Prediction of drug-drug interactions for fluconazole using PBPK – a case with concentration-dependent liver:plasma partition coefficient.

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Objectives

Fluconazole is an antifungal agent widely used in the clinical setting for the treatment of candidiasis and meningitis. It undergoes minimal metabolism and is excreted renally[1].

Fluconazole is a moderate dose-dependent inhibitor of CYP3A4, CYP2C9 and CYP2C19. Saturable hepatic binding is a major determinant of the volume of distribution of fluconazole and the main reason for its nonlinearity. The liver:plasma partition coefficient (Kp) for fluconazole was shown to be concentration-dependent and ranged from 2 to 30 in rat studies[2]. The aim of our study was to predict human pharmacokinetics of fluconazole and the magnitude of its DDIs using physiologically based pharmacokinetics (PBPK), and to test the applicability of concentration-dependent experimental liver Kps for that purpose.

Methods

GastroPlus™ (Simulations Plus, Inc.) was used to build PBPK models of fluconazole's distribution and clearance in humans using intravenous (IV) and oral Cp-time profiles for 100 mg[3,4] and 400 mg[5] doses obtained from the literature. Experimental (rat) Kps were used for drug partitioning between liver:plasma and kidney:plasma, while a modified Rodgers and Rowland predictive method based upon drug properties and tissue composition was applied to calculate Kps for all other tissues. Clearance was fitted to the IV data using the PKPlus™ module in GastroPlus. ADMET Predictor™ (Simulations Plus, Inc.) was used to predict human intestinal permeability for fluconazole. DDIs were predicted using a test version of a steady state DDI Module in GastroPlus that is currently under development.

Results

PBPK models for 100 mg and 400 mg fluconazole doses using two different concentration-related liver Kp values acquired from rat studies[2] provided a very close fit to the experimental plasma concentration-time profiles. Volume of distribution, half-life, and fraction bioavailable were also predicted with high accuracy for both doses. DDI predictions (AUC ratios) obtained for 9 substrates (alfentanil, cyclosporine, midazolam, omeprazole, phenytoin, sirolimus, theophylline, tolbutamide and warfarin) were mostly within 20% of the observed *in vivo* values.

References

1) Debruyne D. and Ryckelynck J. P., Clin. Pharmacokinet. **1993**; 24 : 10-27.
2) Ervine C. M. and Houston J. B., Pharm. Res. **1994**; 11 (7) : 961-965.
3) Yeates R. A. et al., Br. J. Clin. Pharmac. **1994**; 38 : 77-79.
4) Thorpe J. E. etal., Antimicrob. Agents and Chemother., **1990**; 34 (10) : 2032-2033.
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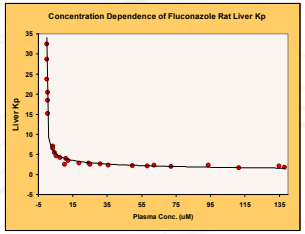
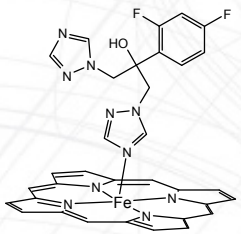
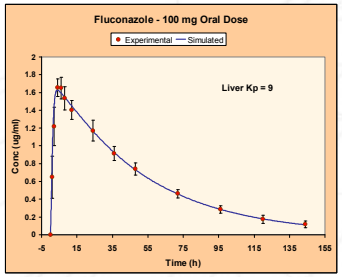


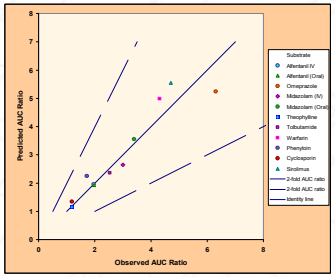
Relationship between liver Kp and plasma concentration of fluconazole in rat based on Ervine et al. data[2].



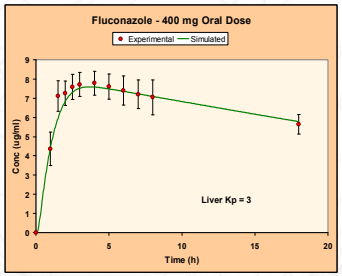
Fluconazole azole group binds to the heme group forming a covalent bond with the iron atom at the distance of 2.108-2.156 Å[6]. This reaction is responsible for saturable hepatic binding of fluconazole.



Experimental (dots) and simulated (line) Cp - time profiles for 100 mg oral dose of fluconazole.



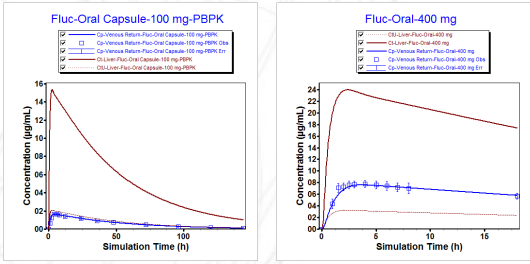
Observed versus predicted AUC ratios for DDI interactions between fluconazole and 9 substrates under steady-state conditions.



Experimental (dots) and simulated (line) Cp - time profiles for 400 mg oral dose of fluconazole.

Substrate	Metabolizing Enzyme	Relative contribution (fm) to the hepatic metabolism	Ki (uM)	Fluconazole Dose (mg)
Alfentanil	3A4	1	15	400
Omeprazole	3A4	0.4	10.7	100
Omeprazole	2C19	0.6	2	100
Midazolam	3A4	0.94	10.7	400
Theophylline	1A2	1	300	200
Tolbutamide	2C9	0.72	22.5	100
Tolbutamide	2C19	0.28	12.3	100
Warfarin	2C9	1	7.5	400
Phenytoin	2C19	0.9	22.5	200
Phenytoin	2C9	0.1	6.5	200
Cyclosporine	3A4	0.71	40	100
Sirolimus	3A4	0.85	10.7	200
Sirolimus	2C9	0.15	6.5	200

Relative CYP contribution to the hepatic metabolism, Ki values used to calculate drug-drug interactions with fluconazole, and the doses of fluconazole given to the subjects for which the interactions were reported.



Fluconazole liver concentrations for 100 mg and 400 mg PO doses.

Conclusions

- The use of concentration-dependent liver:plasma partition coefficients was essential for the accurate simulation of the nonlinear volume of distribution observed for fluconazole.
- The 100 mg and 400 mg doses represent the lower and upper bound of therapeutically applied concentrations in human, with ~3 fold difference in liver:plasma partition coefficients between the two doses. Liver Kps of 3 and 9 used in simulations of the 400 mg and 100 mg PO doses, respectively, gave the best fit to the observed data. The values of rat liver Kps observed for the equivalent fluconazole plasma concentrations were ~2.5 and ~6.5.
- Accurate prediction of the fluconazole unbound liver concentration is of particular importance in explaining and predicting its drug-drug interactions. All predicted AUC ratios were well within 2-fold of the observed values, with most of them being within 20% of the *in vivo* values.

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