Results A two-compartment model best fitted the data. Current weight, post-menstrual age (PMA) and serum creatinine were the significant covariates for clearance (CL). After model validation, simulations showed that a loading dose (25 mg/kg) and a maintenance dose (15 mg/kg twice daily if < 35 weeks PMA and 15 mg/kg three times daily if ≥ 35 weeks PMA) achieved the AUC₀₋₂₄ target earlier than a standard 'Blue Book' dosage regimen in more than 89% of the treated patients.

Conclusions The results of a population meta-analysis of vancomycin data have been used to develop a new dosing regimen for neonatal use and assist in the design of the model-based, multinational European trial, NeoVanc.

Disclosure(s) Nothing to disclose

027

PROSPECTIVE EVALUATION OF A POPULATION PHARMACOKINETIC MODEL OF PANTOPRAZOLE FOR OBESE CHILDREN

¹A Chapron, ^{1,2}S Abdel-Rahman, ^{1,2,3}V Shakhnovich*. ¹Children's Mercy Kansas City; ²University of Missouri-Kansas City School of Medicine, Kansas City, MO; ³University of Kansas Medical Center, Kansas City, KS, USA

10.1136/archdischild-2019-esdppp.27

Background Pharmacokinetic (PK) data for proton pump inhibitors, acid suppressive medications commonly prescribed to children, are lacking for obese children who are at greatest risk for acid related disease. Our aim was to evaluate the performance of the only published population PK model of pantoprazole for obese children, in an independent cohort of obese and non-obese children.

Methods A published 2-compartment structural model,¹ modified to exclude transit compartments for delayed absorption, was used to predict the PK of pantoprazole (PAN) oral suspension, immediate release ($k_a=7.3 \text{ hr}^{-1}$). Calculated population parameters and covariate relationships (e.g., weight, CYP2C19 genotype) were extracted. Predictions were based on dose, sampling times, and covariates from 57 children (6–17 years; 21% obese, 28% overweight) who received a single dose PAN and had plasma PAN concentrations collected at 10 time-points over 8 hours. Model predictive performance was assessed visually and by relative root mean squared error (RMSE), with mean ratio of predicted-to-observed area under the concentration time curve (AUC) compared via one-way ANOVA across weight groups, defined by body mass index for age (10–84th percentile normal-weight, 85–94th percentile overweight, >95th percentile obese; $\alpha=0.05$, R).

Results The model generally over-predicted observed PAN concentrations (RMSE 194%). Ratios of predicted versus observed AUC were not significantly different among obese, overweight and normal-weight children (1.5 vs. 1.7 vs. 2.2, $p=0.06$); however, a trend toward better model prediction was observed in the subset of obese children.

Conclusion Observed PAN PK deviated from model predictions, which may be due to differences in patient demographics or PAN formulation. A validation study using a delayed release PAN formulation is in progress, with the overarching goal of understanding PAN disposition, and appropriate dose selection, for obese children, who are at potential risk for drug over- or under-dosing using commonly employed dosing strategies in pediatrics (e.g., mg/kg, weight-tiered).

REFERENCES

- Shakhnovich, et al. A Population-Based Pharmacokinetic Model Approach to Pantoprazole Dosing for Obese Children and Adolescents. *Paediatr Drugs* 2018 Oct;**20**(5):483–495.

Disclosure(s) Nothing to disclose

028

VARIABILITY IN LIVER ANATOMY AND PHYSIOLOGY IN CHILDREN PARTICIPATING IN PHARMACOKINETIC STUDIES

¹A Friesen, ²J Radford, ^{3,4}S Chan, ^{3,4}N Mardis, ^{1,3,4}V Shakhnovich*. ¹University of Kansas Medical Center, Kansas City; ²Kansas State University, Manhattan, KS; ³Children's Mercy Kansas City; ⁴University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

10.1136/archdischild-2019-esdppp.28

Background Obesity-related changes in liver anatomy and physiology (e.g., hepatic fat infiltration) may be important sources of interindividual variability in hepatic drug metabolism and relevant covariates for physiologically-based pharmacokinetic (PBPK) models. The aim of this investigation was to quantify variability in hepatic fat fraction (HFF) and hepatic volume in children participating in PK studies, utilizing a novel, non-invasive, magnetic resonance imaging (MRI) sequence.¹

Methods Children, without a known diagnosis of fatty liver disease, enrolled in a PK study for hepatic CYP2C19 and CYP3A4 substrates, had hepatic volume and total HFF estimated using MRI proton density fat fraction (PDFF) and HFF assessed via conventional MRI spectroscopy (MRSFF) using a region of interest in the right upper hepatic lobe (LiverLab, Siemens Healthcare). Patient anthropometrics, laboratories and LiverLab outcomes were compared between obese and non-obese children, using independent student t-test, and associations explored via Spearman's correlation (ρ); SPSSv24, $\alpha=0.05$. Obesity was defined by body mass index (BMI) ≥ 95th percentile for age; clinically significant liver adiposity defined as HFF > 5%.

Results 25 children (7–20 years; 56% obese) had evaluable MRI data. Liver volume ranged 911–2227 cm³, MRSFF 1.6–34.8% and PDFF 2.1–31.1%. Liver volume and HFF significantly correlated with BMI (both $\rho=0.6$, $p<0.01$), but not age (both $\rho=0.3$, $p>0.11$). Liver volume (1574.5 ± 367.1 vs 1284.8 ± 216.3 , $p=0.04$), MRSFF (8.9 ± 8.4 vs 2.8 ± 1.2 , $p=0.02$), PDFF (8.9 ± 7.0 vs 3.4 ± 1.3 , $p=0.07$) and alanine aminotransferase (ALT; 37.7 ± 15.8 vs 26.8 ± 3.6 IU/L, $p=0.02$) were higher in obese vs non-obese children. HFF > 5% and ALT > 40 were only observed in obese children.

Conclusion Liver volume and adiposity varied substantially among children and may be important covariates for pediatric PBPK models, especially for obese children. HFF > 5% and ALT > 40 were only observed in obese children. Recently, 24% reduction in clearance of azithromycin, a CYP3A4 substrate, was reported for children with ALT > 40.² Our PK analyses are in progress.

REFERENCES

- Causy C, Reeder SB, Sirlin CB, et al. Noninvasive, quantitative assessment of liver fat by MRI-PDFF as as endpoint in NASH trials. *Haptology* 2018;**68**(2):763–72.
- Zheng Y, Liu SP, Xu BP, et al. Population Pharmacokinetics and Dosing Optimization of Azithromycin in Children with Community-Acquired Pneumonia. *Antimicrob Agents Chemother* 2018;**62** (9):e00686–18.

Disclosure(s) Nothing to disclose

029

PHARMACOMETRIC MODELLING OF FREE THYROXINE DYNAMICS AFTER INITIATION OF ANTITHYROID DRUG TREATMENT IN CHILDREN WITH GRAVES' DISEASE: A TOOL FOR PERSONALIZED DRUG DOSING IN CHILDREN

¹G Koch*, ²V Gotta, ³C Ollagnier, ³D Konrad, ⁴C Flück, ⁵D L'Allemand, ⁶M Steigert, ⁷A Rohner, ⁸F Bachmann, ⁸J Schropp, ⁷G Szinnai, ⁷M Pfister. ¹Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel UKBB; ²University Children's Hospital Basel UKBB, Basel; ³University Children's Hospital Zürich, Zürich; ⁴University Hospital Bern, Bern; ⁵Ostschweizer Kinderspital, St. Gallen; ⁶Kantonsspital Graubünden, Chur; ⁷University Children's Hospital Basel (UKBB), Basel, Switzerland; ⁸University of Konstanz, Konstanz, Germany

10.1136/archdischild-2019-esdppp.29

Background Thyroid hormones are essential for normal growth and puberty in children and adolescents. Graves' disease (GD) is a rare autoimmune disorder associated with thyroid hormone over-production and occurs in 0.5–2:100'000 children (mostly females) in Europe. In contrast to adults, first line treatment of GD is long-term antithyroid drug (ATD) therapy, and radioiodine ablation is usually being reserved for patients after puberty. However, treatment of acquired hyperthyroidism with ATD is difficult since 1) paediatric patients differ considerable in age, weight and diseases severity and 2) minimal ATD dose should be used to avoid mild side effects (occurring in 6–35% of patients), and rare severe side effects such as agranulocytosis and liver failure.

Methods Longitudinal clinical and laboratory data from a Swiss multicentre cohort were analysed retrospectively. Non-linear mixed effects modelling was applied to characterize dynamics of free thyroxine (FT4) during the first 3 months of treatment with carbimazole. Sex, co-medications such as propranolol, and thyroid stimulating hormone receptor antibody were tested as covariates on model parameters. Reference range for FT4 was derived from target levels in clinical practice (12–22 pmol/L).

Results Study cohort comprised 45 children with GD, 78% females, median age 12.2 years (IQR = [8.7,13.6]) with a total of 181 visits. FT4 baseline at diagnosis of GD was 62.3 pmol/L (IQR = [45.7, 86.7]). None of the tested factors showed significant covariate effects. The model allows individual simulations of optimal ATD dosing strategies (starting and maintenance dose) for different GD severities, ages and weights at start of therapy. Personalized dosing examples will be presented.

Conclusions Developed pharmacometric model is able to predict dynamics of FT4 in children with GD depending on four parameters: ATD dose/kg/d, age, weight and disease severity, and can be applied to personalize dosing regimen to avoid over- or under dosing.

Disclosure(s) Nothing to disclose

030

A COMPREHENSIVE ANALYSIS OF ONTOGENY OF RENAL DRUG TRANSPORTERS: MRNA ANALYSES, QUANTITATIVE PROTEOMICS AND LOCALIZATION

^{1,2,3}KWK Cheung*, ⁴BD van Groen*, ^{4,5}E Spaans, ⁶MD van Borselen, ⁷ACJM de Bruijn, ⁷Y Simons-Oosterhuis, ⁴D Tibboel, ⁷JN Samsom, ⁸RM Verdijk, ⁹B Smeets, ¹⁰L Zhang, ²S-M Huang, ¹KM Giacomini**, ^{4,6}SN de Wildt**. ¹University of California, San Francisco, San Francisco, CA; ²Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD; ³Oak Ridge Institute for Science and Education (ORISE Fellow), Oak Ridge, TN, USA; ⁴Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam; ⁵CDTS Consulting BV and SDD Consulting BV, Etten-Leur; ⁶Department of Pharmacology and Toxicology, Radboud University, Nijmegen; ⁷Department of Pediatrics, Erasmus MC-Sophia Children's Hospital; ⁸Department of Pathology, Erasmus MC, Rotterdam; ⁹Department of Pathology, Radboudumc, Nijmegen, The Netherlands; ¹⁰Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

10.1136/archdischild-2019-esdppp.30

Background Postnatal developmental changes of human renal membrane transporters, which are key players of disposition of renally cleared drugs and endogenous substrates, are largely unknown. This study aimed to characterize the ontogeny of 11 human renal transporters to understand changes in the renal clearance of substrate drugs in children.

Methods mRNA levels of known renal transporters: BCRP, MATE1, MATE2-K, MDR1, MRP2, MRP4, URAT1, GLUT2, OAT1, OAT3 and OCT2, and the transcription factor PXR were measured with RT-qPCR in 184 human postmortem frozen renal cortical tissues (preterm newborns - adults; 1 day-75 yrs old) from individuals of European and African descent. Protein expression of all but MRP2, MRP4 and PXR was quantified with LC-MS/MS SRM in 62 of those samples (term newborns - adults; 1 day-29 yrs old). Localization of MRP4 was tested with immunohistochemistry.

Results Expression levels of MDR1, URAT1, OAT1, OAT3, and OCT2 increased with age, but levels of MATE1 and GLUT2 were stable from birth. Protein levels of MATE2-K and BCRP showed no difference from newborns to adults despite age-related changes in mRNA expression. MRP2, MRP4 and PXR expression levels were stable. MRP4 localization in pediatric samples was similar to that in adult samples.

Conclusion Renal drug transporters exhibited different rates and patterns of maturation, suggesting that renal handling of both endogenous and exogenous compounds may change with age. It is important to consider ontogeny of renal transporters during pediatric drug development.

Disclosure(s) The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Views expressed in this paper are those of authors and do not necessarily reflect the official views or policies of the FDA; nor does any mention of trade names, commercial practices, or organization imply endorsement by the U.S. Government.

*Contributed equally,

**Contributed equally