to predict tenofovir concentration in 50 virtual pregnant mothers at term after single administration of 600 mg of tenofovir disoproxil fumarate (272 mg tenofovir). The mechanistic model implemented using the Simcyp Lua interface within the Simcyp Simulator. Fetal as well as maternal tissue to plasma ratio values were predicted using the Rodgers & Rowland method with a scalar of 1.5. Predictions of tenofovir maternal and fetal plasma concentration were compared to reported observations.[4]

Results In spite of the large variability in the observed data, the model adequately replicated the maternal as well as fetal clinical observations.[4] The placenta transfer by cotyledon was changed 10 times the mean reported value from perfusion experiment.[5] All other model parameters were calculated using bottom-up approach.The maternal predicted-to-observed ratio for AUC24hr and Cmax was 1.13 and 1.08, respectively. The predicted fetal exposure was well predicted within the 5th and 95th percentiles and was 0.51 of maternal exposure (AUC24h), the reported value is 0.60.[4]

Conclusion The developed feto-placental-maternal PBPK models can be used to predict drug exposure in fetal organs during in utero growth. The inter-subject variability can be predicted incorporating both the drug physicochemical properties and system (placental, maternal and fetal) parameters.

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P02 ALLOPURINOL COUNTERACTS INADEQUATE MERCAPTOPURINE METABOLISM IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background Mercaptopurine (6-MP), a cornerstone of childhood acute lymphoblastic leukemia (ALL) therapy, is metabolized to active 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine nucleotides (6-MMPN) potentially hepatotoxic (threshold of 5000 pmol/8x10^8 RBC). In few cases, the equilibrium between 6-TGN and 6-MMPN is unbalanced and in favor to 6-MMPN with high risk of inefficacy and toxicities. Here, we treated patients with allopurinol which inhibits Xanthine Oxidase and Thiopurine S-methyl Transferase (*TPMT*) implicated in methylation of thiopurines.

Methods Therapeutic drug monitoring of ALL patients was based on the determination of metabolites concentrations in red blood cells, measured by HPLC-UV after 3 weeks of stable 6-MP dose. After parental consent, individual genotypes are determined for *TPMT* (*2, *3B, *3C), *ITPA* (c.94C>A) and *HLA*B5801* (prior to allopurinol) by TaqMan allelic discrimination.

Results In 8 patients, 6-MMPN/6-TGN ratio was too high, superior to 50 (range: 58–248) with 6-TGN under therapeutic threshold (< 250 pmol/8x10^8 RBC). All patients have a wild-type *TPMT* genotype and for 3 patients, *ITPA* polymorphism could be involved to this disequilibrium. The co-administration of Allopurinol (50 mg n=5, 100 mg n=2), with a reduced 6-MP dose (around -50%) dose had a positive impact on metabolic ratio, inferior to 15 (range: < 1- 13) with metabolites levels inside therapeutic window and on resolving some toxicities (hypoglycemia (n=4), hepatotoxicity (n=3)). For one patient, 200 mg of Allopurinol was administered without reducing 6-MP dose, the metabolic ratio decreased from 115 to 63 but metabolites levels were both at supratherapeutic levels.

Conclusion Allopurinol was effective in redirecting 6-MP metabolism to 6-TGN. A standardized protocol for this co-administration needs to be established and DNA-TGN incorporation dosage could be helpful for this recommendation. Long-term follow-up is required to evaluate impact on safety and efficacy of ALL maintenance therapy.

Disclosure(s) Nothing to disclose

P03 GERMLINE *NUDT15* MUTATION AND THIOPURINES FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: IS IT A PROGNOSTIC FACTOR?

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Background The nudix hydrolase 15 (*NUDT15*) polymorphism recently emerges as a biomarker of severe hematological toxicity during 6-mercaptopurine (6-MP) therapy of children with acute lymphoblastic leukemia (ALL). Initially described restricted to Asian population, recent publications highlighted its presence in patients with European ancestry. In November 2018, the Clinical Pharmacogenetics Implementation Consortium (CPIC) updated the guideline for thiopurines dosing based on Thiopurine S-methyl transferase (*TPMT*) and *NUDT15* genotypes. Here, we presented a feedback from a French monocentric experience in ALL patients.

Methods We retrospectively genotyped 188 children for *NUDT15* c.94C>A treated for ALL at Trousseau hospital, Paris. Parents have given their consent for thiopurines' therapeutic drug monitoring including performing *TPMT* genotype (*2, *3B, *3C). We focused, for patients with a mutated *NUDT15* genotype, on treatment response in terms of morbi-mortality.

Results This *NUDT15* polymorphism was found for 6 patients (3.2%): one patient with a European ancestry and the others with an Asian ancestry. Five children had a *NUDT15* mutated heterozygous genotype without *TPMT* alterations and one patient with a mutated homozygous *NUDT15* genotype associated with *TPMT* *1/*3C. Hematological and/or infectious complications were reported for all patients with this variant with hospitalization in intensive care unit for the one with a mutated *NUDT15* genotype and *TPMT* *1/*3C. Reduced 6-MP dose (between 30% to 50% of the standard dose for heterozygous patients and 3% of the standard dose for mutated homozygous patient) was required for maintenance therapy. Two patients had a relapse.

Conclusion This report supports CPIC guidelines for screening *NUDT15* polymorphism before 6-MP treatment regardless patients' race. The impact of this polymorphism on relapse occurrence is worrying and prospective results with dose adjustments at 6-MP initiation will be crucial to understand if

treatment interruptions and/or reduced dose were at risk of relapse.

Disclosure(s) Nothing to disclose

P04 NON-COMPARTMENTAL ANALYSIS OF VANCOMYCIN PHARMACOKINETICS IN CRITICALLY ILL CHILDREN

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Background Vancomycin is often used as the drug of choice in the treatment of bacteria that are methicillin resistant or in patients sensitive to penicillin. This study describes the pharmacokinetics of vancomycin in critically ill children.

Methods Children aged 1month to 16 years admitted to the paediatric intensive care unit of the Red Cross War Memorial Hospital and on vancomycin treatment for ≥24 hours and ≤72 hours were prospectively recruited. Blood samples were collected around predetermined optimal sampling times. A minimum of three samples per patients was analysed. Non-compartmental analysis was used to determine the volume of distribution (V), clearance (CL), half-life ($t_{1/2}$), area under the concentration-time curve (AUC), elimination constant (Ke) and Mean residence time (MRT). The minimum concentration (Cmin) and maximum concentration (Cmax) of vancomycin were measured directly as trough and peak plasma concentration respectively. Analysis of data was performed using PKNCA version 0.8.5 in R.

Results Forty-nine serum concentrations from 10 patients were included in the analysis. The ratio of male to female was 1:1. Median age (Range) was 1.6 (0.2–15) years, weight = 10.6 (3.1–31.3) kg, baseline serum creatinine (Scr) = 0.31 (0.15–0.78) mg/dL. Patients received daily vancomycin doses ranging from 56 to 78 mg/kg. Mean PK parameters (range) were as follows: CL = 0.12±0.15 (0.018–0.52) L/h/kg, V =0.68 ±0.47 (0.15–1.57) L/kg, Ke = 0.147±0.073 (0.07–0.33) h^{-1}, $t_{1/2}$ =5.54±2.03 (2.11–9.62) h, MRT=8.02±2.92 (3.04–13.88) h, AUC =322.07±245.65 (31.6–850.4) mg/L.h, Cmin =6.21±3.66 (2.0–14.5) mg, Cmax =38.91±31.92 (10.4–97.2) mg. Trough concentration and AUC were not met in >80% and >75% of the patients.

Conclusion Variability in vancomycin pharmacokinetics was observed in patients. At current doses, target trough concentrations and AUC were not met.

Disclosure(s) Nothing to disclose

P05 ESTABLISHING THE INTEGRITY OF THE CONTINUALLY PAEDIATRIC PHARMACOKINETIC BIOANALYSIS FOR CLINICAL TRIAL WITHIN AN ACADEMIA ENVIRONMENT USING QUALITY ASSESSMENT PROCESS

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Background European Medicines Agency (EMA) outlines criterion for validation of bioanalytical assay applied under Good Clinical Laboratory Practice (GCLP) within clinical studies. The validation is performed once and does not inevitably ensures comparable reliability over long duration of assay's applicability. To address this hurdle, the investigator-driven 'Labelling of Enalapril from Neonates up to Adolescents' project (LENA) adapted quality system comparable to industry. A comprehensive set of quality measures was applied to ensure reliability of monthly quantified paediatric samples over duration of 31 months.

Methods A 3-step quality approach analysing the calibration standards (CS), quality controls (QCs) and incurred sample reanalysis (ISR) was used to established reliability of unknown samples. Unknown concentrations were reported only if results of known CS (11 levels) and QCs were within the predefined limits. A maximum deviation of ±15% was acceptable at all five QCs level. ISR was conducted for randomly selected paediatric samples to monitor the assay's performance over time. The acceptable%difference was ±20% for at least 67% of the ISR according to international guidelines. [1,2]

Results 38 analytical runs were conducted for two drugs (enalapril/enalaprilat) from February 2016 to August 2018. Calibration curve evaluation accounted for exclusion of four enalapril and five enalaprilat runs. Additional investigation of QCs resulted in further exclusion of two enalapril and one enalaprilat runs. Within 32 valid runs 820, QCs were measured for enalapril and enalaprilat. 94% enalapril and 89% enalaprilat QCs were within limits (±15%). This set ensured reliable determination of 1262 LENA paediatric study samples. 93 and 104 incurred samples for enalapril and enalaprilat were reanalysed. ISR for enalapril (70%) and enalaprilat (67%) was also within guidelines.[1,2]

Conclusion The analysis of bioanalytical data ensured the reliability of reported unknown concentrations. It ensured consistent and reliable pharmacokinetic data from first to the last LENA study patient.

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P06 PATERNAL EXPOSURE TO METHOTREXATE AND THE RISK OF MISCARRIAGE – A REGISTER BASED NATIONWIDE COHORT STUDY

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Objective To study the association between paternal exposure to methotrexate within three month before conception and during the first trimester of pregnancy and the risk of miscarriage.

Methods We conducted a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2015. All births were identified using the Medical Birth Registry, and all records of induced abortion and miscarriage were from the National Hospital Register. Data on drug use were from the