Developmental and Pediatric Pharmacology

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- Eckenstein-Geigy Professor of Pediatric Pharmacology, University Children’s Hospital Basel, Switzerland
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 Pediatrics
Adverse Drug Reactions - History

• 1956 – neonates who received sulphonamides had more kernicterus than those receiving tetracycline

• Chloramphenicol & “gray baby syndrome”

• “Gasping syndrome”
  – Agents that were reconstituted in benzylalcohol

• Need history repeat itself >50 years later?
## Adverse Drug Reactions by Age and Hospital Location

<table>
<thead>
<tr>
<th>Age</th>
<th>Low Severity</th>
<th>High Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 month</td>
<td>N=897</td>
<td>N=112</td>
</tr>
<tr>
<td>1-12 months</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>1 year - 5 years</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>5 years</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>5 years</td>
<td>54%</td>
<td>71%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Low Severity</th>
<th>High Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Pediatrics</td>
<td>N=964</td>
<td>N=119</td>
</tr>
<tr>
<td>Heme/Onc</td>
<td>36%</td>
<td>19%</td>
</tr>
<tr>
<td>PICU</td>
<td>31%</td>
<td>34%</td>
</tr>
<tr>
<td>NICU</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>7%</td>
</tr>
</tbody>
</table>

## Medication Use in NICU – Pediatrix, Inc. Data for 2007; 72,647 Patients - Rate/1000 Discharges

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rank</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>1</td>
<td>822</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2</td>
<td>726</td>
</tr>
<tr>
<td>Surfactants</td>
<td>3</td>
<td>234</td>
</tr>
<tr>
<td>Caffeine</td>
<td>4</td>
<td>224</td>
</tr>
<tr>
<td>Furosemide</td>
<td>5</td>
<td>199</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6</td>
<td>177</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>Dopamine</td>
<td>9</td>
<td>89</td>
</tr>
<tr>
<td>Midazolam</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Morphine</td>
<td>11</td>
<td>71</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>13</td>
<td>62</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>15</td>
<td>54</td>
</tr>
</tbody>
</table>

Data from Reese Clark
Unlicensed and off-label drug use in pediatric and neonatal intensive care units

% < 28 weeks 28-<37 weeks term neonates infants children adolescents
Determinants of Drug Response in Infants

- Drug Exposure
- Absorption
- Distribution
- Receptor Interaction
- Biotransformation
- Excretion

Factors:
- Disease
- Growth and Development
- Environment
- Genetics

Drug Flow:
- Drug
- Exposure
- Response
The Challenge of Pediatric Clinical Pharmacology: Determining the Source(s) of Variability......

Ontogeny

Pharmacogenetics

Variability
Critical Role of Pharmacokinetics in Pharmacotherapy

- The combination of ADME dictate exposure which dictates dose.
Critical Role of Pharmacokinetics in Pharmacotherapy......

Absorption
Factors Influencing Oral Drug Absorption

- Biliary function
- Gastric pH
- Gastric emptying time
- Intestinal motility
- Intestinal surface area
- Intestinal drug metabolism
- Microbial colonization
- Intestinal drug transport
- Splanchnic blood flow

Biopharmaceutical, Interactions, etc
Drug Absorption
Developmental Changes in Gastric pH

% Adult Activity

Birth 1 wk 2 wk 3 wk 1 mos 3 mos 5-10 yr Adult

Gastrin Pepsin HCl production

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)

Penicillin concentration (U/mL)

Time (hr)

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

Huang et al. J Pediatr 1953;42:657
Developmental Alterations in Gastric Emptying Rate

30 minute gastric retention

<table>
<thead>
<tr>
<th>Postnatal Age</th>
<th>% of meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-12 hr</td>
<td>Pre-term</td>
</tr>
<tr>
<td>22-36 hr</td>
<td>Full term</td>
</tr>
<tr>
<td>46-60 hr</td>
<td></td>
</tr>
</tbody>
</table>

Gupta & Brans *Pediatrics* 1978;62:26
**Influence of developmental alterations in gastric emptying**

<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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<tbody>
<tr>
<td><strong>Cmax (ng/ml)</strong></td>
<td>30.0 (17.5)</td>
<td>23.3 (11.7)</td>
<td>44.5 (19.5)</td>
</tr>
<tr>
<td><strong>Tmax (hr)</strong></td>
<td>5.0 (2.6)</td>
<td>4.3 (3.3)</td>
<td>2.2 (1.1)</td>
</tr>
<tr>
<td><strong>T1/2 (hr)</strong></td>
<td>11.6 (3.0)</td>
<td>11.5 (3.0)</td>
<td>4.8 (3.0)</td>
</tr>
<tr>
<td><strong>AUC (ng/ml*hr)</strong></td>
<td>568 (257)</td>
<td>362 (198)</td>
<td>364 (249)</td>
</tr>
<tr>
<td><strong>VDss/F (L/kg)</strong></td>
<td>7.4 (4.7)</td>
<td>12.7 (9.1)</td>
<td>4.1 (1.5)</td>
</tr>
<tr>
<td><strong>Cl/F (L/hr/kg)</strong></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.)
Factors Influencing Extraoral Drug Absorption

Physicochemical & Mechanical

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

Barrier thickness
Developmental Alterations in Skin thickness

GA: 26 wk
PNA: 1 day

GA: 26 wk
PNA: 16 days

GA: 40 wk
PNA: 1 day

Critical Role of Pharmacokinetics in Pharmacotherapy......
Factors Influencing Drug Distribution Volume

- **Extent**
  - size of body water/adipose compartment
  - degree of plasma/tissue protein binding
  - permeability of cell membranes
  - acid-base balance

- **Rate**
  - regional blood flow
  - organ perfusion pressure
  - cardiac output
Impact of Ontogeny on Drug Distribution

The graph illustrates the impact of ontogeny on drug distribution across different stages of life, from birth to 40 years old. The curves show changes in TBW, ECW, and Body Fat over time.

- **TBW** (Total Body Water) decreases gradually from birth to adulthood, stabilizing around 20 years old.
- **ECW** (Extracellular Water) shows a similar trend but with a slight increase around 10 years old.
- **Body Fat** increases significantly from birth, peaking around 20 years old, and then decreases in later years.

The data points and lines indicate the dynamic changes in body composition and water distribution throughout the lifespan.
# Amikacin Administration in Neonates: Pharmacokinetic Variables

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Vd (L/ kg) mean ± 1 sd</th>
<th>Half-life (h) mean ± 1 sd</th>
<th>Cl (ml/kg/h) mean ± 1 sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28 w</td>
<td>0.700 ± 0.151</td>
<td>12.20 ± 3.83</td>
<td>0.73 ± 0.148</td>
</tr>
<tr>
<td>28 - &lt; 31 w</td>
<td>0.660 ± 0.120</td>
<td>8.40 ± 1.36</td>
<td>0.87 ± 0.127</td>
</tr>
<tr>
<td>31 - &lt; 34 w</td>
<td>0.614 ± 0.013</td>
<td>7.71 ± 0.31</td>
<td>0.98 ± 0.025</td>
</tr>
<tr>
<td>34 - &lt; 37 w</td>
<td>0.573 ± 0.013</td>
<td>6.77 ± 0.32</td>
<td>1.09 ± 0.061</td>
</tr>
<tr>
<td>37 - 41 w</td>
<td>0.520 ± 0.021</td>
<td>5.55 ± 0.49</td>
<td>1.15 ± 0.036</td>
</tr>
</tbody>
</table>

*Langhendries et al, Med Mal Infect, 1993;23:44*
<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 (2.5)</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>8-28</td>
<td>4 (2.5)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>&gt; 28</td>
<td>4 (3)</td>
<td>24</td>
</tr>
<tr>
<td>30-33</td>
<td>0-7</td>
<td>4.5 (3)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>&gt; 7</td>
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<td>24</td>
</tr>
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</tr>
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<td></td>
<td>&gt;7</td>
<td>4 (2.5)</td>
<td>18</td>
</tr>
</tbody>
</table>
Critical Role of Pharmacokinetics in Pharmacotherapy......
Drug Biotransformation

Phase I
- CYPs
- Esterases
- Dehydrogenases

Phase II
- UGTs
- NATs
- STs
- MTs
- GSTs
Sites of drug metabolism

Extrahepatic enzymes

Hepatic enzymes
Factors that effect drug metabolism

- Herbal medicine
- Disease
- Drugs
- Genetics
- Age
- Nutrition
Ontogeny of CYP3A4


Percent Adult Value

0  20  40  60  80  100  120

<mRNA Activity>

$<$30 wk >30 wk <24 hr 1-7 d 8-28 d 1-3 mo 3-12 mo 1-10 yr

Fetus Newborn Infant Activity
## 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>ADH1C</td>
</tr>
<tr>
<td>FMO1</td>
<td>GSTA1</td>
<td>FMO3</td>
</tr>
<tr>
<td>GSTP</td>
<td>GSTA2</td>
<td>AOX</td>
</tr>
<tr>
<td>SULT1E1</td>
<td>SULT1A1</td>
<td>GSTM</td>
</tr>
<tr>
<td>SULT1A3</td>
<td></td>
<td>CYP1A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SULT2A1</td>
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<tr>
<td></td>
<td></td>
<td>CYP2C9</td>
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<tr>
<td></td>
<td></td>
<td>UGT1A1</td>
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<tr>
<td></td>
<td></td>
<td>CYP2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UGT1A6</td>
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<tr>
<td></td>
<td></td>
<td>CYP2E1</td>
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<tr>
<td></td>
<td></td>
<td>UGT2B7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PON1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPHX1</td>
</tr>
</tbody>
</table>

Human DME Ontogeny

DME (pmol/mg protein)

EGA 10-26 wks
EGA >26-40 wks
PNA 0-6 mo
PNA >6 mo-18 yr

SULT1E1
Class 1
SULT1A1
Class 2
CYP2C9
Class 3
Impact of Ontogeny on Drug Metabolism

Changes in Metabolic Capacity

Midazolam Clearance in Neonates


Birth Weight (g)

Clearance (L/hr)
Cisapride

4-F-2-OH-Cis

3-F-4-OH-Cis

Norcisapride
## 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>
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</tr>
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</table>


- Data expressed as mean (S.D.)
<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>$C_{\text{max}}_{\text{norm}}$ (mg/L)</td>
<td>19.7 ± 4.9</td>
<td>17.0 ± 5.2</td>
<td>12.5 ± 3.5</td>
</tr>
<tr>
<td>$C_{12 \text{ pred}}$ (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>
</table>
Linezolid Plasma Clearance Association with PCA
Linezolid plasma clearance in neonates
Critical Role of Pharmacokinetics in Pharmacotherapy......
Maturation of renal function

- **GFR (ml/min/1.73m²)**
- **PAH CL (ml/min/1.73m²)**
- **Kidney length (cm)**
- **Kidney weight (g)**

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.
<table>
<thead>
<tr>
<th>PCA (wks)</th>
<th>PNA (days)</th>
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<tr>
<td></td>
<td>&gt;7</td>
<td>4 (2.5)</td>
<td>18 (8)</td>
</tr>
</tbody>
</table>
Maturation of GFR in neonates as reflected by Amikacin clearance

De Cock, Allegaert, van den Anker, et al. *Clin Pharmacokinet* 2012;51(2):105-17

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose Range</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langhendries <em>et al.</em></td>
<td>15.5-20 mg/kg</td>
<td>24-42 hrs</td>
</tr>
<tr>
<td>Sherwin <em>et al.</em></td>
<td>14-15 mg/kg</td>
<td>24-36 hrs</td>
</tr>
<tr>
<td>Neofax® (2009)</td>
<td>15-18 mg/kg</td>
<td>24-48 hrs</td>
</tr>
<tr>
<td><em>RedBook® (2009)</em></td>
<td>7.5-10 mg/kg</td>
<td>8-24 hrs</td>
</tr>
<tr>
<td>BNFc (2009)</td>
<td>15 mg/kg</td>
<td>24 hrs</td>
</tr>
<tr>
<td>New regimen</td>
<td>12-20 mg/kg</td>
<td>20-48 hrs</td>
</tr>
</tbody>
</table>
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

Anikó Róka, MD⁷, Kis Tamas Melinda, MD⁷, Barna Vásárhelyi, PhD⁷, Tamás Machay, PhD⁷, Denis Azzopardi, MD⁷, Miklós Szabó, PhD⁷

*First Department of Paediatrics, Semmelweis University, Budapest, Hungary; Research Group of Paediatrics and Nephrology, Hungarian Academy of Sciences, Budapest, Hungary; Division of Clinical Sciences, Hammersmith Campus, Imperial College London, United Kingdom

The authors have indicated they have no financial relationships relevant to this article to disclose.

What’s Known on This Subject

Data obtained in adults indicate that even short-term hypothermia may have an effect on the metabolism of major analgesics and other drugs. No data are available for neonates concerning the impact of hypothermia on the pharmacokinetics of morphine.

What This Study Adds

The aim of our observational study, therefore, was to investigate whether morphine pharmacokinetics are altered during prolonged moderate systemic hypothermia in asphyxiated neonates, resulting in excessively high morphine concentrations compared with infants kept at normothermia; this would be important information for clinicians wishing to provide hypothermia.
**FIGURE 1**
Serum morphine concentrations at 72 hours after birth in asphyxiated neonates treated with hypothermia or on normothermia. At this time point, 6 of 7 infants in the hypothermia group and 1 of 6 in the normothermia group had potentially toxic morphine serum levels (>300 ng/mL; *P* = .007).

**FIGURE 2**
Relation between serum morphine concentrations and infusion rates in asphyxiated neonates treated with hypothermia or on normothermia. Morphine concentrations at 24, 48, and 72 hours after birth were related to infusion rate (averaged over previous 24 hours) and hypothermia (adjusted $r^2 = 0.527; P \leq .0001$).
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-nonautaster as an autosomal recessive trait
1954 Hughes et al. Relates isoniazid neuropathy to metabolism – n-acetyltransferase
1956 Carson et al. Discovery of glucose G-6 PD deficiency
1957 Kalow Characterizes acetylcholinesterase deficiency
1957 Motulsky Inherited differences in drug metabolism
1957 Vogel Coins the term ‘pharmakogenetik’
1960 Price Evans Characterization of acetylators polymorphisms
1962 Kalow The first textbook on pharmacogenetics
1979 Eichelbaum et al. Describes sparteine metabolism polymorphism
1982 Eichelbaum et al. Recognition of link between sparteine and debrisoquine metabolism
1984 Wedlund et al. Description of the cytochrome CYP2C19 polymorphism
1988 Gonzalez Explanation for the debrisoquine phenotype
1997 Yates et al. Polymerase chain reaction (PCR) based methods used to detect thiopurine
Cytochrome P450 2D6
CYP2D6
CYP2D6 Pharmacogenetics

Drug

EM

Stable metabolites, Excretion

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


![Graph showing CYP2D6 activity with a distribution of individuals across different activity levels. The graph indicates the number of individuals with faster or slower CYP2D6 activity.]
CYP2D6 Activity: Chinese


Number of Individuals

N = 1,011
N = 695

Faster
CYP2D6 Activity
Slower
Unravelling CYP2D6 Pharmacogenetics

Individuals

EM
Extensive Metabolizer

IM
Intermediate Metabolizer

UM
ultrarapid metabolizer

PM
Poor Metabolizer

Griese et al.
Pharmacogenetics 1998,
Raimundo et al. CPT 2004,
Toscano et al.
Pharmacogenetics 2006
Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

- 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 ng/mL (typical)
Pharmacogenetics of Codeine

Cytochrome P450 2D6

Codeine → Extensive Metabolizer

Morphine

Poor Metabolizer

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

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

**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

![Graph showing the lack of association between CYP2C19 activity score and apparent terminal elimination rate constant.](image-url)
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

\[ y = 0.4625x + 0.098 \]
\[ R^2 = 0.4475 \]
\[ P < 0.001 \]
兰索拉唑和泮托拉唑生物转化

兰索拉唑

- CYP2C19
- CYP3A4

5-OH兰索拉唑
兰索拉唑砜

泮托拉唑

- CYP2C19
- CYP3A4

去甲基泮托拉唑
泮托拉唑砜

磺基转移酶
泮托拉唑硫酸盐
Metabolic Pathways for Selected Proton Pump Inhibitors

- **Metabolites:**
  - Pantoprazole
  - Pantoprazole sulphone
  - CYP3A4
  - CYP2C19
  - Sulfotransferase

- **Reactions:**
  - 5-O-Desmethylomeprazole
  - 3-Hydroxyomeprazole
  - 5-Hydroxyomeprazole
  - Omeprazole sulphone
  - Omeprazole hydroxysulphone
  - Demethylated pantoprazole
  - Pantoprazole sulfate
Target therapy
"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
THANK YOU!