APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING FOR PREDICTION OF BUPRENORPHINE EXPOSURE IN SUBJECTS WITH HEPATIC IMPAIRMENT

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Background

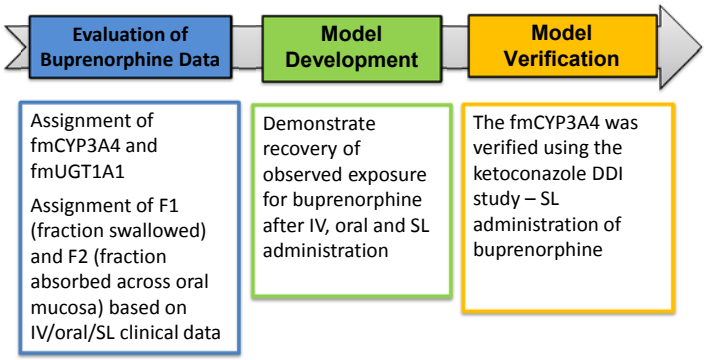
The partial μ-opioid receptor agonist buprenorphine is metabolised extensively by CYP3A4 and UGT1A1, undergoes biliary clearance and is subject to a high degree of first-pass metabolism (Kuhlman *et al*., 1996). After oral and SL administration, the bioavailability ranges from 6 to 8% and from 16 to 29%, respectively. For high extraction drugs, bioavailability can be increased in subjects with liver cirrhosis as a result of decreased first pass metabolism due to porta-caval shunting. A PBPK model incorporating these changes was used to predict the impact of cirrhosis on the exposure of buprenorphine following SL administration.

Methods

Prior *in vitro* data on metabolism, plasma protein binding (PPB) and physicochemical properties of buprenorphine were previously collated (Johnson *et al*., 2016).

After demonstrating that the model was able to recover the observed exposure of buprenorphine after SL administration, the model was then verified using the clinical DDI study with ketoconazole in the Simcyp Simulator (V15) (Figure 1).

Figure 1. General workflow for model development



Results

The buprenorphine PBPK model was able to recover observed plasma exposures of buprenorphine following SL administration (8 mg) in healthy adults and the clinical drug-drug interaction with ketoconazole (predicted and observed increases in exposure were 2.4- and 2.3-fold, respectively).

Changes in hepatic blood flow (to reflect porta-caval shunting), CYP3A4, liver size, PPB and renal function corresponding to Child-Pugh score C (severe) liver cirrhosis were then applied for simulations of subjects with severe HI (Johnson *et al*., 2010)

Figure 2. Simulated and observed exposure of buprenorphine in healthy age matched subjects (A) and patients with cirrhosis (B)

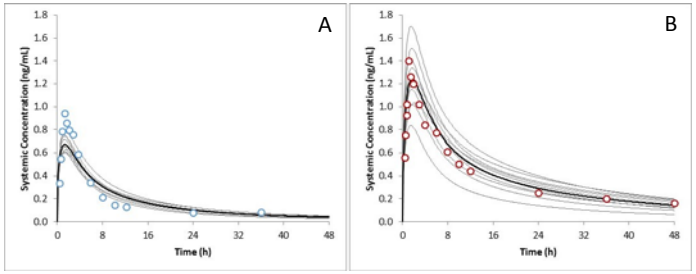
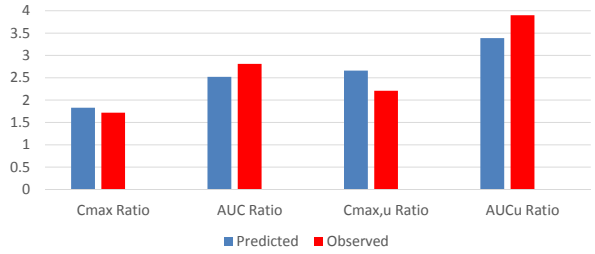


Figure 3. Change in exposure of buprenorphine in patients with cirrhosis relative to healthy age matched subjects



Simulated plasma concentration time profiles of buprenorphine in healthy subjects and those with cirrhosis were reasonably consistent with observed data (Figure 2).

Predicted increases in total and unbound C_{max} and AUC in subjects with severe HI relative to healthy age matched controls were within 1.25-fold of observed data (Figure 3).

Conclusions

- Applying physiological changes associated with severe liver cirrhosis (Child-Pugh score C) to a verified robust PBPK model for buprenorphine based on reliable *in vitro* data, allowed accurate prediction of the increase in exposure of buprenorphine in subjects with severe HI relative to healthy age matched controls (Nasser *et al*., 2015).
- It should be noted that the full extent of the increase in buprenorphine exposure in subjects with severe HI could only be recovered with the PBPK model when changes in hepatic blood flow which reflect porta-caval shunting were considered in addition to changes in CYP3A4 expression, liver size, protein binding and renal function.

Refrences

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Kuhlman JJ, Lalani S, Magluilo J, Levine B and Darwin WD. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol* 1996; 20: 369-378.

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