Prediction of the inhibitory effects of ketoconazole and fluconazole on midazolam and zolpidem clearance from in vitro data using physiologically-based pharmacokinetic modeling

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INTRODUCTION

- Predicting the magnitude of *in vivo* metabolic drug-drug interactions (mDDIs) involving cytochrome P-450 enzymes from *in vitro* data requires accurate knowledge of the inhibition constants (K_i) and an estimate of the inhibitor concentration ([I]) at the enzyme active site.
- The contribution of a given metabolic pathway (fm) to the total clearance of a substrate is also an important determinant of the accurate prediction of drug interactions [1].

AIMS & OBJECTIVES

- We aimed to predict the magnitude of the inhibitory effects of ketoconazole and fluconazole, potent and weaker inhibitors of CYP3A4, respectively, on the clearance of the CYP3A substrate midazolam after intravenous (iv) and oral (po) administration [2,3].
- In addition, the effects of ketoconazole and fluconazole on the oral clearance of zolpidem, a CYP3A and CYP2C9 substrate, were also predicted [4].

METHODS

- Substrate and inhibitor files for midazolam and zolpidem, and ketoconazole and fluconazole, respectively, used for the simulations were found in Simcyp® (version 6.1) libraries.
- Data in these files were collated from published sources, using two electronic databases, "WEB OF SCIENCE" (1981-2004) and "PUBMED" (1966-2006) and complemented by our own unpublished data.
- The K_i values of fluconazole and ketoconazole for different CYP450s used in the simulations are shown in Table 1.
- The maximum average fm (assuming steady state conditions) values for the enzymes that have potential to be inhibited and are involved in the metabolism of midazolam or zolpidem are also shown in Table 1. CYP1A2 and CYP2D6 also contribute to the metabolism of zolpidem but are not shown here.

MODELLING APPROACH

- The data were implemented in a physiologically-based pharmacokinetic model within Simcyp® software (version 6.1).
- The model accounted for time- and concentration-dependent inhibition or inactivation 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 (AU) was set to 6, as determined from the results of a previous study [5].

Table 1. Mean values of the inhibitory potency (K_i) of fluconazole and ketoconazole for different CYP450s and the contribution (fm, %) of each enzyme to the metabolism of midazolam and zolpidem

CYP	2C8	2C9	2C19	3A4	3A5
Ki,u (μM)					
ketoconazole	2.2	8.0	-	0.015	0.11
fluconazole	-	7.9	2.0	10.7	84.6
fm (%)					
midazolam	-	-	-	97	3
zolpidem	-	34	1	43	-

In vitro Ki values for ketoconazole and fluconazole were obtained from a meta-analysis of values weighted by the number of liver samples used in each study and were corrected for non-specific microsomal binding using experimental fu_{mic} values from the literature or estimated values [6]. *In vitro* metabolism data for midazolam and zolpidem were obtained from the literature and were based on recombinant systems heterologously expressing CYP450 with appropriate intersystem extrapolation factors (ISEFs) applied [7].

RESULTS & DISCUSSION

Table 2. Predicted and observed mean AUC ratios for mDDIs

	Ketoconazole		Fluconazole	
	Predicted	Observed	Predicted	Observed
Zolpidem	1.7	1.7	1.4	1.3
Midazolam po	12.6	13.6	2.5	3.6
Midazolam iv	4.4	4.7	1.6	2.0

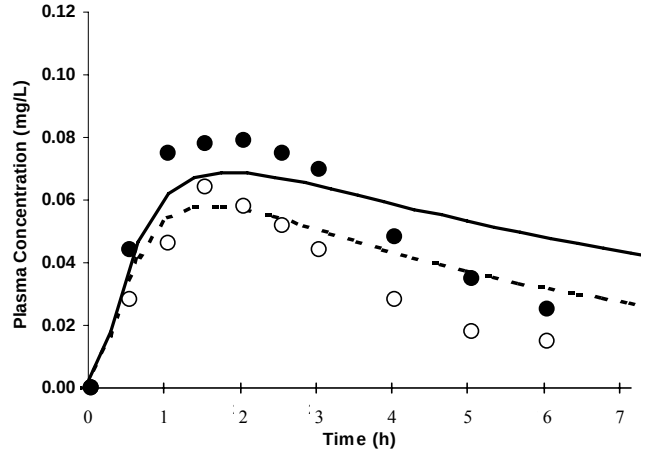

Figure. Observed (circles) versus predicted (lines) plasma concentration-time profile for zolpidem in the absence (○ , -----) and presence (●, ——) of fluconazole [4].

- Simcyp® (version 6.1) was able to predict the magnitude of inhibition by ketoconazole and fluconazole on the systemic clearance and first pass metabolism of midazolam with reasonable precision (Table 2).
- Accurate predictions were obtained irrespective of the substrate used. Importantly, the software has the intrinsic ability to generate the contribution of a given metabolic pathway to total drug clearance.

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