dependent children depends on both the type of drug and the drug levels prior to weaning. In this study, there was insufficient information to characterise midazolam withdrawal dynamics, potentially because of slow midazolam weaning with insufficiently high NRS_{withdrawal} scores.

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034

ITEM RESPONSE THEORY MODELING; OLD KID ON THE BLOCK TO IMPROVE PEDIATRIC DRUG DOSING

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Background Quantification of changes in disease states or clinical conditions is essential to establish drug effects and dosing guidelines. When single endpoints for direct measurements are lacking, multi-factorial observational scales may be used, like for instance pain or sedation scales.^{1,2}

Methods Analysis of data from multi-factorial observational scales is commonly based on total scores. This assumes each item to be equally informative, which is generally not true. Item Response Theory (IRT), a long existing method in social sciences and psychology, has only recently been recognized for its ideal applicability to the analysis of multi-factorial observational scales. In this approach a latent variable is derived from all item-level data and the information that each item adds to establishing the latent variable is being weighted appropriately. The basic concepts, assumptions and applications of IRT in pharmacological research are introduced and illustrated with examples from studies on analgesia and sedation in the PICU and NICU.

Results With IRT modeling, the performance of individual items of the COMFORT and PIPP scales were assessed, and the information or noise that each item adds to the total score was quantified.³ By introducing IRT in a population pharmacokinetic-pharmacodynamic modelling approach, the effect of morphine was established on both procedural pain in preterm neonates⁴ and post-operative pain at rest in children [unpublished data]. For this, statistical significance of drug effects were evaluated based on changes in the latent variable and back calculation to the total score of the observational scales allowed for the clinical interpretation of findings.

Conclusion IRT offers a desperately needed data analysis framework that may revolutionize pharmacological studies for diseases or conditions that cannot be directly quantified in children. New techniques augmenting the performance of the classical IRT approach when assumptions are violated are currently being developed in our group.

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035

MIDAZOLAM PHARMACOKINETICS IN CHILDREN WITH OBESITY

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Background Midazolam is a first-line drug for treatment of status epilepticus,^{1,2} both by buccal and intravenous administration. In children with obesity, the midazolam pharmacokinetics may be altered, and the current dosing guidelines may therefore be insufficient.

The aim of the study was to investigate the pharmacokinetics of midazolam, after intravenous administration, in obese and non-obese children, aged 11–18 years.

Methods Trial subjects were divided into groups by Body Mass Standard Deviation Score (SDS). All children received 1 µg midazolam administered as an intravenous bolus dose. Thirteen blood samples were collected per participant at prespecified timepoints over 9 hours. Plasma concentration-time data was fitted to pharmacokinetic models using non-linear mixed effects modelling (NONMEM, 7.4).

Results Seventy-two children were enrolled in the study, of these 67 children were included in the analysis. The pharmacokinetics of midazolam was best described with a two-compartment model. The changes in pharmacokinetics in children with obesity were best described with a linear function of BMI SDS on inter-compartmental clearance and peripheral volume. Thus, the rate of distribution was faster, and the peripheral volume of distribution was larger in children with obesity as compared to non-obese children. Simulations revealed that long-term infusions based on total body weight, could lead to high plasma concentrations in children with obesity. Furthermore, simulated plasma concentrations after a fixed buccal dose showed that children with obesity may be at risk of subtherapeutic plasma concentrations.

Conclusion BMI SDS was shown to have a significant influence on the peripheral volume of distribution and the inter-compartmental clearance of midazolam. The current Danish dosing guidelines for status epilepticus (<http://www.paediatrii>

dk), where midazolam dose is adjusted to total body weight or age, may lead to both supra- and subtherapeutic doses respectively, in children with obesity. However, confirmatory studies are needed.

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036

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS TO PREDICT FETAL EXPOSURE TO ANTIVIRAL DRUGS

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Background Physiologic changes associated with pregnancy may have a large impact on drug disposition. The goal of this study was to build PBPK maternal-fetal models to predict the fetal exposure to antiviral drugs including emtricitabine and acyclovir.

Methods PBPK models were built in the Open Systems Pharmacology Software Suite version 7.3 (www.open-systems-pharmacology.org). The maternal-fetal PBPK model structure was developed in MoBi and exported to PK-Sim for population simulations. Placental transfer was parameterized based on data from ex vivo cotyledon perfusion experiments. The predictive performance of the PBPK models was evaluated via comparison with in vivo data. The pregnancy data for those drugs were from in vivo maternal and fetal blood samples taken at delivery.

Results In the acyclovir ex vivo experimental data simulation, the fitted was 0.056 L/h (95% confidence interval: 0.043 - 0.069 L/h) and the fitted was 0.49 (95% confidence interval: 0.39 - 0.59). The predicted ratio between acyclovir in vivo concentrations in the umbilical vein plasma and the maternal plasma ranged from 0.37 - 0.77, whereas the observed ratios were slightly higher and ranged from 0.61 - 1.1.¹ The previously published, and CLpl (1.49 l/h) parameters² were applied to the emtricitabine maternal-fetal PBPK model, and the emtricitabine concentrations in the umbilical cord were adequately predicted.

Conclusion These results increase the confidence in applying PBPK models to predict maternal and fetal drug exposure. Improved maternal-fetal PBPK models may streamline and accelerate the performance of pharmacokinetic and safety studies for drugs in pregnant women.

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USE OF ALBENDAZOLE IN CHILDREN WITH ASYMPTOMATIC TOXOCARIASIS

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Background Human toxocariasis is highly prevalent and its global importance may be greatly underestimated. Toxocariasis occurs mainly in childhood by ingestion of parasite eggs from contaminated environment. During migration in human tissues the *Toxocara* larvae can cause several symptoms including eye involvement, but the majority of patients are asymptomatic. Eosinophilia is a marker of activity of this disease. There are no studies supporting the treatment of asymptomatic patients. **Methods** To evaluate the effectiveness of albendazole (10–15 mg/kg/day BID for 15 days) a randomized, placebo-controlled trial was carried out in asymptomatic children (ClinicalTrials.gov #NCT00755560). Treatment response was defined as mean absolute reduction in eosinophil counts, 12 months after treatment.

Demographic, complete blood count, liver and renal function and stool parasite exam were assessed at diagnosis, and every 4 months during follow up. Inclusion criteria: age 2 to 15 years, reactive toxocara excretory-secretory substances (TES) by ELISA, eosinophils >1100/mm³, normal fundoscopy and non geohelminthic infection.

Results The 45 enrolled subjects, median age 5.3 years (range 2–13), were randomized in a 1: 1 relationship.

At 12-month follow-up, eosinophil median was: 1008/mm³ (IQ₂₅₋₇₅:680 to 2023) in placebo group and median of 1360/mm³ (IQ₂₅₋₇₅:761 to 2226) in albendazole group (p = 0.37).

Kinetics of specific antibody titers by the ELISA showed an erratic pattern. No differences were observed in the values between the 2 treatment groups.

Both groups had minor adverse events and no patient needed to discontinue medication. In asymptomatic patients with toxocariasis, albendazole was not effective to reduce eosinophil counts.

Conclusion Given that toxocariasis is a neglected disease, in order to evaluate the effectiveness of albendazole or other drugs, further studies need to be conducted.

Disclosure(s) Nothing to disclose

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POPULATION PHARMACOKINETICS OF GANCICLOVIR AFTER ORAL VALGANCICLOVIR IN RENAL TRANSPLANT CHILDREN

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