Managing Pediatric Poisons: How Important are Accurate Dose Recommendations?

Kevin Watt, MD
Conflicts of Interest

• None
Objectives

• Review barriers to pediatric drug studies
• Discuss the role of modeling and simulation
• Case studies
  – Neonatal sepsis
  – Fungal infection in children on ECMO
Physiologic Differences

Metabolism

Distribution

Renal Function

Absorption

Why are Pediatric PK studies Difficult?

- Limited number of patients with the disease
- No “healthy child/baby volunteer”
- Low rates of parental informed consent
- Perceived study risks
- Limited blood volume and timed sampling
- Sick population – increases variability
- Lack of clinical pharmacology expertise
- Lack of pediatric PK/PD modeling expertise
Modeling and Simulation

- **Disease models**
  - Understand biomarker(s)/outcome relationship(s)
  - Characterize disease processes in the absence of drug

- **Drug models**
  - Exposure-response relationships
  - Exposure-safety relationships
  - Predict differences in PK/PD relationships between healthy, special and diseased populations

- **Trial Models**
  - Account for trial dropout and medication adherence
  - Explore the importance of patient characteristic

Gobburu Ann Rev Pharm Tox 2009
Case Study #1

NEONATAL SEPSIS
Neonatal Sepsis

• Infants with sepsis are 3x as likely to die as infants without sepsis
• Up to 20% of extremely premature infant deaths are caused by sepsis
• Survivors often suffer from significant morbidities
  – Bronchopulmonary dysplasia
  – Neurodevelopmental impairment

Empirical Antibiotics

- Majority of infants admitted to the NICU receive empirical antibiotics
- Use of prolonged courses (≥ 5 days) of empirical antibiotics in preterm infants associated with:
  - necrotizing enterocolitis, death, late-onset infection
- Proportion exposed to prolonged courses
  - 27-85% in NICHD Neonatal Research Network
Antibiotic Therapy

- Clinician has to weigh consequences
  - Short-term – 24 hour mortality
  - Intermediate-term – school age neurodevelopment
  - Long-term – development of resistance and NICU public health
## Phase I Trials: Pediatric Surprises

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preferred adult dosing (mg/kg/day)</th>
<th>Pediatric or infant dosing (mg/kg/day)</th>
<th>Factor Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>30–50</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>10</td>
<td>5</td>
<td>0.5x</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>250–340</td>
<td>150–480</td>
<td>0.6-1.4x</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>30</td>
<td>15</td>
<td>0.5x</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>3–6</td>
<td>12</td>
<td>2-4x</td>
</tr>
<tr>
<td>Micafungin</td>
<td>3</td>
<td>10–15</td>
<td>3-5x</td>
</tr>
</tbody>
</table>
Piperacillin-Tazobactam

• Piperacillin
  – semisynthetic derivative of ampicillin with enhanced activity against resistant Gram-negative bacteria.
• FDA approved ≥ 2 months
  – Appendicitis and peritonitis

Piperacillin-Tazobactam Study Design

• NIH sponsored study
• 4 center, 32 infant, open-label, PK, and safety study
• Inclusion Criteria
  – < 61 days of age
  AND ONE OF THE FOLLOWING
  – Suspected systemic infection
  – Receiving piperacillin-tazobactam as standard of care
Piperacillin Model Development

- Population PK analysis and Monte Carlo simulations were performed in NONMEM v. 7.2

- Model development
  - One and two compartment models were tested
  - Covariate analysis was performed using a forward inclusion ($p=0.05$) and backward elimination ($p=0.001$) approach
  - Model development was guided by goodness of fit plots, plausibility of parameter estimates, VPCs, and parameter precision

\[
V (L) = 0.4 \times Wt \\
CL (L/h) = 0.08 \times Wt \times (PMA / 32)^{1.8} \times \exp(\eta_{Cl})
\]
## Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>1.43 (0.5, 3.9)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>30 (23, 40)</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>8 (1, 60)</td>
</tr>
<tr>
<td>Postmenstrual age (weeks)</td>
<td>32 (25, 48)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.8 (0.3, 2.0)</td>
</tr>
</tbody>
</table>

Values are median (range) for continuous variables and percent for categorical
## Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed Effects</th>
<th>Bootstrap CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point estimate</td>
<td>% RSE</td>
</tr>
<tr>
<td>Fixed Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V (L/kg)</td>
<td>0.4</td>
<td>9.6</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.08</td>
<td>7.9</td>
</tr>
<tr>
<td>Exponent for PMA on CL</td>
<td>1.8</td>
<td>33.6</td>
</tr>
<tr>
<td>Random Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL interindiv var (CV%)</td>
<td>37.1</td>
<td>27.5</td>
</tr>
<tr>
<td>Residual error - prop (CV%)</td>
<td>32.7</td>
<td>9.9</td>
</tr>
<tr>
<td>Residual error - add (mg/L)</td>
<td>6.9</td>
<td>42.6</td>
</tr>
</tbody>
</table>
Visual Predictive Check
Surrogate PD Target

T>MIC for 75% of the dosing interval
Pseudomonas aeruginosa MIC 16-32 mg/L
## Dosing

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Maintenance dose (mg/kg)</th>
<th>Dosing interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>30-35</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>36-49</td>
<td>80</td>
<td>4</td>
</tr>
</tbody>
</table>

Cohen-Wolkowiez, PIDJ 2013
PMA-based Regimen Outperformed Standard Dosing

Cohen-Wolkowiez, PIDJ 2013
Conclusions

• Piperacillin-tazobactam clearance increases with increasing body weight and PMA

• Target concentrations were obtained with a PMA dosing strategy

• A prolonged infusion does not offer benefit over short infusion (0.5 hours) in preterm infants
Future Directions

Establish safety
• SCAMP study
  – Safety of Antimicrobials in Infants with Complicated Intra-Abdominal infections
  – N=350
  – Ampicillin, clindamycin, metronidazole, pip-tazo

Label changes
Case Study #2

FUNGAL INFECTION IN CHILDREN ON ECMO
Extracorporeal Membrane Oxygenation (ECMO)

Illustration by Jürgen Schaub, Creative Commons BY-SA
Infections on ECMO

- Children supported with ECMO are at high risk for infections

- *Candida* species are a common pathogen in this population

- Invasive candidiasis is treated with antifungal drugs and removal of intravascular catheters

- Treatment or prophylaxis on ECMO relies on optimal dosing

Image from Al-Fattani AAC 2004
ECMO Can Alter the PK of Drugs

- ECMO increases the volume of distribution (V) of some drugs (e.g., vancomycin, fluconazole)
  - Addition of a large volume of blood to prime the circuit
  - Adsorption of drug by components of the ECMO circuit

- Renal insufficiency on ECMO can decrease clearance (Cl)

Population PK of Fluconazole in Children on ECMO

- Fluconazole prophylaxis in children on ECMO (n=20)
- Fluconazole loading dose in children (n=12)
- Fluconazole in infants (n=8)

Monte Carlo sims to determine optimal dosing
Population PK Final Model

$CL \ (L/h) = 0.017 \times Wt \times (\text{creatinine} \ / \ 0.6)^{-0.44} \times \exp(\eta_{Cl})$

$V \ (L) = 0.9 \times Wt \times 1.4^{ECMO} \times \exp(\eta_{V}) \quad \text{ECMO=0/1}$
## Bayesian Estimates of PK

<table>
<thead>
<tr>
<th></th>
<th>ECMO</th>
<th>no ECMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (L/kg)</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>(1.2, 1.6)</td>
<td>(0.8, 1.1)</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.018</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>(0.016, 0.020)</td>
<td>(0.011, 0.018)</td>
</tr>
</tbody>
</table>

Values are median (range)
## Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point estimate</th>
<th>% RSE</th>
<th>2.5%</th>
<th>Median</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V (L/kg)</td>
<td>0.9</td>
<td>5.4</td>
<td>0.8</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.017</td>
<td>5.7</td>
<td>0.016</td>
<td>0.017</td>
<td>0.019</td>
</tr>
<tr>
<td>Coefficient for ECMO on V</td>
<td>1.4</td>
<td>7.3</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Exponent for SCR on CL</td>
<td>-0.33</td>
<td>9.1</td>
<td>-0.42</td>
<td>-0.33</td>
<td>-0.27</td>
</tr>
<tr>
<td><strong>Random Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V interindividual var CV%</td>
<td>21.8</td>
<td>29.3</td>
<td>14.8</td>
<td>21.0</td>
<td>27.1</td>
</tr>
<tr>
<td>CL interindividual var (CV%)</td>
<td>33.0</td>
<td>22.0</td>
<td>24.1</td>
<td>32.1</td>
<td>39.7</td>
</tr>
<tr>
<td>Residual error (CV%)</td>
<td>15.8</td>
<td>12.8</td>
<td>13.7</td>
<td>15.8</td>
<td>17.7</td>
</tr>
</tbody>
</table>
Visual Predictive Check

Fluconazole Conc (mg/L)

Time After Dose (h)
Surrogate PD target for treatment

AUC/MIC $>50$ (AUC$>400$ mg$\times$h/L) in first 24h

Median AUC 600-800 mg$\times$h/L at steady state
Fluconazole Treatment: Simulated Exposures

<table>
<thead>
<tr>
<th>LD/MD (mg/kg)</th>
<th>PD Target 24h (%)</th>
<th>Time to SS target (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-/12</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>25/12</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>35/12</td>
<td>89</td>
<td>3</td>
</tr>
</tbody>
</table>

Fluconazole AUC (mg*h/L)

Day of Therapy

- No load; 12 mg/kg daily
- 25 mg/kg load; 12 mg/kg daily
- 35 mg/kg load; 12 mg/kg daily
Fluconazole Prophylaxis: Simulated Exposures

Median AUC 200-400 at steady state

T>MIC 4 mg/L for 50% of dosing interval

<table>
<thead>
<tr>
<th>LD/MD (mg/kg)</th>
<th>PD Target 24h (%)</th>
<th>Time to SS target (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-/6</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>12/6</td>
<td>99</td>
<td>2</td>
</tr>
</tbody>
</table>

Under journal review
Next Steps

Use PBPK models to evaluate the impact of physiologic derangements on drug dosing in children on ECMO

• Determine relationship between drug physicochemical properties and interaction with ECMO circuit
• Develop PBPK models of fluconazole and micafungin in children on ECMO
• Evaluate PBPK models with clinical trials
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