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

REFERENCES

Disclosure(s) Nothing to disclose

O28 VARIABILITY IN LIVER ANATOMY AND PHYSIOLOGY IN CHILDREN PARTICIPATING IN PHARMACOKINETIC STUDIES

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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.

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); SPSS v24, α=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 ρ=0.6, p<0.01), but not age (both ρ=0.3, p>0.01). 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 vary 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.

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Disclosure(s) Nothing to disclose

O29 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

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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 radiiodine 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