POPULATION PHARMACOKINETICS OF FLUCONAZOLE IN EXTREMELY LOW BIRTH WEIGHT INFANTS

Jeremiah D Momper, PharmD, PhD¹, Edmund V Capparelli, PharmD¹, Kelly C Wade, MD, PhD², Girija Natarajan, MD³, Jamie Gao⁴, Matt Laughon, MD, MPH⁵, P Brian Smith, MD, MPH⁴, and Daniel K Benjamin Jr, MD, PhD⁴

1. University of California, San Diego, La Jolla, CA
2. Children's Hospital of Philadelphia, Philadelphia, PA
3. Wayne State University, Detroit, MI
4. Duke University, Durham, NC,
5. University of North Carolina, Chapel Hill, NC
DISCLOSURE STATEMENT

JEREMIAH MOMPER (Presenter)

Dr. Momper has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

<table>
<thead>
<tr>
<th>Affiliation / Financial Interest</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant</td>
<td>Omnitura Therapeutics, Epocrates, Genyous Biomed, Athenahealth</td>
</tr>
<tr>
<td>Ownership interest</td>
<td>Illumina</td>
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Background

- Knowledge of fluconazole pharmacokinetics (PK) is necessary to determine optimal dosing that takes into consideration the rapid maturation in extremely premature infants.
- The objective of this study was to characterize the population PK and dosing requirements of fluconazole in infants <750 g birth weight.
Multi-center, randomized, placebo-controlled trial that evaluated the efficacy and safety of fluconazole in premature infants weighing < 750 g at birth

- Infants received IV or oral fluconazole 6 mg/kg twice weekly for up to 42 days
- Plasma fluconazole concentrations from scheduled and scavenged samples were determined using a validated LC-MS/MS assay

Methods: PK Sampling

**Scheduled PK samples** collected according to 1 of 8 sampling schemes with 3 samples taken around doses 3, 5, 7 or 9 and the final dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of life</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>18</td>
<td>22</td>
<td>25</td>
<td>29</td>
<td>32</td>
<td>36</td>
<td>39</td>
</tr>
</tbody>
</table>

PK sampling Group

1-2 3-4 5-6 7-8

PK sampling scheme*

**Scavenged PK samples** were also collected according to a preferred collection schedule.
Methods: Population PK Analysis

• Concentration-time data were analyzed with nonlinear mixed-effect modeling using NONMEM version 7.2.
• Clearance was scaled by allometric weight ($WT^{0.75}$), and volume of distribution was scaled by weight ($WT^{1.0}$) prior to evaluation of potential covariates.
• Continuous covariates evaluated were PNA, GA, PMA, serum creatinine, and albumin.
• Categorical covariates evaluated were race and ethnicity, intubation status, and birth by Caesarean section.
• Final PK model was used to perform Monte Carlo simulations with a pharmacodynamic target trough concentration of 2 µg/mL.
## Demographic and Clinical Data at First PK Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal age (days)</td>
<td>17 (10 – 25)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>25 (24 – 26)</td>
</tr>
<tr>
<td>Postmenstrual age (weeks)</td>
<td>27.4 (26.2 – 29.1)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.90 (0.6 – 1.2)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.7 (2.2 – 3.1)</td>
</tr>
</tbody>
</table>
Fluconazole Concentrations: Measured vs. Predicted from the Final PK Model

- Scavenged
- Scheduled
# Key Steps in Population PK Analysis

<table>
<thead>
<tr>
<th>Model description</th>
<th>Population model</th>
<th>Objective function value (OFV)</th>
<th>Change in OFV from base model</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (base model)</td>
<td>( CL = \theta_{CL} \cdot (WT)^{0.75} )</td>
<td>9624</td>
<td>---</td>
</tr>
<tr>
<td>PNA</td>
<td>( CL = \theta_{CL} \cdot (WT)^{0.75} \cdot (PNA/25) \theta_{CL-PNA} )</td>
<td>9492</td>
<td>-132</td>
</tr>
<tr>
<td>GA</td>
<td>( CL = \theta_{CL} \cdot (WT)^{0.75} \cdot (GA/25) \theta_{CL-GA} )</td>
<td>9599</td>
<td>-25</td>
</tr>
<tr>
<td>PMA</td>
<td>( CL = \theta_{CL} \cdot (WT)^{0.75} \cdot (PMA/28) \theta_{CL-PMA} )</td>
<td>9450</td>
<td>-174</td>
</tr>
<tr>
<td>SCR</td>
<td>( CL = \theta_{CL} \cdot (WT)^{0.75} \cdot (SCR/0.8) \theta_{CL-SCR} )</td>
<td>9405</td>
<td>-219</td>
</tr>
<tr>
<td>CSCT</td>
<td>( CL = \theta_{CL} \cdot (WT)^{0.75} \cdot \theta_{CL-CSCT}^{\theta_{CSCT}} )</td>
<td>9617</td>
<td>-7</td>
</tr>
<tr>
<td>V (base model)</td>
<td>( V = \theta_v \cdot (WT)^{1.0} )</td>
<td>9624</td>
<td>---</td>
</tr>
<tr>
<td>PMA</td>
<td>( V = \theta_v \cdot (WT)^{1.0} \cdot (PMA/28) \theta_v-PMA )</td>
<td>9620</td>
<td>-4</td>
</tr>
<tr>
<td>SCR</td>
<td>( V = \theta_v \cdot (WT)^{1.0} \cdot (SCR/0.8) \theta_v-SCR )</td>
<td>9600</td>
<td>-24</td>
</tr>
</tbody>
</table>

\( CL \), clearance; \( V \), volume of distribution; \( PNA \), postnatal age; \( GA \), gestational age; \( PMA \), postmenstrual age; \( SCR \), serum creatinine; \( CSCT \), birth by Caesarean section
Fluconazole Clearance is Correlated with Serum Creatinine and Postmenstrual Age
CL increases with PNA: Potential for under-dosing at older ages

PNA is correlated with SCR and is not a significant independent covariate for CL
### Fluconazole Final Population PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Point Estimate</th>
<th>SEE</th>
<th>2.5%</th>
<th>Median</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>(\theta_V)</td>
<td>1.00</td>
<td>0.0378</td>
<td>0.93</td>
<td>1.00</td>
<td>1.08</td>
</tr>
<tr>
<td>CL</td>
<td>(\theta_{CL})</td>
<td>0.0127</td>
<td>0.00033</td>
<td>0.0120</td>
<td>0.0127</td>
<td>0.0133</td>
</tr>
<tr>
<td>F1</td>
<td>(\theta_{F1})</td>
<td>1.00</td>
<td>0.065</td>
<td>0.86</td>
<td>1.00</td>
<td>1.13</td>
</tr>
<tr>
<td>KA</td>
<td>(\theta_{KA})</td>
<td>0.96</td>
<td>0.25</td>
<td>0.52</td>
<td>0.96</td>
<td>1.81</td>
</tr>
<tr>
<td>SCR</td>
<td>(\theta_{SCR})</td>
<td>-0.410</td>
<td>0.0498</td>
<td>-0.53</td>
<td>-0.41</td>
<td>-0.32</td>
</tr>
<tr>
<td>PMA</td>
<td>(\theta_{PMA})</td>
<td>2.05</td>
<td>0.35</td>
<td>1.23</td>
<td>2.05</td>
<td>2.62</td>
</tr>
</tbody>
</table>

\[V \ (L) = \theta_V \times \text{WTKG}\]
\[CL \ (L/h) = \theta_{CL} \times \text{WTKG}^{0.75} \times \left(\frac{\text{SCR}}{0.8}\right)^{\theta_{SCR}} \times \left(\frac{\text{PMA}}{28}\right)^{\theta_{PMA}}\]
\[F1 \ (%) = \theta_{F1}\]
\[KA \ (1/h) = \theta_{KA}\]
Monte Carlo simulations demonstrate that fluconazole dosed at 6 mg/kg twice weekly results in 89.9% of concentrations above the pharmacodynamic target of 2 µg/mL.
Conclusions

• We successfully characterized the PK of fluconazole using population PK techniques with data across 6 weeks of therapy.
• Serum creatinine best predicts developmental changes in fluconazole clearance.
• A twice-weekly dose of 6 mg/kg given orally or intravenously achieves appropriate plasma concentrations for *Candida* prophylaxis in infants <750 g birth weight.
• Scavenged PK sampling is a minimal-risk approach that will facilitate drug studies in difficult populations.