Developmental and Pediatric Pharmacology

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- Professor of Pediatrics, Pharmacology, Physiology & Integrative Systems Biology, GWU, Washington, DC
- Adjunct Professor of Medicine, Pharmacology & Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

Historical Drug “Development” in Children

Teething
Deodorized tincture of opium (1.5%) morphine (1/8 grain)

Colic, diarrhea, cholera & teething alcohol (8.5%)

Historical Drug “Development” in Pediatrics

Sulfanilamide
Chloromycetin

Hydrocortisone Ophthalmic
Unlicensed and off-label drug use in pediatric and neonatal intensive care units

Determinants of Drug Response in Infants

The Challenge of Pediatric Clinical Pharmacology: Determining the Source(s) of Variability...

Growth and Development

Absorption
Distribution
Receptor Interaction
Biotransformation
Excretion

Environment
Genetics

Disease

Drug
Exposure
Response

Ontogeny
Pharmacogenetics

Variability
Critical Role of Pharmacokinetics in Pharmacotherapy

- The combination of A, D, M, E dictate exposure which dictates dose.

Factors Influencing Oral Drug Absorption

Factors that influence oral drug absorption include:

- Biliary function
- Gastric emptying time
- Intestinal motility
- Microbial colonization
- Intestinal drug transport

Physicochemical & Mechanical

Gastric pH

Intestinal drug metabolism
Intestinal surface area

Drug Absorption Developmental Changes in Gastric pH

- HCl production
- Pepsin
- Gastrin

% Adult Activity

Birth - Adult

0 - 250
Developmental Alterations in Intestinal Drug Absorption

Influence of Higher Gastric pH

Orally Administered Penicillin (10,000 U/lb)

![Graph showing penicillin concentration over time for preterm, fullterm neonate, infants, and children.](Huang et al. J Pediatr 1953;42:657)

Developmental Alterations in Gastric Emptying Rate


Influence of developmental alterations in gastric emptying

<table>
<thead>
<tr>
<th>Postconceptional Age</th>
<th>28-36 wks.</th>
<th>36-42 wks.</th>
<th>42-54 wks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 17)</td>
<td>(n = 13)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<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>5.8(2.9)</td>
<td>4.8(1.9)</td>
<td>2.2(1.1)</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>11.5(3.9)</td>
<td>11.5(3.9)</td>
<td>4.8(3.0)</td>
</tr>
<tr>
<td>AUC (ng*ml/hr)</td>
<td>25784(2875)</td>
<td>362(198)</td>
<td>364(249)</td>
</tr>
<tr>
<td>VSS/F (L/kg)</td>
<td>7.4(4.7)</td>
<td>12.7(9.1)</td>
<td>4.7(1.5)</td>
</tr>
<tr>
<td>CL/F (L/hr/kg)</td>
<td>0.42(0.24)</td>
<td>0.72(0.42)</td>
<td>0.93(0.63)</td>
</tr>
</tbody>
</table>

Sources:

Data expressed as mean (S.D.)
**Factors Influencing Extraoral Drug Absorption**

- **Physicochemical & Mechanical**
  - Regional blood flow
  - Temperature
  - Diffusional surface area
  - Hydration
  - Drug-vehicle interactions
  - Local pH
  - Tissue binding sites

**Developmental Alterations in Skin thickness**

- GA: 26 wk, PNA: 1 day
- GA: 26 wk, PNA: 16 days
- GA: 40 wk, PNA: 1 day


**Impact of Ontogeny on Drug Distribution**

- TBW
- ECW
- Body Fat

![Graph showing changes in TBW, ECW, and Body Fat from birth to 40 years]
**Amikacin Administration in Neonates: Pharmacokinetic Variables**

<table>
<thead>
<tr>
<th>Vd (L/kg)</th>
<th>Half-life (h)</th>
<th>Cl (ml/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean ± 1 sd</td>
<td>mean ± 1 sd</td>
<td>mean ± 1 sd</td>
</tr>
<tr>
<td>&lt; 28 w</td>
<td>0.700 ± 0.151</td>
<td>12.20 ± 3.83</td>
</tr>
<tr>
<td>28 - &lt; 31 w</td>
<td>0.660 ± 0.120</td>
<td>8.40 ± 1.36</td>
</tr>
<tr>
<td>31 - &lt; 34 w</td>
<td>0.614 ± 0.013</td>
<td>7.71 ± 0.31</td>
</tr>
<tr>
<td>34 - &lt; 37 w</td>
<td>0.573 ± 0.013</td>
<td>6.77 ± 0.32</td>
</tr>
<tr>
<td>37 - 41 w</td>
<td>0.520 ± 0.021</td>
<td>5.55 ± 0.49</td>
</tr>
</tbody>
</table>

Langhendries et al, Med Mal Infect, 1993; 23:44

**HARRIET LANE 2002 (Gentamicin)**

<table>
<thead>
<tr>
<th>PCA (wks)</th>
<th>PNA (days)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 29</td>
<td>0-28</td>
<td>2.5</td>
<td>24</td>
</tr>
<tr>
<td>&gt; 28</td>
<td>3</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>30-36</td>
<td>0-14</td>
<td>7.5</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 14</td>
<td>3</td>
<td>2.5</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 37</td>
<td>0-7</td>
<td>2.5</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 7</td>
<td>2.5</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

PCA (Premature)
HARRIET LANE 2005 and NEOFAX (Gentamicin)

<table>
<thead>
<tr>
<th>PCA (wks)</th>
<th>PNA (days)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 29</td>
<td>0-7</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>8-28</td>
<td>4</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>&gt; 28</td>
<td>4</td>
<td>24</td>
<td></td>
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Drug Biotransformation

Drug → Phase I (CYPs, Esterases, Dehydrogenases) → Phase II (UGTs, NATs, STs, MTs, GSTs) → Metabolite

Ontogeny of CYP3A4

Human Hepatic DME Ontogeny

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH1A</td>
<td>CYP2C19</td>
<td>ADH1B</td>
</tr>
<tr>
<td>CYP3A7</td>
<td>CYP3A5</td>
<td>CYP3A7</td>
</tr>
<tr>
<td>FMO1</td>
<td>GSTA1</td>
<td>ADH1C</td>
</tr>
<tr>
<td>GSTP</td>
<td>GSTA2</td>
<td>FMO3</td>
</tr>
<tr>
<td>SULT1E1</td>
<td>SULT1A1</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>SULT1A3</td>
<td></td>
<td>GSTA1</td>
</tr>
</tbody>
</table>


Human DME Ontogeny

Impact of Ontogeny on Drug Metabolism

Midazolam Clearance in Neonates

![Graph showing clearance vs. birth weight]

CYP3A4

F - OH

4-F-2-OH-Chl

F

OH

CYP2B6

NH

CYP3A4

NH

3-F-4-OH-Chl

Norcisapride

Cisapride

Single-Dose (0.2 mg/kg) Pharmacokinetics of Cisapride in Neonates and Young Infants

<table>
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<td>44.5(19.5)</td>
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<tr>
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<td>4.8(1.3)</td>
<td>2.2(1.1)</td>
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<tr>
<td>T1/2 (hr)</td>
<td>17.5(3.9)</td>
<td>17.5(3.9)</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>4.3(1.3)</td>
</tr>
<tr>
<td>Cl/F (L/hr/Kg)</td>
<td>4.49(2.26)</td>
<td>8.73(4.45)</td>
<td>9.86(6.83)</td>
</tr>
</tbody>
</table>


Oxazepam: oral route (91)
Parameter | Adult (n=57) | Child (n=44) | Infant (n=10)
--- | --- | --- | ---
Vdss (L/kg) | 0.63 ± 0.13 | 0.71 ± 0.18 | 0.83 ± 0.18
Cl (L/hr/kg) | 0.10 ± 0.01 | 0.30 ± 0.12 | 0.52 ± 0.15
t1/2 (hr) | 4.6 ± 1.7 | 3.3 ± 0.9 | 2.0 ± 0.9
Cmax total (mg/L) | 19.7 ± 4.9 | 17.0 ± 5.2 | 12.5 ± 3.5
C12 pred (mg/L) | 3.3 ± 2.1 | 0.41 ± 0.72 | 0.03 ± 0.05
T>MIC90 (%) | 70-100% | 35-70% | 20-35%

Linezolid Plasma Clearance Association with PCA

Linezolid Plasma Clearance Association with PNA
Linezolid plasma clearance in neonates


Maturation of renal function

Summary of Developmental Alterations Relevant for Pediatric Clinical Pharmacology

• Differences in extravascular absorption rate and extent
• Altered body composition influences distribution
• Marked ontogeny of drug metabolizing enzymes
• Dynamic influence of development on renal function
Factors influencing drug disposition in infants, children and adolescents

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

Elevated Morphine Concentrations in Neonates Treated With Morphine and Prolonged Hypothermia for Hypoxic Ischemic Encephalopathy

Audrey Hill MCh, MCB, Akinwatura Ikpe, MCh, Olusegun Adeyemo, MBBS, FRCS, UK, Yemi Ayodele, MBBS, FRCS, UK

The Department of Paediatrics, University College Hospital, Ibadan, Nigeria. This study was supported by the International Children's Health Network and the Wellcome Trust, UK.

Which factors influence the drug disposition in infants, children, and adolescents?

Which treatment is associated with elevated morphine concentrations in neonates?
Factors influencing drug disposition in neonates, infants, children and adolescents

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

Pharmacogenetics:

“Study of the role of genetics in drug response”

Friedrich Vogel (1957)
Some important milestones in the history of pharmacogenomics

1866 Mendel Lays down the principles of heredity
1909 Garrod Publication of "Inborn Errors of Metabolism"
1932 Snyder Characterization of the phenylthiourea non-taster as an autosomal recessive trait
1954 Hughes et al. Relates isoniazid neuropathy to metabolism – N-acetyltransferase
1957 Kalow Characterization of acetylcholinesterase deficiency
1957 Motulsky Inherited differences in drug metabolism
1957 Vogel Coined the term "pharmakogenetik"
1959 Price Evans Characterization of acetylator polymorphisms
1960 Kalow The first textbook on pharmacogenetics
1962 Kalow et al. Describes sparteine metabolism polymorphism
1984 Wedlund et al. Description of the cytochrome CYP2D6 polymorphism
1997 Eichelbaum et al. Polymerase chain reaction (PCR) based methods used to detect phenotype

Cytochrome P450 2D6
CYP2D6

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: Chinese

Unravelling CYP2D6 Pharmacogenetics

- **Individuals**
  - UM: ultrarapid metabolizer (~10 - 15%)
  - IM: intermediate metabolizer (~10 - 15%)
  - PM: poor metabolizer (~5 - 10% Caucasians)

**Case Report**

**Lancet 2006; 368: 704**

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

- Full-term healthy male infant
- Day 7 pp: intermittent periods of difficulty in breastfeeding
- Day 11: the baby had regained his birthweight
- Day 12: grey skin, milk intake had fallen
- Day 13: the baby was found dead

- Autopsy: no abnormality
- Blood concentration of morphine (metabolite of codeine):
  - 70 ng/mL versus 0.2 - 2.2 ng/mL (typical)

**Pharmacogenetics of Codeine**

- **Codeine**
  - **Site of action**
  - Cytochrome P450
  - Morphine

- Plasma morphine levels after 170 mg codeine p.o.

Eckhardt et al., Pain 1998
Case Report

**Lancet 2006; 368: 704**

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

**Explanation:**

- **Medication mother due to episiotomy pain:**
  - Codeine 60 mg plus paracetamol 1000 mg every 12 hrs for 2 weeks
- **Morphine concentration in stored milk:** 87 ng/mL
- **Mother:**
  - CYP2D6 genotype: CYP2D6*2x2 gene duplication
  - *Ultra rapid metabolizer phenotype*

**Cytochrome P450 2C19**

**CYP2C19**

**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
Drug X: Lack of Association Between CYP2C19 “Activity Score” (AS) and Apparent Terminal Elimination Rate Constant (ke)

Kearns G, Leeder JS, Gaedigk A, Drug Metab Disp 2010;38:894-97

Drug Y: Significant Association Between CYP2C19 “Activity Score” (AS) and Apparent Terminal Elimination Rate Constant (ke)

Kearns G, Leeder JS, Gaedigk A, Drug Metab Disp 2010;38:894-97

兰索拉唑和泮托拉唑生物转化

兰索拉唑

CYP2C19

5-OH兰索拉唑

CYP3A4

去甲基泮托拉唑

CYP2C19

兰索拉唑

去甲基泮托拉唑

CYP3A4

泮托拉唑

CYP2C19

泮托拉唑硫酸盐

去甲基泮托拉唑

磺基转移酶
Metabolic Pathways for Selected Proton Pump Inhibitors

- Pantoprazole
  - Demethylated pantoprazole
  - Pantoprazole sulfate

- Omeprazole
  - 5-O-Desmethylomeprazole
  - 3-Hydroxyomeprazole
  - 5-Hydroxymeprazole
  - Omeprazole hydroxysulphone
  - Omeprazole sulphone

- CYP2C19
- CYP3A4
- Sulfotransferase

Incorporating Genetics into (Pediatric) Clinical Trials
"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

Philipus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus