Physiologically Based Model for Ketoconazole Disposition and Prediction of its Drug-Drug Interactions

Grazyna Fraczkiewicz†, Viera Lukacova†, Neil Parrott‡, Michael B. Bolger†, John R. Crison†, Walter S. Woltosz†, & Thierry Lave‡

†Simulations Plus, Inc., 42505 10th Street West, Lancaster, CA 93534, USA

‡F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Pharma Research, Non-Clinical Development, Non-Clinical Drug Safety, Basel Switzerland.

Objectives

Ketoconazole is a potent inhibitor of the major drug-metabolizing enzyme, CYP3A4 and, as the result of that, is involved in many drug-drug interactions. Pharmacokinetic (PK) information available for ketoconazole is limited since no intravenous human study is available to date, which probably contributes to the lack of published comprehensive PK models for this drug. The aim of our study was to predict human PK of ketoconazole and the magnitude of its drug-drug interactions (DDIs) using physiologically based pharmacokinetics (PBPK).

Methods

GastroPlus™ (Simulations Plus, Inc.) was used to build PBPK models of ketoconazole's distribution and clearance in humans from oral Cp-time profiles for 200, 400, 600 and 800 mg doses obtained from the literature[1]. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™. The program's modified Rodgers and Rowland predictive method based upon drug properties and tissue composition was used to calculate Kps for all tissues. Nonlinear clearance was fitted to oral doses with the program's PKPlus™ module using Michaelis-Menten kinetics. ADMET Predictor™ (Simulations Plus, Inc.) was used to predict human intestinal permeability for ketoconazole. DDIs were predicted using a test version of a new steady state DDI Module in GastroPlus.

Results

PBPK models for 200, 400, 600, and 800 mg ketoconazole oral doses using Kps calculated by the modified Rodgers and Rowland method, along with fitted clearance parameters that included Vmax (0.011417 mg/s) and Km (0.008 mg/L) for CYP3A4, provided a very close fit to the experimental plasma concentration-time profiles. Volume of distribution, half-life, and fraction bioavailable were predicted with high accuracy for all doses. DDI predictions (as AUC ratios with and without ketoconazole) obtained for 7 CYP3A4 substrates (alprazolam, loratidine, midazolam, nisoldipine, sirolimus, tacrolimus, and triazolam,) were mostly within 20% of the observed *in vivo* values.

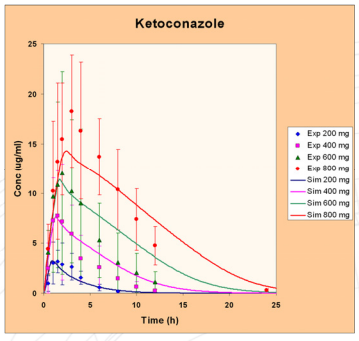

Fig 1. Experimental (dots with error bars) and GastroPlus simulated (lines) Cp-time profiles for 200, 400, 600 and 800 mg ketoconazole doses.

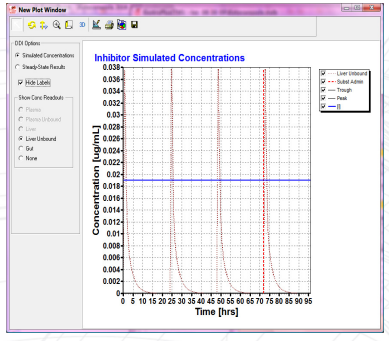

Fig 2. Simulated unbound concentrations in liver for the 200 mg Ketoconazole dose. Nisoldipine was administered on the 4th day.

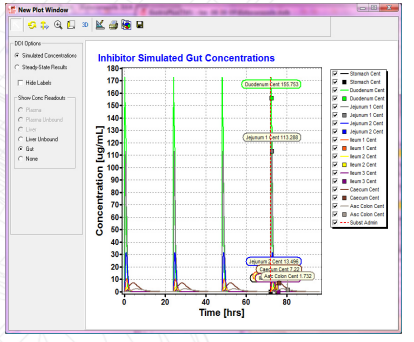

Fig 3. Ketoconazole 200 mg dose simulated gut concentration. Nisoldipine was administered on the 4th day.

Substrate	Ki [μM]	AUC Ratio Gut	AUC Ratio Liver	AUC Ratio Total	AUC Ratio Observed
Triazolam	0.006 [2] 0.023 [2]	2.08	3.78	7.88	9.16 [2]
Midazolam	0.015 [3]	2.43	5.89	14.32	15.9 [4]
Tacrolimus	0.015 [3]	1.45	1.65	2.4	2.39 [5]
Loratidine	0.015 [3]	1.245	2	2.49	3.47 [6]
Nisoldipine	0.015 [3]	7.6	3.16	24.1	25.3 [7]
Sirolimus IV	0.015 [3]	1	1.97	1.97	2.39 [8]
Sirolimus PO	0.015 [3]	2.44	3.47	8.45	10.9 [9]
Alprazolam	0.015 [3]	1.01	2.29	2.31	3.98 [5]

Fig 4. DDI predictions for ketoconazole. *In vitro* unbound Ki (0.015 μM) was used for all the compounds except for triazolam, for which well-characterized Ki values were available for two separate CYP3A4 metabolism pathways.

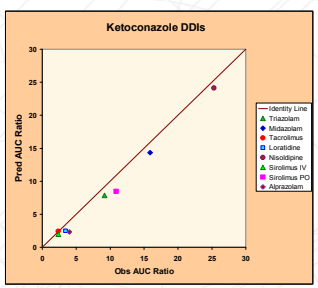

Fig 5. Observed versus predicted AUC ratios for DDI interactions between ketoconazole and different substrates under steady-state conditions.

Conclusions

*Accurate predictions of the unbound ketoconazole liver and gut concentrations were of particular importance in predicting the magnitude of its drug-drug interactions. It was the most evident in sirolimus example, for which interactions were measured for the oral and IV doses, where the contribution of gut wall CYP3A4 metabolism to the interaction with ketoconazole was greater than the liver contribution.

*Application of the steady-state inhibitor concentration [I] at the active site predicted by GastroPlus using a nonlinear kinetics model for both liver and gut CYP3A4 metabolism, together with unbound *in vitro* Ki values, provided exceptional predictions of AUC ratios, with many of them being within less than 20% different from the *in vivo* values.

References

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