Application of Physiologically Based Pharmacokinetic Modelling to Predict Ibuprofen Pharmacokinetics in Preterm Neonates

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Background

Patent ductus arteriosus (PDA) is a frequent complication in premature infants particularly those with respiratory distress syndrome. Ibuprofen is commonly used to close a PDA, possibly with fewer side effects than indomethacin. It is expected that prematurity (< 37 gestational weeks (GW)) and postnatal age (PNA) can affect drug exposure in preterm populations.

Methods

The pharmacokinetics of ibuprofen was investigated in a preterm population after intravenous and oral administration using the Sim-Preterm population within Simcyp Simulator V17. Ibuprofen compound file has been generated using drug related parameters, including *in vitro* kinetics for metabolism collated from the literature and the performance verification has been done against adult populations.

The following scenarios have been used to replicate clinical studies [1-4]:

Intravenous: Total 130 virtual subjects, grouped into 10 trials with mean PNA of 3 days and 28.6 GWs have been generated. Ibuprofen was administered on days 1, 2, and 3 by a 15-minute i.v. infusion of 10, 5 and 5 mg/kg, respectively [1,2].

Oral: Ibuprofen was administered orally as a single dose of 10 mg/kg to 13 preterm subjects born at 28.6 GW [3] and 20 subjects born at 30.5 GW [4]. Simulations were ran with settings similar to the clinical studies using 10 trials with each having the same number as the clinical study. PNA was set to a range of 0-3 days in the simulation.

The redefining subject over time features in the simulator was selected to account for the growth of individual physiology alongside the simulation progress. The ontogeny function for CYP2C9 was derived based on reported abundance values obtained using western blotting for individuals aged between 28 and 44 weeks of gestation [5].

Predictive performance of the PBPK model was evaluated by comparing the simulated to the clinical results. Simulations were also executed for Intravenous ibuprofen for sub-populations with different CYP2C9 phenotypes.

Results

Simulated Ibuprofen concentration profiles for multiple dose iv administration and single dose oral administration were comparable to the clinical observations (Figure 1). In the case of iv Ibuprofen, the predicted PK parameters were within 2-fold ratios (predicted/observed) for all the parameters (Figure 2a). Predicted and observed individual half-life and peak plasma concentration of oral Ibuprofen in preterm neonates were plotted against their body weight as shown in Figure 2b. The plot indicates that the model was also able to predict the absorption aspects in preterm neonates adequately.

High variability in clearance was observed in the clinical studies and replicated in the simulated scenarios. Simulated $AUC_{0.24h}$ was 1.5-fold higher (Figure 3) in CYP2C9 poor metabolizers (PMs) compared with extensive metabolizers (EMs) sub-group, which suggest that CYP2C9 genotype polymorphism may contribute to inter-individual variability in clearance.

Conclusions

Incorporation of prior *in vitro* information on ibuprofen metabolism together with anatomical and physiological developmental changes in the preterm PBPK models produced a successful simulation of the PK of ibuprofen and impact of CYP2C9 phenotypes on clearance in this population. Trial simulations similar to the one shown in this study can be used to optimize the design of clinical PK studies in premature neonates.

Results(cont.)

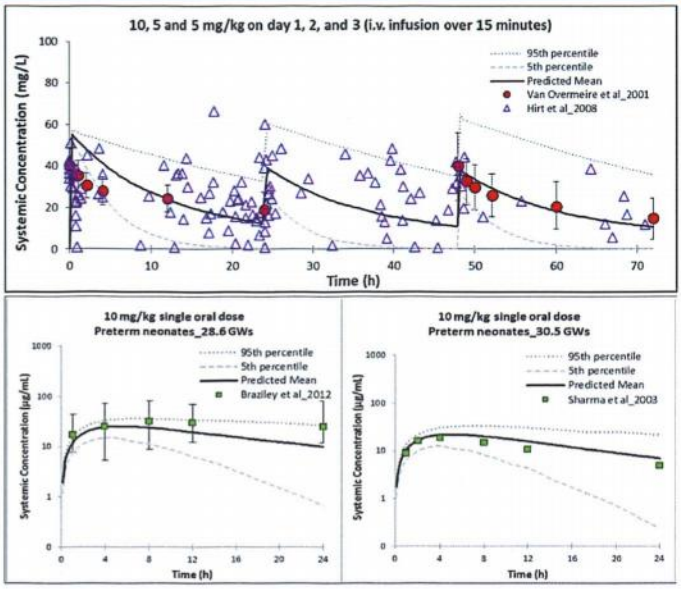

Figure 1. Ibuprofen plasma concentration profile after multiple dose iv (Top figure) and oral (bottom figures) administration of ibuprofen to preterm neonates.

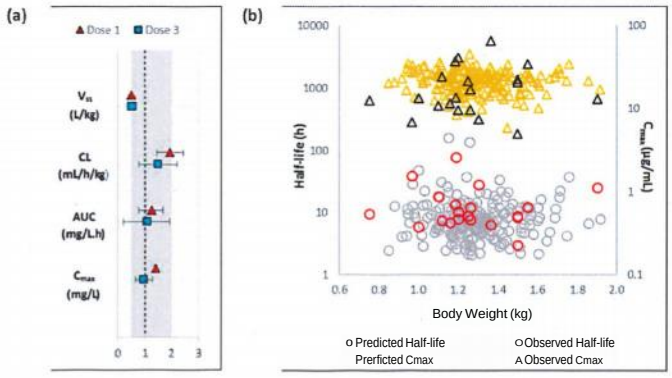

Figure 2. Predictive performance of Ibuprofen in Preterm neonates.

(a) Intravenous Ibuprofen, ratios of predicted over observed of Volume of distribution (VJ, Clearance (CL), area under the curve (AUC) and peak plasma concentration (Cmax): Mean values with SD (bars), The dashed line represents the identity (predicted/observed ratio=I), and the gray shade represents the 0.5-2.0 ratio window; (b) Predicted vs observed individual values of Half-life (t1/2) and Peak plasma concentration (Cmax) of oral Ibuprofen against body weight

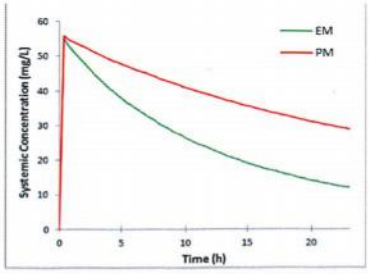

Figure 3. Simulated ibuprofen plasma concentration profile for the first iv ibuprofen dose in CYP2C9 extensive metabolizers (EMs) and poor metabolizers (PMs) preterm neonatal population.

References

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5) Koukouritaki et al. Developmental expression of human hepatic CYP2C9 and CYP2C19. J Pharmacol Exp Ther. 2004 Mar;308(3):965-74.