017 THE BIOAVAILABILITY AND MATURING CLEARANCE OF DOXAPRAM IN PRETERM INFANTS

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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 ($CL_{D\text{-}KD}$) and clearance of doxapram via other routes (CL_D). For an individual of 0.95 kg, GA of 25.9 weeks and PNA of 17 days, $CL_{D\text{-}KD}$ was 0.096 L/h (residual standard error (RSE) 22%) and CL_D0.493 L/h (RSE 13%). Compared to PNA 30 days, estimated $CL_{D\text{-}KD}$ was 13% at PNA day 1 and 69% at day 15, and estimated CL_D was 12% and 68%, respectively. Compared to GA 28 weeks, estimated $CL_{D\text{-}KD}$ was 65% at GA 24 weeks and 80% at 26 weeks, and estimated CL_D 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

018 THERAPEUTIC DELIVERY DURING BREASTFEEDING: A FEASIBILITY STUDY

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Background At an age when breastfeeding is the optimal nutritional support for infants, enteral drug delivery can be physically and emotionally challenging for parents. Delivery during breastfeeding could serve as an alternative to currently existing approaches. This study aimed to explore its feasibility and acceptability.

Methods Vitamin B12 was administered as part of a single-centre feasibility study to breastfed infants at the University of Cambridge Addenbrooke´s Hospital NHS Trust. Hereby a solid formulation (tablet) was placed inside an ultra-thin silicone nipple shield, and worn by a mother during the feed. The study investigated i.) quantitative changes in B12 blood serum levels at baseline and 6–8 hours after the study feed, ii.) mothers' expectations and experiences via a mixed method approach by a single investigator. Local ethics approval was obtained prior to any study procedures being undertaken (18/LO/0551).

Results Twenty dyads completed the study protocol. In all cases, no residual tablet was left after the feed, and the tablet's presence within the shield did not appear to impact feeding. A pharmacokinetic-dependent vitamin B12 increase to 1871 pg/mL (610–4981 pg/mL) from a baseline of 533 pg/mL (236–925 pg/mL) was observed. Mothers described the nipple shield´s surprising ease of use and comfort for delivery, not affecting normal breastfeeding behaviour/sensation, while decreasing infant/maternal distress compared to the use of an oral syringe. All mothers expressed their wish for this approach to become available to parents in the future. Reasoning included the desire (1) of parents to have choices in relation to their infants' health, (2) to replace a medical intervention with one that was felt to be more 'natural'.

Conclusions This study showed that solid formulations can be used for therapeutic delivery whilst breastfeeding and is viewed by mothers as advantageous compared to currently available methods.

Disclosure(s)

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

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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