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

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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 инт) value 889 µL/min per mg protein was extrapolated from the in vivo Clu инт of 54.2 L/h (Huestis et al., 2013). After subtraction of the in vitro Clu инт 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.

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).

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⁻¹kg⁻¹ which were reasonably consistent with observed data (0.23 Lh⁻¹kg⁻¹; n=7) (Barrett et al., 1993) (Figure 3).

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