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 all 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
Rodgers et al. *J. Pediatr Surg* 1978;13:13

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

Hines, Pharmacol & Therap. 118:250-267, 2008

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

From Kearns GL, et al. *N Engl J Med* 2003;349:1157-67

Midazolam Clearance in Neonates

Impact of Age on Linezolid Pharmacokinetics

Kearns GL, Jungbluth GL, Abdel-Rahman SM, Hopkins NK, Welshman IR, Grzebyk RP, Bruss JB, van den Anker JN. Impact of ontogeny on linezolid disposition in neonates and infants. *Clin Pharmacol Ther* 2003:74(5):413-422.

Linezolid Plasma Clearance Association with PCA

Linezolid Plasma Clearance Association with PNA

Propofol clearance almost exclusively depends on metabolic clearance

Chemical structures of Propofol and 4-hydroxypropofol.

Plot sowing Propofol concentration (mg/L) over time (min).

Allegaert K, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term infants. Br J Anesth 2007 dec 99(6):864-70.

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 <u>will</u> 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 → Stable metabolites
Excretion

Drug --PM→ 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"

2	*1x2, *2x2
1	*1, *2, *10x2, *35, *41[2988G]
0.75	*9, *29, *45, *46
0.5	*10, *17, *41[2988A]
0	*3, *4, *5, *6, *7, *8, *11, *12, *15, *36, *40, *42

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)

Postmenstrual Age and CYP2D6 Polymorphisms Determine Tramadol O-Demethylation in Critically ill Neonates and Infants (Allegaert K, van den Anker JN, et al. Pediatr Res, 2008)

CYP2D6 activity score

Postmenstrual Age and CYP2D6 Polymorphisms Determine Tramadol O-Demethylation in Critically ill Neonates and Infants (Allegaert K, van den Anker JN, et al. Pediatr Res, 2008)

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)

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 mephenytion

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.

Sagar M, et al. Gastroenterology 2000;119:670-676

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)