical tolerability, resulting in an $AUC_{0\text{-}46h}$ of 15.8 mg.h/L and dose-limiting neutropenia. 5-FU was continued on a 75% dose. Case 2 was heterozygous for c.1905+1G>A with a DPD activity of 2.4 nmol/h/mg who started FOLFOXIRI on a 25% dose of 5-FU, resulting in an $AUC_{0\text{-}46h}$ of 6.4 mg.h/L. 5-FU dose was gradually escalated to finally achieve an $AUC_{0\text{-}46h}$ of 22.4 mg.h/L in cycle 6 on an 85% 5-FU dose. Case 3 had a reduced DPD activity of 2.2 nmol/h/mg, but no *DPYD* variants were found. FOLFOXIRI-B treatment was started with a 25% 5-FU dose, which was increased to 33% in cycle 2, resulting in an $AUC_{0\text{-}46h}$ of 6 mg.h/L. Dose was gradually escalated to achieve an $AUC_{0\text{-}46h}$ of 24 mg.h/L in cycle 7 on a 75% 5-FU dose.

Conclusions

These cases highlight the added value of combined *DPYD*/DPD testing to accurately identify patients with reduced DPD activity, and the importance of continuous TDM to enable safe dose escalation after initial dose reductions to minimize the risk of 5-FU underexposure in patients with partial DPD deficiency.

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TROPICAL SNAKEBITE IN A HOBBYIST: EFFECTIVE ANTIVENOM TREATMENT AFTER *TRIMERESURUS INSULARIS* ENVENOMATION

Authors
Robert J. van de Peppel MD PhD, Teun van Gelder MD PhD, M.G. Caris MD PhD

Organisations
Leiden University Medical Center, department of Internal Medicine and department of Clinical pharmacology and Toxicology

Introduction
Bites from tropical *Trimeresurus* snakes (green pit vipers) are rare outside their endemic regions. However, in northern and western Europe, they are the second most frequently reported venomous snake bites after the adder, primarily due to pet ownership. Such bites can sometimes lead to severe bleeding disorders as a complication.

Methods
We describe a case of *T. insularis* envenomation complicated by an extensive local reaction and laboratory-confirmed coagulation abnormalities, successfully treated with antivenom.

Results
A 45-year-old man presented to the emergency department with a painful local hematoma following a bite by a two-day-old Indonesian pit viper. The patient was able to identify the exact species, as he keeps several venomous snakes as a hobby. The bite occurred at 14:00, and the patient presented to the emergency department around 17:00, complaining of pain involving the entire hand and forearm. Physical examination showed stable vital signs and a blood blister approximately 1 cm in diameter on the left ring finger (Figure 1), with mild edema of the hand and forearm. Neurological examination was normal. Around 19:00, erythema surrounding the hematoma had extended by approximately 1 cm, but pain and swelling had decreased. The patient left the hospital against medical advice awaiting the laboratory results.Laboratory analysis revealed a slightly decreased fibrinogen level of 2.0 g/L (reference >2.1 g/L) and a markedly elevated D-dimer level above 4000 ng/mL. After consultation with the Poison Control Center, the decision to order anti-venom was made and the patient was called to urge him to return to the hospital. Due to patient delay, the antivenom was administered at 04:00, 14 hours after the bite. Serial coagulation parameters improved and normalized after treatment. No bleeding complications occurred. Outpatient follow-up was arranged to monitor the local reaction and to evaluate for potential serum sickness. Seventeen days after the bite, the patient still reported pain, but the edema had completely resolved and the blood blister had dried out (Figure 2).

Conclusions
Venomous snakebites in Northwestern Europe are rare; however, many national expertise centers have appropriate antivenom available. Consultation with a national expert center is essential for determining optimal management, particularly in cases involving exotic venomous species.

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SEVERE AND FATAL CENTRAL NERVOUS SYSTEM TOXICITY AFTER FLUDARABINE, THIOTEPA AND MELPHALAN CONDITIONING FOR ALLOGENEIC STEM CELL TRANSPLANTATION

Authors Pleun Schonewille[1], Sharon Berendsen[2], Yousra van der Leest[1], Klaartje Nijssen[1], Lotte van der Wagen[1], Laura Daenen[1], Anna van Rhenen[1], Anke Janssen[1], Viola Kraak[1], Bram Kottink[3], Arief Lalmohamed[3], Aurelia de Vries-Schultink[3], Maaike Dirks[2], Jürgen Kuball[1,4], Moniek de Witte[1]

Organisations [1]Department of Hematology, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands
[3]Department of Clinical Pharmacy, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, The Netherlands
[4]Center for Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

Introduction
We observed a cluster of severe central nervous system (CNS) toxicity after conditioning with fludarabine, thiotepa and melphalan (Flu-Thio-Mel), raising concerns about regimen-related and exposure-dependent neurotoxicity. We aimed to characterize neurological complications (NC), identify clinical risk factors, compare with fludarabine–busulfan (Flu-Bu) conditioning, and explore fludarabine plasma exposure as a predictor of CNS toxicity.

Methods
This retrospective study included all 55 adult patients who received allo-SCT conditioning with anti-thymocyte globulin (ATG)-Fresenius and Flu-Thio-Mel between 2019 and 2024 at UMC Utrecht. All new, recurring or worsening NC within one year post-SCT were reviewed for type, location, severity, etiology, clinical course and likeliness to be caused by the conditioning by neurologists. For the comparator cohort, 47 patients received ATG and Flu-Bu conditioning between 2019 and 2022. For patients with available plasma samples within 72 hours after the last Flu dose, Flu exposure was analysed using LC-MS/MS. Non-linear mixed effects modelling for determining Flu exposure was applied via NONMEM.

Results
Potentially toxic NC occurred in 17 patients (30.9%) in the Flu-Thio-Mel and 15 patients (31.9%) in the Flu-Bu cohort. NC after Flu-Thio-Mel occurred earlier (median 46 versus 103 days post-SCT, p=0.043) and were more often fatal (5 versus 0 cases) than NC after Flu-Bu. CNS toxicity was observed in 7 Flu-Thio-Mel patients (12.7%, median onset 32 days, range 6-139 days) but in none of the Flu-Bu patients (p=0.014). NC occurred in three distinct clinical patterns with CTCAE grades 2 through 5. 3 patients developed fatal leukoencephalopathy, 2 patients developed severe encephalomyelopathy with remaining deficits, and 2 patients developed myeloneuropathy with minimal sequelae. Patients with CNS toxicity were older (median 66 versus 54.5 years, p=0.024) and had a lower baseline renal function (median eGFR 73 versus 105 mL/min/1.73m2, p=0.024) than those without. Of interest, patients with CNS toxicity had higher cumulative fludarabine exposure (mean area under the curve (AUCcum) 29.8 mg·h/L) compared with patients without NC (23.8 mg·h/L), especially for patients with leukoencephalopathy (31.6 mg·h/L) and encephalomyelopathy (31.1 mg·h/L). No association was found between CNS toxicity and sex, diagnosis, donor type, prior chemotherapy, neurological history, or graft-versus-host-disease (GVHD).

Conclusions
This case series highlights the Flu-Thio-Mel combination specifically as a potential contributing factor towards severe, and in some cases fatal, CNS toxicity and suggest that this combination may be contra-indicated in older patients and those with a (mild) renal impairment. Our findings point towards a possible association between higher Flu exposure as a predisposing factor for developing NC.

USE OF CIMETIDINE TO ENHANCE SYSTEMIC ACYCLOVIR CONCENTRATIONS IN PATIENTS WITH INEFFECTIVE SUPPRESSIVE THERAPY FOR RECURRING HERPES SIMPLEX VIRUS INFECTIONS: A NOVEL PURPOSE FOR AN OLD DRUG

Authors
D.G. Stuijt[1*], V.M. Cnossen[1*], A.F.Y.S.M. Osman[2], T. van Gelder[2], S.M. Arend[3]

Organisations
[*] These authors contributed equally.
[1] Centre for Human Drug Research (CHDR), Leiden, The Netherlands
[2] Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands
[3] Leiden University Centre for Infectious Diseases (LU-CID), Leiden University Medical Centre, The Netherlands

Introduction
Herpes simplex virus (HSV) is a common cause of oral or genital ulcerative infections, which may recur frequently. Valacyclovir may be used as suppressive therapy, but is insufficiently effective for some patients. To date, no guidelines are available for patients with ineffective suppression; we present a case series in which valacyclovir dose is guided by pharmacokinetic data, as well as the addition of cimetidine (a tubular transporter agonist competitive to acyclovir) to enhance systemic antiviral concentrations.

Methods
Four patients with frequently recurring HSV infections were included in this case series. Blood acyclovir concentrations were measured before, and 1 and 2 hours after valacyclovir administration. Prescribed valacyclovir doses were determined individually based on clinical effects and pharmacokinetic concentrations.

Results
All four patients were shown to have subtherapeutic levels of acyclovir with a regimen of either 500 or 1000 mg of valacyclovir. For three patients, addition of cimetidine to 1000 mg resulted in therapeutic levels; for one patient, valacyclovir dose was increased to 1500mg to achieve a sufficient concentration. All patients tolerated their therapy well over years of continuous use. A satisfactory clinical effect was achieved in all four patients.

Conclusions
Ineffective suppressive therapy of valacyclovir may reflect subtherapeutic systemic drug levels. Increase of valacyclovir dose or addition of cimetidine may result in sufficient concentrations and consequently achieve good clinical effects.

CORRELATION BETWEEN LEVETIRACETAM PLASMA CONCENTRATION AND ADVERSE EFFECTS AND EFFICACY IN PATIENTS WITH EPILEPSY

Authors
M.H. Butterhoff[1], L.C. van Loo[1], P.A.D. Bouma[2], K.C.M. van der Elst[3], T. Bognàr[3], P.D. van er Linden[1], M. van Nuland[1]

Organisations
[1] Department of Pharmacy, Tergooi Medical Center, Hilversum, the Netherlands; [2] Department of Neurology, Tergooi Medical Center, Hilversum, the Netherlands; [3] Department of Clinical Pharmacy, University Medical Center; Utrecht, Utrecht, The Netherlands;

Introduction
Therapeutic drug monitoring (TDM) of levetiracetam is frequently performed in clinical practice, particularly in patients with persistent seizures or suspected adverse effects. However, evidence regarding the relationship between levetiracetam plasma concentrations and both efficacy and tolerability remains limited.

Methods
This multicenter, retrospective observational study included real-world data from patients with epilepsy in whom levetiracetam plasma concentrations were measured between January 2019 and September 2024. Data were extracted from electronic medical records from the Tergooi Medical Center and University Medical Center Utrecht. Associations between levetiracetam plasma concentrations and adverse effects as well as treatment efficacy were evaluated using multivariate analyses.Age, body weight, sex, estimated glomerular filtration rate (eGFR) and seizure type were included in multivariate analyses.

Results
A total of 273 patients were included, of whom 261 were evaluable for adverse effect analyses. Adverse effects were reported in 36% of patients. Median levetiracetam plasma concentrations were significantly higher in patients with adverse effects compared to those without (respectively 25.6 mg/L and 19.5 mg/L, p = 0.009). Patients with concentrations above 25 mg/L experienced more adverse effects than those with lower concentrations (p = 0.006). Multivariate analysis demonstrated that supra-therapeutic concentrations (25-45 mg/L) were associated with a higher risk of adverse effects compared to therapeutic concentrations (5–24 mg/L) (adjusted OR 1.95; 95% CI 1.04–3.64). No significant association was found between levetiracetam plasma concentration and treatment efficacy, defined as seizure-free months.

Conclusions
Higher levetiracetam plasma concentrations are associated with an increased risk of adverse effects but not with improved treatment efficacy. These findings suggest that TDM of levetiracetam is valuable for evaluating suspected toxicity, while its role in predicting clinical response is not yet established.

BREASTFEEDING RISK ASSESSMENT FOR ANTIVIRAL MEDICATIONS: COMPARISON OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING AND MODIFIED ALLOMETRIC APPROACHES

Authors
W.Saffaf[1,2], P. Mian[1,2], P. Malik[3]

Organisations
[1] Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands
[2] Pharmacometrics Expertise Center Of the Northern Netherlands, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[3] Ionis Pharmaceuticals, Carlsbad, California, United States

Introduction
Antiretroviral drugs (ARVs) taken by mothers during lactation transfer into breast milk and may lead to unintended infant exposure. Quantifying this exposure is challenging because infant blood sampling is limited for ethical and logistical reasons. This study compared physiologically based pharmacokinetic (PBPK) modeling with a modified allometric scaling approach to predict plasma concentrations of zidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP) in breastfed infants.

Methods
Adult PBPK models for ZDV and 3TC were developed and verified in adults; a published and verified PBPK model was used for NVP. PBPK models were scaled to infants aged 0–6 months incorporating literature-reported breast-milk concentrations, weight-normalized milk intake, and enzyme ontogeny (PK-Sim default, Farhan for UGT2B7, Upreti for CYPs). Infant clearance was also estimated using a modified allometric equation based on body weight scaling from adult values. Predicted average infant plasma concentrations (C_avg) were compared with literature clinical data; predictions within two-fold geometric mean fold error (0.5 – 2.0) (GMFE) were considered acceptable.

Results
Both PBPK and allometric scaling predicted negligible ZDV exposure (<0.11 ng/mL), consistent with undetectable clinical concentrations from literature. For NVP, predictions were accurate with GMFE of 0.75 (PBPK Upreti ontogeny), 1.57 (PBPK PK-Sim ontogeny), and 0.65 (allometric scaling). For 3TC, GMFE was 0.50 (PBPK) and 1.02 (allometric scaling), indicating better performance of allometric scaling for 3TC.

Conclusions
Both PBPK and allometric scaling reliably predicted infant plasma concentration of ZDV, NVP, and 3TC, with allometric scaling showing better performance for 3TC. These complementary approaches can support clinical guidance, optimization of antiretroviral therapy during lactation, and evidence-based breastfeeding guidelines.

FUTHER ABBREVIATING A LIMITED SAMPLING STRATEGY FOR AREA UNDER THE CURVE ESTIMATION OF TACROLIMUS EXPOSURE IN PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS

Authors

R.D.C. Francisca[1], P. van den Broek[2], F.H.M. Vrieling-Prince[3], M.G. Mooij[3], H. de Jong[3], B.C.M de Winter[2]

Organisations

1.Erasmus Medical Centre, Department of Internal Medicine

2.Erasmus Medical Centre, Hospital Pharmacy

3.Erasmus Medical Centre, Department of Pediatric Nephrology

Introduction

Multiple models have been developed with limited sampling strategies (LSS) to estimate the area under curve as a measure of the total tacrolimus exposure in pediatric kidney transplant recipients. Our LSS includes 6 tacrolimus levels. We investigated whether our area under the curve (AUC) estimation was equally precise with fewer samples.

Methods

We performed a retrospective cross-sectional study with secondary data collected from electronic health care records. We included in-patient and out-patient kidney transplant recipients aged 18 and younger at Erasmus Medical Centre's Sophia Children's Hospital, treated with tacrolimus and for whom an AUC was calculated between November 1st 2024 and December 31st 2025.

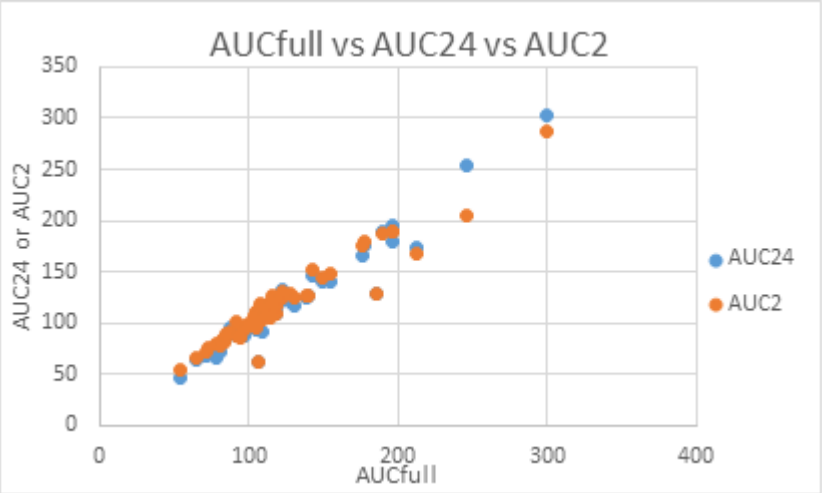
We compared abbreviated sampling schedules with 2 samples (=AUC2: through level, T =2 hours) and 3 samples (=AUC24: through level, T = 2 hours, T = 4 hours) with the current LSS by calculating Pearson's correlation coefficient. We also tested for differences using paired T-tests.

Results

53 patients were included in our study. Median age was 11 years old (interquartile range (IQR) 9 years), 66% were male, median BMI was 19 (IQR 3).

Median difference between the AUCfull and AUC24 was -3.6 ng/ml (IQR 9.4 ng/ml), $p < 0.01$). Pearson's correlation coefficient was 0.97.

Median difference between the AUCfull and AUC2 was -1.3 ng/ml (IQR 9.8 ng/ml), $p = 0.03$). Pearson's correlation coefficient was 0.96.



Conclusions

The AUC estimated with the abbreviated schedule correlated well with the current LSS. Though the difference was statically significant, it was small enough not to be clinically relevant.

MASS SPECTROMETRIC CHARACTERISATION OF FLUCLUXACILLIN BINDING TO SERUM ALBUMIN IN HOSPITALISED PATIENTS WITH HYPOALBUMINEMIA: AN OBSERVATIONAL PILOT STUDY

Authors Sjoerd D. Meenks[1,2,3,4], Heleen Bouman[5], Fatma Karapinar[2,4], Bas C.T. van Bussel[4,6,7], Paddy K.C. Janssen[2,3], Douwe de Boer[8,9]

Organisations [1] Department of Clinical Pharmacy, Catharina Hospital Eindhoven, Eindhoven, the Netherlands, [2] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, the Netherlands, [3] Department of Hospital Pharmacy, VieCuri Medical Centre, Venlo, the Netherlands, [4] Cardiovascular research institute Maastricht (Carim), Maastricht University, Maastricht, the Netherlands, [5] Division of Nephrology, Department of Internal Medicine, Maastricht University Medical Centre+, University Maastricht, Maastricht, the Netherlands, [6] Department of Intensive Care Medicine, Maastricht University Medical Centre+, University Maastricht, Maastricht, the Netherlands, [7] Care and Public Health Research Institute (Caphri), Maastricht University, Maastricht, the Netherlands, [8] Unit of Clinical Chemistry, Central Diagnostic Laboratory, Maastricht University Medical Centre+, 6202 AZ Maastricht, the Netherlands, [9] Nutrim, School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, the Netherlands

Introduction Novel insights are needed into flucloxacillin pharmacokinetics (PK) and serum protein binding in critically ill patients to facilitate antibiotic dose optimisation. Therefore, we assessed the number of flucloxacillin molecules bound to a serum albumin molecule (stoichiometry) in hospitalised patients with hypoalbuminaemia.

Methods Adult hospitalised patients with serum hypoalbuminaemia who were administered intravenous flucloxacillin were enrolled in this prospective, observational, single-centre pilot study. Patients treated with piperacillin/tazobactam or amoxicillin/clavulanic acid served as controls. Matrix-assisted laser desorption-ionisation time-of-flight mass spectrometry (MALDI-TOF MS) measurements were performed to calculate the stoichiometry of the antibiotic/albumin complexes. In addition, the associations between the stoichiometry and antibiotic treatment duration, serum albumin concentration or time since flucloxacillin treatment cessation were assessed using association plots.

Results
Eleven patients treated with flucloxacillin and four control patients were enrolled. A total of 251 stoichiometric measurements were considered. Large intra- and inter-individual differences were observed in the stoichiometry, ranging from 0 to 6 flucloxacillin molecules bound to albumin. An increase in the stoichiometry with the number of flucloxacillin treatment days was confirmed in 8 patients (72%). In addition, the stoichiometry increased at lower albumin concentrations. A stoichiometry of ≥ 3 was observed for 2 to 8 days after flucloxacillin treatment cessation.

Conclusions
Longer flucloxacillin treatment and lower serum albumin concentrations were associated with a higher stoichiometry of flucloxacillin/albumin complexes in hospitalised patients with serum hypoalbuminaemia. This study illustrates that protein binding is not a constant, which contributes to our understanding of the PK, effectiveness and toxicity of flucloxacillin.

SWITCHING STANDARD DOSED INTRAVENOUS TO SUBCUTANEOUS INFLIXIMAB LEADS TO SIMILAR DRUG EXPOSURE INDEPENDENT OF CONCOMITANT IMMUNE SUPPRESSANTS (SHUFFLE STUDY)

Authors
Lieke M.J. van de Ven - van Dinter (PharmD)[1], Mariëlle J.L. Romberg-Camps (MD, PhD)[2], Dennis R. Wong (PharmD, PhD)[1], Adriaan A. van Bodegraven (MD, PhD)[2,*], Niels W. Boone (PharmD, PhD)[1,*].

Organisations
[1]*Department of Clinical Pharmacy, Pharmacology and Toxicology, Zuyderland Medical Centre, Heerlen/Sittard-Geleen, The Netherlands*
[2]*Department of Gastroenterology, Zuyderland Medical Centre, Heerlen/Sittard-Geleen, The Netherlands*
[*]*These authors should be considered joint senior authors.*

Introduction:
Subcutaneous (SC) flat-dose infliximab (IFX) biosimilar was introduced, offering potential advantages over intravenous (IV) weight-based dosing. Prospective pharmacokinetic-data and clinical outcomes in Inflammatory Bowel Disease (IBD) are scarce. The main objective of this study to compare IFX exposure during IV and SC therapy in IBD patients and address the effect of immune suppressants.

Methods:
In this single-centre, prospective study, adult IBD patients in clinical remission on a 6-8 weekly IFX IV-dosing interval were switched to biweekly SC IFX and followed for 24 weeks. Primary endpoint was the Area Under the Concentration-time curves (AUCs). Secondary endpoints included trough levels, time burden and quality-of-life (IBDQ-NL). Trough levels at ≥12 months were compared across IFX mono-, combination-, and immune suppressant discontinuation groups.

Results:
35 patients were evaluated: 20 received IFX monotherapy and 15 IFX in combination with methotrexate or thiopurine. Mean $AUCs_{6\text{-}8\ weeks}$ were comparable between IV and SC administration, independent of immune suppressant. Median IFX trough levels increased on SC IFX 4.6 mg/L to 16.1 mg/L ($p<0.05$), independent of immune suppressive drug use. These trough level results were consistent after one year, regardless of monotherapy, combination therapy, or immune suppressant discontinuation. Time burden decreased (median 9.3 hours/6 months, $p<0.05$) and IBDQ-NL score increased (189 to 197, $p<0.05$). There were no exacerbations during follow-up. After 6 months, 97% were still being treated with IFX SC. After 1 year, treatment persistence was 100% (n=26) in patients who consented to extended follow-up, regardless of monotherapy, concomitant or stopped immunosuppressants.

Conclusions:
SC IFX in IBD patients maintained equivalent drug exposure with higher trough levels, reduced time burden and stable quality-of-life, independent of immune suppressants.

VALIDATING THE SAMPLING WINDOW FOR THERAPEUTIC DRUG MONITORING OF ONCE-DAILY DOSED CLOZAPINE

Authors
Abdul Roda A.[1], Kaya L.[3], Musters M.[3], van Hest R.M. [1], Beex-Oosterhuis M.M.[4], Mulder F.Ph.[2], Mathôt R.A.A.[1], Veerman S.R.T. [3], Bank P.C.D.[2].

Organisations: 1. Hospital Pharmacy, Amsterdam UMC
2. Hospital Pharmacy, Noordwest Ziekenhuisgroep
3. GGZ Noord-Holland-Noord
4. Hospital Pharmacy, Albert Schweitzer Ziekenhuis

Introduction

Therapeutic drug monitoring (TDM) guidelines for clozapine treatment recommend sampling 12(±2) hours after intake. However, this window is mainly based on twice-daily dosing and has not been validated for once-daily dosing (1dd). The primary objective of this study was to assess the validity of the current sampling window for 1dd clozapine. The secondary objective was to externally validate a population pharmacokinetic (popPK) model.

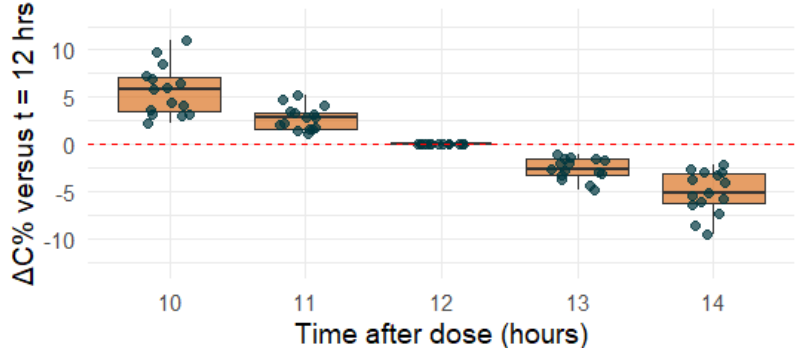
Methods

Patients with schizophrenia or schizoaffective disorder on 1dd clozapine were included. Clozapine plasma concentrations were obtained during routine care. The concentrations at other time points were predicted on basis of the popPK model by Beex et al [1]. Model predicted concentrations at t=10, 11, 13, and 14 hours were compared with those at t=12 hours. Deviations ≤20% were considered acceptable.

Results

Fifty-two clozapine samples from 15 patients were analysed. The existing popPK model significantly underpredicted the observed concentrations with a relative mean error of -17%, (95%CI: -35.8-1.4%) and a normalized root mean squared error of 52.4% (95%CI: 44.0-64.8%). The clozapine clearance was re-estimated including fluvoxamine use as a covariate. This significantly improved the popPK model fit ($p<0.01$) with a 50% reduction in clearance due to fluvoxamine use. Predicted concentrations at t=10-14 hours deviated ≤20% from the concentration at t=12 hours (figure 1).

Figure 1 - ΔConcentrations (ΔC)% versus t = 12



Conclusions

For 1dd clozapine, a sampling window of t=10-14 hours is suitable for TDM. The lower clearance observed in this population was significantly associated with the concomitant use of fluvoxamine.

[1] Beex-Oosterhuis MM, Lau C, Verloop S et al. The impact of once-daily dosing on the pharmacokinetics of clozapine and norclozapine. Unpublished, PhD thesis. 2023.

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DUTCH SOCIETY FOR CLINICAL FARMACOLOGY AND BIOPHARMACY (NVKFB)

info@nvkfb.nl