Application of a PBPK model for prediction of the DDI between Lorazepam and Probenecid.

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Background

Drug-drug interactions (DDIs) between lorazepam and probenecid have been observed *in vivo* with a notable decrease in clearance and increase in AUC (Abernethy *et al.*, 1985). It is suggested this is the result of inhibition of UGT2B7 glucuronide formation, as there is evidence lorazepam is metabolised mainly by UGT2B7 (Zhang *et al.*, 2007).

Objectives

To apply Physiologically-Based Pharmacokinetic (PBPK) models to assess the UGT2B7-mediated DDI between lorazepam and probenecid in healthy volunteers.

Methods

Lorazepam and Probenecid

Physicochemical, *in vitro* and *in vivo* information relating to lorazepam and probenecid was obtained from the literature. A full PBPK model was developed for lorazepam within the Simcyp Population-based Simulator (V13 release 2). Reported *in vivo* CL_{iv} and CL_r were used in combination with *in vitro* fm data for UGTs to back-calculate a metabolic intrinsic clearance using a retrograde approach. This was then incorporated into the model as UGT2B7 elimination data from a recombinant system. A Kp scalar was applied for the distribution to recover the observed V_{ss}.

Simulations were run to generate concentration-time profiles of lorazepam following single (SD) and multiple (MD), intravenous (i.v.) or oral (p.o.) doses over a range of doses (1 mg to ~4.5 mg (0.057 mg/kg)) and compared to the available *in vivo* data.

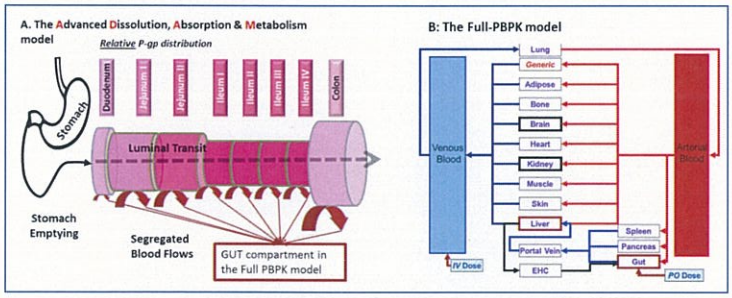

Figure 1 *- The Full-PBPK model within Simcyp V13 release 2 and the permeability-limited model for gut. Both models have been used for the inhibitor, Probenecid. The first order absorption model and the full PBPK has been used for the substrate, Lorazepam.*

Similarly, a full PBPK model was also developed for the UGT2B7 inhibitor probenecid. The ADAM (Advanced Dissolution, Absorption and Metabolism) model was utilised to describe the absorption for this compound; reported *in vivo* CL_{iv} and CL_r were used to back-calculate a metabolic intrinsic clearance using a retrograde approach. Due to the lack of *in vitro* fm data this was assigned as an additional human liver microsomal CL_{int} within the model. Simulations were run to generate concentration-time profiles of probenecid alone at the inhibitor dose of 500 mg and compared to the available *in vivo* data.

DDI study

In vitro Ki data relating to inhibition of UGT2B7 glucuronide formation by probenecid for the DDI study were optimised from a Zidovudine interaction study. This was in agreement with the observations by Uchaipichat *et al.* (2004) that the *in vitro* Ki is below 500 µM, and Rowland *et al.* (2006) that this Ki value, like Km values, should be reduced in the presence of fatty acids. These data were incorporated into the PBPK model and used to investigate the effects of probenecid on the systemic exposure of lorazepam. The results were compared to observed *in vivo* data.

References

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Results

Simulations of PK profiles of lorazepam and probenecid

The simulated concentration-time profiles of lorazepam were consistent with observed data from 4 independent studies (Figure 2).

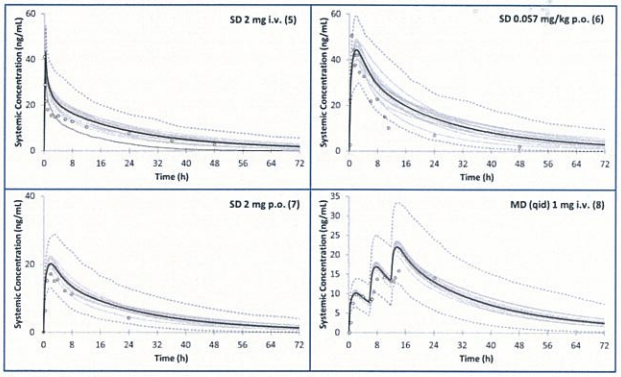

Figure 2. *Simulated lorazepam concentration-time profiles. The solid black line represents the simulated mean profile, dashed lines represent upper and lower percentiles from simulations and the thin grey lines are the individual trials. Observed data are represented by open circles.*

The simulated concentration-time profiles for probenecid were consistent with observed data for 2 independent studies at the inhibitor dose of 500 mg (Figure 3).

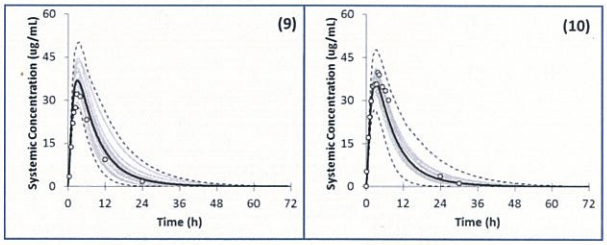

Figure 3. *Simulated probenecid concentration-time profiles. The solid black line represents the simulated mean profile, dashed lines represent upper and lower percentiles from simulations and the thin grey lines are the individual trials. Observed data are represented by open circles.*

Simulations of UGT2B7-mediated DDI

The predicted concentration-time profile, indicating the increase in exposure of lorazepam (2 mg SD iv) following administration of probenecid was similar to the observed data (Figure 4). The predicted and observed ratios of the area under the plasma concentration-time profile are shown in table 1. The under-prediction of the DDI may be due to the contribution of additional UGTs (in liver and kidney) that have not been accounted for so far as probenecid is a potent inhibitor towards many UGTs (Uchaipichat *et al.*, 2004).

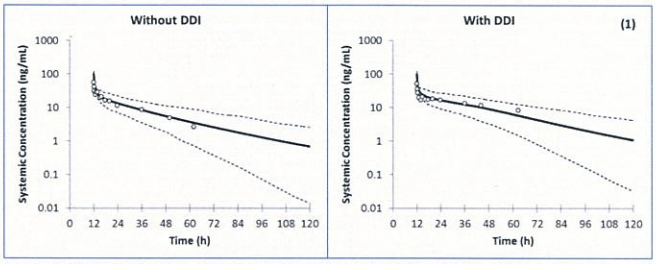

Figure 4. *Simulated lorazepam concentration-time profiles with and without interaction. The solid black line represents the simulated mean profile, dashed lines represent upper and lower percentiles from simulations Observed data are represented by open circles.*

Table 1. Comparisons of observed and predicted AUC values.

AUC ratio	Observed	Predicted
Mean	1.83	1.37
Min	0.97	1.14
Max	2.82	1.79

Conclusions

PBPK modelling in conjunction with reliable inhibition data can be used to assess the importance of interactions affecting the glucuronidation pathways. The reported PBPK models can also be used to evaluate other UGT2B7-mediated DDIs using lorazepam and probenecid as victim and perpetrator, respectively.