THE BIOAVAILABILITY AND MATURING CLEARANCE OF DOXAPRAM IN PRETERM INFANTS

Background
Doxapram is used for intravenous and oral treatment of apnea of prematurity in preterm infants. Dosing is currently based on bodyweight, however pharmacokinetic and bioavailability data are limited. To develop individualized dosing strategies, we characterized pharmacokinetics of doxapram in this vulnerable patient population.

Methods
Data (302 samples) from 75 neonates were included with median (range) gestational age (GA) 25.9 (23.9–29.4) weeks, bodyweight 0.95 (0.48–1.61) kg, postnatal age (PNA) 17 (1–52) days at start of continuous treatment, and treatment duration of 16.8 (1.4–26.9) days. A population pharmacokinetic model was developed for doxapram and keto-doxapram.

Results
A two-compartment model best described the pharmacokinetics of doxapram and its metabolite. PNA and GA affected the formation clearance of keto-doxapram (CLD-KD) and clearance of doxapram via other routes (CLD). For an individual of 0.95 kg, GA of 25.9 weeks and PNA of 17 days, CLD-KD was 0.096 L/h (residual standard error (RSE) 22%) and CLD 0.493 L/h (RSE 13%). Compared to PNA 30 days, estimated CLD-KD was 13% at PNA day 1 and 69% at day 15, and estimated CLD was 12% and 68%, respectively. Compared to GA 28 weeks, estimated CLD-KD was 63% at GA 24 weeks and 80% at 26 weeks, and estimated CLD was 67% and 81%, respectively. Oral bioavailability was estimated 74% (RSE 13%).

Conclusions
With bodyweight-based dosing alone, preterm infants with the lowest PNA and GA had relatively low doxapram CL and the highest exposure. Therefore, the dose may be reduced by 50% up to PNA day 9, and by 25% for day 10–15. In addition, for GA dose may be reduced by 40% and 20% in newborns with GA of 24–25 weeks and 26–27 weeks, respectively, compared to 28–29 weeks. For switch to oral therapy a 33% dose increase is required to maintain plasma concentrations.

Disclosure(s)
Nothing to disclose

DEVELOPMENT OF A PEDIATRIC BRAIN PBPK MODEL IN CHILDREN WITH AND WITHOUT MENINGITIS

Background
Several paediatric physiologically-based pharmacokinetic (PBPK) models have been developed that incorporate developmental changes affecting plasma drug concentrations. Disposition into cerebrospinal fluid (CSF) is also age-related and influenced by physiological factors, including CSF production rate, but also by brain diseases, such as meningitis, which are associated with impaired blood-brain barrier integrity. Our aim was to develop a paediatric brain PBPK model to predict CSF drug concentrations in children with and without meningitis.

Methods
A paediatric PBPK model was developed incorporating age-appropriate parameters and associated inter-individual
variability. The model was validated for paracetamol, ibuprofen, flurbiprofen and naproxen, and for a paediatric meningitis population by estimating meropenem blood-brain barrier penetration using sensitivity analysis. Plasma and CSF drug concentrations derived from literature were used to perform visual predictive checks and to calculate ratios between simulated and observed AUCs in order to evaluate model performance.

**Results** Simulated data were comparable to observed over a broad age range (1 day - 15 y postnatal age), for all drugs investigated. The ratios between observed and simulated AUCs were within 2-fold difference both in plasma and in CSF, indicating acceptable model performance. Disposition of meropenem into the brain was slow and CSF concentrations were lower compared to plasma concentrations. In addition, several days were needed to achieve CSF steady-state concentration.

**Conclusions** Our paediatric brain PBPK model provides a new tool to predict CSF concentrations in children with and without meningitis and can be used as a template model for other drugs acting in the CNS.

**Disclosure(s)** Nothing to disclose