Prediction of *in vivo* drug interactions from *in vitro* enzyme kinetic data: time-based versus steady state simulations

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Introduction

Predicting the magnitude of *in vivo* metabolic drug-drug (mDDIs) interactions involving cytochrome P-450 enzymes from *in vitro* data requires accurate knowledge of the inhibition constants (Ki) and an estimate of the inhibitor concentration ([I]) at the enzyme active site.

Although predictions using the [I]/Ki approach may be improved significantly by incorporating the effects of parallel drug elimination pathways and accounting for inhibition of CYP3A-mediated metabolism in the intestine, this method assumes that [I] is time-invariant, and it cannot accommodate complex *in vivo* study designs [1].

In this study, we have predicted the magnitude of mDDIs observed in 25 clinical studies involving three CYP3A inhibitors (fluconazole, ketoconazole, itraconazole) and 5 substrates that are predominantly metabolised by CYP3A (alprazolam, midazolam, simvastatin, zolpidem and triazolam).

Methods

Substrate and inhibitor data for compounds used in the simulations are found in substrate and inhibitor libraries within the Simcyp© software (version 6.2).

The data were implemented in a physiologically-based pharmacokinetic (PBPK) model incorporated in Simcyp® (www.simcyp.com). The model accounted for time- and concentration-dependent inhibition of active enzyme using unbound plasma drug concentration [I] as the driving force. For ketoconazole, the concentration gradient between unbound drug in hepatocytes and plasma was set to 6, as determined from the results of a previous study [2]. Simulations based on actual clinical trial designs were performed under time-dependent conditions and were then repeated assuming steady state conditions.

The bias of both sets of predictions (steady state and time-based) was assessed from the mean of the ratio of predicted and observed values (average fold error [AFE]). The root mean squared prediction error (RMSE) provided a measure of precision for the prediction of increase in AUC ratio.

Results

Predicted mean increases in AUC ratios were within 2-fold of the observed *in vivo* values in 18 out of 25 studies (72%) for both time-based and steady state simulations (Figure 1).

There was a decrease in bias (AFE values: 0.93 vs 1.35) and increase in precision (MSE values: 2.35 vs 4.89) for time-based versus steady state simulations.

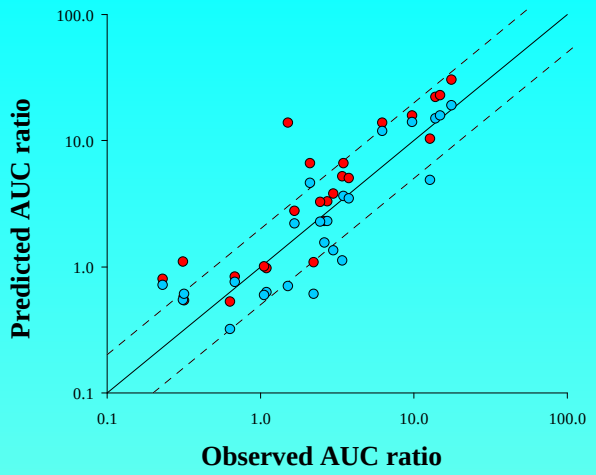

Figure 1. Observed versus predicted AUC ratios for 25 clinical studies under time-dependent (○) and steady state (●) conditions.

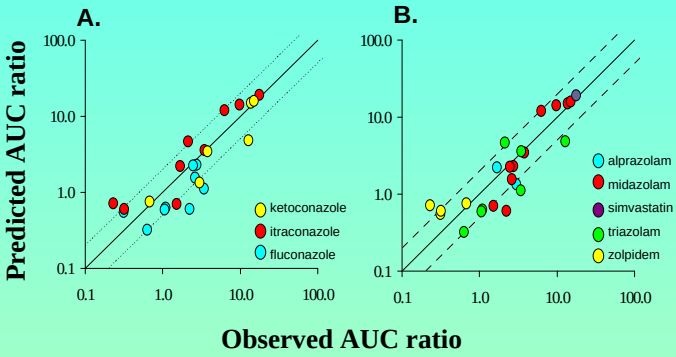

Figure 2. Observed versus predicted AUC ratios for 25 clinical studies under time-dependent conditions based on inhibitor (A) and substrate (B) selection.

Reasonably accurate predictions were obtained using time-based simulations irrespective of the inhibitor or substrate used (Figure 2).

Discussion

The decrease in bias and increase in precision for time-based simulations when compared against those run under steady state conditions, indicate that comprehensive PBPK models which accommodate complex study designs and temporal changes in [I] should be used to predict the magnitude of mDDIs.

References

1)Rostami-Hodjegan & Tucker (2004) *Drug Discovery Today Technologies* 4.
2)Yang *et al.* (2001) *Br J Clin Pharmacol* 52: 472-3.