ADME Issues in Children: Pediatric Pharmacokinetics

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The George Washington School of Medicine and Health Sciences
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Historical Drug “Development” in Children

- Teething Deodorized tincture of opium (1.5%)
- Sulfanilamide
- Chloromycetin (Chloramphenicol) Hydrocortisone Ophthalmic
For adults: Take a teaspoonful about one-half hour before meals and when retiring.

For children: Half dose. If the taste is not liked, it may be combined with milk or water or a mouthful of water may be taken immediately after.

DIRECTIONS

Contains 12% of alcohol by weight or 14% per volume. Used as a solvent.

Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but... it has its own independent range and horizon.

Dr. Abraham Jacobi, 1889

Historical Drug “Development” in Children

Dr. Abraham Jacobi, 1889

"Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but... it has its own independent range and horizon."

Dr. Abraham Jacobi, 1889
Inadequacy of traditional dosing schema

Comparison of total daily gabapentin (Neurontin®) maintenance doses calculated via “traditional” and current dosing guidelines for a 4-year-old, 17 kg child

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Cowling</th>
<th>Clark</th>
<th>BSA</th>
<th>2003 Peds Dosing Handbook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction of adult dose</td>
<td>25%</td>
<td>21%</td>
<td>25%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>225 – 450</td>
<td>391-783</td>
<td>680</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total daily dose (mg/kg)</td>
<td>13 - 26</td>
<td>23 - 46</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Developmental Continuum

- Fetus
  - Newborn
  - Infant
  - Preschooler
  - School-age
  - Adolescent
    - Weight doubles by 5 months; triples by 1 year
    - Body surface area doubles by 1 year
    - Caloric expenditures increase 3- to 4-fold by 1 year
    - Adolescence: transition to adulthood
    - Changes incomprehensible to most adults
- Adult
The Developmental Continuum

Fetus
Newborn
Infant
Preschooler
School-age
Adolescent
Adult

Determinants of Drug Response in Children

Disease
Growth and Development

Environment

Genetics

Drug

Absorption
Distribution
Receptor Interaction
Biotransformation
Excretion

Exposure
Response
Critical Role of Pharmacokinetics in Pharmacotherapy……

- The combination of ADME dictate exposure which dictates dose.

- Exposure along with the interaction with therapeutic targets (e.g., receptors) dictates response.
Drug Absorption
Developmental Changes in Gastric pH

\[
\text{% Adult Activity}
\]

<table>
<thead>
<tr>
<th>Age Group</th>
<th>HCl Production</th>
<th>Pepsin</th>
<th>Gastrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Developmental Alterations in Intestinal Drug Absorption
Influence of Higher Gastric pH

Orally Administered Penicillin (10,000 U/lb)

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin concentration (U/mL)</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
</tbody>
</table>

Huang et al. J Pediatr 1953;42:657

Agunod et al. Amer J Digest Dis 1969;14:400
Mozam et al. J Pediatr 1985;106:467
Drug distribution
Age-dependent changes in body composition

Impact of Age on Linezolid Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult (n=57)</th>
<th>Child (n=44)</th>
<th>Infant (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vdss (L/kg)</td>
<td>0.63 ± 0.13</td>
<td>0.71 ± 0.18</td>
<td>0.83 ± 0.18</td>
</tr>
<tr>
<td>Cl (L/hr/kg)</td>
<td>0.10 ± 0.03</td>
<td>0.30 ± 0.12</td>
<td>0.52 ± 0.15</td>
</tr>
<tr>
<td>t_{1/2} (hr)</td>
<td>4.6 ± 1.7</td>
<td>3.3 ± 0.9</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>C_{max_norm} (mg/L)</td>
<td>19.7 ± 4.9</td>
<td>17.0 ± 5.2</td>
<td>12.5 ± 3.5</td>
</tr>
<tr>
<td>C_{12_pred} (mg/L)</td>
<td>3.3 ± 2.1</td>
<td>0.41 ± 0.72</td>
<td>0.03 ± 0.05</td>
</tr>
<tr>
<td>T&gt;MIC_{90} (%)</td>
<td>70-100%</td>
<td>35-70%</td>
<td>20-35%</td>
</tr>
</tbody>
</table>

**Drug Biotransformation**

Drug → Phase I → Metabolite
- CYPs
- Esterases
- Dehydrogenases

Phase II → Metabolite
- UGTs
- NATs
- STs
- MTs
- GSTs

---

**Ontogeny of CYP3A4**


<table>
<thead>
<tr>
<th>Stage</th>
<th>Percent Adult Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus</td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td></td>
</tr>
<tr>
<td>Infant</td>
<td></td>
</tr>
<tr>
<td>mRNA</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td></td>
</tr>
</tbody>
</table>
**Single-Dose (0.2 mg/kg)**
Pharmacokinetics of Cisapride in Neonates and Young Infants

<table>
<thead>
<tr>
<th>Postconceptional Age</th>
<th>28-36 wks. (n = 17)</th>
<th>36-42 wks. (n = 13)</th>
<th>42-54 wks. (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>30.0(17.5)</td>
<td>23.3(11.7)</td>
<td>44.5(19.5)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>5.0(2.6)</td>
<td>4.3(3.3)</td>
<td>2.2(1.1)</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>11.6(3.0)</td>
<td>11.5(3.0)</td>
<td>4.8(3.0)</td>
</tr>
<tr>
<td>AUC (ng/ml*hr)</td>
<td>568(257)</td>
<td>362(198)</td>
<td>364(249)</td>
</tr>
<tr>
<td>VDss/F (L/kg)</td>
<td>7.4(4.7)</td>
<td>12.7(9.1)</td>
<td>4.1(1.5)</td>
</tr>
<tr>
<td>Cl/F (L/hr/kg)</td>
<td>0.45(0.26)</td>
<td>0.75(0.46)</td>
<td>0.85(0.69)</td>
</tr>
</tbody>
</table>


-Data expressed as mean (S.D.)

**Impact of Development on Cisapride Elimination in Infants**

Cisapride in Neonates and Infants: Kel vs. Postconceptional Age

![Graph showing the correlation between PCA (weeks) and Kel (1/hr) for Cisapride in neonates and infants.](image-url)
Impact of Age on Linezolid Pharmacokinetics

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<td>0.03 ± 0.05</td>
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<td>20-35%</td>
</tr>
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Linezolid Plasma Clearance Association with PCA

[Graph showing Linezolid Plasma Clearance Association with PCA]
Linezolid Plasma Clearance Association with PNA

Drug Biotransformation

Drug → Metabolite → Metabolite

Phase I
- CYPs
- Esterases
- Dehydrogenases

Phase II
- UGTs
- NATs
- STs
- MTs
- GSTs
NEWBORN RENAL FUNCTION

- Very low Glomerular Filtration Rate (GFR)
- Delicate balance between vasoconstrictor and vasodilatory renal forces
- Low mean arterial pressure and high intrarenal vascular resistance
- Limited postnatal renal functional adaptation to endogenous or exogenous stress

Figure 2. Linear regression analysis of total body clearance of amoxicillin (mL/h) versus gestational age (weeks) in 17 preterm infants on day 3 after birth

\( r=0.75, \ p<0.001, \ y=8.88x – 181.2 \)

Meropenem pharmacokinetics in the newborn

Factors influencing drug disposition in infants, children and adolescents............

- Genetics
- Environment
- Disease
- Treatment
- Growth and development

PHARMACOGENOMICS

PHARMACOGENETICS

PHARMACOKINETICS

PHARMACODYNAMICS

Leeder, 2002
PHARMACOGENETICS

The study of the role of genetic factors in drug disposition, response and toxicity - relating variation in human genes to variation in drug responses at the level of the individual patient (the right drug for the right patient)

CYP2C19 Pharmacogenetics

- 1984: Unusual sedation in a subject receiving anticonvulsant mephenytoin
- Impaired 4-hydroxylation of S-mephenytoin
- Affects 2-5% of Caucasians; 20-25% of Asians
- Affected drugs include omeprazole, lansoprazole, pantoprazole, diazepam
- Major clinical consequence at present related to omeprazole pharmacodynamics and efficacy
Impact of CYP2C19 Pharmacogenetics on Omeprazole PK and PD

Omeprazole PK After a Single 20 mg Oral Dose

Functional Alleles
- 2 (n=5)
- 1 (n=4)
- 0 (n=6)

Mean Intragastric pH

\[ r = 0.873 \]
\[ p < 0.0001 \]

Lack of an Effect of CYP2C19 Genotype on Omeprazole Exposure in Pediatric EMs

CYP2D6 Pharmacogenetics

- CYP2D6 activity displays bimodal distribution in Caucasian subjects
- 5-10% of Caucasian population deficient in CYP2D6 activity
- "Poor metabolizers" or "PMs" have two "inactive" forms (alleles) of the CYP2D6 gene
- PMs at increased risk for concentration-dependent side effects with "normal" drug doses
- Some drugs may not work (codeine; tramadol)
CYP2D6 Pharmacogenetics: Caucasians


\[ N = 1,011 \]

Number of Individuals

\[
\begin{align*}
&0.01 & 0.1 & 1 & 10 & 100 \\
&0 & 40 & 80 & 120 & \\
&Faster \quad \text{CYP2D6 Activity} \quad \text{Slower}
\end{align*}
\]

---

CYP2D6 Activity: Chinese


\[ N = 1,011 \]
\[ N = 695 \]

Number of Individuals

\[
\begin{align*}
&0.01 & 0.1 & 1 & 10 & 100 \\
&0 & 40 & 80 & 120 & \\
&Faster \quad \text{CYP2D6 Activity} \quad \text{Slower}
\end{align*}
\]
THIS DRUG'S FOR YOU
NEW TARGETED MEDICINES PROMISE BREAKTHROUGH CURES

U.S. News and World Report, 14 January 2003
• µ-opioid receptor gene (OPRM)

The genetic polymorphism A118G of the human µ-opioid receptor gene decreases effect of morphine-6-glucuronide
Lotsch et al 2002, Pharmacogenetics 12:3-9
### μ-opioid receptor gene

The genetic polymorphism A118G of the human μ-opioid receptor gene decreases effect of morphine-6-glucuronide

Lotsch et al. 2002, Pharmacogenetics 12:3-9

![Graph](image)

Concentration-effect relationship of W9G and morphine in subjects with the A118G SNP in the proximal promoter gene and without effects. The curves were calculated from the individual estimates of the parameters of the sigmoid Emax model (Table 1) and described the dose–response relationship. They represent the mean ± SD per group. White box with “H” resulted in a right shift of the curve for W9G, indicating a decrease in receptor density. It had no effect on the potency of morphine. A schematic overview of the Emax model with indication of the parameter estimation is also given.

### OPRM and COMT

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>N</th>
<th>DNA Collection</th>
<th>Successful Genotyping</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>morphine vs placebo, ventilated neonates</td>
<td>150</td>
<td>informed consent + collection (N = 132)</td>
<td>OPRM: N = 118, COMT: N = 88</td>
</tr>
<tr>
<td>II</td>
<td>morphine ± acetaminophen, postsurgical infants (0-1 year)</td>
<td>71</td>
<td>informed consent + collection (N = 54)</td>
<td>OPRM: N = 40, COMT: N = 32</td>
</tr>
<tr>
<td>III</td>
<td>continuous vs intermittent morphine, postsurgical infants (0-3 years)</td>
<td>204</td>
<td>informed consent + collection (N = 150)</td>
<td>OPRM: N = 125, COMT: N = 95</td>
</tr>
</tbody>
</table>

Included in current analyses:
OPRM: N = 283
COMT: N = 215
μ-opioid receptor gene (OPRM)

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRM gene (asn40asp)</td>
<td>OPRM gene (asn40asp)</td>
<td>OPRM gene (asn40asp)</td>
</tr>
<tr>
<td>Wild type</td>
<td>Heterozygous</td>
<td>Homozygous</td>
</tr>
<tr>
<td>84</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Total</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>118</strong></td>
<td><strong>40</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>


OPRM and COMT

Simons SH, et al. JAMA 2003;290:2419-2427

Study I
- morphine vs placebo
- ventilated neonates
- N = 150
- DNA informed consent + collection (N = 132)
- Successful genotyping: OPRM: N = 118
  COMT: N = 88

Study II
- morphine ± acetaminophen
- postsurgical infants (0-1 year)
- N = 71
- DNA informed consent + collection (N = 54)
- Successful genotyping: OPRM: N = 40
  COMT: N = 32

Study III
- continuous vs intermittent morphine
- postsurgical infants (0-3 years)
- N = 204
- DNA informed consent + collection (N = 150)
- Successful genotyping: OPRM: N = 125
  COMT: N = 95

Included in current analyses
- OPRM: N = 283
  COMT: N = 215
Catechol-O-methyl transferase (COMT)

COMT is an enzyme that metabolises catecholamines that work as neurotransmitters.

The Val158Met variant influences the human experience of pain:

patients with Met/Met variant experience more pain

(Zubieta 2003, Science)

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>21</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>47</td>
<td>17</td>
<td>41</td>
</tr>
<tr>
<td>Homozygous</td>
<td>20</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>88</td>
<td>32</td>
<td>95</td>
</tr>
</tbody>
</table>

Simons, et al.
Ped Research 2004;55:275A
Future perspectives: The Perfect Neonatal Pain Assessment Instrument

The need for drug studies in children

- Drug studies in adults or animal models may not adequately predict pharmacokinetic or pharmacodynamic properties in pediatric patients
- Unable to reliably extrapolate adult data to the pediatric population
- Drugs must be studied in children to determine their pharmacokinetics, pharmacodynamics, appropriate dose, safety and efficacy
There are two ways to live your life.
One is as though nothing is a miracle.
The other is as though everything is a miracle.

Albert Einstein (1879–1955)