Developmental and Pediatric Pharmacology

John N. van den Anker, MD, PhD

March 10, 2010

Evan and Cindy Jones Chair in Pediatric Clinical Pharmacology
Vice Chair of Pediatrics for Experimental Therapeutics
Professor of Pediatrics, Pharmacology and Physiology, The George Washington School of Medicine and Health Sciences/Children’s National Medical Center, Washington, DC
Adjunct Professor of Pediatrics, Erasmus MC-Sophia Children’s Hospital, Rotterdam, the Netherlands
Teething Deodorized tincture of opium (1.5%)
Unlicensed and « off-label drugs » in paediatric and neonatal intensive care units

- < 28 weeks
- 28-<37 weeks
- term neonates
- infants
- children
- adolescents

Treluyer et al 1999
Determinants of Drug Response in Infants

Disease
Growth and Development

Environment
Genetics

Drug
Exposure
Response

Absorption
Distribution
Receptor Interaction
Biotransformation
Excretion
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.

- Exposure along with the interaction with therapeutic targets (e.g., receptors) dictates response.
Drug Absorption
Developmental Changes in Gastric pH

% Adult Activity

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

HCl production
Gastrin
Pepsin

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)

Time (hr)

Penicillin concentration (U/mL)

- 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

Drug distribution
Age-dependent changes in body composition

Drug distribution
Age-dependent changes in body composition
Drug Biotransformation

- **Drug**
  - Phase I: CYPs, Esterases, Dehydrogenases
  - Phase II: UGTs, NATs, STs, MTs, GSTs
- **Metabolite**
Ontogeny of CYP3A4


Fetus - Newborn - Infant - Activity

mRNA

Percent Adult Value

<30 wk >30 wk <24 hr 1-7 d 8-28 d 1-3 mo 3-12 mo 1-10 yr
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>AOX</td>
</tr>
<tr>
<td>SULT1A3</td>
<td></td>
<td>GSTM</td>
</tr>
</tbody>
</table>

Human DME Ontogeny

DME (pmol/mg protein)

EGA
10-26 wks
>26-40 wks

PNA
0-6 mo
>6 mo-18 yr

SULT1E1
Class 1

SULT1A1
Class 2

CYP2C9
Class 3
CYP3A (pmol/mg)

Fetus  Neonate  >1-24 mo  >2-18 yrs  Adult

Birth

CYP3A4  CYP3A7

CYP3A (pmol/mg)
Impact of Ontogeny on Drug Metabolism

Changes in Metabolic Capacity

% of Adult Activity

- CYP3A4
- CYP1A2
- CYP2D6
- UGT2B7

<24hr 1-7d 8-28d 1-3m 3-12m 1-10yr

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>$t_{1/2}$ (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

![Graph showing Linezolid Plasma Clearance Association with PCA]

- **CLEARANCE, mL/min/kg**
- **POSTCONCEPTIONAL AGE, weeks**

Legend:
- ○ Preterm; < 5 days
- ● Preterm; > 5 days
- ▲ Full term; < 3 days
- ▼ Full term; > 3 days
Linezolid Plasma Clearance Association with PNA
Linezolid plasma clearance in neonates

![Graph showing linezolid plasma clearance in neonates. The graph displays the relationship between post-natal age and clearance, with different symbols representing different groups of neonates.]
Propofol clearance almost exclusively depends on metabolic clearance

Propofol

4-hydroxypropofol

- CYP? (24 - 60%)
- UGT1A9 (40 - 76%)
- Glucuronide and sulphate metabolites
- Eliminated (mainly in urine)

- UGT?
- SULT?
GFR (ml/min/1.73m²)

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

<table>
<thead>
<tr>
<th>Term</th>
<th>Preterm (&lt;2000gm)</th>
<th>Preterm (&lt;1500 gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-9 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-16 d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.
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

Objective: Our objective was to study the pharmacokinetics of ibuprofen in premature infants with patent ductus arteriosus on day 5 and day 10 after birth.

Methods: Ibuprofen was administered on days 3, 4, and 5 by a 15-minute intravenous infusion of 10, 5, and 5 mg/kg, respectively, with the aim of closing the ductus arteriosus. Blood samples were drawn at time zero and at 0.5, 1, 2, 4, 12, and 24 hours after the first and third doses. Ibuprofen plasma concentrations were assayed by HPLC.

Results: A total of 27 premature infants were included (gestational age, 28.6 ± 1.9 weeks; birth weight, 1289 ± 616 g; values are mean ± standard deviation). Ibuprofen pharmacokinetics followed a 2-compartment open model. Between the first and third doses (day 3 and day 5) there was a significant decrease of the volume of distribution of the central compartment (Vd1) (0.244 versus 0.171 L/kg; P < .01) and area under the plasma concentration-time curve (524 versus 647 mg·h/L; P < .01). The decrease in Vd1 was most pronounced in patients with a closing ductus. Total body clearance and plasma half-life did not change significantly. No significant differences were observed in ibuprofen peak plasma concentrations after the first and third doses in relation to decile status or treatment.

Conclusions: Ibuprofen pharmacokinetics showed a large interindividual variation in premature infants during treatment for patent ductus arteriosus, and significant changes may occur between day 3 and day 5 after birth in these infants with a closing ductus. These findings may have implications for the treatment schedule with ibuprofen in patients with patent ductus arteriosus. (Clin Pharmacol Ther 2001;70:388-393.)

Bart Van Overmeire, MD, PhD, Daan Touw, PharmD, PhD, Paul J. C. Schepens, PhD, Gregory L. Kearns, PharmD, and John N. van den Anker, MD, PhD
Eugene and Winnie Nijhoff, Amsterdam and Rotterdam, The Netherlands; Kansas City, Mo; and Columbus, Ohio
Elevated Morphine Concentrations in Neonates Treated With Morphine and Prolonged Hypothermia for Hypoxic Ischemic Encephalopathy

Ankó Róka, MD*, Klis Tamás Melinda, MD*, Barna Vásárhelyi, PhD*, Tamás Machay, PhD*, Denis Azzopardi, MD*, Miklós Szabó, PhD*

*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 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 normothermia. Morphine concentrations at 24, 48, and 72 hours after birth were related to infusion rate (averaged over previous 24 hours) and hypothermia (adjusted \( R^2 = 0.327, P < .001 \)).
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-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
CYP2D6
slow
intermediate
rapid
ultrarapid

CYP2C19
Poor metabolizer
normal

anti-convulsants, proton pump inhibitors, benzodiazepines, anti-malarials

anti-depressants, anti-psychotics, anti-arrhythmics, beta-blockers, pain medications, anti-emetics, anti-cancer drugs
CYP2D6 Pharmacogenetics

Drug \(\rightarrow\) EM
Stable metabolites, Excretion

Drug \(\rightarrow\) 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)
Unravelling CYP2D6 Pharmacogenetics

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

Inferring CYP2D6 Phenotype from Genotype: “Activity Score”

2  *1x2, *2x2


0.75  *9, *29, *45, *46

0.5  *10, *17, *41[2988A]

Relationship between CYP2D6 activity (DM/DX) and Activity Score

Blake M, et al. 2007
CYP2D6 Genotype-Phenotype Correlation in First Year of Life
Developmental Trajectories: Pediatric Pharmacogenetics
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

Cytochrome P450 2D6

Site of action

Blood brain barrier

Morphine

Plasma morphine levels after 170 mg codeine p.o.

Eckhardt et al., Pain 1998
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
CYP2C19 Pharmacogenetics

- 1984: Unusual sedation in a subject receiving anticonvulsant mephenyton
- 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

**Mean Intragastric pH**

<table>
<thead>
<tr>
<th>Functional Alleles</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

**OPZ AUC (ng/ml/hr)**

$r = 0.873$

$p < 0.0001$

*Sagar M, et al. Gastroenterology 2000;119:670-676*
Drug X: no relationship between CYP2C19 activity score and Clearance
Drug Y: a clear relationship between CYP2C19 activity score and Clearance

\[ y = 0.4625x + 0.098 \]

\[ R^2 = 0.4475 \]

\[ P < 0.001 \]
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
  - 泮托拉唑硫酸盐
Metabolic Pathways for Selected Proton Pump Inhibitors

- **5-O-Desmethylomeprazole**
  - CYP2C19

- **Omeprazole**
  - CYP3A4

- **5-Hydroxyomeprazole**
  - CYP3A4
  - CYP2C19
  - Omeprazole hydroxysulphone

- **3-Hydroxyomeprazole**
  - CYP3A4

- **Omeprazole sulphone**
  - CYP2C19

- **Pantoprazole**
  - CYP2C19
  - CYP3A4
  - Pantoprazole sulphone
  - Demethylated pantoprazole
  - Sulfotransferase
  - 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
Target therapy
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)