Azole Antifungals: Physiologically-Based Pharmacokinetic (PBPK) Modeling and Prediction of Drug-Drug Interactions (DDIs)

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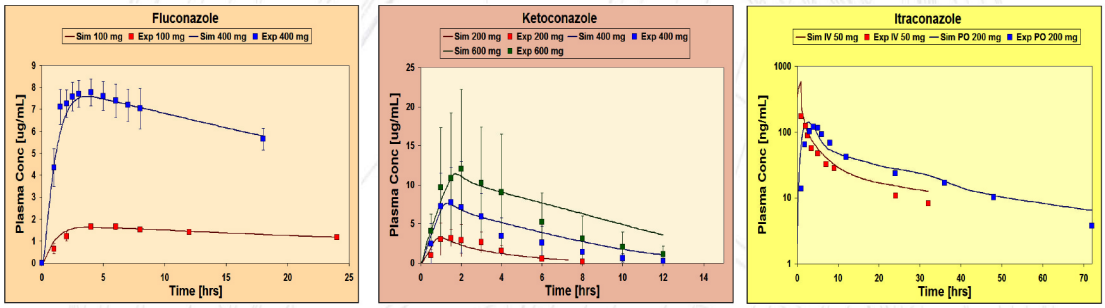
Purpose: Develop PBPK models for azole antifungals for prediction of DDIs.

Methods: The absorption and pharmacokinetics of azole antifungals were simulated using GastroPlus™ 6.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental and Transit (ACAT) model described the absorption and intestinal first pass extraction of the drugs, while pharmacokinetics was simulated with a PBPK model. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™. Experimental tissue/plasma partition coefficients (Kps) were used where available. A modified Rodgers algorithm [1,2] based on tissue composition and *in vitro* and *in silico* physicochemical properties from ADMET Predictor™ 4.0 (Simulations Plus, Inc., Lancaster, CA) were used to estimate the remaining Kps. Metabolic clearances in gut and liver were estimated from *in vitro* enzyme kinetic constants for relevant enzymes combined with built-in *in vitro* values for the distribution of 3A4 in gut [3], and the average expressions of all relevant enzymes in liver [4]. A test version of a new DDI Module in GastroPlus was used to predict the DDIs of azole antifungals with different drugs.



Simulated and experimental [5-10] Cp-time profiles for fluconazole, ketoconazole and itraconazole that were used to validate the absorption/PBPK models for all compounds (for clarity only few selected profiles are shown for each compound)

Itraconazole, ketoconazole and fluconazole are reversible inhibitors of 3A4 [11] and the steady-state equation below was used to predict the DDI as a ratio of AUCs. Simulated gut and liver unbound concentrations were used for inhibitor concentrations.

$$\frac{AUC^{inh}_{PO}}{AUC_{PO}} = \frac{1}{F_g + (1 - F_g)\cdot\left(\frac{fm^g_1}{1+\frac{I_g}{Ki_1}} + \frac{fm^g_2}{1+\frac{I_g}{Ki_2}} + \ldots + \frac{fm^g_n}{1+\frac{I_g}{Ki_n}} + fm^g_{other}\right)}$$

Gut Contribution to DDI

$$\times \frac{1}{\left(\frac{fm^L_1}{1+\frac{I_L}{Ki_1}} + \frac{fm^L_2}{1+\frac{I_L}{Ki_2}} + \ldots + \frac{fm^L_n}{1+\frac{I_L}{Ki_n}}\right) + fm^L_{other}}$$

Liver Contribution to DDI

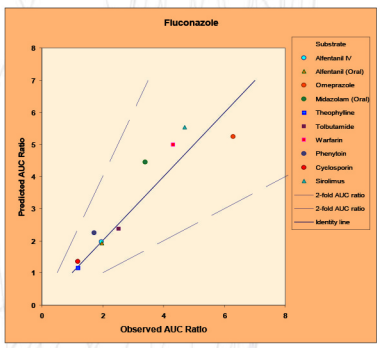
DDI predictions for Midazolam

Inhibitor	Ki [uM]	AUC Ratio Gut	AUC Ratio Liver	AUC Ratio predicted	AUC Ratio observed
Fluconazole	9.21 [12]	2.22	2	4.44	3.4 [17]
Ketoconazole	0.015 [13]	2.43	5.89	14.32	15.9 [16]
Itraconazole	0.0013 [14]	2.43	1.03	2.5	6.2 [15]

The total DDI is underpredicted for Itraconazole – this result was expected because there are significant inhibitory effects of Itraconazole metabolites on 3A4 [14] which were not considered in the current study. In line with the observed effect [11], itraconazole is predicted to nearly completely inhibit intestinal 3A4 (with Fg = 40% and predicted increase in AUC ratio due to gut = 2.43, the Fg would increase to ~ 97%).

Results and Conclusions:

- Simulated plasma concentration-time profiles for *i.v.* and *p.o.* doses for different dose levels closely matched *in vivo* data reported in literature.
- The simulated liver and gut unbound concentrations, which were used as estimates of effective inhibitor concentrations, were able to predict DDIs for all compounds.
- As previously reported for fluconazole [18], accurate simulations of various drugs' uptake by liver tissue were essential in predicting contribution of inhibition of liver metabolism to the total observed DDI.
- Similar to experimental observations for ketoconazole and itraconazole [11], the predictions show significant contribution of inhibition of intestinal metabolism to the total observed DDI.



Observed versus predicted AUC ratios for DDI interactions between fluconazole and different substrates under steady-state conditions.

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