Developmental and Pediatric Pharmacology

John N. van den Anker MD PhD

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• Professor of Pediatrics, Pharmacology, Physiology & Integrative Systems Biology, GWU, Washington, DC
• 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></th>
<th>Low Severity</th>
<th>High Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>1-12 months</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>1 year - 5 years</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>5 years</td>
<td>54%</td>
<td>71%</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>N=964</td>
<td>N=112</td>
</tr>
<tr>
<td>General Pediatrics</td>
<td>36%</td>
<td>19%</td>
</tr>
<tr>
<td>Heme/Onc</td>
<td>31%</td>
<td>34%</td>
</tr>
<tr>
<td>PICU</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>NICU</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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28 weeks</td>
<td>70%</td>
</tr>
<tr>
<td>28-&lt;37 weeks</td>
<td>60%</td>
</tr>
<tr>
<td>Term neonates</td>
<td>50%</td>
</tr>
<tr>
<td>Infants</td>
<td>40%</td>
</tr>
<tr>
<td>Children</td>
<td>30%</td>
</tr>
<tr>
<td>Adolescents</td>
<td>20%</td>
</tr>
</tbody>
</table>
Determinants of Drug Response in Infants

Disease
Growth and Development

Environment Genetics

Absorption Distribution Receptor Interaction Biotransformation Excretion

Drug Exposure Response
The Challenge of Pediatric Clinical Pharmacology: Determining the Source(s) of Variability......
Critical Role of Pharmacokinetics in Pharmacotherapy……

- The combination of ADME dictate exposure which dictates dose.
Critical Role of Pharmacokinetics in Pharmacotherapy......
Factors Influencing Oral Drug Absorption

Physicochemical & Mechanical

- Gastric pH
- Splanchnic blood flow
- Intestinal drug metabolism
- Intestinal surface area
- Intestinal drug transport
- Biopharmaceutical, Interactions, etc

Gastric emptying time

- Intestinal motility
- Microbial colonization
- Biliary function
Drug Absorption
Developmental Changes in Gastric pH

% Adult Activity

Gastrin
Pepsin
HCl production

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

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)

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

30 minute gastric retention

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>
</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>
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<td>AUC (ng/ml*hr)</td>
<td>568(257)</td>
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<td>364(249)</td>
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<td>VDss/F (L/kg)</td>
<td>7.4(4.7)</td>
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<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.)
Factors Influencing Extraoral Drug Absorption

Physicochemical & Mechanical

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

Barrier thickness
Developmental Alterations in Skin thickness

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 shows the impact of ontogeny on drug distribution over different age ranges. The x-axis represents age with intervals from birth to 40 years, while the y-axis indicates the percentage of total body water (TBW), extracellular water (ECW), and body fat. The curves illustrate how these components change as age progresses, highlighting the differences in drug distribution across various stages of ontogeny.
### Amikacin Administration in Neonates: Pharmacokinetic Variables

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Vd (L/kg)</th>
<th>Half-life (h)</th>
<th>Cl (ml/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</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</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</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</td>
<td>0.573 ± 0.013</td>
<td>6.77 ± 0.32</td>
<td>1.09 ± 0.061</td>
</tr>
<tr>
<td>37 - 41</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>
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<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>
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<td></td>
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<td>4 (3)</td>
<td>24</td>
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</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>4 (2.5)</td>
<td>18</td>
</tr>
</tbody>
</table>
Critical Role of Pharmacokinetics in Pharmacotherapy......

Metabolism
Drug Biotransformation

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

Metabolite → Metabolite
- 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


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>ADH1C</td>
</tr>
<tr>
<td>FMO1</td>
<td>GSTA1</td>
<td>AOX</td>
</tr>
<tr>
<td>GSTP</td>
<td>GSTA2</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>SULT1E1</td>
<td>SULT1A1</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>SULT1A3</td>
<td></td>
<td>CYP2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2E1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPHX1</td>
</tr>
</tbody>
</table>

Human DME Ontogeny

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

DME (pmol/mg protein)

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

Changes in Metabolic Capacity

Midazolam Clearance in Neonates


MID
CYP3A4
1-OH Mid
CYP3A5
CYP3A4
4-OH Mid

Birth Weight (g)

Clearance (L/hr)
Cisapride

\[
\text{CYP3A4} \xrightarrow{4-F-2-OH-Cis} \text{CYP3A4} \xrightarrow{3-F-4-OH-Cis}
\]

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

<table>
<thead>
<tr>
<th>Postconceptional Age</th>
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<td>0.85(0.69)</td>
</tr>
</tbody>
</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&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>4.6 ± 1.7</td>
<td>3.3 ± 0.9</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;&lt;sub&gt;norm&lt;/sub&gt; (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&lt;sub&gt;12 pred&lt;/sub&gt; (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&lt;sub&gt;90&lt;/sub&gt; (%)</td>
<td>70-100%</td>
<td>35-70%</td>
<td>20-35%</td>
</tr>
</tbody>
</table>

Linezolid Plasma Clearance Association with PCA

![Graph showing Linezolid Plasma Clearance Association with PCA](image-url)
Linezolid plasma clearance in neonates

![Graph showing linezolid plasma clearance in neonates. The graph plots POST-NATAL AGE in days on the x-axis and CLEARANCE in mL/min/kg on the y-axis. Different symbols represent different age groups: preterm (< 8 days), preterm (> 8 days), full term (< 8 days), and full term (> 8 days).]
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)

GFR (ml/min/1.73m$^2$)

- Term
- Preterm (<2000gm)
- Preterm (<1500 gm)

Term: 
- 1-2 d: 
- 8-9 d: 
- 15-16 d: 

Preterm (<2000gm): 
- 1-2 d: 
- 8-9 d: 
- 15-16 d: 

Preterm (<1500 gm): 
- 1-2 d: 
- 8-9 d: 
- 15-16 d:
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>
<th>Dose (mg/kg)</th>
<th>Interval (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 29</td>
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<td>24 (12)</td>
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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>Regimen</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><strong>RedBook® (2009)</strong></td>
<td>7.5-10 mg/kg</td>
<td><strong>8-24 hrs</strong></td>
</tr>
<tr>
<td>BNFc (2009)</td>
<td>15 mg/kg</td>
<td>24 hrs</td>
</tr>
<tr>
<td><strong>New regimen</strong></td>
<td>12-20 mg/kg</td>
<td><strong>20-48 hrs</strong></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, MD*, Kiss Tamás Melinda, MD*, Barna Vásárhelyi, PhD*, Tamás Machay, PhD*, Denis Azzopardi, MD*, Mihlós Szabó, PhD*

*First Department of Pediatrics, Semmelweis University, Budapest, Hungary; †Research Group of Pediatrics 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.

<table>
<thead>
<tr>
<th>What's Known on This Subject</th>
<th>What This Study Adds</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>
FIGURE 1
Serum morphine concentrations at 72 hours after birth in asphyxiated neonates treated with hypothermia or normothermia. At this time point, 8 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 normothermia. Morphine concentrations at 24, 48, and 72 hours after birth were related to infusion rate (averaged over previous 24 hours) and hypothermia (adjusted $r^2 = 0.227, P = .001$).
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
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

Drug

*PM*

“Functional” overdose

Stable metabolites, Excretion
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


Number of Individuals

N = 1,011

0 1 10 100

$0.01 \quad 0.1 \quad 1 \quad 10$

Faster CYP2D6 Activity Slower

12.6
CYP2D6 Activity: Chinese


Number of Individuals

N = 1,011
N = 695

Faster CYP2D6 Activity Slower
Unravelling CYP2D6 Pharmacogenetics

Individuals

EM Extensive Metabolizer

UM ultrarapid metabolizer

IM Intermediate Metabolizer

PM Poor Metabolizer

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

Gideon Koren, James Cairns, David Chitayat, Andrea Goodlgk, 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

Codeine is metabolized by Cytochrome P450 CYP2D6 to morphine. Morphine is the active metabolite of codeine, and its site of action is in the brain.

Plasma morphine levels after 170 mg codeine p.o. are shown in the graph. The graph shows the plasma morphine levels for both extensive metabolizers and poor metabolizers over time.

Eckhardt et al., Pain 1998
Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Goodligk, 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

CYP2C19 Activity Score
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

\[ y = 0.4625x + 0.098 \]
\[ R^2 = 0.4475 \]

CYP2C19 Activity Score

\( P < 0.001 \)
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  →  兰索拉唑砜

泮托拉唑

CYP2C19  →  去甲基泮托拉唑

CYP3A4  →  泮托拉唑砜

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

Omeprazole
- 5-O-Desmethylomeprazole (CYP2C19)
- 3-Hydroxyomeprazole (CYP3A4)
- 5-Hydroxyomeprazole (CYP3A4)
- Omeprazole hydroxysulphone (CYP2C19)

Pantoprazole
- Demethylated pantoprazole sulphone (Sulotransferase)
- Pantoprazole sulphone (CYP2C19)
- Pantoprazole sulfate (CYP3A4)

CYP2C19
CYP3A4
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!