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ACCOUNTING FOR KETOCONAZOLE ABSORPTION VARIABILITY IMPROVES PREDICTION OF ITS INHIBITORY EFFECT ON MIDAZOLAM KINETICS

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PURPOSE

Several clinical studies have reported a high variability of observed Ketoconazole (KTZ) plasma concentration in humans which can be a result of variation in formulation, food and disease. This variability in KTZ exposure can affect the outcome of drug-drug interaction (DDI) studies. We aim at using modelling and simulation to assess the impact of perpetrator kinetics on the variability of the KTZ midazolam (MDZ) DDI.

Table 1: Pharmacokinetic and metabolic parameters for MDZ used in the PBPK model predictions. .

Dose	**5 mg**	**$K_{mu,1OH}$**	**µM**
		CYP3A4	**2.16**
fa	1	**CYP3A5**	**4.16**
ka	3.02 h^{-1}		
fu	0.034	**$V_{max,4OH}$**	pmol/min/pmol P450
		CYP3A4	5.2
B:P	0.55	**CYP3A5**	4.03
V	1.07 L/kg		
$V_{max,1OH}$	pmol/min/pmol P450	**$K_{mu,4OH}$**	µM
CYP3A4	5.23	**CYP3A4**	31.8
CYP3A5	19.7	**CYP3A5**	34.8

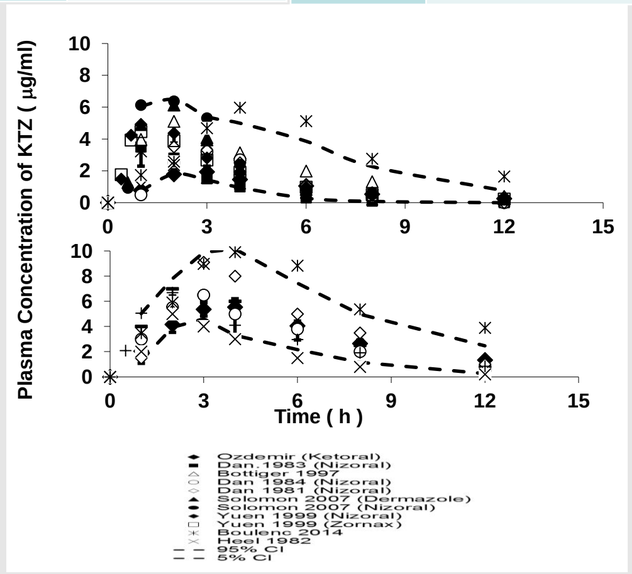

Figure 1. Mean plasma concentrations of KTZ measured after oral doses of (A) 200 and (B) 400 mg in published studies

References: Liu et al, The Impact of Dose, Dose-Staggering and the Absorption Kinetics of Ketoconazole on Inhibition of the Metabolism of Midazolam: Implications for the Evaluation of Variability in the Outcome of Drug-Drug Interaction Studies. Biopharmaceutics & Drug Disposition (Submitted)

METHOD

DDI simulations were run in Simcyp Simulator Version 12 Release 2 to replicate a clinical study where a single dose of MDZ 5mg was administered concomitantly with 100, 200 and 400mg KTZ. The simulation study used both the Simcyp library KTZ compound model (default) and an optimised KTZ model developed from the observed profiles in the DDI study. The fa and ka (1/h) for the default KTZ model order absorption model were 1 and 0.78, respectively. The Simcyp Advanced Dissolution Absorption and Metabolism model was used in the optimized model. The absorption parameters including disintegration time, supersaturation ratio and precipitation rate of KTZ were estimated from the observed data. 20 trials of the virtual subjects with the same number, age range and sex ratios as the in vivo studies were simulated.

Table 2: The parameters used in the KTZ Study Specific Kinetics model

Permeability (cm/s) ×10^{-4}	**4.95**	**Dose: 100 and 200 mg**	
Intrinsic Solubility (mg/mL)	0.0133	**Disintegration parameter (Weibull function)***	alpha×100 0.12; beta 10.52; Lag time (s) 0.5
Particle radius (µm)	10		
SAC parameters		**Supersaturation**	MSR. 11.21; PRC. ×1000 (1/h) 0.13
k_{in} (SAC) (1/h)	0		
k_{out}(SAC) (1/h)	0.0116		
V_{sac} (SAC) (L/kg)	1e-6	**Dose: 400 mg**	
Dose (mg)	**100, 200, 400**	**Disintegration parameter (Weibull function)***	alpha×100 0.15; beta 5.9
fu	0.029		
B:P	0.62		
Log $P_{o:w}$	4.04	**Supersaturation**	MSR. 14.28; PRC. (1/h) 0.01
V (L/kg)	0.345		

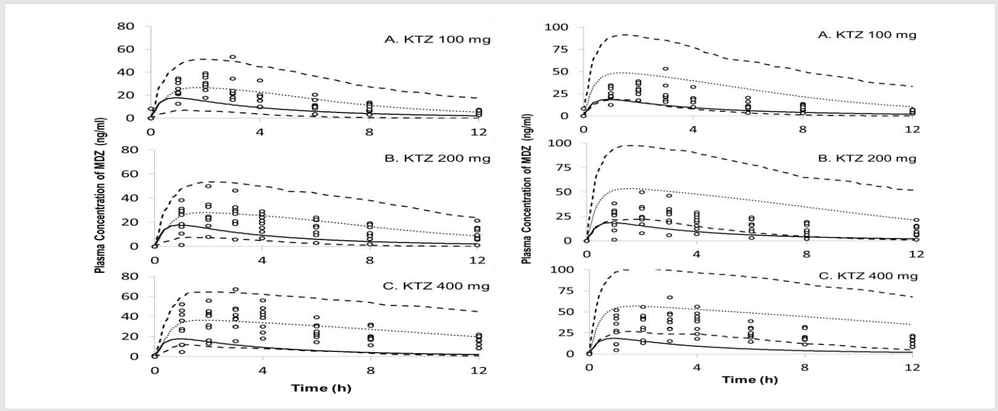

Figure 3. Predicted (SSK Model = Left panel; GLD Model = Right panel) and individual observed plasma concentrations of MDZ (5 mg dose) given at the same time as single oral doses of A. 100mg, B. 200 mg and C. 400 mg of KTZ. Mean predicted MDZ concentrations after inhibition (dotted line), mean predicted MDZ concentrations without inhibition (black line), 95% confidence limits are indicated by the break lines, and individual observed values by the circles.

RESULTS

DDI prediction accuracy is increased using the study specific kinetics (**SSK model**) KTZ model with predicted/observed AUC ratios decreasing from 2.1, 2.8 and 2.3 using the default KTZ model to 1.0, 1.1 and 1.2 with the optimised model for doses of 100, 200 and 400mg KTZ. A similar, though less marked effect was also observed for C_{max} with predicted/observed ratios decreasing from 1.6, 2.0 and 1.6 using the default KTZ model to 0.8, 1 and 0.9 with the optimised model.

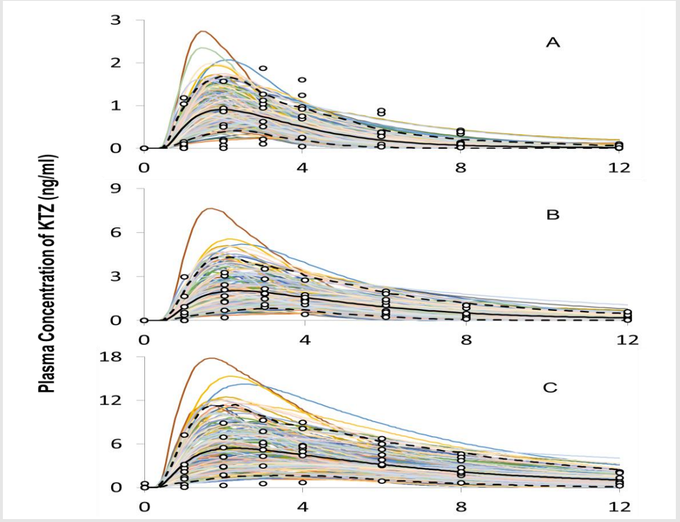

Figure 2. Predicted (SSK model) and observed plasma concentrations of KTZ after single oral doses of A. 100 mg; B. 200 mg; C. 400 mg. Predictions for individual subjects are indicated by the coloured lines; the predicted means and 95% confidence limits by the continuous black and broken lines, respectively. The individual observed data are indicated by open circles.

CONCLUSION

The results of this study show that incorporation of absorption variability of KTZ, and as a result its exposure, can improve the prediction performance for KTZ and MDZ DDI studies. It also demonstrates that the use of more advanced models helps with accounting for variation in formulation and physiological factors.

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