maternal and fetal acetaminophen concentrations were compared with those observed in the literature. umbilical cord data at birth.

Results The 3 different approaches to predicted acetaminophen PK in the umbilical vein were found to yield broadly similar results. Acetaminophen exposure was similar in maternal blood compared to venous umbilical cord blood. Prediction of the median dose fraction of acetaminophen converted to its metabolites (f_m) revealed higher maternal acetaminophen-glucuronide formation clearance and sulphate formation compared to that in the fetal liver ($f_{m_glucuronide}$ 52.2 vs 0% and $f_{m_sulphate}$ 30.4 vs 0.8%, respectively) and higher fraction of acetaminophen converted to the reactive metabolite N-acetyl-*p*-benzoquinone-imine (f_{m_NAPQI} 6.5 vs 0.06%) in pregnant women compared to their fetus.

Conclusion No differences were observed in the 3 approaches for integration of placental drug transfer. Differences in acetaminophen biotransformation to its metabolites between pregnant women and their fetuses were quantitatively predicted.

Disclosure(s) Paola Mian received a Short term Minor (STM-2017) grant from the Stichting Sophia Kinderziekenhuis fonds to conduct this research.

P67

IMPACT OF ENANTIOMER-SPECIFIC MATURATIONAL CHANGES IN PHARMACOKINETICS ON THE RACEMIC KETOROLAC TARGET TROUGH CONCENTRATION

¹M Cloesmeijer, ¹E Krekels, ¹M van Esdonk, ²A Lynn, ³A Smits, ⁴D Tibboel, ⁵Y Daali, ⁶K Olkkola, ^{7,8}K Allegaert, ⁴P Mian*. ¹Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands; ²Department of Anesthesiology and Pain Medicine, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA, USA; ³Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium; ⁴Department of Paediatric Surgery and Intensive Care, Erasmus MC – Sophia Childrens Hospital, Rotterdam, The Netherlands; ⁵Division of Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland; ⁶Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; ⁷Cluster Woman and Child, Department of Development and Regeneration, Biomedical Sciences, KU Leuven, Leuven, Belgium; ⁸Department of Pediatrics, Division of Neonatology, Erasmus MC – Sophia Childrens Hospital, Rotterdam, The Netherlands

10.1136/archdischild-2019-esdppp.105

Introduction Ketorolac is a racemic drug with analgesic effects specific to its S-enantiomer. This study aimed to describe enantiomer-specific maturational pharmacokinetics (PK). Simulations were performed to describe how S-ketorolac exposure in infants differs from adults, and how this affects the adult racemic analgesic trough threshold EC_{50} ($EC_{50_thr_adult}$ 0.37 mg/L) in infants ($EC_{50_thr_infant}$) when the same S-target is applied.

Methods A population PK analysis (NONMEM 7.3) was performed based on 1020 plasma samples from 5 studies including 80 patients (adults, children, infants) following single intravenous ketorolac administration.

Results S-ketorolac PK was best described with a 2-compartment model in infants and 3-compartment model in adults, while R-ketorolac PK was best described with a 2-compartment model in all. S-ketorolac clearance [mean population value: 3.45 L/h/56 kg] and central volume of distribution (V1) [4.27 L/56kg] increased exponentially with bodyweight (0.75, 0.59 respectively). R-ketorolac clearance [0.93 L/h/56kg], peripheral volume of distribution (V2) and inter-compartmental clearance (Q) increased exponentially with bodyweight (0.62, 1.20, 0.76 respectively), V1 [4.11 L/56kg] linearly with

bodyweight. Simulations revealed $EC_{50_thr_adult}$ (0.37 mg/L) contained 0.048 mg/L S-ketorolac as mean in typical adults (BW 48.6–99.6 kg), while $EC_{50_thr_adult}$ contained 0.032–0.036 mg/L S-ketorolac in typical infants (BW 5.3–10.6 kg). To reach adult S-enantiomer concentration (0.048 mg/L) in typical infants (BW 5.3–10.6 kg), $EC_{50_thr_infant}$ should be 0.49–0.46 mg/L, respectively.

Conclusion Enantiomer-specific maturational PK of ketorolac were described. Subsequent simulations displayed differences in proportion of S- and R-ketorolac on the racemic threshold EC_{50} . A The same S-ketorolac concentration necessitates a higher $EC_{50_thr_infant}$ to $EC_{50_thr_adult}$.

Disclosure(s) Nothing to disclose

P68

SIGNIFICANT ORAL DRUG USE IN CRITICALLY ILL CHILDREN: RATIONAL THERAPY OR A BLACK BOX?

^{1,2}M Mooij*, ³J Windster, ³J van Rosmalen, ⁴L Hanff, ³D Tibboel, ^{3,5}S de Wildt. ¹Erasmus MC – Sophia Childrens Hospital, Rotterdam; ²Willem-Alexander Children's Hospital, Leiden University Medical Centre, Leiden; ³Erasmus MC – Sophia Children's Hospital, Rotterdam; ⁴Princess Maxima Centre for Pediatric Oncology, Utrecht; ⁵Radboud University Medical Center, Nijmegen, The Netherlands

10.1136/archdischild-2019-esdppp.106

Background The disposition of orally prescribed drugs in critically ill children may be affected critical illness in addition to age, resulting in erratic effects and safety. We aimed to study oral drug prescribing in the neonatal and pediatric intensive care unit (NICU and PICU).

Methods A one-year retrospective cohort study of all drug prescriptions, including route of administration for all children admitted to the NICU and PICU of the Erasmus MC-Sophia's children's hospital.

Results 1723 children with 2091 unique admissions received per admission (median [IQR]) 5 (3–10) drugs; 1 (0–2) orally and 3 (1–7) intravenously (IV). During mechanical ventilation 15% and 75% of drugs were given orally and IV, respectively. In non-ventilated patients, 27% of drugs were given orally and 60% IV. The 5 most frequently orally prescribed drugs were: vitamin K, spironolactone, oral probiotics, amphotericin B (prophylaxis) and trimethoprim.

Discussion Critically ill infants receive a considerable proportion of drugs orally. Considering that critical illness may significantly impact intestinal drug absorption, this may expose them to an increased risk of ineffective or unsafe drug therapy.

Disclosure(s) Nothing to disclose

P69

PHARMACOKINETICS OF A CONTINUOUS INFUSION OF PIPERACILLIN/TAZOBACTAM TO CHILDREN USING AN ELASTOMERIC PUMP (POPPET STUDY): PILOT DATA FROM DOUBLE LUMEN CENTRAL LINES

^{1,2}J Moss*, ¹V Price, ^{1,2}S Paulus, ³V Ramos-Martin, ¹A Melaine, ¹E Evans, ¹P Newland, ³W Hope, ^{1,2}D Hawcutt, ^{1,2}B Pizer. ¹Alder Hey Children's NHS Foundation Trust; ²Department of Women's and Children's Health, Institute of Translational Medicine; ³Antimicrobial Pharmacodynamics and Clinical Pharmacology, University of Liverpool, Liverpool, UK

10.1136/archdischild-2019-esdppp.107

Background Piperacillin/Tazobactam is the first-line antibiotic for the treatment of febrile neutropenia in the UK. There is

increasing interest in administration by continuous infusion in adult studies, but paediatric data is lacking. A continuous infusion, if given via an elastomeric pump could also facilitate earlier discharge from hospital.

Methods Children with an oncology/haematology diagnosis admitted to Alder Hey Children's Hospital with febrile neutropenia, normally treated with Piperacillin/Tazobactam via elastomeric device were considered eligible for the study. Patients received 24–36 hours of intermittent dosing before continuous dosing commenced via elastomeric pump. We analysed the data from 5 patients with double lumen central lines as a pilot phase to determine if expanded recruitment to include patients with single lumen lines was possible.

Results Five patients were recruited, four of which had the continuous infusion. The mean C_{max} following intermittent dosing of piperacillin and tazobactam from the lumen used for drug administration were 189.7 mg/L, 95% CI [71.7 - 307.9] and 18.5 mg/L, 95% CI [10.7, 26.3] respectively. The mean C_{max} following intermittent dosing for the 'empty' lumen were 160.5 mg/L, 95% CI [121.6 - 199.4] for piperacillin and 13.7 mg/L, 95% CI [11.2 - 16.3] for tazobactam. The largest difference seen was on patient 002 with a concentration of piperacillin almost double that seen in the 'empty' lumen (429 mg/L vs 233 mg/L).

Conclusion The lumen used for drug administration has enough residual drug to influence the results, so expanding recruitment to include single lumen lines is not going to be undertaken. The study has been amended to recognise this, and recruitment will continue with double lumen central lines only.

Disclosure(s) Nothing to disclose

P70

IDENTIFYING AND MANAGING PROBLEMATIC POLYPHARMACY IN CHILDREN AND YOUNG PEOPLE?

^{1,2}J Moss*, ³R Austin, ^{3,4}D Hawcutt. ¹Paediatric Medicines Research Unit, Alder Hey Children's NHS Foundation Trust; ²Department of Women's and Children's Health, Institute of Translational Medicine; ³Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool; ⁴NIHR Alder Hey Clinical Research Facility, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

10.1136/archdischild-2019-esdppp.108

Background Polypharmacy may be necessary in a patient with complex disease or multiple illnesses. Problematic polypharmacy (PP) is defined as the prescribing of multiple medications inappropriately, or where the intended benefit of the medication is not realised. Identification and management of PP already occurs in adult medicine, with evidence based guidelines and deprescribing tools available. This work aims to establish the extent of polypharmacy affecting children at our centre, and the existence of evidence based de-prescribing guidelines to manage potential PP.

Methods Audit of children and young people prescribed medications at a secondary and tertiary children's hospital, January - December 2017. A systematic review looking for evidence of such a deprescribing tool or guideline was registered with PROSPERO, and undertaken. Inclusion criteria specified the need for a guideline or deprescribing tool in children from

birth to < 18yrs of age. Two independent reviewers performed the review with a third reviewer resolving any discrepancies.

Results Within a secondary and tertiary care children's hospital, 668 children were identified as receiving ≥ 10 drugs concurrently, while 30 were receiving ≥ 20 drugs at one time.

The systematic review identified 563 papers initially, with 482 remaining once duplicates were removed. After application of inclusion and exclusion criteria, two studies were included, POPI (Prot-Labarthe et al, 2014) and PIPc (Barry et al, 2016). These papers discuss systems to identify inappropriate prescriptions. No evidence based guidelines related to the management of potential PP in children were identified.

Conclusion There are children receiving a large number of medicines concurrently, putting them at risk of PP. No specific deprescribing guideline or tools to guide management were identified. Paediatric clinical pharmacology is well placed to create and implement such guidelines.

Disclosure(s) Nothing to disclose

P71

POPULATION PHARMACOKINETICS AND PHARMACOGENETICS OF CAFFEINE IN CHINESE PREMATURE INFANTS WITH APNOEA OF PREMATURITY

¹S Ni*, ²X-B Gao, ³Hu Y-E, ²C-H Wang, ²Z-H Jiang, ³F Yang, ³Y Zheng, ⁴W Zhao. ¹The National Clinical Trial Institute; ²Children's Hospital, Zhejiang University School of Medicine, Hangzhou; ³School of Pharmaceutical Sciences, Shandong University; ⁴Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, China

10.1136/archdischild-2019-esdppp.109

Background Caffeine is commonly regarded as the treatment of choice for neonatal apnoea. However, limited data on the developmental pharmacokinetics and pharmacogenetics were available in Chinese premature infants. The objective of this study was to develop a population pharmacokinetic model of caffeine after intravenous administration to Chinese neonates with apnoea of prematurity (AOP) and evaluate the impact of developmental pharmacogenetics of CYP1A2.

Methods Sparse pharmacokinetic samples were collected from AOP newborns receiving caffeine citrate at a loading dose of 20 mg/kg/d and maintenance dose of 5–10 mg/kg/d. Population pharmacokinetic-pharmacogenetic analysis of caffeine was performed using NONMEM. Eight CYP1A2 polymorphisms were genotyped.

Results A total of 99 newborns with a mean (SD) postmenstrual age of 32.0 (2.16) (range 22.3 - 38.0) weeks were included in the present study. Pharmacokinetic data fitted an one-compartment model with first-order absorption and elimination. Current weight, postmenstrual age and serum creatinine concentration were significant covariates influencing caffeine clearance. None of tested CYP1A2 polymorphisms had significant impact on caffeine pharmacokinetics.

Conclusion The population pharmacokinetics-pharmacogenetics of caffeine was evaluated in Chinese AOP premature infants. This developmental pharmacokinetic model can be helpful to individualize caffeine therapy.

Disclosure(s) Nothing to disclose