

Conclusion This pilot showed that, when evidence is inconclusive, consensus on dosing regimens in neonates can be obtained by comparing local regimens and analysing the available evidence. For more uniform use, these new recommendations will be published in the DPF.

Disclosure(s) This project was funded by the federation of medical specialists for qualitative improvement (Stichting Kwaleitsgeld Medisch Specialisten (SKMS)).

P27 THE JUVENILE PIG AS ANIMAL MODEL FOR UNRAVELING RENAL DRUG ELIMINATION PROCESSES IN CHILDREN

¹L Dhondt*, ¹S Croubels, ²P De Paepe, ^{2,3,4}P De Cock, ¹M Devreese. ¹Department of Pharmacology, Toxicology and Biochemistry, Ghent University, Merelbeke; ²Heymans Institute of Pharmacology, Ghent University; ³Department of Pharmacy; ⁴Department of Paediatric Intensive Care, Ghent University Hospital, Ghent, Belgium

10.1136/archdischild-2019-esdppp.65

Background Over the years pigs were promoted as potential animal model for humans due to their high degree of anatomical and physiological similarities with humans. Gasthuys et al. demonstrated that the maturation of the kidney function in terms of the glomerular filtration rate (GFR) in growing pigs was comparable to humans, but no data are currently available on renal plasma flow, renal tubular secretion and reabsorption.¹ The aim of this pilot study was to unravel the contribution of distinct renal elimination processes in juvenile pigs and to compare with reported human values.

Methods Eight seven-week-old pigs were intravenously administered a single bolus of a cocktail of following renal markers: iohexol (64.7 mg/kg body weight (BW), GFR), para-aminohippuric acid (PAH, 10 mg/kg BW, effective renal plasma flow (ERPF) and anion secretion), pindolol (0.05 mg/kg BW, cation secretion) and fluconazole (0.5 mg/kg, tubular reabsorption). Plasma and urinary concentrations were determined for PAH, pindolol and fluconazole at several time points. Only plasma concentrations were assessed for iohexol. PK modelling was performed with Phoenix[®] WinNonlin[®].

Results The clearance of iohexol was 97.9 ± 16.1 ml/min/m² (mean \pm SD). The ERPF, calculated as the renal clearance of PAH, was 9.5 ± 2.1 ml/min/kg. These GFR and ERPF values are approximately a factor 1.3 higher than the values observed in humans, namely 63.5–75.0 mL/min/m² and 6.5 ± 2.0 mL/min/kg.^{2,3} The net tubular secretion of PAH was 5.4 ± 1.8 mL/min/kg, which was comparable with the values obtained in humans (5.0 ± 1.8 mL/min/kg).³ Results for cation secretion and tubular reabsorption are not yet available (to be presented at the congress).

Conclusion The net tubular secretion of PAH was comparable between the juvenile pigs and humans. The GFR and ERPF were generally a factor 1.3 higher in juvenile pigs compared to humans.

REFERENCES

- Gasthuys E, et al., Postnatal maturation of the glomerular filtration rate in conventional growing piglets as potential juvenile animal model for preclinical pharmaceutical research. *Frontiers in Pharmacology* 2017; 8.
- Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatric Nephrology* 2007;**22**(11):1839–1848.
- Gross AS, et al., Simultaneous administration of a cocktail of markers to measure renal drug elimination pathways: absence of a pharmacokinetic interaction between fluconazole and sinistrin, p-aminohippuric acid and pindolol. *British Journal of Clinical Pharmacology* 2001. **51**(6):547–555.

Disclosure(s) This study was funded by the Special Research Fund of Ghent University (BOF16/DOC/285).

P28 PHARMACOKINETICS AND IMPLICATIONS FOR DRUG DOSING IN CHILDREN WITH SICKLE CELL DISEASE: A SYSTEMATIC REVIEW

¹N Dia*, ^{1,2,3}J Autmizguine, ^{3,4}Y Pastore, ^{1,2,3}C Litalien, ⁵A Rémy, ⁶M Amélie, ^{1,3,7}Y Théorêt, ^{1,2,3}N Kleiber. ¹Clinical Pharmacology Unit, Université de Montréal; ²Department of Pediatrics; ³Research Center; ⁴Division of Hematology-Oncology, Department of Pediatrics, CHU Sainte-Justine, Université de Montréal, Montreal, QC, Canada; ⁵Department of Pediatrics, Université de Lille, Lille, France; ⁶Department of Pharmacy, Université de Montréal; ⁷Department of Pharmacology and Physiology, CHU Sainte-Justine, Université de Montréal, Montreal, QC, Canada

10.1136/archdischild-2019-esdppp.66

Background Children with sickle cell disease (SCD) are at high risk of intractable pain and severe infections despite early and aggressive drug treatment. SCD is a multisystemic disease potentially leading to liver and renal dysfunction. Altogether, those may lead to pharmacokinetic (PK) alterations, which may contribute to therapeutic failure or drug toxicity. We performed a systematic literature review to describe the current evidence on the effect of SCD on drug disposition in children.

Methods A systematic literature search was conducted by a librarian on 5 databases until 08.2018 and independently assessed by two reviewers. All full-text articles, containing PK data in children, were included. The reported differences in PK parameters between SCD and non-SCD children were examined.

Results Among 4213 retrieved abstracts, 50 full-text articles were assessed and 27 studies were included (13 exclusively children). Data on 15 drugs was available from which 5 were exclusively developed for SCD (impeding any comparison). From the remaining 10 drugs, a comparison of PK parameters was available in 8. Six were investigated in adults and children. Three (37.5%) showed significant PK alterations (morphine, cefotaxime, lidocaine) while 5 did not (hydroxyurea, sulfadoxine-pyrimethamine, methadone, rofecoxib, arginine butyrate). In children with SCD, clearance was higher by 42–61% for IV morphine, and by 24–62% for cefotaxime, compared with non-SCD controls. This difference led to a new dosing recommendation only for cefotaxime (400 mg/kg/day). Hepatic drug metabolism assessed by lidocaine was impaired in children with SCD compared to healthy controls.

Conclusion SCD alters drug disposition of commonly used drugs but data is scarce. A significant increase in clearance of morphine and cefotaxime, two commonly used drugs in patients with SCD, suggests that recommended doses may not be sufficient to provide adequate analgesia and antimicrobial control. PK data is urgently needed to ensure adequate drug efficacy and safety in this high-risk population.

REFERENCES

- Dong M, McGann PT, Mizuno T, et al. Development of a pharmacokinetic-guided dose individualization strategy for hydroxyurea treatment in children with sickle cell anaemia. *Brit J Clin Pharmacol*. 2016;**81**:742–52.
- Gremse DA, et al. Hepatic function as assessed by lidocaine metabolism in sickle cell disease. *J Pediatr* 1998;**132**:989–93.
- Dampier CD, et al. Intravenous morphine pharmacokinetics in pediatric patients with sickle cell disease. *J Pediatr* 1995;**126**:461–7.
- Kopecky EA, et al. Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. *Clin Pharmacol Ther* 2004;**75**:140–6.