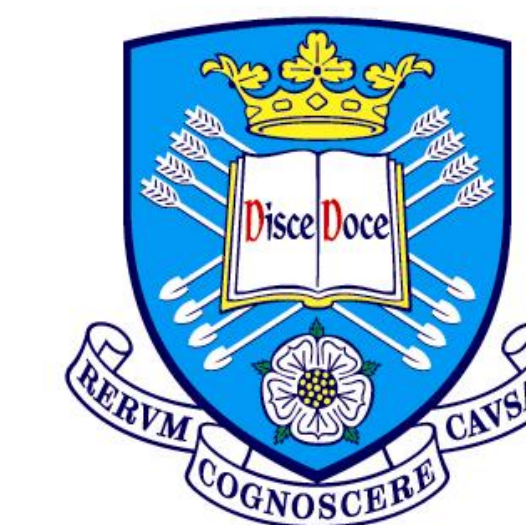


Prediction of time-dependent CYP3A4-mediated *in vivo* drug-drug interactions from *in vitro* data using biological information on enzyme turnover implemented within a physiologically based model

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Introduction

Predicting the magnitude of time-dependent metabolic drug-drug (mDDIs) interactions involving cytochrome P-450 3A4 (CYP3A4) from *in vitro* data requires accurate knowledge of the metabolism of the substrate (fm), of the inactivation parameters of the inhibitor (K_I , k_{inact}), of the turnover of the enzyme (k_{deg}) in both gut and liver and an estimate of the inhibitor concentration ([I]) at the enzyme active site (1).

We have predicted the magnitude and variability of mDDIs observed in 30 clinical studies involving 5 mechanism based inhibitors of CYP3A of variable potency (azithromycin, clarithromycin, diltiazem, erythromycin and verapamil) and 7 substrates predominantly metabolised by CYP3A but to different extents in the gut and liver (alprazolam, cyclosporine, midazolam, nifedipine, quinidine, simvastatin, triazolam). None of the inhibitors are known to cause concomitant enzyme induction.

Methods

The data were implemented in a physiologically-based pharmacokinetic (PBPK) model incorporating the effects of parallel pathways of drug elimination and accounting for CYP3A-mediated metabolism in the liver and intestine (Simcyp version 8.1; www.simcyp.com) without any optimization or fitting of any parameters. A meta-analysis of the literature determined best estimates of the relevant variables, including inactivation parameters for the 5 inhibitors (Table 1) and k_{deg} (weighted mean values of 0.0077 [n=10 studies] and 0.029 hr⁻¹ [n=4 studies] for liver and gut, respectively; (2) and references therein).

Simulations of full plasma drug concentration-time profiles, reproducing actual clinical trial designs enabled rigorous prediction of the combined effects of competitive and mechanism-based enzyme inhibition of enzyme using unbound inhibitor concentration either in the liver ($[Iu_{liver}]$) or the portal vein ($[Iu_{pv}]$) as the driving force for inhibitory effects in the liver.

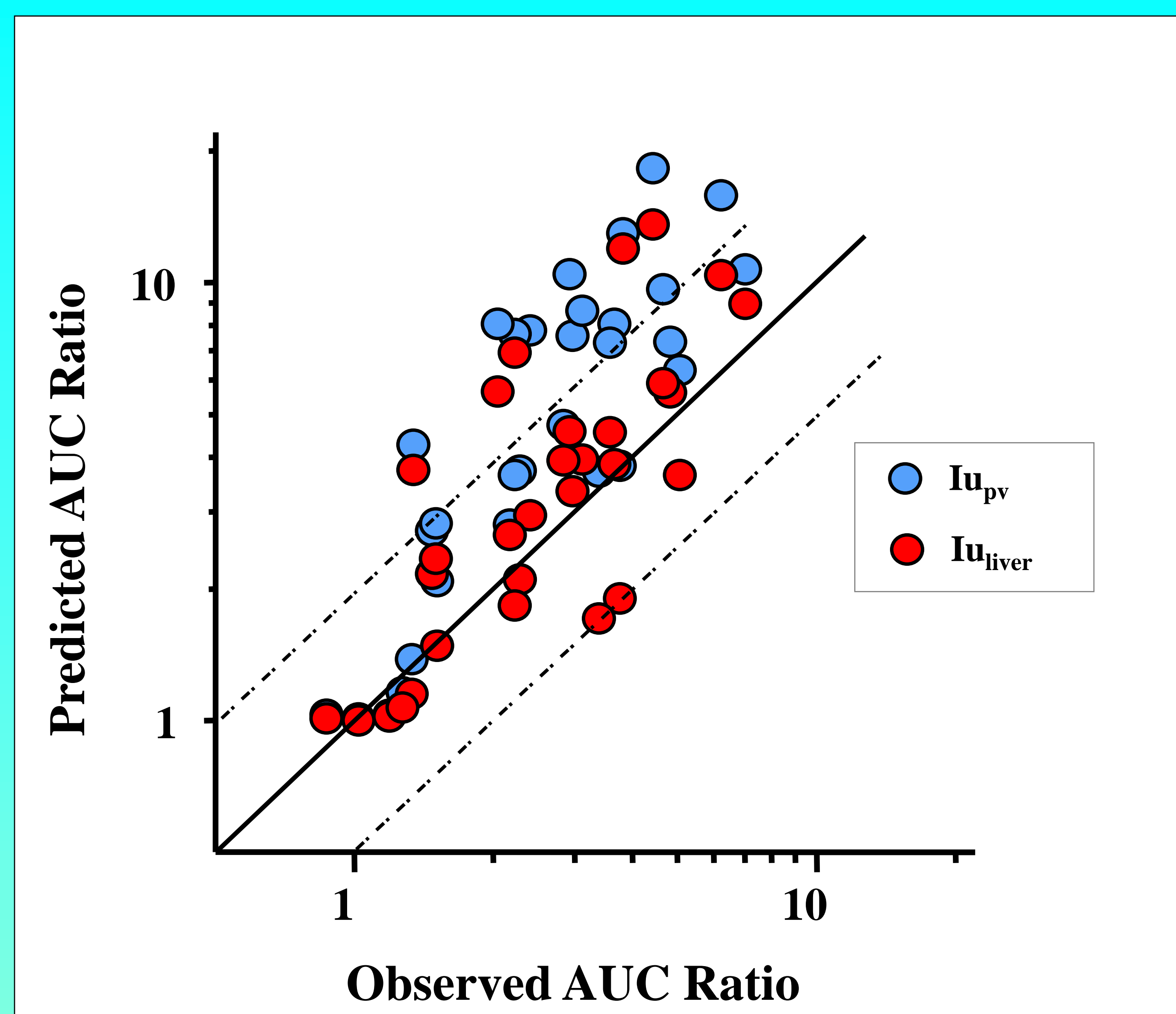


Figure 1. Predicted versus observed AUC ratios for 30 clinical studies using Iu_{liver} or Iu_{pv} as the driving force for inhibitory effects in the liver (dotted lines indicate 2-fold range).

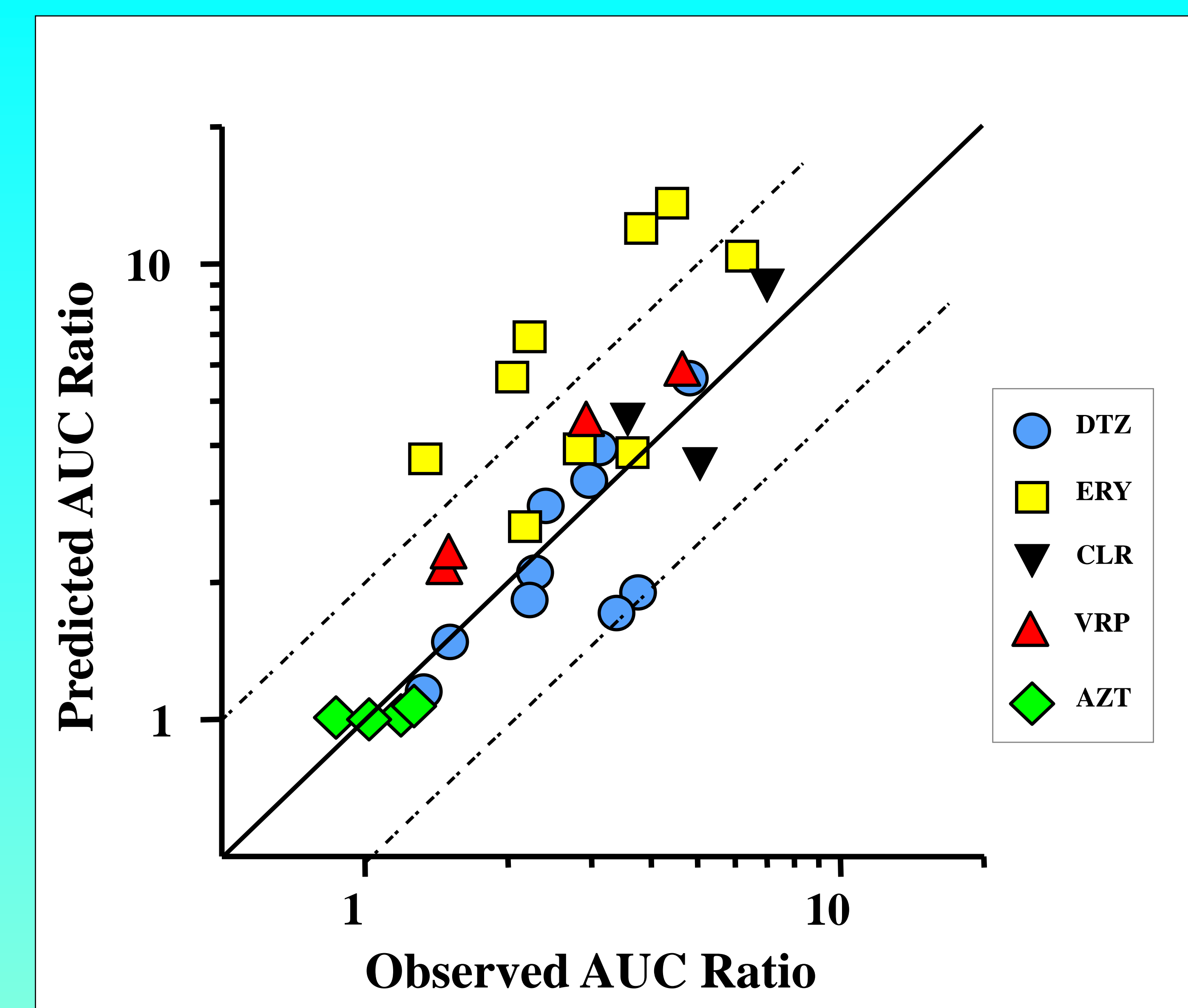


Figure 2. Predicted (using Iu_{liver}) versus observed AUC ratios for different inhibitors (DTZ - diltiazem; ERY - erythromycin; CLR - clarithromycin; VRP - verapamil; AZT - azithromycin; dotted lines indicate 2-fold range).

Results

The use of Iu_{liver} compared to Iu_{pv} resulted in decreased bias (average fold error 1.26 vs 1.85) and increased precision (root mean squared error 2.77 vs 4.72) of the predictions.

Predicted median increases in ratios of area-under-the-curve (AUC) in the absence and presence of inhibitor and the 90% confidence interval/AUC ratio (as an assessment of variability) were within 2-fold of the observed *in vivo* values for 24 (80%) and 17 (57%) of the 30 studies, respectively (Figures 1 and 2).

Table 1. Inactivation parameters for the 5 inhibitors

Inhibitor	k_{inact} hr ⁻¹	K_I μM	References
Azithromycin	1.22	521.34	3
Clarithromycin	2.30	26.51	3,4
Erythromycin	2.62	13.52	3,5,6,7,8,9
Diltiazem	0.88	1.37	6,7,9,10,11
Verapamil	2.79	1.23	7,10,11,12

Conclusion

Comprehensive PBPK models that incorporate the concentration-time profiles of substrates and inhibitors and that replicate the exact design of *in vivo* studies are recommended for the accurate prediction of the extent of mDDIs.

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