A Physiologically Based Pharmacokinetic Model Incorporating Extrahepatic Metabolism Explains Voriconazole Pediatric Bioavailability Differences
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Introduction
Voriconazole, a potent antifungal used for life-threatening infections, is cleared predominantly via oxidative metabolism by cytochrome P450 (CYP) 34A, CYP2C19, and flavin containing monoxygenase (FMO). Its clearance is 3-fold higher & oral bioavailability is approximately half in children compared to adults. The difference in the metabolism of voriconazole by liver microsomes from children forms voriconazole N-oxide, the major circulating metabolite of voriconazole, at approximately 3X the rate in adults, reflecting the observed differences in voriconazole disposition between adults and children. The central hypotheses are that (i) age-dependent changes in the pattern and extent of expression in CYP & FMO enzymes play a pivotal role in determining the clearance and exposure of voriconazole in the pediatric population and (ii) clearance and bioavailability of drugs cleared predominantly by oxidative metabolism can be predicted in children using a physiologically-based pharmacokinetic (PBPK) model based on relevant in vitro metabolism data. The overall goal is to develop experimental & modeling approaches to predict pharmacokinetic (PK) for the purpose of developing safe and effective dosing regimens in children with life-threatening diseases. The approach involves relating clinical PK behavior of metabolically cleared drugs to their in vitro metabolism in relevant systems, and developing a PBPK model based on in vitro data to predict PK in target pediatric populations.

Materials and Methods

Chemicals, Reagents & Metabolic Assays
Frozen tissues from adults & children were obtained from Comparative Human Tissue Network (Columbus, OH) under an approved UNC-Chapel Hill IRB. Normal liver tissues, free of disease, were snap frozen within 6 hours post mortem from 10 adults and 10 donors aged between 2 to 8 years old and adults donors aged >18 years old. Hepatic in vitro PK parameters, $V_{max}$ and $K_{m}$ for voriconazole metabolism were derived from these adult and pediatric tissue donors.

Model Structure
Model development employed Simcyp software (version 12.1; Certara). Simulated outputs were created from healthy volunteer and pediatric population simulators and included 100 patients (10 trials with 10 patients in each trial). Physiological characteristics, such as body weight, cardiac output, organ flows and volumes, were predicted for each population applying Method 1 (Paulin and Thal). Physiochemical properties, generated intrinsic elimination, absorption and distribution parameters of voriconazole are listed in Table 1. These input parameters were combined into a full PBPK model utilizing whole organ metabolic clearance. Trial design and dosing was based on published clinical trials as represented in Table 2.3,4 Simulation output included concentration versus time data as well as pertinent PK parameters.

Model Validation
Simulations yielded PK parameters which were compared against published values and were deemed acceptable if they were within 30%-30% of the published geometric mean. Visual predictive checks were employed to validate models. Visual predictive checks with observed values of the simulated concentration 2.5% confidence intervals were employed to validate models.

Results

Figure 2: Semi-logarithmic Plots of Adult 4mg/kg IV & 200mg Oral Overlays

Figure 3: Semi-logarithmic Plots of the Pediatric 4- and 6mg/kg IV Intusion Overlays

Figure 5: Semi-logarithmic Plots of Pediatric 6mg/kg Oral Overlays

Conclusions and Discussion

1. The PBPK model provided a sound initial base model for voriconazole behavior in humans, with the majority of calculated PK parameters agreeing well with clinical observations.

2. Unexpectedly, predicted oral bioavailability of voriconazole in adults was similar to the observed value but was over-predicted in children by nearly 2-fold when intestinal metabolism was not included in the model.

3. However, pediatric bioavailability was within range of published values when intestinal first-pass metabolism was included in the model, suggesting extrahepatic first-pass metabolism of voriconazole in children compared to adults.

4. Further studies are planned to investigate the in vitro metabolism of voriconazole using microsomes prepared from pediatric intestinal tissues.

References


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