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 (ZTcL) [1] was implemented in the open-source R package mrsvolve [2]. The most influential ZT parameters were investigated through sensitivity analyses, followed by optimization (optim function). Improvement of previous over-prediction following adult oral dosing was investigated with inclusion of intestinal clearance (Clint). Clint was calculated from hepatic clearance as the relative difference in expression of voriconazole metabolizing enzymes in liver and intestine (ClL,ClInt).

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. Clint added to adults (and pediatrics) provided notable improvement in predictions of adult oral dosing: AUC from ZT was different between adults and ZTcL was different between adults and ZTcL was different between adults and pediatrics. For example, estimated Clint 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 mrsvolve, 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

Voriconazole 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 flow and Cl represents clearance while the subscripts Al, Br, Br, Gu, Ho, He, Ke, Li, Lu, Mu, Sp and Bu refer to adipose, bone, brain, gut, kidneys, liver, lungs, muscle, spleen and rest of the body compartments, respectively. He is the hepatic artery. k4, k5, and k6 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]. ZTL refers to the Zane and Thakker model with integrated intestinal absorption. BP refers to the Poulin and Theil method [3] in calculating partition coefficients. PBP is the effective permeability.

General Model Equation

\[
\frac{dA}{dt} = Q(T_{in} - T_{out}) - Cl_{int} C_{int} T_{int}
\]

where \(A\) and \(C\) are the amount and concentration of drug in the tissue, \(T_{in}\) is the drug concentration in the arterial blood compartment, \(T_{out}\) is the tissue:plasma partition coefficient, \(C_{int}\) is the tissue clearance and \(C_{int}\) 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/Clint, Cmax, t1/2, and AUC).

Conclusion

• A flow-limited PBPK model of the anti-fungal voriconazole was developed in the open-source freely available R package mrsvolve and the predictions given were comparable to the observed data and to the predictions of the previously published ZT model.
• The flexibility of mrsvolve 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