Modeling Fluconazole – 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) 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 using physiologically based pharmacokinetics (PBPK) and to test the applicability of static 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 (PO) Cp-time profiles for 100 mg(3,4) and 400 mg(5) doses obtained from the literature. The models were based on human physiologies for 69 kg and 72 kg males, reflecting mean body weights of subjects in studies with 100 mg and 400 mg PO doses, respectively. Experimental liver:plasma and kidney:plasma Kps obtained from rat were used. A modified Rodgers and Rowland method based upon drug properties and tissue composition was used 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 the studied compound.

Results

PBPK models for 100 mg and 400 mg PO fluconazole doses using two different static (i.e., not time-dependent) concentration-related liver Kp values obtained 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.

References

1) Debruyne D. and Ryckelynck J. P., Clin. Pharmacokinet. **1993**; 24 : 10-27.
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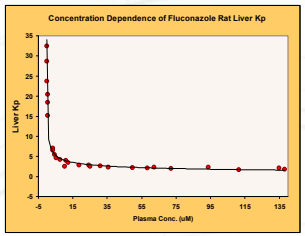
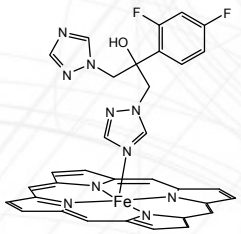
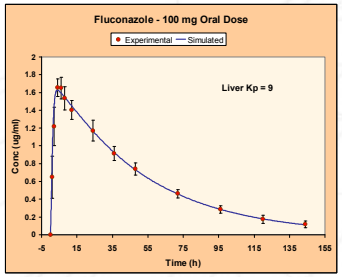
4) Thorpe J. E. etal., Antimicrob. Agents and Chemother., **1990**; 34 (10) : 2032-2033.
5) Ahonen J. et al., Eur. J. Clin. Pharmacol. **1997**; 51 : 415-419.
6) Balding P. R., J. Phys. Chem. A, **2008**; 112 (50) : 12911-12918.



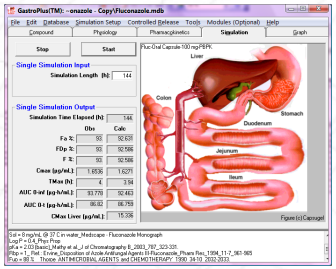
Relationship between liver Kp and plasma concentration of fluconazole in rat based on Ervine et al. data(2).



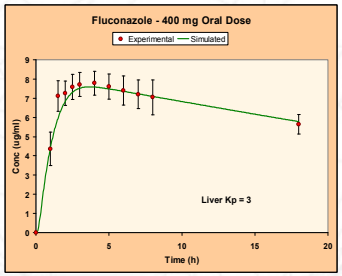
Fluconazole azole group binds to the heme group forming a covalent bond with the iron atom at the distance of 2.108-2.156 Å(6). This reaction is responsible for saturable hepatic binding of fluconazole.



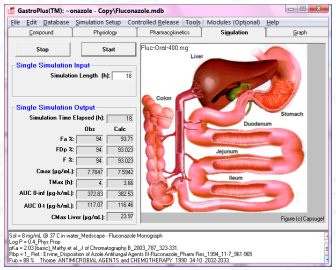
Experimental and simulated Cp - time profiles for 100 mg oral dose of fluconazole.



Experimental vs. simulated PK parameters for 100 mg PO dose of fluconazole. Simulated Vss = 51.7 L (or 0.75 L/kg) and $t_{1/2}$ = 35.8 h.



Experimental and simulated Cp - time profiles for 400 mg oral dose of fluconazole.



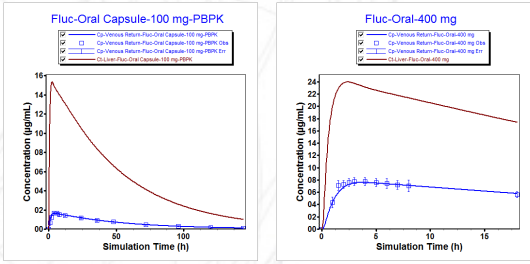
Experimental vs. simulated PK parameters for 400 mg PO dose of fluconazole. Simulated Vss = 43.7 L (0.6 L/kg) and $t_{1/2}$ = 30.3 h.

Conclusions

♦ Application of concentration-dependent liver:plasma partition coefficients was essential for the fluconazole modeling and allowed simulation of the nonlinear volume of distribution observed for this compound.

♦ 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 liver concentration is of particular importance in explaining and predicting drug-drug interactions. Although static values for liver Kps were adequate for these simulations, time-dependent, concentration-dependent Kps may be required under other conditions.



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

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