Developmental and Pediatric Pharmacology

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Photo of two packages of early medicines for babies called Kopp’s “Baby’s Friend” and Tott’s Teething Cordial. Kopp’s “Baby’s Friend” was apparently for the treatment of colic, diarrhea, cholera & teething. It apparently contained alcohol (8.5%) and morphine (1.8 grain).

Tott’s Teething Cordial apparently contained deodorized tincture of opium (1.5%)
Photograph of two other early medicines. One medicine was called Elixir Sulfanilamide and the other medical was called Chloromycetin (Chloramphenicol) hydrocortisone ophthalmic.
Unlicensed and off-label drugs in paediatric and neonatal intensive care units

Bar chart showing the percent of drug (from 0 to 70%) at < 28 weeks, 28-<37 weeks, term neonates, infants, children, and adolescents.

Trelyuer et al 1999
Determinants of Drug Response in Infants
The Challenge of Pediatric Clinical Pharmacology: Determining the Source(s) of Variability
Critical Role of Pharmacokinetics in Pharmacotherapy……
Drug Absorption
Developmental Changes in Gastric pH

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

Huang et al. *J Pediatr* 1953;42:657
Drug distribution
Age-dependent changes in body composition
Bar chart showing peak Gentamicin Ccn (mg/L per mg/kg dose) from 0 to 3.5 for infant, child, adolescent, and adult. The dose rises from infant to child and then rises even higher for adolescent and then very slightly dips for adult.
Drug Biotransformation
Ontogeny of CYP3A4
Human Hepatic DME Ontogeny

Human DME Ontogeny
Graphic illustration of CYP3A (pmol/mg) from 0 to 500 for fetus, neonate, >1-24 mo age, 2-18 yrs, and adult.
Impact of Ontogeny on Drug Metabolism

Midazolam Clearance in Neonates
Impact of Age on Linezolid Pharmacokinetics
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

Chemical structures of Propofol and 4-hydroxypropofol.
Plot sowing Propofol concentration (mg/L) over time (min).

Bar chart showing GFR (ml/min/1.73m$^2$) over 1-2 d, 8-9 d, and 15-16 d for term, preterm (<2000gm) and preterm (<1500gm).
Plot showing total body clearance (mL/h) from 10 to 160 over gestational age (weeks) from 25 to 37.
Graphic illustration of an infant showing various internal organs with arrows pointing from the infant’s organs to five different graphs depicting 1) changes in metabolic capacity, 2) Integumentary development, 3) acquisition of renal function, 4) changes in gastrointestinal function, and 5) developmental changes in distribution sites.

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

Photograph of a toddler sitting on a stool and looking at her midsection.
Copy of an article from a medical publication entitled Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus by Bart Van Overmeire, MD, Ph.D. et al
Copy of the beginning of a medical article entitled Elevated Morphine concentrations in Neonates Treated with Morphine and Prolonged Hypothermia for Hypoxic Ischemic Encephalopathy by Aniko Roka, MD, et al.
Two plots from a medical publication. The first figure shows serum morphine concentration, ng x mL\(^{-1}\) over Hypothermia and Normothermia. The second figure shows serum morphine concentration ng x mL\(^{-1}\) over morphine infusion rate, μg x kg\(^{-1}\) per h.
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

Photograph of a shelf in an early pharmacy.
Photograph of a small AmpliChip CYP450 Array held in a man’s hand
CYP2D6 Pharmacogenetics

Drug $\rightarrow$ Stable metabolites
   Excretion

Drug  --PM$\rightarrow$ Stable metabolites
       Excretopm

"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)
Unraveling CYP2D6 Pharmacogenetics

**EM**
Extensive Metabolizer

**UM**
ultrarapid metabolizer
~ 10-15%

**IM**
Intermediate Metabolizer
~ 10-15%

**PM**
Poor Metabolizer
~ 5-10% Caucasians

Griese et al. Pharmacogenetics 1998,
Raimundo et al. CPT 2004,
Toscano et al.
Pharmacogenetics 2006
Inferring CYP2D6 Phenotype from Genotype: “Activity Score”

<table>
<thead>
<tr>
<th>Score</th>
<th>Genotypes</th>
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<tbody>
<tr>
<td>2</td>
<td>*1x2, *2x2</td>
</tr>
<tr>
<td>0.75</td>
<td>*9, *29, *45, *46</td>
</tr>
<tr>
<td>0.5</td>
<td>*10, *17, *41[2988A]</td>
</tr>
</tbody>
</table>
Relationship between CYP2D6 activity (DM/DX) and Activity Score

Blake M, et al. 2007
CYP2D6 Genotype-Phenotype Correlation in First Year of Life

Plot showing urinary DM/DX ratio over Age (months)

CYP2D6 activity score

CYP2D6 activity score
Developmental Trajectories: Pediatric Pharmacogenetics

Activity (from 0 to 100) over age (years)
Cover of a Newsweek magazine (date of which is not apparent) with the cover story entitled “Where Health Begins. Obesity, Cancer and Heart Attacks: How Your odds are set in the Womb”. Photograph or graphic illustration of a fetus. In addition, there are two other photos or graphic illustrations of fetuses, and two photos of premature infants, one of which has sensors attached to it to medical equipment the other infant is photographed being held in adult male hands.
Case Report

Lancet 2006;368:704

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

Gideon Koren et al

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

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 et al

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 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

Mean Intragastric pH from 01.0 to 6.0 over OPZ AUC (ng/ml/hr) from 0 to 7,000.

Drug X: no relationship between CYP2C19 activity score and Clearance

CYP2C19 Activity Score
Drug Y: a clear relationship between CYP2C19 activity score and Clearance
Graphic illustration of CYP2C19 and CYP3A4 and CYP2C19 and CYP3A4
Metabolic Pathways for Selected Proton Pump Inhibitors

Flow charts for Omeprazole and Pantoprazole
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
Photograph of a glacier reflected in water in which the reflection is many times larger than the glacier.
Target therapy

Graphic illustration of a dart hitting the middle of the target.
Two photographs - each of adult male hands cradling a premature infant.

“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)