A Physiologically-based Pharmacokinetic Model for Voriconazole Explores Differences in Pharmacokinetics between Adults and Children

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Abstract

Objectives: Characterize voriconazole pharmacokinetics (PK), including potential influence of intestinal, first-pass metabolism following oral dosing, in adults and pediatrics using physiologically-based pharmacokinetic (PBPK) modeling.

Methods: A reported voriconazole PBPK model without (ZT) and with intestinal clearance in pediatrics (ZT_{Gu}) [**1**] was implemented in the open-source R package *mrgsolve* [**2**]. The most influential ZT parameters were investigated through sensitivity analyses, followed by optimization (*optim* function). Improvement of previous overprediction following adult oral dosing was investigated with inclusion of intestinal clearance (Cl_{Gu}). Cl_{Gu} was calculated from hepatic clearance as the relative difference in expression of voriconazole metabolizing enzymes in liver and intestine ($Cl_{Gu,calc}$).

Results: Sensitivity analyses highlighted muscle:plasma partition coefficient and blood:plasma concentration ratio as the two most influential parameters. Optimization of these parameters yielded improved model predictions for IV infusion dosing that were comparable to ZT predictions; RMSE = 0.49 and 0.38 compared with 0.55 and 0.34 from ZT, for adults and pediatrics, respectively. Cl_{Gu} added to adults (and pediatrics) provided notable improvement in predictions of adult oral dosing: $AUC_{ss,0-12}/C_{max}$ were 12.17/2.01 (observed), and 21.05/2.24 and 17.1/2.02 mg.h.L^{-1}/mg.L^{-1} from ZT and Cl_{Gu} models, respectively. Estimated Cl_{Gu} was different between adults and pediatrics. For example, estimated Cl_{Gu} in a 19 kg, 5 yo pediatric patient was 0.22 mL/min/kg, or about 3-fold that of a 73 kg, 30 yo adult patient (0.08 mL/min/kg).

Conclusions: A voriconazole PBPK model translated using *mrgsolve*, with further development and optimization, notably improved predictions of IV and oral voriconazole PK in pediatrics and adults. The model suggested a difference between oral voriconazole PK in adults and children may be attributed to the magnitude of intestinal metabolism between the populations and this difference suggests the need for a higher oral dose for pediatrics (6-8 mg/kg) compared to adults (3 mg/kg) to achieve similar exposure.

Methods

Voriconale PBPK Model Structure and Workflow

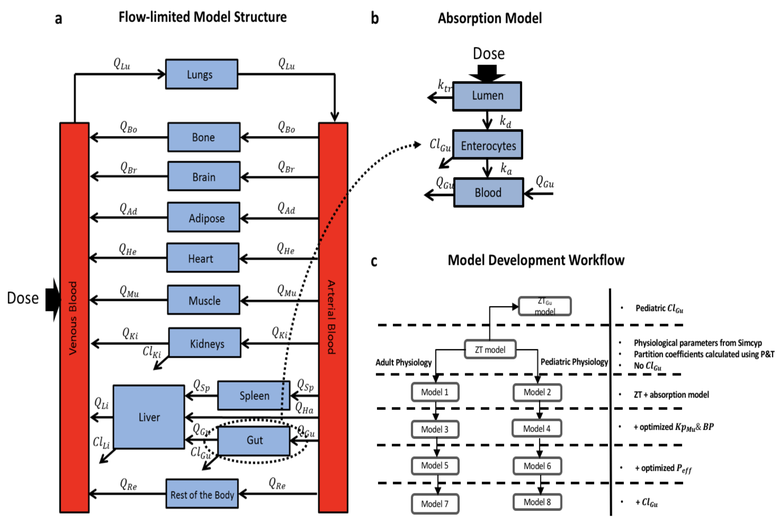

Fig.1 (a) Flow-limited full PBPK model structure. (b) Proposed absorption model structure. (c) Model development workflow. Q represents the blood flows and Cl represents clearance while the subscripts Ad, Bo, Br, Gu, He, Ki, Li, Lu, Mu, Sp and Re refer to adipose, bone, brain, gut, heart, kidneys, liver, lungs, muscle, spleen and rest of the body compartments, respectively. Ha is the hepatic artery. k_{tr}, k_d and k_a are the first-order absorption rate constants for intestinal transit, disappearance from intestinal lumen and absorption into the systemic circulation. ZT refers to the previously published Zane and Thakker PBPK model [**1**], ZT_{Gu} refers to the Zane and Thakker model with integrated pediatric intestinal clearance, P&T refers to the Poulin and Theil method [**3**] in calculating partition coefficients. P_{eff} is the effective permeability.

General Model Equation

$$\frac{dA_T}{dt} = Q_T(C_A - \frac{C_T}{Kp_T}) - Cl_T.C_{T,free}$$

where A_T and C_T are the amount and concentration of drug in the tissue T, C_A is the drug concentration in the arterial blood compartment, Kp_T is the tissue:plasma partition coefficient, Cl_T is the tissue clearance and $C_{T,free}$ is the free drug concentration in tissue.

Model Validation

Model predictions were compared to observed data via point-by-point $RMSE$ and by comparing PK parameters $AUC_{ss,0-12}$, C_{max} and t_{max}.

Results: Estimation Model Comparisons

Model Predictions Under Initial Assumptions

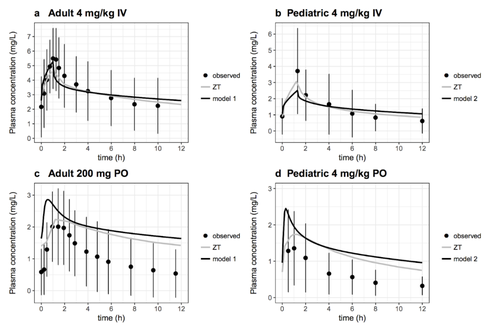

Fig.2 Plasma concentration-time profiles for 4 mg/kg IV infusion dosing for adults (a) and children (b) and 200 mg and 4 mg/kg oral dosing for adults (c) and children (d). The plots show the observed data (black dots), ZT predictions (grey lines) and the corresponding predictions from models 1&2 (black lines). Error Bars represent standard deviation.

Sensitivity Analysis to Detect Most Influential Parameters

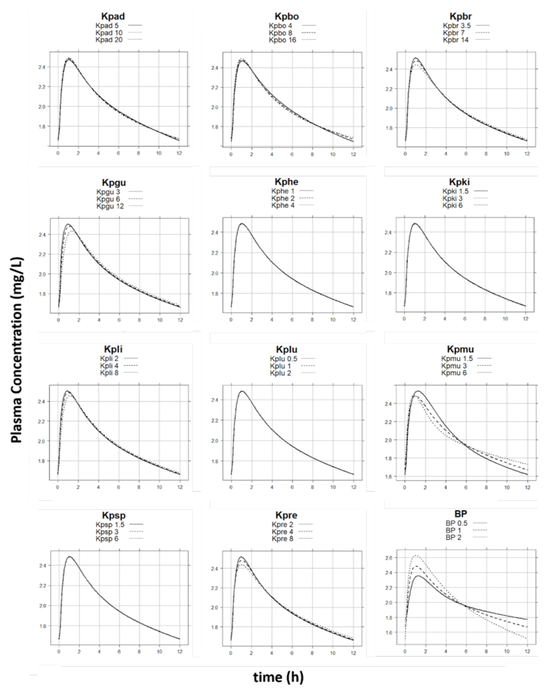

Fig.3 The analyses were done on the 200 mg oral adult dosing model with three different values for each parameter; the approximated predicted value by Poulin and Theil method and 50 and 200% of these predicted values. Kp represents the tissue:plasma partition coefficient with the same subscripts used in Fig. 1. BP is the blood:plasma concentration ratio. Results indicated that Kp_{Mu} and BP are the most influential parameters.

Optimization of Most Influential Parameters

Table 1 Univariate and bivariate optimization of most influential parameters.

Parameter	Model 1			Model 3			ZT
	Value	AIC	$RMSE$	Value (95% CI)	AIC	$RMSE$	$RMSE$
Kp_{Mu}	2.9	-6.6	0.7	0.8 (0.1-5.3)	-10.5	0.5	0.6
BP	1			1.2 (0.4-3.3)			
σ^2	-			0.016 (0.008-0.035)			

σ^2 is the variance.

Model Predictions with Optimized Parameters and Intestinal Clearance

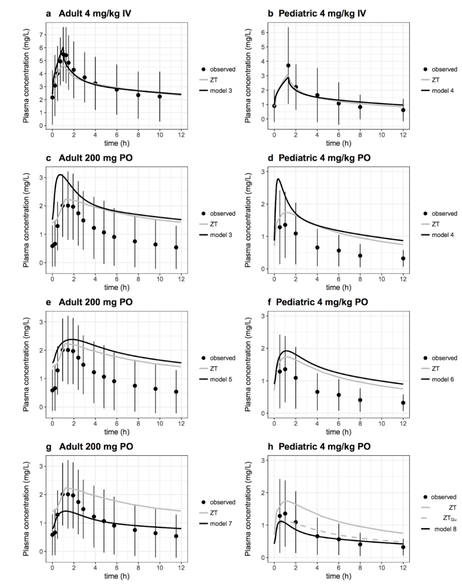

Fig.4 (a), (b), (c) and (d) are the same plots from Fig. 2a, b, c and d except with models 3&4 (optimized Kp_{Mu} and BP as described in Fig. 1c). (e) and (f) are the same as (c) and (d) but using optimized P_{eff} (models 5&6). (g) and (h) are the same as (e) and (f) but incorporating the additional intestinal clearance (models 7&8) for adults (g) and children (h). Black dots represent observed data and grey lines represent the corresponding ZT predictions. Error bars represent standard deviations.

Comparing PK Parameters

Table 2 PK parameters following IV infusion dosing.

Parameter	Adult 4 mg/kg			Pediatric 4 mg/kg		
	Observed	ZT	Model 3	Observed	ZT	Model 4
$AUC_{ss,0-12}$ (mg.h/L)	32.1	36.6	37.9	16.5	16.8	17.4
C_{max} (mg/L)	5.5	4.6	6	3.7	3.1	2.9
t_{max} (h)	1	1	1	1	1	1
$RMSE$	-	0.6	0.5	-	0.3	0.4

Table 3 PK parameters following oral dosing.

Parameter	Adult 200 mg				Pediatric 4 mg/kg			
	Observed	ZT	Model 7	Base Model 1	Observed	ZT_{Gu}	Model 8	Base Model 2
$AUC_{ss,0-12}$ (mg.h/L)	12.2	21.1	12.4	17.1	7.7	8.9	7.6	8.6
C_{max} (mg/L)	2	2.2	1.4	2.1	1.4	1.1	1.1	1.2
t_{max} (h)	1	1	1	1	1	1	1	1
RMSE	-	0.7	0.4	0.5	-	0.2	0.2	0.1

Comparing Adult and Pediatric Exposures Following Different Oral Doses

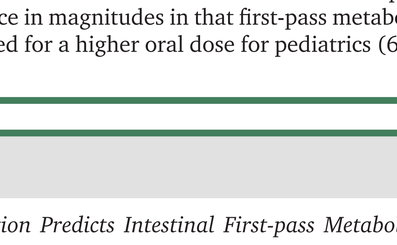

Fig.5 Comparing the adult steady state exposure after an oral standard dose of 200 mg to the pediatric steady state exposures after 4, 6, 8 and 10 mg/kg doses. Intestinal clearances were included in simulations. Black dots are observed data and error bars are standard deviations. The adult standard dose matches a pediatric dosing that falls between 6 and 8 mg/kg.

Conclusion

- A flow-limited PBPK model of the anti-fungal voriconazole was developed in the open-source freely available R package *mrgsolve* and the predictions given were comparable to the observed data and to the predictions of the previously published ZT model.
- The flexibility of *mrgsolve* allowed for further model development through sensitivity analyses followed by parameter optimization. This process resulted in a reduction in prediction errors and more precise predictions than those previously reported.
- A detailed absorption model was implemented to describe the mechanistic factors affecting voriconazole absorption as drug permeability and intestinal clearance.
- The model suggested the involvement of an additional intestinal first-pass metabolism in both adults and children and that the discrepancy in voriconazole PK between these populations following oral administration could be attributed to the difference in magnitudes in that first-pass metabolism pathway where the pediatric intestinal clearance is about 3-fold that of adults. This difference suggests the need for a higher oral dose for pediatrics (6-8 mg/kg) compared to adults (3 mg/kg) to achieve similar exposure.

References

[1] Zane NR, Thakker DR *A Physiologically Based Pharmacokinetic Model for Voriconazole Disposition Predicts Intestinal First-pass Metabolism in Children* Clin Pharmacokinet. 2014;53: 1171-1182.

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