Evaluation of a PBPK Model for Preterm Neonates by Predicting Paracetamol Pharmacokinetics

Karina Claassen[1], Stefan Willmann[2], Kirstin Thelen[2], Katrin Coboeken[2], Karel Allegaert[3], Joerg Lippert[2]

[1] Jacobs University Bremen gGmbH, Bioinformatics, Bremen, Germany

[2] Bayer Technology Services GmbH, Systems Biology & Computational Solutions, Leverkusen, Germany

[3] University Hospitals Leuven, Department of Pediatrics, Leuven, Belgium

Objectives

Due to their immaturity, preterm neonates are the most vulnerable population among pediatric patients. Because the pharmacokinetics of drugs can greatly differ between preterm and term neonates, infants and adults, dose and dosing regimen decisions can be extremely difficult for pediatricians and are usually empirically derived from adult regimens on the basis of extrapolations solely based on body weight. Additionally, despite recent US and EU legislation enforcing pediatric development trials, pharmacotherapy in children still suffers from the frequent need for off-label use. For these reasons, children and in particular preterm neonates undergoing pharmacotherapy could greatly benefit from tools and techniques that support the pediatrician to find a safe and efficient dose or dosing scheme tailored to the individual patient and that can aid the progress of licensing drugs for the pediatric population. One possibility represents the use of physiologically-based pharmacokinetic (PBPK) modeling. PBPK modeling represents a mechanistic method to predict absorption, distribution, metabolization and excretion (ADME) processes of drugs and drug candidates in laboratory animals and humans, thereby facilitating dose regimen decisions. A whole-body PBPK model for preterm neonates has recently been developed enabling the prediction of pharmacokinetics of drugs in preterms [1]. For the development of the PBPK model for preterms neonates, data about organ weights and blood flow rates, tissue composition, as well as ontogeny information about metabolic and elimination processes in the liver and kidney have been reviewed in dependence of gestational and postnatal ages. The model has recently been validated with pharmacokinetic data of amikacin, a drug eliminated exclusively via the kidneys. The model was shown to be able to adequately predict the distribution and elimination behavior of amikacin. However, as metabolism can be considered to represent the most frequent drug clearance mechanism [2] the proper implementation of enzyme ontogeny is a prerequisite for achieving a predictive model.
This work aimed to validate the hepatic maturation processes included in the recently presented PBPK model for preterm neonates [1] by predicting the pharmacokinetics of paracetamol, a drug that undergoes extensive hepatic metabolization reactions in addition to a small contribution of elimination via the kidneys. Additionally, it was the aim of this work to evaluate the proper implementation of postnatal changes in physiological parameters and their effect on paracetamol pharmacokinetics for preterm neonates spanning a wide range of gestational ages (GA).

Methods

1) The recently established PBPK model for preterm neonates, that had been validated by predicting PK of amikacin in in preterms with different gestational and postnatal ages, was used.
2) In this part of the study, the model was extended by integrating information about hepatic enzyme ontogeny in fetuses and preterm neonates. Paracetamol (acetaminophen), frequently administered as its prodrug propacetamol, was chosen as a model drug due to the number of enzymes involved in paracetamol metabolism. Physicochemical properties of Paracetamol are summarized in Table 1.

- Propacetamol is rapidly hydrolyzed to paracetamol by plasma esterases. After intravenous (IV) administration of 2000 mg of propacetamol, the prodrug is hydrolyzed to 1000 mg of paracetamol [3].
- Elimination of paracetamol occurs primarily by hepatic metabolism with the renal clearance accounting for only about 5% of total body clearance [4].
- Paracetamol is metabolized as follows [4,6]:

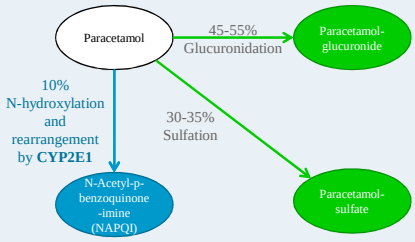

Fig. 1: Metabolism of Paracetamol [4,6]. Green indicates pathways to non-toxic metabolites, blue indicates the CYP-mediated formation of toxic metabolites. Percent values indicate the amount from total metabolization process.

- Enzyme activity for CYP2E1 in preterm neonates and fetuses is reduced to 0-10% of enzyme activity in adults, to 62% for SULT1A1 and to 1-10% for UGT1A6 [6].
- For the evaluation of the model predictions, therapeutic drug monitoring (TDM) data obtained in 48 neonates were available [3, 6]. In this study, preterm neonates with a postmenstrual age (PMA) of 27 to 43 weeks of gestation and a postnatal age (PNA) of one to 76 days were given either single (n=30) or multiple doses (n=18) of propacetamol as an infusion over 15 minutes.
- Simulated populations consisted of 500 male and 500 female preterm subjects for each PMA ranging from 24 to 40 weeks of gestation with growing steps of one day. From these simulations, 10 individuals with the same PMA at birth and minimal differences in body weight compared to the patients were selected for the individual simulations. Pharmacokinetics of paracetamol were predicted on the basis of an established paracetamol model for adults taking into account the anatomy and physiology of preterm neonates and postnatal changes such as body weight gain, changes in organ composition and blood flow changes.

Table 1: Physicochemical Properties of Paracetamol

Lipophilicity (Log MA)	0.78
Molecular weight	151.16 g/mol
Fraction unbound	0.82

Results

After integration of the developmental changes occurring postnatally in preterm and term neonates and integration of data on enzyme ontogeny, individual paracetamol plasma concentrations could successfully be predicted with the help of the extended PBPK model for preterm neonates for all postmenstrual and postnatal ages included in this study. Statistics revealed that 90% of predicted paracetamol plasma concentrations had a maximal deviation of factor two or smaller compared to the TDM data. The predictions of plasma concentrations of 98% of cases fall within a factor three deviation and 99% have a maximal deviation of factor ten from the TDM data. No biases, e.g. related to age, were detected. (see Fig 2). Selected plasma concentration time profiles for three individuals are presented in Fig.3.

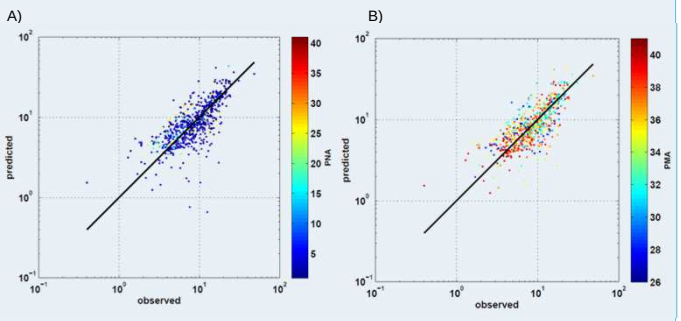

Fig. 2: Comparison of plasma paracetamol concentrations from population simulations with paracetamol TDM data [3, 6] from preterm neonates at A) different PMA's and B) different PNAs. The identity-line indicates perfect matches of predicted vs. observed plasma concentrations of paracetamol. Increasing postmenstrual and postnatal ages are illustrated by a shift in color of the data points.

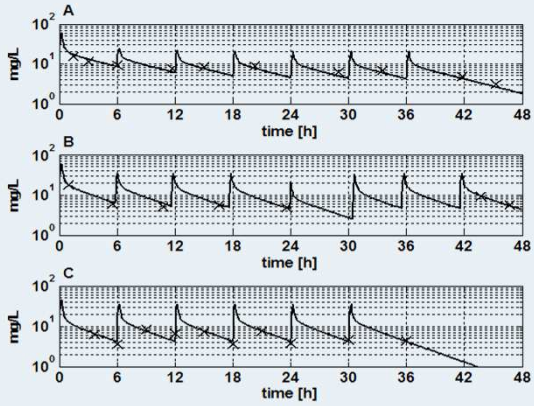

Fig. 3: Comparison of patient data (x) with predicted plasma concentration time curves (solid line) for multiple doses of paracetamol in three different patients at the ages of A) 31 weeks GA, PNA 2 days B) 36 weeks GA, PNA 17 days GA C) 40 weeks GA, PNA 4 days .

Discussion and Conclusion

In summary, the almost perfect prediction of paracetamol PK, including the prediction of hepatic elimination of the drug, indicates a reasonable description of the ontogeny of the eliminating organs and the enzymes involved. Postnatal and postmenstrual maturation processes important for PBPK modeling are successfully described by the physiological data included in the collected database. In the future, this PBPK model will help to facilitate dose and dosing regimen decisions in preterm neonates and can aid the progress of licensing drugs for the pediatric populations. The current assessment of the preterm model allows PK predictions for preterm neonates and thereby adds a new predictive tool for drug development but also for clinical decision support improving the treatment options for the very young ones.

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