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Physiologically Based Pharmacokinetic Model for Voriconazole and Prediction of its Interactions with Midazolam and Alfentanil

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PURPOSE

Voriconazole (formerly known as UK-109,496), is a second-generation triazole antifungal agent widely used in the treatment of invasive fungal infections. Voriconazole is a potent competitive (reversible) and time-dependent inhibitor of CYP3A4, which metabolizes ~50% of the marketed drugs. Coadministration of CYP3A4 substrates with voriconazole is highly likely to result in clinically relevant drug-drug interactions (DDIs).

The primary route for voriconazole elimination is metabolism, mainly catalyzed by the isoenzyme CYP2C19 with minor contributions of other enzymes. Therefore, pharmacokinetics (PK) and the extent of DDIs is influenced by the CYP2C19 genotype.

OBJECTIVE

The goal of this work was to develop and validate a mechanistic absorption model (MAM) and physiologically based pharmacokinetic (PBPK) model of voriconazole that could be used for quantitative prediction of DDIs with co-administered CYP3A4 substrates.

METHODS

- A mechanistic absorption and PBPK model of voriconazole was developed in GastroPlus® 9.6 (Simulations Plus, Inc.).
- Physicochemical and biopharmaceutical inputs were either obtained from literature or predicted by ADMET Predictor™ 9.0.
- Metabolism of voriconazole by CYP2C19, CYP3A4, and FMO3 enzymes was modeled by Michaelis-Menten kinetics. Autoinhibitory effects of CYP2C19 and 3A4 were included in the model. V_{max} values were fitted to *in vivo* data. K_m and inhibition parameters are listed in **Table 1**.

Table 1: DDI model parameters.

Enzymes	K_m (µM)	IC_{50} reversible (µM)	K_i irreversible (µM)	K_{inact} (min^{-1})
CYP2C19	3.5 [1]		8*	0.11*
CYP3A4	235 [1]		2.97 [3]#	0.006*
FMO3	3400 [2]	9.3 [4]		

- *Fitted to *in vivo* data after 200 mg twice daily oral voriconazole doses for 13 days and a single 200 mg dose on day 14 in mostly Caucasian subjects (90% of subjects were CYP2C19 extensive metabolizers) [5]. #Assumed similar to non-competitive inhibition.
- The model was validated by comparing simulated and observed plasma concentration-time (Cp-time) profiles of oral voriconazole for different dosing regimen from a different study (83% extensive metabolizers) [6]. Drug-drug interactions of midazolam [7, 8] and alfentanil [9] mediated mainly by CYP3A4 inhibition were predicted through dynamic simulations using the validated midazolam (standard DDI database of GastroPlus) and alfentanil [10] PBPK models.

RESULTS

The developed PBPK model adequately captured the observed voriconazole Cp-time profile following oral administration as shown in **Figure 1**. Simulated area under the Cp-time curve from time zero to time extrapolated to infinity ($AUC_{0\text{-}inf}$) and/or maximum plasma concentration (C_{max}) following oral administration were within 0.8-1.25 of clinically observed mean data under fasted state in healthy subjects.

The predicted effects of voriconazole on midazolam and alfentanil $AUC_{0\text{-}inf}$ and/or C_{max} were in close agreement with observed values for different dosing regimens following both intravenous and oral routes of administrations of voriconazole and victim compounds (**Table 2**). Full simulated and observed Cp-time profiles for one of the studies are shown in **Figure 2**. The proposed model accurately captured higher magnitude of DDIs for high dose of voriconazole with oral administration of midazolam. These results showed that dynamic simulations adequately predicted the effect of CYP3A4 competitive and time-dependent inhibition by voriconazole on the PK of midazolam and alfentanil.

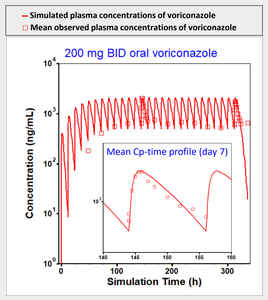
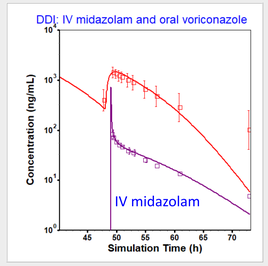


Figure 1: Experimental (points) mean [5] and simulated (red line) Cp-time profile for voriconazole after 200 mg twice daily doses of tablet for 13 days and a single 200 mg dose on day 14. The inlet shows the mean Cp-time profile in logarithmic scale for only day 7.

This simulation was run in the DDI module in GastroPlus to account for the autoinhibitory effect of voriconazole on its own metabolism mediated by CYP3A4 and CYP2C19 which allowed to explain observed Cp-time profile following oral administration of voriconazole.

Table 2: Comparison of observed and predicted fold changes in PK of midazolam and alfentanil after voriconazole treatment.

Voriconazole		Victim drugs			Observed fold change		Predicted fold change		Ref
Dose (mg)	Route	Names	Dose	Route	C_{max}	$AUC_{0\text{-}inf}$	C_{max}	$AUC_{0\text{-}inf}$	
400 bid-day 1, 200 bid-day 2	oral	Midazolam	0.05 mg/kg	IV inf		3.53		2.53	7
400 bid-day 1, 200 bid-day 2	oral	Midazolam	7.5 mg	oral	3.59	9.39	4.71	8.91	7
a single dose of 50	oral	Midazolam	3 µg	oral	1.42	1.83	2.41	2.36	8
a single dose of 400	oral	Midazolam	3 µg	oral	2.71	6.91	3.99	5.79	8
a single dose of 50	oral	Midazolam	1 µg	IV inf	0.75	0.98	1.01	1.02	8
a single dose of 400	oral	Midazolam	1 µg	IV inf	0.69	2.02	1.02	1.60	8
a single dose of 50	IV inf	Midazolam	3 µg	oral	1.03	1.13	1.07	1.07	8
a single dose of 400	IV inf	Midazolam	3 µg	oral	1.79	3.89	1.82	2.54	8
a single dose of 50	IV inf	Midazolam	1 µg	IV inf	0.72	0.96	1.00	1.02	8
a single dose of 400	IV inf	Midazolam	1 µg	IV inf	0.89	2.15	1.01	1.43	8
400 bid-day 1, 200 bid-day 2	oral	Alfentanil	20 µg/kg	IV inf		5.92		5.87	9



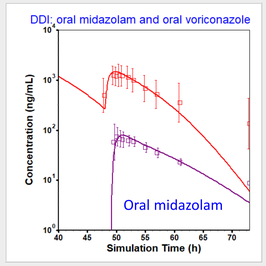


Figure 2: Experimental (points) mean [7] and simulated (lines) Cp-time profiles of voriconazole (red) and midazolam (purple) upon administrations of voriconazole (day 1: 400 mg twice daily, day 2: 200 mg twice daily and day 3: a single 200 mg dose) and a single IV (0.05 mg/kg) or oral (7.5 mg) dose of midazolam (1 h after the last dose of voriconazole) on day 3.

Simulated plasma concentrations of voriconazole
Mean observed plasma concentrations of voriconazole
Mean observed plasma concentrations of midazolam
Simulated plasma concentrations of midazolam

CONCLUSIONS

The work demonstrates the utility of the MAM/PBPK approach to predict DDIs. The mechanistic absorption and PK of voriconazole were adequately described using physiological and drug-specific parameters along with the enzyme kinetics. The model was successfully applied to capture the gut and liver metabolism of voriconazole mainly by CYP2C19.

The model successfully captured the dose and time-dependent PK of voriconazole when irreversible inhibition due to enzyme deactivation of CYP3A4 and CYP2C19 by voriconazole was included.

The proposed model adequately predicted its DDIs with midazolam and alfentanil, -primarily related to voriconazole competitive and time-dependent inhibition of CYP3A4-mediated metabolism. This model can be utilized for quantitative prediction of DDIs effect of voriconazole on other CYP3A4 substrates.

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