The pharmacokinetics of caffeine in preterm newborns: no influence of doxapram but important maturation with age

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LETTER TO THE EDITOR

Comment on: "Preterm Physiologically Based Pharmacokinetic Model, Part I and Part II"

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Dear Editor

We read with interest the two recent articles in Clinical Pharmacokinetcs by Abduljalil et al. describing a preterm physiologically based pharmacokinetic model and evaluate its performance for eight hepatically and renally cleared drugs [1, 2].

The lack of adequate dosing regimens mostly due to off-label use and the high interindividual variability in both pharmacokinetics (PK) and pharmacodynamics (PD) make these infants more prone to suffer from overexposure, adverse effects and treatment failure [3]. To solve these issues, most recent papers focus on using state-of-the-art population modelling and simulation approaches to describe the pharmacokinetics of one individual drug in plasma. However, we need to reach a better understanding of the rapid physiological changes during this early phase of life, as conducting studies for each drug puts a high additional burden on both patients and their parents. Physiology based models can be a tool that can help us understand the underlying processes and to choose the dose for future First-in-Neonate trials.

We therefore highly value the efforts by Abduljalil et al. to get one step closer to being able to predict the PK in preterm neonates; however, we believe this can only be a first stepping stone towards better PK predictions, and some points deserve further attention before the model can be used in practice.

Abduljalil and colleagues used postmenstrual age (PMA) to describe all relevant maturation processes in preterm neonates. While this might seem a smart approach as one can describe the data of all preterm neonates with one function, it has one major drawback—it does not take into account the effect of birth on maturational processes. Birth leads to complex physiological changes in multiple organ systems, independent from gestational age, including the cardiovascular, respiratory, hepatic and renal systems, all of which impact the maturation of the PK of drugs [4–6]. The effect of birth has been repeatedly shown in population PK models for both hepatically cleared [7–9] and renally cleared drugs [10, 11]. In those studies, the combination of gestational age or birthweight with postnatal age, and not PMA, were the best predictors of PK in a large heterogeneous group of preterm neonates. When it comes to renal function, the impact of birth on the maturation of glomerular filtration rate has recently been clearly shown by Salem et al. [12].

We therefore believe that, for a physiologically based PK (PBPK) model, it is crucial to take into account the different maturation rates for different gestational ages. To this end, PMA does not appear to be the best predictor of maturation for the population of preterm neonates with varying PMA of between 28 and 44 weeks.

We observed that due to the lack of available data in preterms, the developed model was based on many assumptions. Although we fully understand that very limited and sometimes conflicting information is available, these assumptions might heavily influence the predictions of the model. For example, preterm neonates were assumed to have

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the same tissue blood flow to organs as full-term neonates and cardiac output was calculated based on bodyweight only, which does not seem very likely. In addition, a significantly higher chance of a patent ductus arteriosus (PDA) in children born at lower gestational ages [6] makes it likely that cardiac output also differs in children with and without PDA. Due to this, blood flow to organs might also vary.

Another drawback is the way in which cytochrome P450 (CYP) metabolism has been implemented into the model. We agree with the authors that much about the ontogeny still remains unknown; however, not implementing CYP3A7 metabolism, which is the major route of hepatic elimination in neonates [13], into the model because of the lack of data on its ontogeny can be a major pitfall. Although Abduljalil et al. acknowledge this problem and state that ontogeny functions can be manually adjusted, their second paper shows the major drawback of their approach. The PK of the four hepatically cleared drugs studied (alfentanil, midazolam, caffeine, ibuprofen) could not be adequately predicted, while the fit for the two renally cleared drugs (gentamicin, vancomycin) looked satisfactory. The authors extensively discuss the drawbacks of each of the clinical studies used, but are, in our opinion, less critical towards the drawbacks of their own model design, most importantly the lack of CYP3A7 metabolism in the model.

In their model, Abduljalil et al. did not consider extremely premature neonates with gestational ages below 28 weeks, however, these neonates have the highest need for intensive care and pharmacological treatment. Furthermore, these very young infants are so small that repetitive blood sampling is difficult, and they would benefit most from insights gained from a PBPK model. Unfortunately, the authors do not discuss why they excluded this important subpopulation, but we believe that possible explanations could be the lack of physiological data in this population and/or the poor performance of their model in this age group. Another population that has not been taken into account in this model is infants who are small for gestational age. Due to intrauterine growth restrictions, these children may develop at a different pace compared with children who are appropriate for their gestational age. We believe that, for the future, it would be extremely valuable to also include these two subpopulations to cover the whole preterm population.

With this PBPK model, the authors have made a valuable step towards better prediction of the PK of drugs in preterm infants. However, potential users need to be very aware of its limitations and can only use the model to get a very rough idea of the potential concentrations in a subpopulation of preterm infants. Including preterm infants with a gestational age below 28 weeks and infants who are small for gestational age in the next version would already make the model applicable for the whole preterm population. After that, crucial next steps would be to first take the effect of birth into account in the maturation function, thereby recognizing the separate influence of intra- and extrauterine maturation, and then to obtain a better description of hepatic elimination.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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