Application of physiologically based pharmacokinetic modelling to predict the pharmacokinetics of zidovudine and its interaction with fluconazole using recombinant UGT2B7 CL_{int} inputs and UGT tissue scalars

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BACKGROUND

- Intrinsic clearance (CL_{int}) data from recombinantly expressed UGT enzymes can be extrapolated to *in vivo* clearance (CL) values using appropriate tissues scalars (similar to relative activity factors).
- Robust scalars are also required for accurate prediction of the fractional contribution of an enzyme to the elimination of a drug (fm) which is critical for the prediction of DDIs.
- The antiretroviral drug, zidovudine, is a probe substrate for UGT2B7 with 65-75% of a dose excreted in the urine as the glucuronide. Following coadministration of the UGT2B7 inhibitor fluconazole, a 1.75-fold increase in the exposure of zidovudine was observed (Sahai *et al*., 1994).

AIMS

- To derive robust *in vitro* tissue scalar values for UGT2B7-mediated metabolism of zidovudine
- To apply these scalars to predict *in vivo* clearance for zidovudine from *in vitro* recombinant UGT2B7 data, incorporating liver, kidney and intestinal metabolism.
- To use PBPK modelling to assess the drug-drug interaction (DDI) between zidovudine and fluconazole (UGT inhibitor)

METHODS AND RESULTS

Model Development

- Tissue scalars were derived for zidovudine using the following equation:

$$\text{rhUGT/tissuescalar} = \frac{CL_{int}(HLM/HIM/HKM)}{CL_{int}(rhUGT)}$$

- *In vitro* CL_{int} data from microsomes expressing recombinant UGT2B7 (rhUGT; BD Gentest, n=3 studies) and microsomes from human liver (HLM; n=5 studies), from kidney (HKM; n=1 study and the intestine (HIM; n=2 studies) were used to derive the tissue scalars shown in the table below.

Liver scalar	Kidney scalar	Intestinal scalar
3.12	1.64	0.32

- *In vitro* metabolism data for zidovudine (rhUGT2B7 - K_m 320µM and V_{max} 3100 pmol/mg/min; Walsky *et al* 2012) were scaled to whole organ values using the relevant scalars as shown in Fig. 1.
- These data were then combined with physicochemical data in a minimal PBPK model implemented in the Simcyp Population-based Simulator (V12) (Jamei *et al*., 2009).

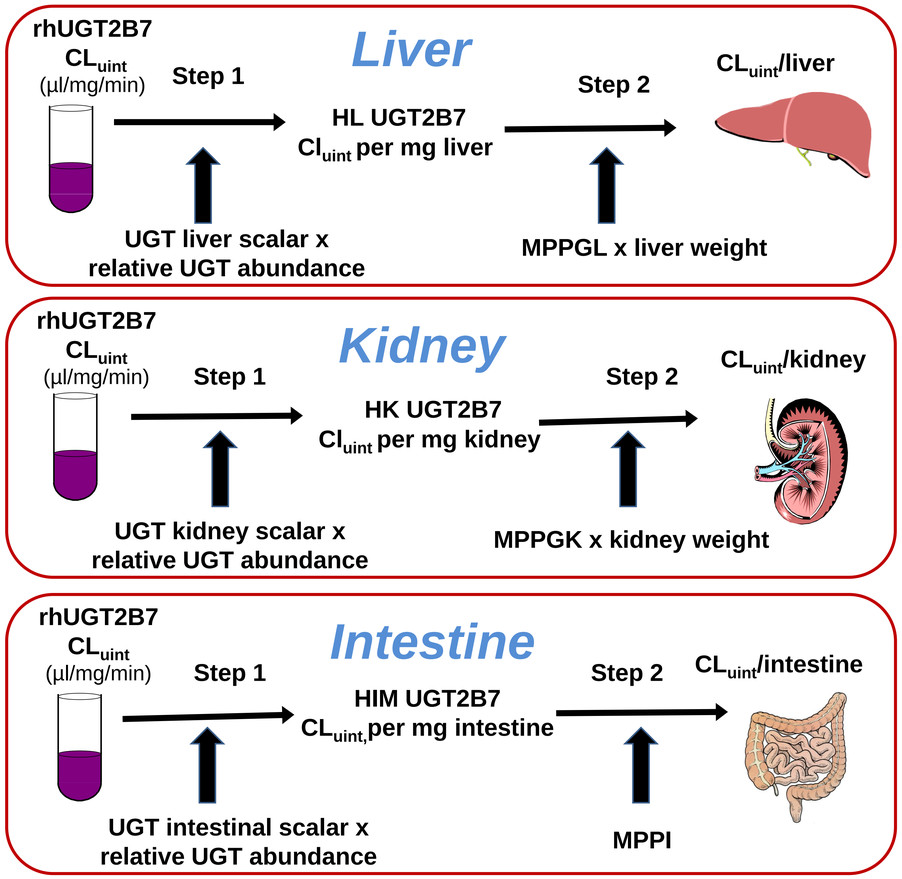

Fig1. Strategy for scaling rhUGT CL_{int} data to whole organ UGT Cl_{int}. MPPGL = microsomal protein per gram of liver; MPPGK = microsomal protein per gram of kidney; MPPI = microsomal protein per intestine. Variability is incorporated into relative UGT abundance, MPPGL, MPPGK, MPPI and organ weight.

Model Verification

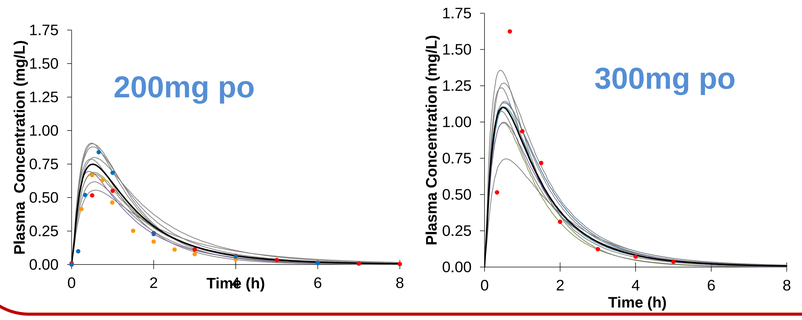

Fig 2. Concentration time profiles of simulated (lines) and observed (circles) data after oral administration of zidovudine (Singlas *et al*., 1989; Anderson *et al*., 2000)

- Following oral administration of zidovudine, simulated concentration-time profiles were reasonably consistent with observed data (Fig 2).
- The predicted oral CL (162.6 L/h) compared well with observed data (153.7 L/h; Singlas *et al.,* 1989) reported in the literature.

Model Application

- The predicted AUC ratio for zidovudine in the presence of the UGT2B7 inhibitor, fluconazole (Ki of 73µM Uchaipichat *et al.,* 2006), was in good agreement with the observed value (Fig 3).

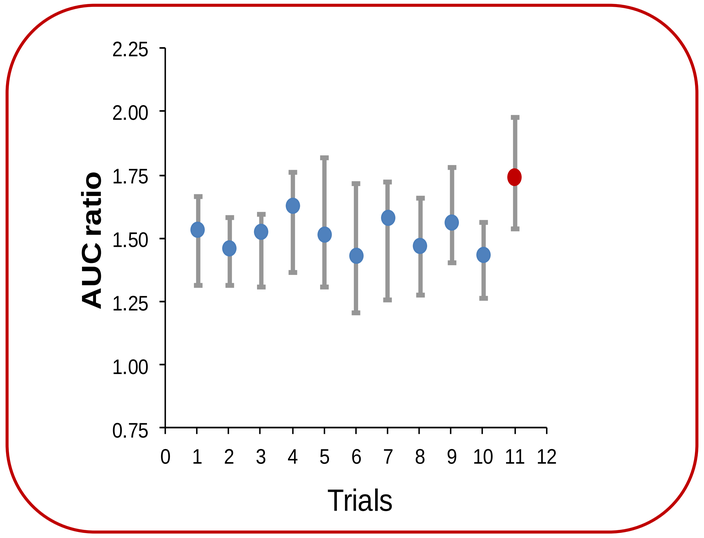

Fig 3 Predicted median AUC ratios (95% confidence intervals) of zidovudine following a single oral dose of 200 mg in the absence of fluconazole and co-administered with fluconazole (400 mg q.d. for 7 days) in 10 different trials of virtual subjects. The red circle indicates observed data (Sahai *et al*., 1994)

CONCLUSIONS

- This study demonstrates the utility of the *in vitro in vivo* scaling approach for UGT data.
- In addition, when this approach is combined with PBPK modelling, it is possible to accurately predict both clearance and DDIs mediated via UGTs.

References

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