FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING
Comparison of Various Renal Function Models in Neonates

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Disclaimer: My remarks today are my own personal views and do not represent those of the FDA
Highlights

• **Target population**: neonatal or child

• **Specific population issues prime for PBPK as a tool**: rapidly changing GFR in neonates and children <2 years old

• **Why PBPK may out-perform other pharmacometric tools**: both PBPK models and traditional compartment models with covariates rely on empirical equations to fit observed data
Outline

• Overview of various models for renal function quantification in neonates

• Evaluation of models with new data

• Summary
Available Models for GFR Quantification in Neonates


• GastroPlus model
Equations

• Schwartz model
  • eGFR (mL/min/1.73m2)=k*HT (cm)/Scr (mg/dL) (k=0.45 for <1 yr or 0.55)

• Simcyp default model
  • eGFR (L/hr) = ((-6.616*BSA^2) + (99.054*BSA) - 17.74)/1000*60

• Rhodin model
  • eGFR (L/hr) =((WT/70)^0.75*(PMA^3.4/(PMA^3.4+47.7^3.4))*7.26

• Gastroplus model (Confidential)
  • Simulated by providing age (full term infant)

• Modified Rhodin model
  • eGFR (L/hr) =((WT/70)^0.75*(PMA^3.4/(PMA^3.4+47.7^3.4))*CL_{adult}

• PNA+GA model*
  • eGFR (L/hr) =((WT/70)^0.75 (1-(1-0.404*(GA/37)^3.3)*exp(-PNA*0.693/20.8)) *7.2

Data Source for Schwartz Model

### Data Source for Simcyp Model

#### Table II. Studies measuring glomerular filtration rate (mL/min/1.73m²) with age in children used to define renal drug clearance with age in the Simcyp® Paediatric model

<table>
<thead>
<tr>
<th>Probe</th>
<th>Neonate</th>
<th>Infant</th>
<th>Child</th>
<th>Adult</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;24h</td>
<td>1–7d</td>
<td>8–28d</td>
<td>1–3mo</td>
<td>3–12mo</td>
</tr>
<tr>
<td>$^{51}$Cr-EDTA</td>
<td>45</td>
<td></td>
<td></td>
<td>90 (6mo)</td>
<td>105 (2y)</td>
</tr>
<tr>
<td>Mannitol</td>
<td>40</td>
<td>43</td>
<td>45</td>
<td>75</td>
<td>98 (6mo)</td>
</tr>
<tr>
<td>Inulin</td>
<td>18.6 ± 6.7</td>
<td>19.6 ± 4.7</td>
<td>38.5 ± 11.7</td>
<td>58</td>
<td>103</td>
</tr>
<tr>
<td>Inulin</td>
<td>20.1</td>
<td></td>
<td>37.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inulin</td>
<td>31.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inulin</td>
<td>29.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>43</td>
<td>45</td>
<td>48 ± 9.7</td>
<td>67.8 ± 8.7</td>
<td>90.6 ± 27</td>
</tr>
<tr>
<td>Inulin</td>
<td>39</td>
<td>47</td>
<td></td>
<td>58</td>
<td>103</td>
</tr>
<tr>
<td>Inulin</td>
<td>38.5</td>
<td></td>
<td></td>
<td>70.2</td>
<td>110</td>
</tr>
</tbody>
</table>

The development of renal function was studied in neonates with gestational ages ranging from 28 to 43 weeks. The effect of gestational age on the maturation of renal function was assessed in newborn infants studied during the first 72 h of life.

We have reviewed the studies that provide the current standards of reference for glomerular filtration rate (GFR) in normal children from 14 days to 12 years of postnatal age.

Renal function was studied serially in 17 healthy term infants during the hours immediately following birth.

The kidneys of neonates are inefficient at drug elimination, leading initially to prolonged elimination half-lives of many drugs.

<table>
<thead>
<tr>
<th>Characteristics of the study</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Method</td>
<td>Cr-EDTA</td>
</tr>
<tr>
<td>Number</td>
<td>185</td>
</tr>
<tr>
<td>Mean PMA (range)</td>
<td>384 weeks (87–1652)</td>
</tr>
<tr>
<td>Mean PNA (range)</td>
<td>6.6 years (0.9–14.2)</td>
</tr>
<tr>
<td>Mean weight (range)</td>
<td>22.5 kg (8–45.4)</td>
</tr>
<tr>
<td>Mean GFR (range)</td>
<td>107 ml/min (107–131 ml/min)</td>
</tr>
<tr>
<td>Sex reported</td>
<td>No</td>
</tr>
<tr>
<td>More than one observation/subject</td>
<td>No</td>
</tr>
<tr>
<td>Pathology</td>
<td>No diagnoses available</td>
</tr>
</tbody>
</table>

GFR Glomerular filtration rate; PMA postmenstrual age; PNA postnatal age

Data Source and Model Validation for Gastroplus Model

Figure 4-28: Plot of GFR vs post-menstrual age (PMA) for neonates up to 12 weeks old (left) and born after 27-33 (dark blue), 34 (light blue), 35 (magenta), 36 (green), 38 (orange) and 40 (red) weeks of gestation (left) and plot of calculated vs observed GFR for the same data (right). Points represent experimental data (Arant 1978, Coulthard 1985, DeWoskin 2008, Fawer 1979) lines show GFR calculated in GastroPlus.

Figure 4-29: Plot of GFR vs post-menstrual age (PMA) for infants and children up to 6 years old. Points represent experimental data (Bird 2003, Kearns 2003, Peters 1994, Rubin 1949, Stevens 2007) line shows GFR calculated in GastroPlus for infants and children from 12 weeks to 6 years.
### Table 1: Drug clearance and renal clearance in adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total clearance (L/hour)</th>
<th>Renal clearance (L/hour)</th>
<th>% Renal clearance</th>
<th>Contribution of nonrenal elimination pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin²⁵</td>
<td>6.0 ± 0.5</td>
<td>5.0 ± 0.9</td>
<td>94</td>
<td>&lt; 5% metabolism</td>
</tr>
<tr>
<td>Gadobutrol²⁶</td>
<td>6.2</td>
<td>6.2</td>
<td>&gt; 99</td>
<td>No metabolism</td>
</tr>
<tr>
<td>Gadoterate²⁷</td>
<td>7.1</td>
<td>7.1</td>
<td>&gt; 99</td>
<td>No metabolism</td>
</tr>
<tr>
<td>Vancomycin²⁸</td>
<td>5.9 ± 1.5</td>
<td>5.3 ± 2.0</td>
<td>~ 90</td>
<td>~ 10% metabolism</td>
</tr>
</tbody>
</table>

### Table 2: Distribution of newborns and infants in age categories

<table>
<thead>
<tr>
<th>Drugs (n)</th>
<th>≥ 42 weeks PMA (n)</th>
<th>&lt; 42 weeks PMA (n)</th>
<th>PNA (days)</th>
<th>GA (weeks)</th>
<th>PMA (weeks)</th>
<th>Body weight (kg)</th>
<th>SCR (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (108)</td>
<td>22</td>
<td>11</td>
<td>75</td>
<td>(3–625)</td>
<td>29</td>
<td>(23–41)</td>
<td>31</td>
</tr>
<tr>
<td>Gadobutrol (43)</td>
<td>39</td>
<td>4</td>
<td>0</td>
<td>(6–696)</td>
<td>40</td>
<td>(40–40)</td>
<td>70</td>
</tr>
<tr>
<td>Gadoterate (45)</td>
<td>41</td>
<td>4</td>
<td>0</td>
<td>(4–721)</td>
<td>40</td>
<td>78</td>
<td>(39–143)</td>
</tr>
<tr>
<td>Vancomycin (92)</td>
<td>22</td>
<td>31</td>
<td>39</td>
<td>(13–2–367)</td>
<td>36</td>
<td>39</td>
<td>(24–41)</td>
</tr>
</tbody>
</table>

Model Validation for PNA+GA Model

Figure S2. Overall performance of clearance prediction for drugs 60 - 80% renally- eliminated in newborns and infants using GA+PNA based model. The circles represent patients with gestational age >= 37 weeks and the triangles represent patients with gestational age < 37 weeks. The colors of red, blue, dark-green represent < 37 weeks PMA, 37 to < 42 weeks PMA, ≥ 42 weeks PMA, respectively. The dotted lines represent 0.5 and 2-fold for the ratio of model predicted clearance relative to the observed value (population PK estimated CL).

Macrocyclic, gadolinium-based contrast agent (GBCA)

Complete GFR elimination, ideal compounds for estimating renal maturation function. (CL: 6.2 L/hr and 7.07 L/hr in 70 kg adults)

Approved Indication: for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
Study Design in Pediatric Patients < 2 yo

- **Gadavist**
  - term newborns.
  - N=43 (38 subjects >1 months, 5 subjects < 1 months)
  - Sparse Sampling scheme: 3 blood samples per subject; one during each time window (15 min to 60 min, 2.0 hours to 4.0 hours and 6.0 hours to 8.0 hours post-injection)

- **Dotarem**
  - term newborns.
  - N=45 (40 subjects >1 months, 5 subjects < 1 months)
  - Sparse Sampling scheme: 3 blood samples per subject; one during each time window (10 min to 60 min, 2.0 hours to 4.0 hours and 6.0 hours to 8.0 hours post-injection)
Predicted GFR/Observed GFR Based on Gadovist Pediatric Data

<table>
<thead>
<tr>
<th></th>
<th>Gastro+</th>
<th>SimCYP</th>
<th>Rhodin</th>
<th>Rhodin+</th>
<th>Schwartz</th>
<th>PNA+GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted/Observed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMA (weeks)</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
</tbody>
</table>

Observed GFR is individual CL estimate from neonate/infant popPK analysis
Predicted GFR/Observed GFR Based on Dotarem Pediatric Data

- Observed GFR is individual CL estimate from neonate/infant popPK analysis.
A Direct Comparison of All Models
Summary

• Different GFR models were built from different data sources

• Significant differences exist between these models

• More high quality data are needed to support an optimal model
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THANK YOU
yaning.wang@fda.hhs.gov
Division of Pharmacometrics (DPM) /Office of Clinical Pharmacology (OCP) is Hiring!

Positions
• PBPK reviewer and Pharmacometrics reviewers

Responsibility
• Approve and label the drug product with particular attention to drug dosing at the individual and population levels.
• Provide advice on trial design and development path decisions to sponsors.
• Conduct research to create new knowledge based on the unique data available at the FDA (i.e. prior submissions) and literature to inform better regulatory decisions by the FDA and drug development decisions by sponsors.

Minimum requirements
• An earned Ph.D. or other professional doctorate in PKPD, Statistics, Engineering, Clinical Pharmacology, or relevant fields
• Hands-on experience with modeling and simulation software (e.g. NONMEM, SAS, Splus/R, Trial Simulator, WinBUGs, Phoenix, Monolix, GastroPlus, PKSIM, SimCYP, etc.)
• Good knowledge of PK/PD modeling principles and statistics.
• Good communication and interpersonal skills.
• Candidates should have continuous residence in the US for the last 3 years.

How to apply
• Send your CV to Yaning.Wang@fda.hhs.gov or Hao.Zhu@fda.hhs.gov