031 LEVETIRACETAM MONITORING IN BREAST-MILK: HIGH INTER-INDIVIDUAL VARIABILITY

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Background Anti-epileptic drug therapy is a great challenge for the practitioners during pregnancy and lactation. Levetiracetam (LEV) is commonly prescribed to pregnant women, however, there are only few publications on its use during lactation with small number of participants.

Objective To monitor LEV levels in breast-milk of epileptic mothers treated with LEV.

Methods Breastfeeding women treated with LEV during pregnancy and after delivery were recruited. Milk sample was collected before administration of the drug and other samples were collected at time points of 1,3,6,9, and 12 hours after drug administration. Breastmilk and blood LEV levels were measured using HPLC.

Results Fourteen breastfeeding women participated in the study: 9 infants were fully breastfed whereas 5 were partially breastfed. Maternal average daily dose of LEV was 2517 mg. Average infant's age was 8 weeks (3–22w). Average infant's weight 4368 gr (3300–7000 gr). Milk/Plasma LEV concentration ratio was 0.88 (0.23–1.1). Relative Infant Dose (RID) was 40% in partial breast feeding, and 61% in full breastfeeding. Estimated average daily dose that all infants received through milk was 158 mg/d (83–250 mg). The normalized dose for the average infant weight per day was 36 mg, which is 15% less than the maximal daily dose of LEV in infants (max. daily dose in infants 1–6 months in 42 mg/d). No adverse reactions were observed in the breastfeed infants.

Conclusions Although the RID of LEV were found to be high, no adverse reactions were observed in the infants; Nevertheless, further studies are needed to elucidate the high variability of LEV excretion into breastmilk.

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032 ONTOGENY OF HUMAN KIDNEY OCT2 EXPRESSION ACROSS THE PAEDIATRIC AGE RANGE

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Background In adults, the organic cation transporter 2 (protein name OCT2, gene name SLC22A2) is localised in the kidney proximal tubules where it mediates organic cation secretion. Hence, the transporter plays a role in the disposition and excretion of several drugs and drug-drug interactions. To better understand the disposition of OCT2 substrate drugs in children, we studied OCT2 localisation and expression in paediatric kidney tissue.

Methods The expression of OCT2 was visualised in tissue using immunohistochemical staining. Tissues were derived post-mortem from children aged 0–14 years. Gestational age

varied between 24 and 40 weeks. Intensity of the staining at the basolateral membrane was scored by two individual observers using three categories; negative, detectible and high. Agreement between two observers was determined using Cohen's kappa.

Results 44 kidney samples (n=17 neonates, n=17 infants, n=7 children, n=3 adolescent) were analysed and scored. There was substantial agreement between two judgements with a kappa of 0.773 (p< 0.005). No age related pattern was observed in the expression of OCT2. Even in the youngest age group, the expression of OCT2 was clearly visible.

Conclusion The kidney expression of OCT2 did not show an age-related pattern. In all age groups, expression levels were similar and OCT2 was properly localised at the basolateral membrane. These findings suggest that, with increasing age, OCT2 will not influence the renal excretion of its substrates.

Disclosure(s) Nothing to disclose

033 TOWARDS PERSONALISED WEANING OF SEDATIVES AND ANALGESICS USING MECHANISM-BASED MODELLING OF IATROGENIC WITHDRAWAL IN CRITICALLY ILL CHILDREN

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Background Prolonged treatment with analgesics and sedatives can result in iatrogenic withdrawal syndrome (IWS) in children being weaned from these drugs.¹ Personalized weaning strategies might lower the incidence of IWS, but this requires a quantitative understanding of withdrawal over time in individual patients.

Methods Data from 81 children (aged 1 month to 17 years) collected during an observational clinical study on IWS² were used, including a total of 1782 withdrawal assessments performed by PICU nurses, on a numerical rating scale (NRS_{withdrawal}) from 0 (no withdrawal) to 10 (worst withdrawal possible). Population pharmacokinetic models from literature were used to generate concentration-time profiles in each patient of all key analgesics and sedatives: morphine, fentanyl, methadone, midazolam, lorazepam, propofol, esketamine and clonidine. A mechanism-based withdrawal model was developed using NONMEM 7.3 to quantify IWS over time. The final model was used to perform simulations in which different weaning strategies were compared.

Results A novel mechanism-based withdrawal model structure was developed with a hypothetical compartment, which equilibrates with the central pharmacokinetic compartment, and which characterizes the development and disappearance of drug dependence over time. With this model and available data, withdrawal dynamics could be established with statistical significance for fentanyl (p< 10⁻⁶), morphine (p=0.043) and esketamine (p=0.002), and not for any of the other drugs. Compared with fentanyl, development and disappearance of esketamine and morphine dependence is slower.

Conclusions Given the patient's use of fentanyl, morphine and esketamine, the developed model can dynamically predict IWS from these substances under different weaning strategies. The results show that the optimal strategy for weaning of drug

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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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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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>