Population Pharmacokinetics of Levofloxacin in Children Treated for, or Exposed to, Multidrug-Resistant Tuberculosis

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Levofloxacin

- Synthetic broad-spectrum fluoroquinolone, active vs. TB
- Currently second-line therapy for active TB disease
- In children, use limited to serious infections (e.g., anthrax) or drug resistant pathogens (due to concerns about cartilage damage in some juvenile animal models)

**Pharmacokinetics**

- Absorption: rapid and complete; Bioavailability ~ 99%
- Distribution: 74-112 L; Protein binding: 24-38%
- Metabolism: minimal
- Elimination: largely excreted unchanged in urine (~ 80%)

Methods

Dataset

- 50 children (1-15 years) treated for or exposed to multi-drug resistant tuberculosis
  - Federated States of Micronesia (FSM, island of Chuuk) and
  - Republic of Marshall Islands (RMI, city of Majuro)
- Plasma samples were taken after ≥ 6 weeks of DOT
- Dose varied between 5-20 mg/kg/day
- Plasma samples were taken at 1, 2, and 6 hours post-dose, and for subjects in the Republic of Marshall Islands, a 0 hour time point collected too
Methods

- Software
  - Noncompartmental analysis performed in WinNonlin
  - Population PK analysis performed in NONMEM 7.2 (FOCE w/ interaction, SAEM)
  - NONMEM execution and run management in Pirana
  - Prediction corrected visual predictive checks (pcVPC) and bootstrapping using Perl-speaks-NONMEM (PsN)
  - Covariates tested using GAM in Xpose R package
Methods

- Population analyses
  - One- and two-compartment body model tested
  - Model development guided by GOF plots, VPCs, plausibility of parameter estimates, and shrinkage and objective function values
  - For nested models, a p-value of 0.05 was used
  - Inter-individual variability was estimated for all parameters using an exponential variance model
  - The final population PK model was used to perform exposure simulations and evaluate target attainment
Methods

A fixed exponent allometric model was applied

\[
\frac{CL}{F} = CL_{std} \times \left( \frac{WT_i}{70 \text{kg}} \right)^{0.75}
\]

\[
\frac{V}{F} = V_{std} \times \left( \frac{WT_i}{70 \text{kg}} \right)^{1}
\]
PK Plots

Chuuk, FSM

Majuro, RMI
## Noncompartmental Analysis

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>N</th>
<th>Lambda_\text{z} (hours(^{-1}))</th>
<th>V/F (liters/kg)</th>
<th>CL/F (liters/hour/kg)</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 to 2</td>
<td>3</td>
<td>0.39 (0.31)</td>
<td>0.74 (0.46)</td>
<td>0.26 (0.15)</td>
<td>2.46 (1.38)</td>
</tr>
<tr>
<td>2 to 5</td>
<td>7</td>
<td>0.19 (0.05)</td>
<td>1.24 (0.43)</td>
<td>0.24 (0.11)</td>
<td>3.83 (1.12)</td>
</tr>
<tr>
<td>5 to 10</td>
<td>18</td>
<td>0.18 (0.07)</td>
<td>1.49 (0.73)</td>
<td>0.23 (0.07)</td>
<td>4.89 (3.08)</td>
</tr>
<tr>
<td>10 to 12</td>
<td>5</td>
<td>0.18 (0.05)</td>
<td>1.36 (0.30)</td>
<td>0.25 (0.12)</td>
<td>4.03 (0.89)</td>
</tr>
<tr>
<td>12 to 17</td>
<td>17</td>
<td>0.14 (0.05)</td>
<td>1.38 (0.44)</td>
<td>0.18 (0.06)</td>
<td>5.45 (1.69)</td>
</tr>
</tbody>
</table>
## Noncompartmental Analysis

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>N</th>
<th>C&lt;sub&gt;MAX&lt;/sub&gt; (µg/ml)</th>
<th>T&lt;sub&gt;MAX&lt;/sub&gt; (hours)</th>
<th>AUC&lt;sub&gt;0-6&lt;/sub&gt; (hours*µg/ml)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (hours*µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 to 2</td>
<td>3</td>
<td>13.54 (3.58)</td>
<td>1.00 (0.00)</td>
<td>52.47 (23.18)</td>
<td>70.09 (42.66)</td>
</tr>
<tr>
<td>2 to 5</td>
<td>7</td>
<td>10.58 (3.62)</td>
<td>1.14 (0.38)</td>
<td>44.79 (15.20)</td>
<td>70.11 (29.56)</td>
</tr>
<tr>
<td>5 to 10</td>
<td>18</td>
<td>6.77 (2.69)</td>
<td>1.44 (0.51)</td>
<td>28.18 (10.22)</td>
<td>47.30 (23.53)</td>
</tr>
<tr>
<td>10 to 12</td>
<td>5</td>
<td>6.95 (1.97)</td>
<td>1.20 (0.45)</td>
<td>29.37 (9.25)</td>
<td>47.82 (19.23)</td>
</tr>
<tr>
<td>12 to 17</td>
<td>17</td>
<td>7.41 (2.17)</td>
<td>1.35 (0.49)</td>
<td>32.17 (10.90)</td>
<td>60.66 (25.09)</td>
</tr>
<tr>
<td>Structural Model</td>
<td>PARAMETER ESTIMATE</td>
<td>RSE (%)</td>
<td>BOOTSTRAP ESTIMATE (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
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<td></td>
</tr>
<tr>
<td>$K_A$ (HOUR$^{-1}$)</td>
<td>2.69</td>
<td>22</td>
<td>2.77 (1.89 - 5.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F (L/H)</td>
<td>11.61</td>
<td>5</td>
<td>11.61 (10.34 - 12.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V/F (L)</td>
<td>88.39</td>
<td>4</td>
<td>87.86 (80.80 - 95.26)</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inter-individual Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega$ ($K_A$)</td>
</tr>
<tr>
<td>$\omega$ (CL/F)</td>
</tr>
<tr>
<td>$\omega$ (V/F)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Residual Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROPORTIONAL (%)</td>
</tr>
<tr>
<td>ADDITIVE ($\mu$g/ml)</td>
</tr>
</tbody>
</table>
Goodness of Fit Plots

**Population Prediction**

**Individual Prediction**
Conditional Weighted Residuals
Visual Predictive Check
Exposure Simulations

Comparisons to adult fAUC 24

- Adult, 1000 mg
- Adult, 750 mg
- Adult, 500 mg

X axis: Pediatric doses

Dosage (mg/kg)

Simulated Steady-State fAUC (0)
Target Attainment Analysis

4 possible exposure targets:

4 possible doses:

4 possible MICs:

4 possible exposure targets:

4 possible doses:

4 possible MICs:
Conclusions

- Levofloxacin may be an effective treatment option for children with MDR-TB or presumed MDR LTBI.

- A population model was created that effectively captured the available data.

- V/F and Cl/F were well described by the model. Estimates of $ka$ were more variable, reflecting in part very limited sampling during the absorption phase.

- Further clinical research is needed to evaluate appropriate targets for PK/PD indices that can be used to optimize drug dosing.

- LEVO doses up to 20 mg / kg may be needed.