Voriconazole, a potent antifungal agent used for life-threatening infections, is cleared predominantly via oxidative metabolism by cytochrome P450 (CYP) 3A4, CYP2C19, and flavin containing monooxygenase (FMO). Its clearance is 3-fold higher and oral bioavailability is approximately 50% in children compared to adults. In vitro oxidative metabolism of voriconazole by liver microsomes from children Voriconazole N-oxide, the major circulating metabolite of voriconazole, at approximately 3X the rate in adults, which reflects the observed differences in voriconazole disposition between adults and children. The aim of this study is to use in vitro voriconazole metabolism data to develop a physiologically based pharmacokinetic (PBPK) model that describes the time course of voriconazole plasma concentrations and its disposition.

Materials and Methods

Frozen tissues from adults and children were obtained from the 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 children donors aged between 2 to 8 years old and adult donors aged >18 years old. Characterization & metabolic assays were performed as previously described.1

Physiologic Characteristics & Model Structure

Tissue-plasma partition coefficients (Ka), age-dependent physiologic volumes, and perfusion rates were generated utilizing GastroPlus (version 7.0, Simulations Plus, Lancaster, CA). Children's target organs were generated utilizing Poulin & Theil (Homogenous) prediction method. Physiochemical & elimination properties are shown in Table 1. Berkeley Madonna (version 8.3.18; University of California at Berkeley, Berkeley, CA) was utilized to run simulations. In order to simulate differences in in vitro exposure due to changes in physiologic characteristics, children were split into groups of 2-, 5-, 8- & 10 year olds. Adult physiologic characteristics were used for humans aged 35 years old, which has been the reference age used in previously published review articles. The Population Estimates for Age-Related Physiology yielded average body weight, cardiac output, tissue volumes and perfusion rates based on gender, age, and American heritage.

Male & female characteristics were averaged. Volumes of each organ and the "other" compartment were combined to equal the average body weight. Flow rates to each organ were converted to a fraction of the total cardiac output and then compared against published pediatric fractional flow rates.2,3 The sum of all the flow rates totaled the cardiac output. A perfusion limited model (Figure 1) was utilized for an initial model, with compartments determining distribution in human tissues based on published data. The "other" compartment grouped tissues not specified in the model for mass balance.

Figure 1. Model Structure

Pharmacokinetic (PK) Analysis

In order to assess differences between age groups, blood concentration simulations were generated for a single IV infusion dose of 7- and 6 mg/kg in children and adults, respectively. Next, determination of model linearity was made for 3-6 mg/kg doses in children and adults. Finally, clinically effective doses, based on previously published clinical trials, were used for single IV infusion, multiple IV infusion and multiple oral dosing simulations (Table 2).4 The output was analyzed using non-compartmental analysis with Phoenix WinNonlin (version 6.2, Pharsight Mountain View, CA). Final PK parameters included AUCC0-t, AUCC0-t/V, Cn, Teq, Vc, and bioavailability (F) using the linear pharmacokinetic method. Lastly, in order to determine bioavailability for each age group, the area under the curve values from the multiple oral and infusions were used.

Model Validation

A dosing regimen was performed to examine and validate the variation in the generated blood concentrations model output corresponding to the input parameters. Sensitivity coefficients are reported as log-normalized values. Relevant metabolic and dosing parameters, including Vmax, Km, body weight & renal clearance, were included in the analysis.

Table 2. Dosing Regimens of Voriconazole

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single IV Dose</td>
<td>6 mg/kg</td>
<td>7 mg/kg</td>
</tr>
<tr>
<td>Multiple IV Dose</td>
<td>4 mg/ml q3h x 74 h</td>
<td>7 mg/ml q2h x 74 h</td>
</tr>
</tbody>
</table>

Voriconazole PK parameters in children and adults with increasing concentrations, with and without a bolus dose of 2 mg/kg. All simulations were performed with non-compartmental pharmacokinetics.

Table 3: Pharmacokinetic Parameters in Children vs Adults with Increasing Doses of Voriconazole

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>AUCC0-t</th>
<th>AUCC0-t/V</th>
<th>Teq</th>
<th>Vc</th>
<th>F</th>
<th>Vmax</th>
<th>Km</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>519</td>
<td>519/1</td>
<td>19.1</td>
<td>212</td>
<td>0.34</td>
<td>188</td>
<td>1.82</td>
</tr>
<tr>
<td>4</td>
<td>722</td>
<td>722/1</td>
<td>22.6</td>
<td>333</td>
<td>0.37</td>
<td>408</td>
<td>1.53</td>
</tr>
<tr>
<td>6</td>
<td>925</td>
<td>925/1</td>
<td>26.3</td>
<td>434</td>
<td>0.41</td>
<td>615</td>
<td>1.48</td>
</tr>
</tbody>
</table>

Figure 3: Semi-logarithmic Plots of Blood Concentration vs Time for Single IV Infusion

Figure 4: Semi-logarithmic Plots of Blood Concentration vs Time for Multiple IV & Oral Dosing of Voriconazole

Figure 5: Semi-logarithmic Plots of Blood Concentration vs Time for Multiple IV Infusions

Figure 6: Normalized Sensitivity Analysis

Normalized sensitivity coefficients of Vmax, renal clearance (Cl), renal body weight (BW), and the first-order absorption constant (Ks) for AUC during IV infusions and oral dosing of voriconazole stratified by age.

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, calculated oral bioavailability in adults was similar to the observed value but was over-predicted in children by nearly 2-fold.

3. Since the model incorporated only hepatic and renal clearance as routes of elimination, the results suggest that voriconazole undergoes intestinal first-pass metabolism in children but not in adults.

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

References


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A Physiologically Based Pharmacokinetic Model of Voriconazole Disposition in Children Suggests Extrathoracic First-Pass Metabolism

Nicole R. Zane1, Garrett R. Ainslie2, Mary F. Paine3, and Dhiren R. Thakker1

1Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, and 2Curriculum in Toxicology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599.