Application of PBPK Approach to Investigate the Role of Intestinal and Hepatic P-Glycoprotein in Digoxin Disposition in Newborn Children. Is there an Ontogeny Function ?

Khaled, Abduljalil, Trevor N Johnson, Sibylle Neuhoff

Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK

Khaled.Abduljalil@certara.com

Introduction

The transporter P-glycoprotein (P-gp) is an important determinant of Digoxin PK in adults but its contribution in different paediatric age groups is largely unknown. The ontogeny function of intestinal and hepatic P-gp is contradictory, one study suggests that protein expression across the paediatric age range is the same as adults [1], while another indicates that P-gp expression in neonates is about 25-60 % of adult values [2].

The **aim** of this work is to apply the PBPK approach to investigate the ontogeny of both intestinal and hepatic P-gp after birth using digoxin as a probe.

Methods

The Simcyp Paediatric Simulator V16R1 was used to replicate two clinical studies by Wettrell G. 1977 [3], where digoxin (0.014 and 0.022 mg/kg given as an iv injection over 2 to 3 min) was administered to 7 full-term neonates and infants with heart failure (aged 2 - 81 days. These settings were used to generate 140 virtual children (20 trials of 7 individuals to match the clinical study) and administration of 0.017 mg/kg dose.

The SV-Digoxin compound file has been verified in adult populations [4,5]. The file inputs include: a full physiological distribution model (Rodgers & Rowland method) and liver permeability liver model (hepatic canalicular P-gp kinetics J_{max}=434 µL/min/10^6 hepatocytes, K_m=177 µM, fu_{inc}=1, RAF/REF=1.5) in addition to additional Hep CL_{int} of 0.37µL/min/10^6 hepatocytes and CL_R= 9.66 L/h. The enterohepatic circulation is enabled after intravenous administration and hence the intestinal P-gp is accounted for in the ADAM model with J_{max}=434 pmol/min, K_m=177 µM, fu_{inc}=1, and RAF/REF=2.

The Simulator accounts for age-dependent system parameters including user defined transporter ontogeny. The P-gp ontogeny profile was assumed to be 0.25, 0.5, 0.75 and 1.0 of adult expression. The predicted profiles were compared to the clinical data [3] to verify the P-gp ontogeny assumptions. Ontogeny with best fitting then was used to predict digoxin concentration profiles after oral dosing of 0.013 mg/kg within the first week of life. Predictions were compared to a clinical study [6], where 3 patients aged between 6 - 7 days received single dose between 0.011 – 0.015 mg/kg.

Results

The simulated concentration-time profiles of digoxin after IV bolus administration together with observed values are shown in Figure 1. Observed data suggested that the neonatal P-gp (Expression/activity) are operated at half to full adult activity at term. The oral profiles are given in Figure 2 for half and full adult P-gp activity.

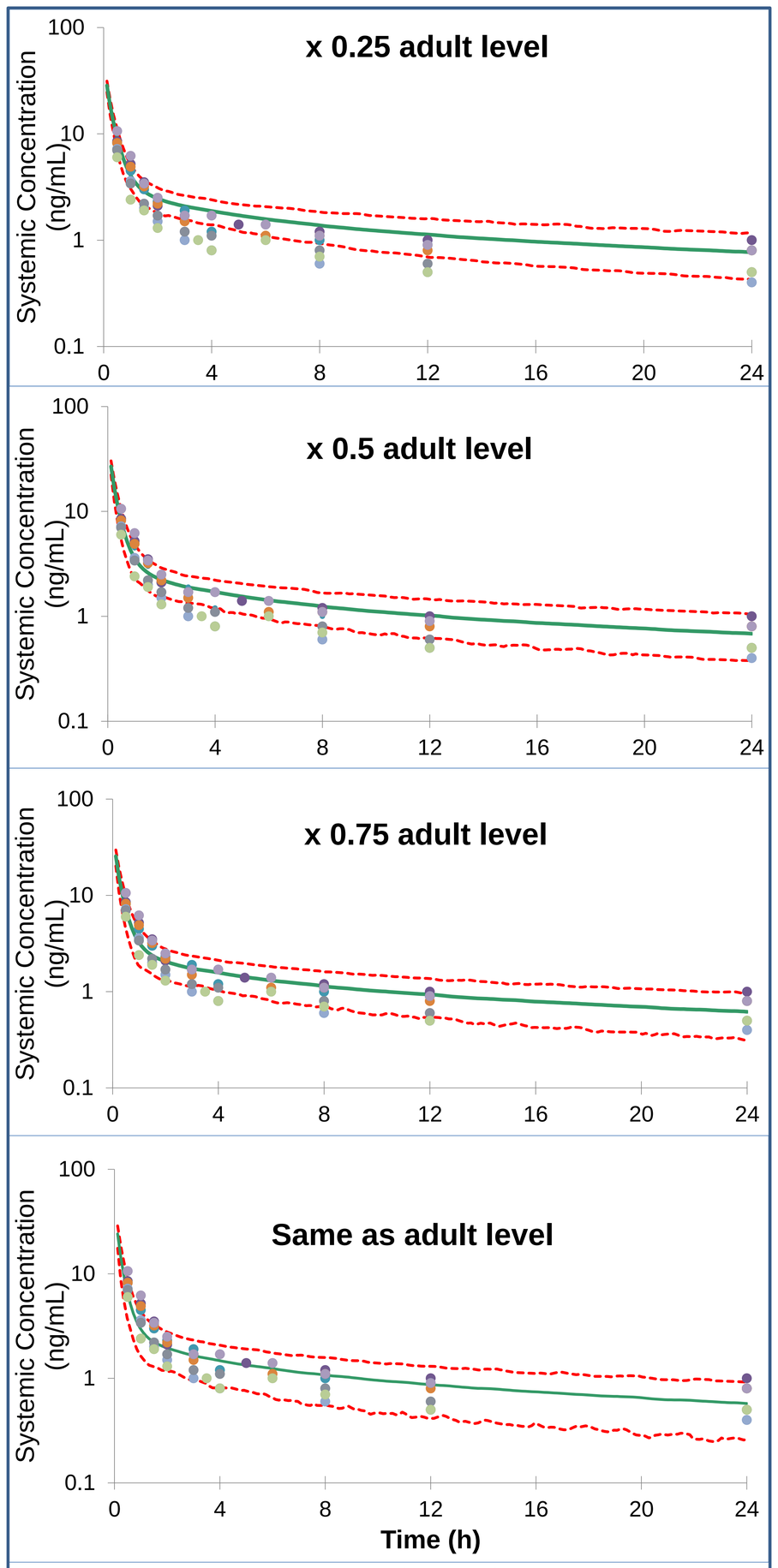

Figure 1. Average (dotted lines are 5th and 95th percentiles) of predicted versus observed [3] digoxin concentration levels over time in neonates after single i.v. bolus dose of 0.017 mg/kg assuming different fraction of adult P-gp expression level in the liver.

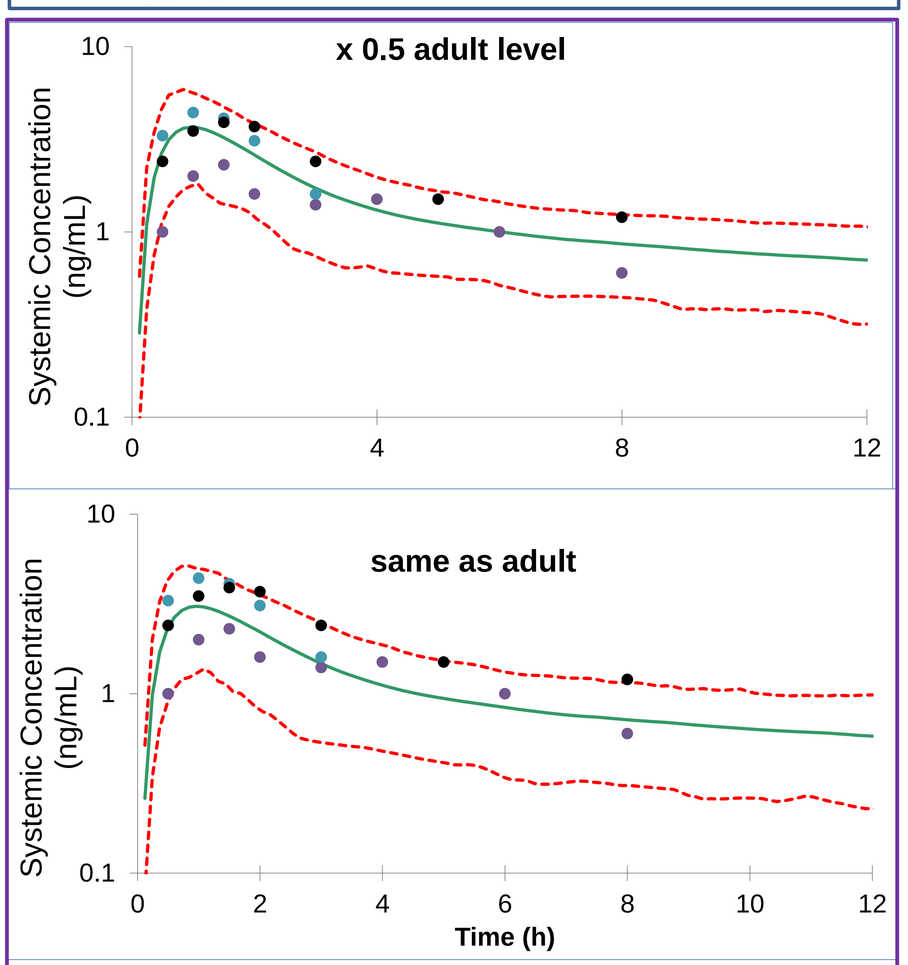

Figure 2. Average (with 5th – 95th percentiles) of predicted versus observed [6] digoxin concentration levels over time in neonates after single oral bolus dose of 0.013 mg/kg assuming half (top) and full (bottom) adult P-gp activity in the gut and liver.

Conclusions

This work suggests that developmental activity of hepatic P-gp is at least 50% of adult levels soon after birth, this is in agreement with recent findings by Prasad *et al* [2], who found that P-gp expression increased to about 50-60% of adult level in the first week post birth. The results are also in agreement with Johnson *et al* [7] who using a similar approach using azithromycin and digoxin concluded that 'P-gp as a canalicular transporter is at or near adult activity just after birth'. The oral data are also confirming that the P-gp activity in the intestine is at least 50% of adult. The simulations did not show to what extent the expression in higher age group as this requires an additional validation set of data.

References

1. Mooij *et al.* 2016. Proteomic Analysis of the Developmental Trajectory of Human Hepatic Membrane Transporter Proteins in the First Three Months of Life. Drug Metab Dispos. 44(7):1005-13.
2. Prasad *et al.* 2016. Ontogeny of Hepatic Drug Transporters as Quantified by LC-MS/MS Proteomics.Clin Pharmacol Ther. 100(4):362-70.
3. Wettrell G. 1977. Distribution and elimination of digoxin in infants. Eur J Clin Pharmacol.11(5):329-35
4. Neuhoff *et al.* 2013a.Application of permeability-limited physiologically-based pharmacokinetic models: part I-digoxin pharmacokinetics incorporating P-glycoprotein-mediated efflux.J Pharm Sci. 102(9):3145-60.
5. Neuhoff *et al.* 2013b. Application of permeability-limited physiologically-based pharmacokinetic models: part II- prediction of P-glycoprotein mediated drug-drug interactions with digoxin.J Pharm Sci. 102(9):3161-73.
6. Wettrell & Andersson. 1975. Absorption of digoxin in infants. Eur J Clin Pharmacol.9(1):49-55.
7. Johnson *et al.* 2016. How does in vivo biliary elimination of drugs change with age? Evidence from in vitro and clinical data using a systems pharmacology approach. Drug Metab Dispos. 44: 1090-1098