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

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

Developmental and Pediatric Pharmacology

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Teething Cordial
Unlicensed and « off-label drugs » in paediatric and neonatal intensive care units

Treluyer et al 1999

Determinants of Drug Response in Infants

Disease
Growth and Development

Environment
Genetics

Drug
Absorption
Distribution
Receptor Interaction
Biotransformation
Excretion

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.

- Exposure along with the interaction with therapeutic targets (e.g., receptors) dictates response.

Drug Absorption

Developmental Changes in Gastric pH

Developmental Alterations in Intestinal Drug Absorption

Influence of Higher Gastric pH
**Drug distribution**

Age-dependent changes in body composition

![Graph showing changes in body composition over age]

- TBW
- ECW
- Body Fat

**Drug Biotransformation**

- **Phase I**
  - CYPs
  - Esterases
  - Dehydrogenases

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

**Drug** → **Metabolite** → **Phase I** → **Metabolite** → **Phase II**
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>EPHX2</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>GSTM</td>
</tr>
<tr>
<td>SULT1A3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Human DME Ontogeny

<table>
<thead>
<tr>
<th></th>
<th>SULT1E1</th>
<th>SULT1A1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class 1</td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGA</td>
<td>0-6 mo</td>
<td>&gt;6 mo</td>
</tr>
<tr>
<td>10-26 wks</td>
<td></td>
<td>&gt;26-40 wks</td>
</tr>
</tbody>
</table>

PNA PNA PNA

Impact of Ontogeny on Drug Metabolism

Midazolam Clearance in Neonates

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>t₁/₂ (hr)</td>
<td>4.6 ± 1.7</td>
<td>3.3 ± 0.9</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>19.7 ± 4.9</td>
<td>17.0 ± 5.2</td>
<td>12.5 ± 3.5</td>
</tr>
<tr>
<td>C₁₂ 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;MIC₉₀ (%)</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 Association with PNA
Linezolid plasma clearance in neonates

Propofol clearance almost exclusively depends on metabolic clearance

Figure 1. Linear regression analysis of total body clearance of ceftriaxone (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis.

Ref: Kearns et al, NEJM 2003
All neonates are not created equal

- post-conceptional age
- gestational age
- postnatal age
- asphyxia at birth
- PDA
- prenatal drug exposure

These will increase variability in outcome measures

Factors influencing drug disposition in infants, children, and adolescents

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

Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus
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)
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 (PTU) non-taster as an autosomal recessive trait
1954: Hughes et al. relate isoniazid neuropathy to metabolism -N-acetyltransferase
1956: Carson et al. discovery of glycoside G-6-PD deficiency
1957: Kalow characterizes acetylcholinesterase deficiency
1957: Motulsky identifies differences in drug metabolism
1957: Vogel coins the term "pharmakogenetik"
1958: Price Evans characterization of acetylators and non-acetylators
1958: Kalow the first textbook on pharmacogenetics
1959: Eichelbaum et al. describes sparteine metabolism
1962: Wedlund et al. description of the cytochrome CYP2D6 polymorphism
1965: Gonzalez explanation for the debrisoquine phenotype
1979: Eichelbaum et al. recognition of link between sparteine and debrisoquine metabolism
1982: Wedlund et al. description of the cytochrome CYP2D6 polymorphism
1997: Yates et al. Polymerscape chain reaction (PCR) based method used to detect response.

CYP2D6 Pharmacogenetics

Drug EM Stable metabolites, Excretion
PM "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)

**Unravelling CYP2D6 Pharmacogenetics**

![Distribution of CYP2D6 Phenotypes](image)

- EM: Extensive Metabolizer
- IM: Intermediate Metabolizer
- UM: Ultrarapid Metabolizer
- PM: Poor Metabolizer

**Inferring CYP2D6 Phenotype from Genotype: “Activity Scores”**

- **2**: *1x2, *2x2
- **1**: *1, *2, *10x2, *35, *41[2988G]
- **0.75**: *9, *29, *45, *46
- **0.5**: *10, *17, *41[2988A]
Relationship between CYP2D6 activity (DM/DX) and Activity Score

![Graph showing the relationship between CYP2D6 activity (DM/DX) and Activity Score.](image)

CYP2D6 Genotype-Phenotype Correlation in First Year of Life

![Graph showing CYP2D6 Genotype-Phenotype Correlation in First Year of Life.](image)


![Graph showing the relationship between CYP2D6 activity score and some other measure.](image)

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Developmental Trajectories: Pediatric Pharmacogenetics

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Pharmacogenetics of Codeine

**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 ng/mL (typical)

**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

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Pharmacogenetics of Codeine

- Codeine
  - Site of action
  - Cytochrome P450
  - Extensive Metabolizer
  - Poor Metabolizer

Plasma morphine levels after 170 mg codeine p.o.

Eckhardt et al., Pain 199

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**Explanation:**

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  - Ultra rapid metabolizer phenotype
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

Developmental Alterations in CYP2C19 Expression

Koukouritaki et al. J Pharmacol Exp Ther 2004;308:965

CYP2C19 Pharmacogenetics

Omeprazole PK After a Single 20 mg Oral Dose

**Drug X: no relationship between CYP2C19 activity score and Clearance**

![Graph showing no relationship between CYP2C19 activity score and Clearance](image)

**Drug Y: a clear relationship between CYP2C19 activity score and Clearance**

![Graph showing a clear relationship between CYP2C19 activity score and Clearance](image)

![Laostorazole and pantoprazole biotransformation](image)
Metabolic Pathways for Selected Proton Pump Inhibitors

5-O-Desmethylomeprazole → Omeprazole → CYP2C19

3-Hydroxyomeprazole → Omeprazole sulphone → CYP3A4

5-Hydroxomeprazole → Omeprazole hydroxysulphone → CYP2C19

Pantoprazole demethylated → CYP2C19

Pantoprazole sulphone → CYP3A4

Pantoprazole sulfate

The need for drug studies in critically ill preterm infants

- Drug studies in adults or animal models may not adequately predict pharmacokinetic or pharmacodynamic properties in neonatal patients
- Unable to reliably extrapolate adult data to the neonatal population
- Drugs must be studied in neonates to determine their pharmacokinetics, pharmacodynamics, appropriate dose, safety and efficacy