The Elephant, the Mouse & the Child
-Paediatric & Neonatal Pharmacology

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Reading Material


• Koren G. Chapter 60. Special aspects of perinatal and pediatric pharmacology. In Basic & Clinical Pharmacology ed Katzung BG, Appleton & Lange


• Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet 2009; 24 (1): 25-36

• Anderson BJ, Meakin GH. Scaling for size; some implications for paediatric anaesthesia dosing. Paediatr Anaesthesia 2002; 12: 205-219

• Bartelink IH, rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 2006; 45: 1077-1097

Foetal Drug Exposure
Adverse Effects

• lithium, carbimazole Goitre
• tetracycline Abnormal teeth/bones
• NSAIDs Closure of ductus arteriosus
• ethanol Foetal alcohol syndrome
• nicotine Low birth weight, increased mortality
• Methadone Withdrawal syndrome

THERAPEUTIC ORPHAN

Dr Harry Shirkey 1963

•Disasters
  – thalidomide, chloramphenicol, alcohol, iodine
  – fentanyl, bupivacaine, gastric prokinetics, propofol

•Incentives (USA)
  – pediatric exclusivity 1997
    • patent extension
  – final pediatric rule 1998
    • rules requiring investigation of new drugs
  – Pediatric Research Equity Act 2003
  – FDA statutory authority to mandate pediatric studies

Differences in the young

• Size
  – Smaller
    • Distances shorter, faster BMR, faster onset time

• Maturation
  – Body composition changing (V)
  – Drug metabolism immature (CL)
  – Response to drugs different

• Toxicity
  – Short term (e.g. verapamil and arrest)
  – Long term (e.g. tetracycline and teeth)

Definitions

• Neonate
  – first 6 weeks of life

• Infant
  – 6 weeks -2 years

• Child
  – 2 years +
    • teenager
    • adolescent
What do we want to know to determine dose?

- Concentration-response relationship (PD)
- Target effect
- Target concentration
- Dose to achieve concentration (PK)
- Covariate effects
  - age, weight, disease
- Toxicity data

Paediatric Differences

- Size
- Growth & development
- Ethics
  - Autonomy, beneficence, blood loss, min distress
- Disease spectrum
  - Bronchiolitis and bronchodilators
- Potential for future harm
  - Stilboestrol - vaginal adenocarcinoma

Growth

Separation of
Size usually kg
Maturation

The Major PK Covariates in Children

- SIZE
- AGE
- Organ Function
- Body Composition
- Drug interactions
- Pharmacogenetics
- Environmental factors
- Circadian rhythms
Paracetamol clearance – weight or age?

**Body size is primary covariate**

- 200x weight difference (e.g. 0.5-100 kg)
- Parameters expressed as function of size
- Common size models
  - per kilogram
    - Under estimates under 40 kg
  - body surface area
    - Overestimates under 20 kg
  - Allometric

**SIZE MODELS**

- PER KILOGRAM MODEL
- BODY SURFACE AREA MODEL
- ALLOMETRIC MODEL

**PER KILOGRAM MODEL**

- Under predicts dose if weight < 47 kg
- Error increases as size decreases
- Explanations for under prediction fallacious
  - Morphine – relative big liver
  - Fentanyl – increased hepatic blood flow
  - Remifentanil - ???

Hypothetical Drug

Sotolol clearance changes with age

Laer S. J Am Coll Cardiol 46:1322-30
Body Surface Area Model

- Nomogram required
  \[ BSA = W^{0.425} \times H^{0.725} \times 0.007184 \]

- Original model from only 10 individuals
  - Du Bois D. Arch Intern Med 1916;17:863

- Works reasonably well 7-100 kg
  - Can be estimated using \( W^{2/3} \)

Who among the following was NOT one of the nine subjects used to derive the DuBois Formula?

- 1 ¾ y; Measured 2 h after death, had rickets
- 12 ½ y; Well-formed, no signs of puberty
- 18 y; Tall, thin, emaciated from diabetes
- 26 y; Sculptor’s model, well-proportioned
- 36 y; Cretin, physical development of 8 yr. old child

Body Mass vs Metabolic Rate (Peters HP. Cambridge 1983)

Fractal Geometry

West GB. Science 1999;284:1677
**Allometric Theory**

\[
\text{CL} = \text{CL}_{\text{std}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{std}}}\right)^{3/4}
\]

\[
V = V_{\text{std}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{std}}}\right)^{4/4}
\]

\[
T = T_{\text{std}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{std}}}\right)^{1/4}
\]


**NOTE** Surface area model can be approximated by exponent of 2/3

Holford S. J Pharmacol Clin Toxicol 2014

**Allometric Examples**


**Clearance changes with weight**

**CLEARANCE: A Mechanism Based Model**

\[
\text{CL}_{\text{GRP}} = \text{CL}_{\text{STD}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{STD}}}\right)^{3/4} \times \text{MF} \times \text{OF}
\]

Size

Maturation

Organ Function


**PAEDIATRIC DOSING**

<table>
<thead>
<tr>
<th>Term</th>
<th>WT</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>3.5 kg</td>
<td>12%</td>
</tr>
<tr>
<td>3 mo</td>
<td>6.0 kg</td>
<td>15%</td>
</tr>
<tr>
<td>6 mo</td>
<td>7.5 kg</td>
<td>20%</td>
</tr>
<tr>
<td>1 yr</td>
<td>10 kg</td>
<td>25%</td>
</tr>
<tr>
<td>3 yr</td>
<td>14 kg</td>
<td>33%</td>
</tr>
<tr>
<td>7 yr</td>
<td>22 kg</td>
<td>50%</td>
</tr>
<tr>
<td>10 yr</td>
<td>30 kg</td>
<td>60%</td>
</tr>
</tbody>
</table>
Evidence for Allometry in Humans


Remifentanil clearance

- Rapid hydrolysis by non-specific tissue and plasma esterases
- 2-cmt, first order elimination
- Allometric scaling describes clearance changes with age

Clinical Considerations

- Propofol Infusion
  - Adult: bolus 1 mg/kg then 10-8.6 mg/kg/h
  - Child: bolus 1 mg/kg then 15-13-10 mg/kg/h

Maintenance Dose in Child

$$CL_{CHILD} = CL_{ADULT} \times \left(\frac{\text{weight}_{CHILD}}{\text{weight}_{ADULT}}\right)^{3/4}$$

Allometry alone fails under 10 kg for propofol


Barker N. Pediatr Anesth 2007

Table 1: Examples that support the proposal that CL scales allometrically with brain size.

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Clearance (L/h/70kg)</th>
<th>65% confidence interval</th>
<th>CS Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>25</td>
<td>3-48 yrs</td>
<td>Range: 3-18.8</td>
<td>8.70</td>
<td>1.61, 16.84, 15.7%</td>
<td>(30)</td>
</tr>
<tr>
<td>Propofol</td>
<td>22</td>
<td>3-17 months</td>
<td>Range: 8.2-12.9</td>
<td>6.74</td>
<td>5.55, 8.00, 14.7%</td>
<td>(45)</td>
</tr>
<tr>
<td>Propofol</td>
<td>20</td>
<td>3 months-10 years</td>
<td>Range: 8.3-10.5</td>
<td>8.83</td>
<td>5.98, 9.87, 3.7%</td>
<td></td>
</tr>
<tr>
<td>Patent</td>
<td>1</td>
<td>18.4-30.7 yrs</td>
<td>Range: 8.6-30.5</td>
<td>8.93</td>
<td>6.74, 10.3, 11.3%</td>
<td>(35)</td>
</tr>
<tr>
<td>Preterm</td>
<td>80</td>
<td>1 week-36 weeks</td>
<td>Range: 8.6-30.5</td>
<td>4.35</td>
<td>3.47, 5.10, 5.0%</td>
<td>(54)</td>
</tr>
<tr>
<td>Full-term</td>
<td>40</td>
<td>3 months-17 years</td>
<td>Range: 8.6-30.5</td>
<td>4.46</td>
<td>3.58, 5.70, 4.0%</td>
<td>(54)</td>
</tr>
<tr>
<td>Teenager</td>
<td>25</td>
<td>17.3-18 years</td>
<td>Range: 8.6-30.5</td>
<td>4.46</td>
<td>3.58, 5.70, 4.0%</td>
<td>(54)</td>
</tr>
<tr>
<td>Adult</td>
<td>75</td>
<td>0.5-1.5 years</td>
<td>Mean: 8.6-30.5</td>
<td>8.58</td>
<td>6.32, 8.74, 14.4%</td>
<td>(34)</td>
</tr>
</tbody>
</table>

Clearance changes with weight

Age and Maturation

\[ CL_{GRP} = CL_{STD} \times \left( \frac{WT}{WT_{STD}} \right)^{3/4} \]

- \( CL_{GRP} \) = Group clearance
- \( CL_{STD} \) = Population standard clearance
- \( WT \) = Total Body Weight
- \( WT_{STD} \) = Standard weight e.g. 70 kg

Maturation Models

- Linear increase (Lemahl & Reith 2005)
  - OK for small age ranges e.g. premature neonates
- Exponential increase (Anderson 2000)
  - OK for premature and term children but not adult values
- Asymptotic Exponential (Hayton 2002)
  - OK for term and adult children but too fast for premature neonates
- Sigmoid Emax (Tod et al. 2001)
  - Matches theory and observation across all ages

How to Describe Clearance Maturation?

- **Theory**
  - Should be close to zero at conception
  - \( CL \) will appear during development in utero
  - Should reach adult values around age 20

- **Observations**
  - Slow changes after premature birth
  - Rapid changes around time of normal gestation
  - Slow change in older children

Which Age?

- Post-natal age (PNA)
  - Does not account for in utero maturation
- Post-menstrual age (PMA)
  - On average 2 weeks longer than biological age
- Post-conception age (PCA)
  - The biological age but not widely recorded

Maturation Models
### Morphine Clearance

- CLmax = 84.2 L/h/70kg
- TM50 = 58 weeks PMA
- Hill = 3.92
- 449 Preterm
- 23-32 weeks PMA
- 184 Infants
- 0-3 years PNA

### Clearance changes with age

#### Allometric size model + Maturation model

**Morphine infusion**

- Target concentration 10 mg/L

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</tr>
<tr>
<td>2 Year</td>
<td>16</td>
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### Ventilated premature neonates in NICU have reduced morphine clearance


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#### Organ Function

\[ CL_{GRP} = CL_{STD} \left( \frac{WT}{WT_{STD}} \right)^{3/4} \]

- **CL**<sub>GRP</sub> = Group clearance
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- WT = Total Body Weight
- WT<sub>STD</sub> = Standard weight e.g. 70 kg

**Postmenstrual age (weeks)**

**Clearance (L/h/70kg)**

- **CL premature**
- **CL term**
- **POPCL term**
- **POPCL prem**

---

### Potts A. Pediatr Anesth 2009

- Postnatal age (PNA) – Does not account for in utero maturation
- Post-conception age (PCA) – The biological age but not widely recorded
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### Ventilated premature neonates in NICU have reduced morphine clearance

A PKPD approach to determine dose

\[
TC = \frac{C_T \times E_T}{E_{\max} \times E_T}
\]

Equation 1

\[
SCE = \left(\frac{WT}{WT_{\text{std}}}\right)^\frac{1}{\gamma}
\]

Equation 2

\[
WT_{\text{std}} = \text{Weight in a standard individual (e.g. 70 kg)}
\]

\[
\text{Maturation} = \frac{PMA}{PMA_{\text{std}}}
\]

Equation 3

\[
\text{Hill} = \text{Steepness of the maturation function}
\]

\[
\text{OrganFunction} = \frac{OF_{\text{actual}}}{OF_{\text{normal}}}
\]

Equation 4

\[
\text{CL}_{\text{STD}} = \text{the CL in an individual with standard covariates (e.g. WT, GFR)}
\]

Equation 5

\[
TC \times CL_{MDR} = \text{Equation 6}
\]

ALTERED PHARMACOKINETICS

- Absorption
- Metabolism
- Volume of distribution
- Bioavailability
- Protein binding

Neonatal Absorption

- Skin thickness
- \(\uparrow\) intragastric pH
  - \(\uparrow\) bioavailability acid-labile compounds e.g. Penicillin G
  - \(\downarrow\) bioavailability weak acids e.g. pentobarbitone
- Delayed gastric emptying
  - \(\text{Tmax delayed}\)
- Reduced transport bile salts
  - \(\downarrow\) entero-hepatic circulation opioids

Oral Absorption of Paracetamol

Volume of distribution

- \(\text{Body composition changes}\)
- \(\text{Vd determines initial plasma concentration (Cp) after an intravenous dose of a drug}\)

\[
\text{Dose} = \text{Cp} \times \text{Vd}
\]
Body Water

Vd - Physiological Basis

Tiny  - warfarin  10 L. less than ECF, greater than blood, plasma protein binding
Small - gentamicin 18 L  approx. ECF
Medium - theophylline  35 L  Total Body Water
Large - digoxin  500 L  Na+ K+ ATPase binding

Predicting Vd in infants

- Morphine - ↓ Vd in neonates
- Pethidine - ↑ Vd in neonates

Vd determined by
- body composition (muscle bulk, fat content etc)
- drug properties (lipophilicity, protein binding etc)

Post Natal Drug Disposition

- Volume of Distribution
  - "Size" predicted by Wt
  - simple L/kg rule
- Water
  - 'Wet' at birth ECF 50% of Wt
  - adult 'dry' ECF 25% of Wt within 3 months
- Fat
  - 'Skinny' at birth Fat 10% of Wt
  - adult Fat 20% of Wt within 3 months

Clearance

- Immature hepatic enzymes
  glucuronide
- Renal function reduced
  aminoglycosides

CYP Maturation

- cytochrome P450
  - CYP2E1 surges after birth
  - CYP2D6 soon thereafter
  - CYP3A4, 2C 1st week
  - CYP1A2 last to appear

- Normal maturation unknown
CYP2C9 Maturation (Phase I)

- **Growth**
  - organ size
  - organ blood flow

Maturation of CYP 2D6
Tramadol as substrate

CYP maturation (Phase 1)

- Immature at birth
- Different CYPs mature at different rates

Practical Implication

- Reduce Infusion rates in neonates
  - Concentration = infusion rate/CL
  - Bupivacaine (CYP1A2)
    - continuous epidural infusion rates in neonates (0.2 mg/kg/h) are less than children (0.4 mg/kg/h)

GFR Growth Curves

Renal and Metabolic Maturation


Propofol Metabolism
Glucuronide CYP2B6, CYP2C9 or CYP3A4

928 patients
22 weeks PCA to 32 y

CLmax=6.84 L/h/70kg
TM50=46.4 weeks PCA
Hill=3.43

Median and 95% Intervals

CLmax=6.84 L/h/70kg
TM50=46.4 weeks PCA
Hill=3.43

928 patients
22 weeks PCA to 32 y

Paracetamol
TM50 52.2 weeks
Hill 3.4

Morphine
TM50 54.2 weeks
Hill 3.92

Dexmedetomidine
TM50 46.5 weeks
Hill 2.78

Propofol
TM50 38.5 weeks
Hill 4.6
The kick at birth (GFR)

Foetal circulation
- Increased oxygen
- Increased blood flow

Minimal impact

Caffeine - a long acting stimulant in neonates

- Good central respiratory stimulant
- Poor hepatic clearance Immature P450 CYP1A2
- Immature renal clearance
- T1/2 days in neonate, hours in adults

Impact of Gender

- P-glycoprotein expression, CYP3A4
- Renal Function (Cockcroft and Gault)
  - Cockcroft DW. Nephron 16:31-41

Post Natal Drug Disposition

- Clearance
  - ‘Size’ predicted by Wt3/4
    - Kleiber’s law (or BSA)
  - Kidney
    - 30% of size predicted value at birth
    - ‘Adult’ function within 6 months
  - Liver
    - 20-50% of size predicted value at birth
    - ‘Adult’ function within 1 year

Relative Bioavailability

How much drug available?

- Skin thickness
- Gut bacterial colonisation
- Enzyme pathways
- Rectal insertion height

Relative bioavailability of a paracetamol suppository

Dose-concentration variability after paracetamol elixir 12.5 mg/kg 6 h

The Major PK Covariates in Children

- **SIZE**
- **AGE**
- **Body Composition**
  - Total body water and ECF are increased in neonates
  
  Fat is 3% in a 1.5 kg premature neonate and 12% in a term neonate; this proportion doubles by 4-5 months of age.
  
  “Baby fat” is lost when infants start walking and protein mass increases (20% in a term neonate, 50% in an adult)
  
  Reduced binding proteins e.g. AAG
  
  Spinal column takes greater proportion body mass

- **Disease**
- Drug interactions
- Pharmacogenetics
- Environmental factors
- Circadian rhythms

Body Composition

- **Growth**
  - organ size
  - organ blood flow

Protein binding - AAG

- Alpha-1 acid glycoprotein reduced in neonates
- Bupivacaine is bound to AAG

Bolus epidural dose of bupivacaine in neonates is lower than in children (1.5-2 mg/kg vs. 2.5 mg/kg) because a greater proportion will be unbound drug and it is unbound drug that exerts effect
Spinal Column

- Preterm and full-term infants have a much greater CSF volume relative to weight than a child (4 ml/kg in children < 15 kg) or adult (2 ml/kg) – this may account in part for the increased dose (mg/kg) of local anesthetic required in infants to produce a successful subarachnoid block. Duration of blockade is shorter in neonates and this may be due to a higher CSF turnover rate than adults.

- The epidural space in infants has increased vascularity and a smaller absorptive surface for local anaesthetics. Epidural fat is spongy and gelatinous in appearance with distinct spaces between individual fat globules. With increasing age, fat becomes more tightly packed and fibrous. – The absorption half time of epidural levobupivacaine decreases with age. This slower absorption may contribute to increased rostral spread of local anaesthetic and the consequent longer duration of caudal analgesia observed in infants.

Disease Processes

- Malignancy ...↑ resistance to muscle relaxants
  - ↑ clearance Vm
- R → L cardiac shunts....inhalation agent uptake
- PDA....↑ Vd aminoglycosides, indomethacin
- ↑ intra-abdominal pressure → ↓ hepatic blood flow
  → ↓ fentanyl clearance

Formulations & Delivery

- children prefer liquid formulations
- iv may need lots of diluent
- exact dose may be hard to give
- use of iv formulations orally
- Dose splitting
- taste

Paracetamol taste

Frequency of Key Phrases

unpublished (David Herd)

![Paracetamol taste chart]

Altered Pharmacodynamics

- Bronchodilators (sm muscle↓)
- Warfarin (sensitivity ↑)
- Cyclosporin (immunosuppression ↑)
- Midazolam (GABBA$_A$ receptor ↑)
- Calcium and neonatal heart
- Gastric prokinetics (↓ sensitivity)
Isoflurane MAC changes with age (LeDez, 1987)

Variation in quantal content of the end-plate potential with age in phrenic nerve hemidiaphragm preparations from young rats (Wareham, 1994)

Potential Role of Pharmacogenomics in Reducing Adverse Drug Reaction

A Systematic Review

Kathleen N. Phillips, PhD
Robert L. Stover, MD, FACP
Gayle D. Bird
Jon A. Low, PhD
Wolfgang Arano, MD

S

Pharmaco genomics is the study of the relationship between a person's genetic makeup and their response to drugs. This field is rapidly growing and 100,000 or more individuals have been genotyped in GWAS (genetic association studies). Pharmacogenomics has the potential to significantly reduce adverse drug reactions and improve the efficacy and safety of drugs.

Opioids – PK or PD?

(Way WL, Clin Pharmacol Ther 1965;6:454)

Context: Adverse drug reactions are a significant cause of morbidity and mortality, although many adverse drug reactions are considered unpredictable, quantal opioid sensitivity may be modulated through examination of drug disposition parameters. Opioids can undergo a variety of metabolic transformation, and the resulting metabolites may play a role in opioid pharmacodynamics.

To determine whether the sensitivity of opioids at the neuromuscular junction (NMJ) is modulated by age, a study was conducted in rats and compared to humans.

Methods: Rats were divided into three age groups: young (2-3 weeks), adult (6-9 weeks), and old (12-18 weeks). The sensitivity of the NMJ to opioids was assessed using quantal release techniques.

Results: The sensitivity of opioids at the NMJ was found to be significantly lower in young rats compared to adult and old rats.

Conclusions: These findings suggest that the sensitivity of opioids to the NMJ is modulated by age, with young rats being less sensitive than adult and old rats.

FIGURE 1

GENETICS OF CYP 206 METABOLIZING EFFECTS ON NORTRIPYLINE

CYP2D6 polymorphism (P500). The radiometric rate of parent debrisoquine + metabolic OH-debrisoquine.

**Impact of CYP2D6 on Tramadol Clearance**

![Graph showing the impact of CYP2D6 on Tramadol Clearance](image)

**Contributors to analgesic variability**

- **Cytochrome P450**
  - CYP2E1 surges after birth
  - CYP2D6 soon thereafter
  - CYP3A4, 2C 1st week
  - CYP1A2 last to appear

**CYP Maturation**

- **cytochrome P450**
  - Normal maturation unknown

**Impact Pharmacogenetics**

- Limited impact neonates
- Enzyme responsible for ≥ 50% CL
- Steep dose-response curve and narrow therapeutic window
- Active metabolite formed by enzyme

**CYP 2C9 & celecoxib**

- Stempak D. Clin Pharmacol Ther 2005

**Isoniazid acetylation metabolic ratio during maturation in children**

Isoniazid acetylation metabolic ratio (MR) was studied in 61 children with tuberculosis after administration of isoniazid. MR was calculated as the molar acetylated to isoniazid concentration ratio. MR was used as a probe for N-acetyltransferase activity and to determine the acetylation phenotype. MR had a bimodal distribution with an antimode between 0.68 and 0.77. MR and the percentage of fast acetylators increased significantly with age. The cumulative frequency of fast acetylators increased with age, with a plateau reached around 4 years. MR value was checked during treatment in 44 children. All children but one who initially appeared as fast acetylators remained in this group after repeated testing. Among the 30 slow acetylators, 12 became fast acetylators, and 10 showed a variable phenotype at different ages. A bimodal distribution of the isoniazid acetylation MR was shown in children, with an antimode close to that described in the thiaminase and a maturation of isoniazid acetylation during the first 4 years. (Ciba Clin Pharmacol Ther 1997;62:277-84.)

Ann Pariente Khayat, MD, Elisabeth Ray, PharmD, Dominique Gendrel, MD, PhD, Françoise Vaussard-Roverbuen, MD, Odile Creminier, MD, Philippe d’Athis, PhD, Jean Badonat, MD, Georges Olive, MD, and Gérard Pons, MD, PhD Paris, France

**N-acetyltransferase activity maturation with age**


Impossible to determine fast or slow under 1 year
Tramadol M1 metabolite formation clearance (CYP2D6) increases with postmenstrual age. Rate of increase varies with genotype expression (Allegaert, 2008)

In reality

- CYP2D6, CYP3A, CYP2C9 - 70%
- CYP1A2, CYP2C19, CYP2E1 - 20%
- NAT 2
- G-6-P dehydrogenase
- CYP2D6
codeine, tramadol, chlorpromazine, propanolol, mexiletine

Gene Chip vs TDM (& Bayesian Forecasting)

- Practical use
- Availability
- Cost
- Use
  - Adverse drug reactions
  - Active metabolites
  - Taylor therapy

Propofol Toxicity in Neonates
- an immediate effect

- Neonatal data from neonatologists
  - Papoff P. Pediatrics 2008; 121:448-9
  - Ghanta S. Pediatrics 2007; 119:e1248-e1255
- Concerns BP

Ketamine and the neonate
- a long term effect

Concerns about widespread neuronal apoptosis and long-term memory deficits

Other long term effects due to impact at critical time:
Thalidomide - phocomelia
Stilboesterol - vaginal carcinoma
Tetracycline - tooth staining
Drugs in breast milk

Neonatal concentration

- How much drug in breast milk (milk/plasma)
  - Diffusion, ion trapping, lipid partition
  - Maternal concentration
- How much breast milk ingested
- Bioavailability
- Clearance

Phenobarbitone in 3 kg Neonate

- Rate In
  - \( F \times MPR \times \text{MilkFlow} \times \text{Maternal Conc} \)
  - \( 1.0 \times 0.5 \times 18.8 \text{ mL/h} \times 10 \text{ mg/L} = 0.094 \text{ mg/h} \)
- Neonatal Clearance
  - \( F_{devCL} \times \text{CLstd} \times \left( \frac{Wt}{Wtstd} \right)^{3/4} \)
  - \( 0.33 \times 0.3 \text{ L/h} \times \left( \frac{3}{70} \right)^{3/4} = 0.0093 \text{ L/h} \)
- Neonate Conc
  - \( \frac{\text{Rate In}}{\text{Neonatal Clearance}} = 10.05 \text{ mg/L} \)

Fluoxetine in 3 kg Neonate

- Rate In
  - \( F \times MPR \times \text{MilkFlow} \times \text{Maternal Conc} \)
  - \( 1.0 \times 1.0 \times 18.8 \text{ mL/h} \times 10 \text{ mg/L} = 0.188 \text{ mg/h} \)
- Neonatal Clearance
  - \( F_{devCL} \times \text{CLstd} \times \left( \frac{Wt}{Wtstd} \right)^{3/4} \)
  - \( 0.33 \times 40 \text{ L/h} \times \left( \frac{3}{70} \right)^{3/4} = 1.24 \text{ L/h} \)
- Neonate Conc
  - \( \frac{\text{Rate In}}{\text{Neonatal Clearance}} = 0.15 \text{ mg/L} \)

Infant Exposure

<table>
<thead>
<tr>
<th>MPR</th>
<th>CLmat</th>
<th>Age</th>
<th>Wt (kg)</th>
<th>FdevCL</th>
<th>CRInfMat</th>
<th>DRInfMat</th>
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<td>0.3</td>
<td>Premature</td>
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<td>0.1</td>
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<td>73%</td>
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<td>0.5</td>
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<td>Neonate</td>
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<td>72%</td>
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<td>Infant</td>
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<td>73%</td>
</tr>
<tr>
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<td>3%</td>
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<tr>
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<td>9</td>
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<td>0.33</td>
<td>2%</td>
<td>3%</td>
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<tr>
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<td>9</td>
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<td>2%</td>
<td>3%</td>
</tr>
<tr>
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<td>1%</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Infant</td>
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<td>1</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Clearance is the key difference between medicines

Dosing During Breast Feeding

- 30-60 min after nursing
- 3-4 h before next feed

Postnatal Adverse Effects

- Neonate
  - opioids: resp depression; withdrawal
  - aspirin: bleeding
  - diazepam: apnoea, poor feeding

- Puberty
  - stilboestrol: vaginal adenocarcinoma
Summary

- size important - allometric models satisfactory out of infancy
- other covariates contributing to PK variability poorly described
- PK maturation over 1st year of life
- PD differences poorly described

-More work required before we can predict the correct target concentration

Time for an Aphorism Change

Children are not Small Adults

Adults are BIG Children

Children are OLD Babies