Modeling Pediatric Pharmacokinetics: Physiologically based pharmacokinetic (PBPK) modeling and simulation

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Conflict of Interest Statement

I am co-owner of the PBPK consulting company, Design2Code Inc.
Key messages

1. Appropriate pediatric PBPK model development is a **systematic process** encompassing biologically plausible virtual individual/population creation along with justifiable drug-specific parameterization.

2. PBPK model evaluation methods define the appropriateness of the model for its intended use (e.g. pediatric clinical trial planning).

3. PBPK models are currently used to generate **pediatric clinical trial doses**.

4. Their use in **risk assessment** for environmental compounds (e.g. pesticides) is common and is likely to become important also for medications (e.g. exposure through breastmilk).
Use of PBPK models

- Pediatrics is represented in 17% of submissions using PBPK to the FDA.
- Primarily used in the planning of pediatric clinical PK trials and not in the replacement of these trials.

Grillo JA. In: AAPS Meeting. San Diego, 2014

IND/NDA submitted to the FDA Office of Clinical Pharmacology (2008-2014) (n=136)
Pediatric Drug Development

• FDA and EMA require pediatric trials plans
• Best Pharmaceuticals for Children Act (BPCA); Pediatric Research Equity Act (PREA)
  • 530 labeling changes have been made (up to 2014) since enactment of BPCA and PREA

• *44 unique products had failed pediatric drug development trials submitted to FDA between 2007 and 2014 due to:
  • #1 lack of efficacy (suboptimal dosing, diff. in adult and pediatric disease process)
  • #2 safety issues

Utility of Structured Workflows for Development of Pediatric PBPK Models


Leong R et al. CPT, 2012
Utility of a Structured Workflow

A Workflow Example of PBPK Modeling to Support Pediatric Research and Development: Case Study with Lorazepam

DOI: 10.1208/s12248-013-9451-0
A. R. Maharaj,¹ J. S. Barrett,² and A. N. Edginton¹,³

**Objective**

Provide an informative example (lorazepam) of how adult PK data can be leveraged for pediatric PBPK model development using a structure workflow
1. Develop and evaluate an adult PBPK model describing the PK of IV lorazepam

<table>
<thead>
<tr>
<th>Data for initial parameterization</th>
<th>virtual population n=100</th>
<th>Greenblatt DJ et al. J Pharm Sci, 1979</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(- -)5th,95th percentiles</td>
<td>Greenblatt DJ et al. J Pharm Sci, 1982</td>
</tr>
</tbody>
</table>

| Physicochemical                   | LogP 2.39 (34)              |                      |
| pKa                               | 1.3 (base), 11.5 (acid) (35)|                      |
| ADME                             | fu 0.11 (11-13)              |                      |
|                                  | CLint(bep-U/GT287) 0.439 ml/min/g liver (13,15,20-22) |                      |
|                                  | CLGFR 0.01 ml/min/kg (14-16) |                      |
|                                  | B/P 0.642 (36)               |                      |
| Anatomic/physiologic             | Organ size Generated using simple demographic information |                      |
|                                  | Organ blood flow (sex, male; age, 26.6 years; weight, 68 kg) by the |                      |
|                                  | Tissue composition methods described in Willman et al. (23) |                      |

Plasma Concentration (ng/mL) vs Time (hr)
2. Extrapolate evaluated adult PBPK model towards pediatrics

Scale anatomy/physiology

Scale clearance

Scale protein binding

n = 40 pediatric subjects
centralities dose normalized to 0.05 mg/kg
Dose needed to achieve similar unbound exposure as in adults (red dots; shaded region is 90th percentile of adults)

3. Define doses for clinical trial planning (examples)
PBPK provides *a priori* predictions of CL and $V_{ss}$ that are similar to PopPK

- For 15 subjects, intensive PK sampling was conducted; Chamberlain JM et al. J Pediatr, 2011.
- PBPK and PopPK predicted CL and $V_{ss}$ were compared to values derived via noncompartmental analysis

<table>
<thead>
<tr>
<th></th>
<th><strong>CL</strong></th>
<th></th>
<th><strong>V_{ss}</strong></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PBPK</td>
<td>PopPK</td>
<td>PBPK</td>
</tr>
<tr>
<td>1.25-fold</td>
<td>6 (40%)</td>
<td>7 (47%)</td>
<td>1.25-fold</td>
</tr>
<tr>
<td>1.5-fold</td>
<td>9 (60%)</td>
<td>10 (67%)</td>
<td>1.5-fold</td>
</tr>
<tr>
<td>2-fold</td>
<td>12 (80%)</td>
<td>12 (80%)</td>
<td>2-fold</td>
</tr>
</tbody>
</table>

fold error = \( \frac{\text{predicted}}{\text{observed}} \)
Summary

1. The use of structure workflows ensures that pediatric PBPK models are developed rationally by appropriately leveraging the relative wealth of PK data in adults.

2. However, use of such workflows does NOT guarantee accurate pediatric predictions.

3. Accurate PK predictions – Effective Parameterization Required!!
   - Intrinsic understanding of PK in adults
   - Quantitative knowledge of the ontogeny of parameters that effect drug PK
Anatomy and physiology

Development and Evaluation of a Generic Physiologically Based Pharmacokinetic Model for Children

Andrea N. Edginton, Walter Schmitt and Stefan Willmann
Competence Center Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany

Human Organ/Tissue Growth Algorithms that Include Obese Individuals and Black/White Population Organ Weight Similarities from Autopsy Data

John F. Young¹, Richard H. Luecke², Bruce A. Pearce³, Taewon Lee¹, Hongshik Ahn⁴, Songjoon Baek², Hojin Moon⁵, Daniel W. Dye⁶, Thomas M. Davis⁶, and Susan J. Taylor¹

¹Division of Personalized Nutrition & Medicine, National Center for Toxictological Research, Jefferson, Arkansas, ²Department of Chemical Engineering, University of Missouri–Columbia, Columbia, Missouri, ³Information Technology Staff, National Center for Toxictological Research, Jefferson, Arkansas, ⁴Department of Applied Mathematics and Statistics, Stony Brook University, Stony Brook, New York, ⁵Department of Mathematics and Statistics, California State University–Long Beach, Long Beach, California, and ⁶Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
Clearance scaling: Adults to children

- Numerous studies on the age-dependence of amount of enzyme protein/gram liver
- Enzyme maturation an important model input

\[
\text{CLint}_{\text{child}} \text{ (L/min/g tissue)} = \text{CLint}_{\text{adult}} \text{ (L/min/g tissue)} \times \% \text{ of adult activity/protein}
\]

- AUC greatly dependent on CLint for low to moderate extraction ratio drugs

Clearance scaling: Adults to children

**In vitro to in vivo**

- Relate abundance of isoform in vitro to in vivo abundance
  - Abundance of CYP isoform/mg microsomal protein
  - Microsomal protein/g liver

\[
CYP3A4 \text{ CL}_{int,child} \rightarrow \text{CYP3A4 CL}_{int,child}
\]

\[
CYP1A2 \text{ CL}_{int,child} \rightarrow \text{CYP1A2 CL}_{int,child}
\]

**In vivo \text{adult} to in vivo \text{child}**

\[
CL_{H,1A2} = CL_{total} \times f_{m,1A2}
\]

\[
Q_{liver,adult} \times LW_{adult} \times f_{u,adult}
\]

\[
\text{CYP1A2 CL}_{int,adult}(\text{e.g. L/min/g liver})
\]

\[
\text{CYP1A2 CL}_{int,child}
\]

Clearance scaling: Pitfalls

• Pathways of clearance sometimes difficult to assess
• Age dependence of relevant enzyme activity absent. Less common enzymes (e.g. conjugating enzymes: arylamine N-acetyltransferases and methyltransferases) lack clear maturation functions.
• Role and age dependence of transporter activity
Developmental differences in plasma protein concentrations exist between children and adults

- Plasma protein-binding ($f_{up}$) can have a profound impact on both CL and V

$$CL_{hepatic (child)} = \frac{Q_h (child) \times f_{u,p}(child) \times CL_{int (child) total \ liver}}{Q_h (child) + \left( f_{u,p}(child) \times CL_{int (child) total \ liver} \right) / B/P_{(child)}}$$

$$V_{ss} = V_p + \sum \frac{f_{up}}{f_{ur}} \cdot V_t$$

- Two main plasma proteins: albumin (acidic compounds)
  a1-acid glycoprotein (AAG; basic compounds)
Issues associated with AAG ontogeny

• widely used equation (McNamara and Alcorn) depicting the ontogeny of AAG over-predicts protein concentration in neonates

• AAG is an acute phase reactant that increases in concentration by 3-5 fold in response to inflammation, systemic injury, or infection

\[ \text{AAG Level} \% = 0.01137 \times \text{Days} + 53.4 \]

McNamara PJ and Alcorn JA. AAPS PharmSci, 2002
A sigmoid Emax model was found to best depict the ontogeny of AAG in both healthy and infected subjects.

\[
\frac{AAG_{max} \cdot AGE^P}{K_{50}^P + AGE^P}
\]

Youngest children = 5 days old

* The Pharmacokinetics of Anti-Staphylococcal Antibiotics in Infants Clinical Trial (Staph Trio; NICHD-2012-STA01, ClinicalTrials.gov NCT01728363; IND 115,396), Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (PTN POPS; NICHD-2011-POP01, ClinicalTrials.gov NCT01431326; IND 113,645), and Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin Pediatric Subjects With BMI ≥ 85th Percentile (CLIN01; NICHD-2012-CLN01, ClinicalTrials.gov NCT01744730; IND 115,396).
AAG ontogeny is similar in healthy and infected subjects

AAG levels >2 fold higher than healthy subjects

Normalized AAG levels (fraction of adult levels) indicate the similar trajectory in AAG ontogeny

\[ f_{\text{ped}} = \frac{1}{1 - \frac{P_{\text{ped}}}{P_{\text{adult}}}} \]
Sigmoid Emax model produced superior estimates of $f_{u_p}$

- accuracy of $f_u$ estimates -- compared to 17 observed pediatric (<1 year; primarily from 7 days and younger) $f_u$ values for compounds that preferentially bind to AAG

$$f_{u_{ped}} = \frac{1}{1 + \frac{p_{ped}}{p_{adult}} \cdot \frac{1 - f_{u_{adult}}}{f_{u_{adult}}}}$$

<table>
<thead>
<tr>
<th>Maharaj et al. (i.e. current analysis) (Sigmoid Emax)$^a$</th>
<th>McNamara &amp; Alcorn (Linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AFE$ (bias)</td>
<td>0.979</td>
</tr>
<tr>
<td>$AAFE$ (precision)</td>
<td>1.239</td>
</tr>
</tbody>
</table>
**Model Evaluation: sensitivity & uncertainty**


**Methods** for sensitivity analysis (Zhang et al. 2016. CPT Pharmacometrics Syst Pharmacol. 4, 69–79)
- Local sensitivity analysis
- Global sensitivity analysis
  - Sobol
  - Partial rank correlation coefficients

Sensitivity analysis for pediatric PBPK models

Sensitivity analysis using AUC as the outcome in the adult PBPK model would identify $CL_{int}$ as being **VERY** important and $CL_{int}$ as being **LESS** important.

$CL_{int\_child} \ (L/\text{min/g liver}) = CL_{int\_adult} \ (L/\text{min/g liver}) \times \text{Maturation Factor}$
Sensitivity analysis for pediatric PBPK models

Sensitivity analysis using AUC as the outcome in the pediatric PBPK model would identify \( CL_{\text{int}} \) as being LESS important and \( CL_{\text{int}} \) as being VERY important.

\[
CL_{\text{int, child}} \text{ (L/min/g liver)} = CL_{\text{int, adult}} \text{ (L/min/g liver)} \times \text{Maturation Factor}
\]

Sensitivity analysis should be done in the population that is being predicted.
Motivating example

In adults: expectation of increased AUC in the presence of a strong CYP3A4 inhibitor

$$\text{CL}_{\text{int, child}} (\text{L/min/g liver}) = \text{CL}_{\text{int, adult}} (\text{L/min/g liver}) \times \text{Maturation Factor}$$
Motivating example

**Maturation Factor (MF)**

In very young children: AUC increase would be minimal in presence of strong CYP3A4 inhibitor.

\[
\text{CLint}_{\text{child}} \text{ (L/min/g liver)} = \text{CLint}_{\text{adult}} \text{ (L/min/g liver)} \times \text{Maturation Factor}
\]
Question: is that red Maturation Function well characterized?

Oh no! can be dealt with by:

1. Benchmarking with another compound that is similarly metabolised for which there is pediatric PK data
2. Assessing the implications in the resulting dosing algorithm and altering trial design
3. Experimentation
Mid-presentation summary...

- PBPK modeling is seeing increased usage in pharma
- PBPK model extrapolation to children requires knowledge of growth and maturation
- Systems-level knowledge gaps increase pediatric model uncertainty
- The importance of those knowledge gaps can be assessed using sensitivity analysis
- Uncertainty can be reduced using experimentation
A future for PBPK models

- Good enough to replace a dedicated PK trial?
  - Drug-drug interaction – yes!
  - Pediatrics – not yet (but getting there)

- Planning trials to assess importance of:
  - Genotype
  - Renal impairment
  - Hepatic impairment
  - DDIs
  - Pregnancy
Infant exposure via breastmilk

Working with Dr. Shinya Ito, SickKids, Toronto, Ontario, Canada

**Goal**: Establish an *approach* to generate population level PK data for risk assessment of infants exposed to maternal medications excreted into breast milk.

Currently developing linked breastmilk – infant model to predict age dependent exposure given exposure to the mother.
Infant exposure via breastmilk

Milk concentrations for given maternal dose (experimental)

Virtual population of neonates (preterm & term), infants

Exposure as a function of age/weight

How would you interpret this?

Volume of milk/feed/kg/day (literature based)

Incorporates size, maturation and associated variability

# feeds/day/kg (literature based)
Infant exposure via breastmilk- why PBPK?

• What resources would be needed to examine infant exposure of all drugs in breastfed infants?

• Can we use PBPK to reduce the needed resources?

  1. Rank drugs with respect to risk categorization
     pediatric AUC/adult mean therapeutic AUC
     e.g. <0.1 – low risk of unwanted effects
          >0.1-0.5 – moderate risk
          >0.5 – significant risk – focus resources here

  2. Given actual infant exposures (n = low), estimate the expected inter-individual exposure variability

  3. Identify subgroups most likely to reach ‘significant risk’ exposure (e.g. CYP2D6 extensive metabolizers)
Pediatric PBPK- Clindamycin (IV)

• Hypothesis: combining opportunistic and literature data will allow us to develop a well parameterized pediatric PBPK model for the lincosamide antibiotic, clindamycin

• Opportunistic PK studies capitalize on standard of care procedures by timing collection of samples to occur optimally at the time of routine laboratory blood draws.

• Can we use these concentrations to evaluate a PBPK model, which can then be used to inform labelling?

• Clindamycin is already labelled for children – this study is proof of principle

Department of Pediatrics, Duke University School of Medicine & UNC Eshelman School of Pharmacy [NIH 1R01-HD076676-01A1 – Micky Cohen-Wolkowiez (PI)] – currently in peer-review
Adult PBPK Model Development

Clindamycin Phosphate $\rightarrow$ Renal (0.35%)

Alkaline Phosphatase (>99%)

Clindamycin

CYP3A4
CYP3A5
Renal (tubular secretion and filtration)
## Pediatric Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Range) or N (%)</th>
<th>0 – 1 year</th>
<th>2 – 5 years</th>
<th>6 – 11 years</th>
<th>12 – 18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>9</td>
<td>11</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Gestational age&lt;sup&gt;a&lt;/sup&gt; (weeks)</td>
<td>39 (37.3 – 40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postnatal age (years)</td>
<td>0.1 (0.03 – 0.3)</td>
<td>3.3 (2.0 – 5.9)</td>
<td>10.2 (7.5 – 11.5)</td>
<td>17.0 (12.7 – 19.0)</td>
<td></td>
</tr>
<tr>
<td>Postmenstrual age&lt;sup&gt;b&lt;/sup&gt; (weeks)</td>
<td>42 (41 – 53)</td>
<td>212 (145 – 349)</td>
<td>570 (430 – 639)</td>
<td>928 (702 – 1030)</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>4.2 (2.7 – 6.0)</td>
<td>17.2 (10.3 – 24.6)</td>
<td>31.7 (23.6 – 47.7)</td>
<td>67.9 (28.6 – 87)</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>3 (33)</td>
<td>5 (45)</td>
<td>6 (60)</td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (100)</td>
<td>9 (82)</td>
<td>5 (50)</td>
<td>13 (72)</td>
<td></td>
</tr>
<tr>
<td>Black or African</td>
<td>0</td>
<td>1 (9)</td>
<td>3 (30)</td>
<td>4 (22)</td>
<td></td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other Race</td>
<td>0</td>
<td>1 (9)</td>
<td>0</td>
<td>1 (6)</td>
<td></td>
</tr>
</tbody>
</table>

68 plasma samples from 48 participants

1.4 [1 - 6] samples/child
## Results

1. Number of concentration data out of 90% prediction interval of the pediatric population PBPK model.

<table>
<thead>
<tr>
<th></th>
<th>0 – 1 year</th>
<th>2 – 5 years</th>
<th>6 – 11 years</th>
<th>12 – 18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of</strong></td>
<td>9</td>
<td>11</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td><strong>subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total number of data</strong></td>
<td>14</td>
<td>16</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td><strong>points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number (%) of data points outside of the 90% prediction interval</strong></td>
<td>1 (7)</td>
<td>6 (37.5)</td>
<td>2 (18)</td>
<td>4. (22)</td>
</tr>
</tbody>
</table>
Results

2. Model-generated pediatric doses that produce adult AUCs are similar to those recommended by the Infectious Diseases Society of America for the treatment of community acquired MRSA.

3. Predicted concentrations in target tissues including bone, skin, and lungs, were >MRSA MIC (0.5 mg/L) for at least 50% of the dosing interval in ≥88% of subjects.
Clindamycin take-away

• An evaluated pediatric PBPK model (birth to 17 yrs) was able to generate doses that are recommended already using other methods (proof of principle)
• Very few samples were used to achieve this goal
• What about new drugs? Old drugs without pediatric labelling but off-label use?
Key messages

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2. PBPK model evaluation methods define the appropriateness of the model for its intended use (e.g. pediatric clinical trial planning).

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