APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELLING FOR PREDICTION OF THE EXPOSURE OF BUPRENORPHINE IN NEONATES: INCORPORATION OF CYP3A4 AND UGT1A1 ONTOGENIES

Karen Rowland Yeo[1], Trevor Johnson[1], Maurice Dickins[1], Amin Rostami-Hodjegan[1,2]

[1] [1]Simcyp Limited, Blades Enterprise Centre, Sheffield, UK; [2]Centre for Applied Pharmacokinetic Research, The School of Pharmacy and Pharmaceutical Sciences, The University of Manchester, Manchester, UK

BACKGROUND

During gestation, neonates may be exposed to various legal and illicit substances which can result in varying degrees of withdrawal after delivery. The partial μ-opioid receptor agonist buprenorphine is recommended for infants requiring treatment for neonatal abstinence syndrome. Buprenorphine is metabolised extensively by CYP3A4 and UGT1A1 and undergoes biliary clearance (CL). A PBPK model incorporating ontogeny data relating to these processes was used to predict the exposure of buprenorphine in neonates.

METHODS

Prior *in vitro* data on metabolism, protein binding and physicochemical properties of buprenorphine were obtained from the literature and incorporated into a PBPK model within the Simcyp Simulator (Version 13 R2). A metabolic intrinsic clearance (Clu_{int}) value 889 μL/min per mg protein was extrapolated from the *in vivo* CL_{IV} of 54.2 L/h (Huestis *et al*., 2013). After subtraction of the *in vitro* CLu_{int} values of 472 (53.1%) and 279 μl/min/mg protein (31.4%) for CYP3A4 and UGT1A1, respectively (Kilford *et al*., 2009), the remaining 138 μl/min per mg protein was assigned to biliary clearance, consistent with mass balance data.

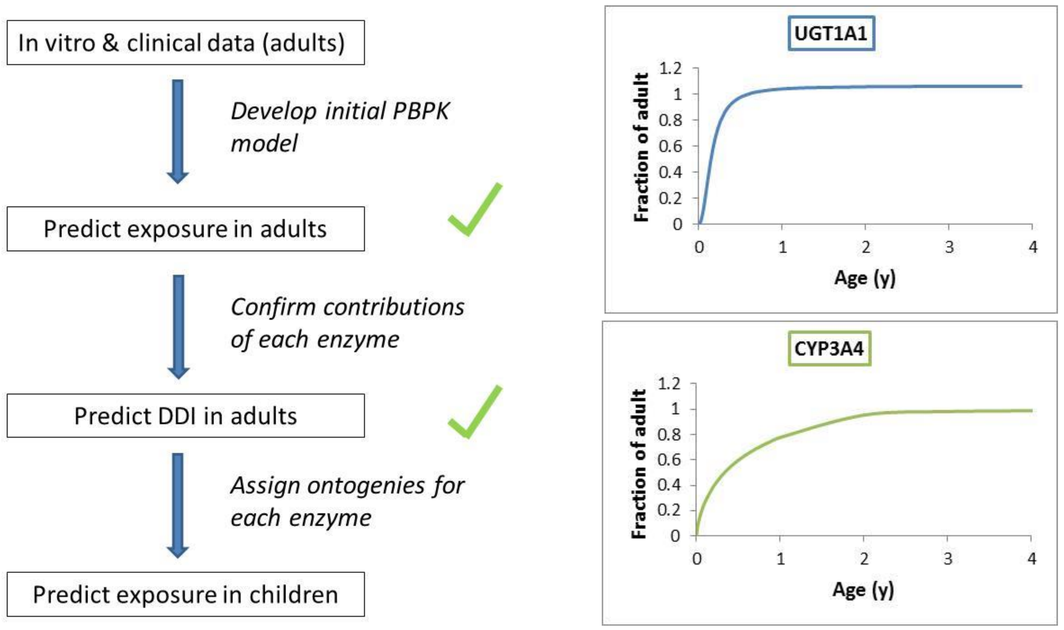
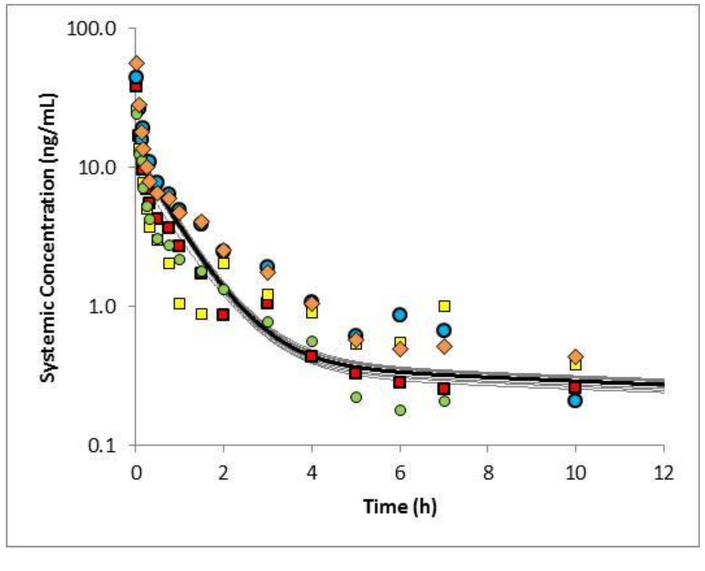


Figure 1. Strategy for developing a PBPK model for buprenorphine in paediatric subjects – incorporation of UGT1A1 and CYP3A4 ontogenies

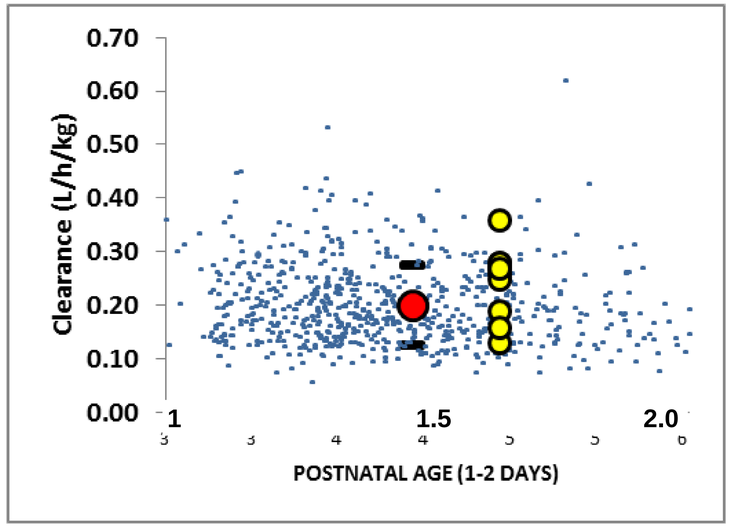
The strategy for the development of the PBPK model for buprenorphine in paediatric subjects is shown in Figure 1. Once the buprenorphine model was validated in adults, data on developmental physiology and CYP3A4 and UGT1A1 ontogenies were applied in conjunction with other physiological changes to predict the kinetics in paediatric subjects (Johnson *et al*., 2006). Various maturation functions for biliary CL were investigated with the purpose of recovering observed data under the so called "middle-out" modelling framework.

RESULTS



The PBPK model was able to recover the exposure of buprenorphine in adults (Figure 2) and the DDI with ketoconazole - predicted and observed AUC ratios of 2.5 and 2.0, respectively (buprenorphine NDA 20-732 and NDA20-733).

Figure 2. Simulated mean (lines) and observed (symbols; n=5; Kuhlman *et al*., 1996) plasma concentrations of buprenorphine after an IV dose of 1.2 mg administered over 1 minute in adults.



For simulations in neonates (postnatal age 1 - 2 days), integration of a moderate maturation function (compared with CYP3A4/UGT1A1) for biliary CL was necessary to obtain predicted mean CL values of 0.20 $Lh^{-1}kg^{-1}$ which were reasonably consistent with observed data (0.23 $Lh^{-1}kg^{-1}$; n=7) (Barrett *et al.*,1993) (Figure 3).

Figure 3. Simulated (individuals - blue dots; mean and standard deviation – red circle and solid lines) and observed (yellow circles; n=10) paediatric clearance values following a IV bolus dose (3 μg/kg)and a continuous infusion rate of 0.72 μg/kg/h.

CONCLUSIONS

Combining bottom-up PBPK modelling with reliable *in vitro* data allowed elucidation of the disposition of buprenorphine in neonates based on top-down analysis of observed data.

REFERENCES

Barrett *et al.* (1993) *Br J Clin Pharmacol* 36: 215-9; Johnson *et al*. (2006) *Clin Pharmacokinet* 45(9): 931-56; Kilford PJ, et al. (2009) *Drug Metab Dispos* **37**: 82-89.; Kuhlman JJ, et al. (1996) *J Anal Toxicol* **20**: 369-378 (1996); Huestis MA, *et al*. (2013) *Drug Alcohol Depend.* 2013; 131(3): 258-262; NDA 20-732 Buprenorphine Hydrochloride