Application of Physiologically Based Pharmacokinetic Modelling to Predict Caffeine Pharmacokinetics in a Preterm Neonatal Population

Khaled Abduljalil (1), Amita Pansari (1), Trevor N. Johnson (1)
Simcyp Ltd (a Certara Company), Sheffield, UK
Khaled.Abduljalil@certara.com

Background

In 2005 the World Health Organisation estimated about 9.6% of all births were preterm, this translates to about 12.9 million births [1]. Preterm infants may develop respiratory distress due to structural immaturity of the lungs. Nearly all infants born at <29 weeks gestation or <1kg body weight experience episodes of apnea [2] involving 15 to 20 seconds of breathing cessation. Caffeine is the most commonly used drug for the treatment of apnea of prematurity and its effect has been well established in increasing respiratory drive, lowering the threshold of sensitivity to hypercapnia, and increasing contractility of the diaphragm [3,4]. Caffeine disposition varies with postnatal age [5] and can differ markedly between premature and term neonates.

Objectives

The objective of this study is to use a PBPK approach to predict caffeine concentration time profiles after intravenous and oral administration to extremely preterm neonates [6].

Methods

The Sim-Preterm population has been introduced as an extension to the Simcyp Paediatric Simulator V17R1. The population was build based on meta-analysis of system parameters relevant to this population including demographics, cardiac output, renal function and tissue volume, composition & blood perfusion.

The default caffeine compound file was selected from the Simcyp library. This consists of first order oral absorption with ka of =1.48 h^{-1} [6], full PBPK distribution model (Rodgers & Rowland method was used to predict tissues Kp), while the default elimination selection (enzyme kinetics, mainly CYP1A2) was used to predict caffeine clearance.

The trial design was set to match the clinical studies, ten trials of 10 preterm neonates, 28 gestational weeks was run for 7 days, the postnatal age was uniformly distributed between 0.03 and 0.07 years. Two dosage regimen were replicated based on the original study:

Regimen A: 10 mg/kg caffeine base on day one followed by 2.5 mg/kg/day for 6 days administered as either orally or intravenous (IV) infusion over 15 minutes.

Regimen B: 40 mg/kg caffeine base on day one followed by 10 mg/kg/day for 6 days administered as either orally or IV infusion over 15 minutes.

Redefining subject over time features were selected to allow the growth of individual physiology alongside the simulation progress. While the default ontogeny function is zero by default, the value at birth (0.24 fraction of adult) was over-predicting clearance in these preterm neonates. Sensitivity analysis gave a value of 0.1 as a fraction of adult CYP1A2 expression in this population (28 gestational weeks and 15–30 days postnatal days). The developed model was used to compare PK parameters after a single oral dose of 10 mg/kg in four preterm sub-groups born at different specific GW (Group 1, 2 ,3 ,4 = 28, 30, 32, 34 GW, respectively), but with PNA (0–30 days).

Results

Simulated profiles for caffeine at high or low dosage regimen after intravenous or oral administration were in agreement with the reported concentration time profiles (Figure 1). Similar results were generated assuming the low dose given orally and high dose given by IV infusion (results not shown). One limitation is the maximum simulated PNA is 30 days, while the reported one was 45 days and the reported gestational week ranged from 24–29 (mean 27.6) weeks (simulated GW was 28 weeks). Also the original data were not stratified based on these ages, but in terms of the dosage regimen.

PK Parameters for preterm sub-populations are given in Figure 2.

Results (Cont)

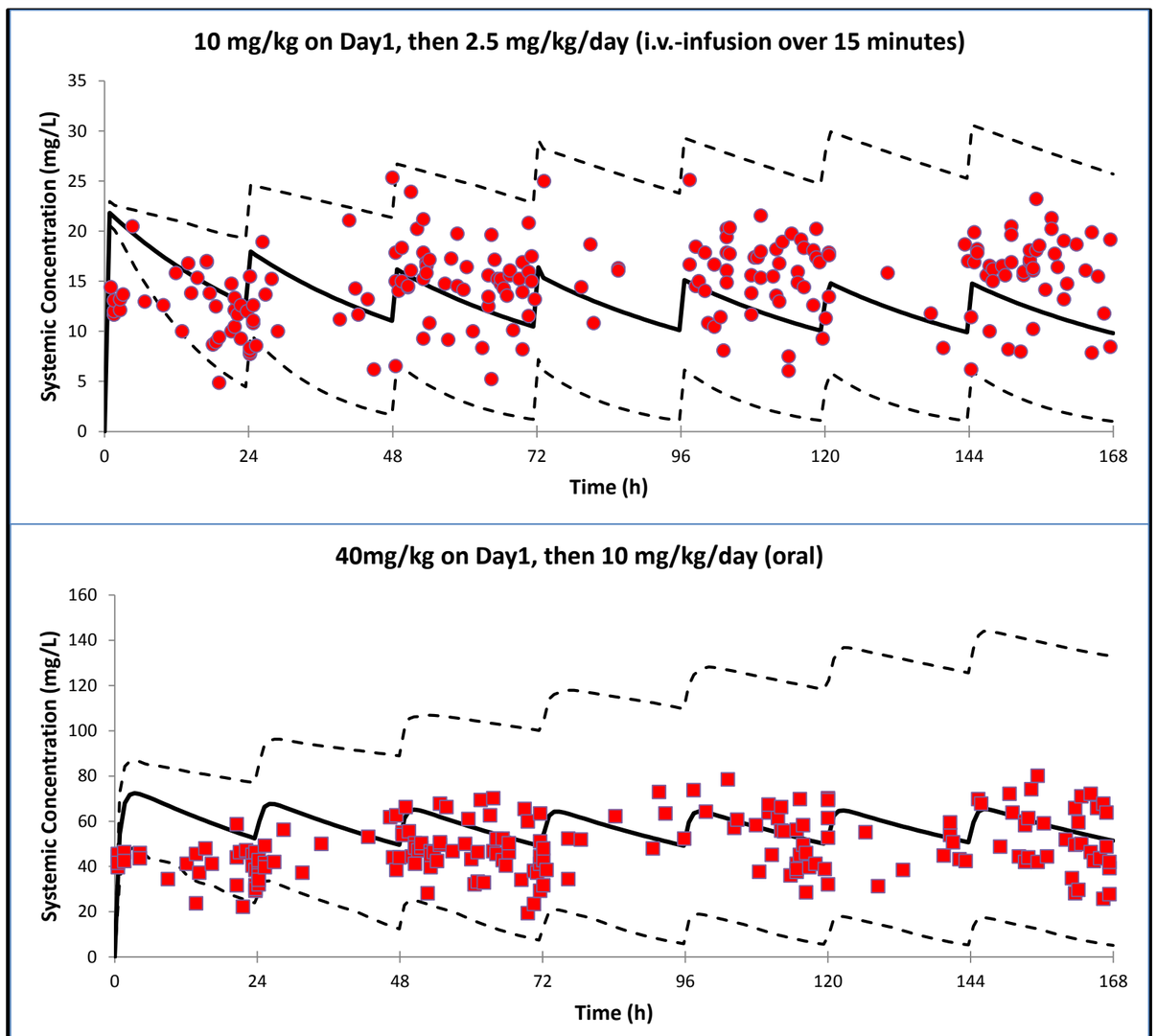

Figure 1. Representative Plasma concentration profiles assuming intravenous (top) and oral (bottom) administration to preterm neonates. Predicted mean (solid lines), Predicted 90% interval (dashed line) and reported [Ref. 6] (filled circles and squares)

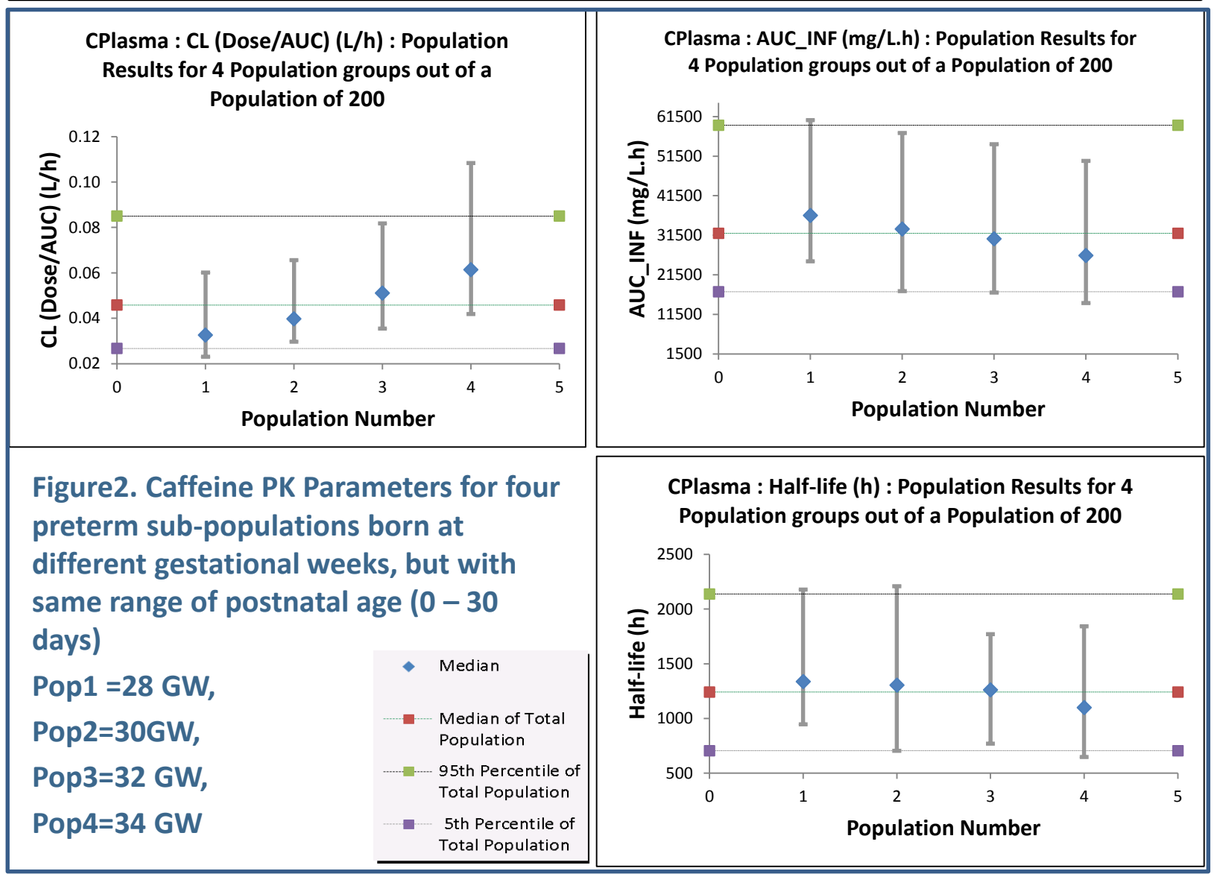

Figure2. Caffeine PK Parameters for four preterm sub-populations born at different gestational weeks, but with same range of postnatal age (0 – 30 days)

Pop1 =28 GW,
Pop2=30GW,
Pop3=32 GW,
Pop4=34 GW

Conclusion

A preterm PBPK model was build and integrated successfully within the Simcyp Simulator. The preterm PBPK model was able to replicate the clinical observations for caffeine. One design aspect of the clinical study was that both oral and IV administration was used for each dosage regimen, in agreement with the clinical data the simulated results were similar regardless of administration route. This reiterates the interchangeability of administration route in the clinic.

References

[1] WHO 2010. Bulletin of the World Health Organization 2010;88:31-38. doi: 10.2471/BLT.08.062554 (http://www.who.int/bulletin/volumes/88/1/08-062554/en/)

[2] Robertson et al., Outcomes for the extremely premature infant: what is new? And where are we going? Pediatr Neurol. 2009 Mar; 40(3):189-96.

[3]Aranda et al. Effect of caffeine and theophylline on control of breathing in infantile apnea. J Pediatr. 1983;89:F499–F503.

[4] Supinski et al. The effects of caffeine and theophylline on diaphragm contractility. Am Rev Resp Dis. 1984;130:429–433.

[5] Johnson et al. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children.Clin Pharmacokinet. 2006;45(9):931-56.

[6] Charles et al. Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. Ther Drug Monit. 2008 Dec;30(6):709-16.