ADME Issues in Children: Pediatric Pharmacokinetics

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The George Washington School of Medicine and Health Sciences
Adjunct Professor of Pediatrics, Erasmus MC-Sophia Children’s Hospital, Rotterdam, the Netherlands
Historical Drug “Development” in Children

Colic, diarrhea, cholera & teething
alcohol (8.5%)
morphine (1/8 grain)

Teething
Deodorized tincture of
opium (1.5%)
Historical Drug “Development” in Children
ECKMAN’S ALTERNATIVE

Contains Twelve Per Cent. of Alcohol by Weight, or Fourteen Per Cent. by Volume. Used as a Solvent.

FOR ALL THROAT and LUNG DISEASES INCLUDING BRONCHITIS, BRONCHIAL CATARRH, ASTHMA, HAY FEVER, COUGHS and Colds, and CATARRH OF THE STOMACH and BOWELS, and TUBERCULOSIS (CONSUMPTION)

DIRECTIONS

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.

Contains 12% of alcohol by weight or 14% per volume.

Used as a solvent.

Historical Drug “Development” in Children
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**
  - 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

- **Newborn**
  - Adolescence: transition to adulthood
  - Changes incomprehensible to most adults

- **Infant**
  - 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

- **Preschooler**
  - Adolescence: transition to adulthood
  - Changes incomprehensible to most adults

- **School-age**

- **Adolescent**

- **Adult**
The Developmental Continuum

- Fetus
- Newborn
- Infant
- Preschooler
- School-age
- Adolescent
- Adult
Determinants of Drug Response in Children

Disease

Growth and Development

Environment

Genetics

Absorption
Distribution
Receptor Interaction
Biotransformation
Excretion

Drug

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

<table>
<thead>
<tr>
<th>% Adult Activity</th>
<th>Birth</th>
<th>1 wk</th>
<th>2 wk</th>
<th>3 wk</th>
<th>1 mos</th>
<th>3 mos</th>
<th>5-10 yr</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl production</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>Pepsin</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>Gastrin</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>150</td>
<td>100</td>
</tr>
</tbody>
</table>

Agunod et al. *Amer J Digest Dis* 1969;14:400
Mozam et al. *J Pediatr* 1985;106:467
Developmental Alterations in Intestinal Drug Absorption
Influence of Higher Gastric pH

Orally Administered Penicillin (10,000 U/lb)

- Preterm neonate
- Fullterm neonate
- Infants (2 wk-2 yr)
- Children (2-13 yr)

Huang et al. J Pediatr 1953;42:657
Drug distribution
Age-dependent changes in body composition

TBW
ECW
Body Fat
## 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>
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<tr>
<td>C_{max\text{ norm}} (mg/L)</td>
<td>19.7 ± 4.9</td>
<td>17.0 ± 5.2</td>
<td>12.5 ± 3.5</td>
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<tr>
<td>C_{12\text{ 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>
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Drug Biotransformation

Phase I
- CYPs
- Esterases
- Dehydrogenases

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

Drug → Metabolite → Metabolite
Ontogeny of CYP3A4


The graph illustrates the ontogeny of CYP3A4 mRNA activity from fetal to adult stages. The x-axis represents different stages: <30 wk, 30 wk, <24 hr, 1-7 d, 8-28 d, 1-3 mo, 3-12 mo, 1-10 yr. The y-axis represents the percent adult value. The graph shows a significant increase in mRNA activity from the fetal stage to adulthood, with the highest activity observed in the 1-10 yr age group.
Midazolam Clearance in Neonates

Cisapride

4-F-2-OH-Cis

3-F-4-OH-Cis

Norcisapride

CYP3A4

CYP2B6
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>
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<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>
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<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>
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- Data expressed as mean (S.D.)
Impact of Development on Cisapride Elimination in Infants

Cisapride in Neonates and Infants: Kel vs. Postconceptional Age

Kel - 1/hr

0.000 0.100 0.200 0.300 0.400

PCA - wks

0 20 30 40 50 60

<30 wk >30 wk <24 hr 1-7 d 8-28 d 1-3 mo 3-12 mo 1-10 yr
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Linezolid Plasma Clearance Association with PCA
Linezolid Plasma Clearance Association with PNA
Drug Biotransformation

Drug → 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

\( r = 0.75, p < 0.001, y = 8.88x - 181.2 \)
Figure 1. Linear regression analysis of total body clearance of ceftazidime (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis.
Meropenem pharmacokinetics in the newborn

\[ y = 0.7301x - 19.519 \]

\[ R^2 = 0.6652 \]
Factors influencing drug disposition in infants, children and adolescents

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

Mean Intragastric pH

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

r=0.873
p<0.0001

Lack of an Effect of \textit{CYP2C19} Genotype on Omeprazole Exposure in Pediatric EMs

CYP2D6 Pharmacogenetics

Drug | EM | Stable metabolites, Excretion

Drug | PM | Stable metabolites, Excretion

“Functional” overdose
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


CYP2D6 Activity

Number of Individuals

N = 1,011
CYP2D6 Activity: Chinese


Number of Individuals

0 40 80 120

0.01 0.1 1 10 100

N = 1,011
N = 695

Faster

CYP2D6 Activity

Slower
THIS DRUG'S FOR YOU

NEW TARGETED MEDICINES PROMISE BREAKTHROUGH CURES

U.S. News and World Report, 14 January 2003
Morphine → Morphine-3-glucuronide
Morphine-6-glucuronide

μ-opioid receptor
Catechol-O-methyltransferase

EFFECT
• 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
The genetic polymorphism A118G of the human \(\mu\)-opioid receptor gene decreases effect of morphine-6-glucuronide.

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
### μ-opioid receptor gene (OPRM)

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRM gene (asn40asp)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>84</td>
<td>30</td>
<td>100</td>
<td>214</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>30</td>
<td>9</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>Homozygous</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>40</td>
<td>125</td>
<td>283</td>
</tr>
</tbody>
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Simons, et al.
*Ped Research 2004;55:275A*
OPRM and COMT

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

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*N = 150*

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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)
## Catechol-O-methyl transferase (COMT)

<table>
<thead>
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<tr>
<td><strong>COMT gene (val\textsuperscript{158}met)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>21</td>
<td>7</td>
<td>26</td>
<td>54</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>47</td>
<td>17</td>
<td>41</td>
<td>105</td>
</tr>
<tr>
<td>Homozygous</td>
<td>20</td>
<td>8</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>88</td>
<td>32</td>
<td>95</td>
<td>215</td>
</tr>
</tbody>
</table>

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

Pain: 6.8
GIVE MORPHINE
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)