Drug Use in Children

Anna Ponnampalam
Department of Physiology
University of Auckland

Acknowledgement
Associate Professor Brian Anderson

"Paediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but... it has its own independent range and horizon..."
Dr Abraham Jacobi 1889

Objectives
- Understand the major sources of variability affecting the response to medicines in children
- Appreciate the relative contributions of body size, body composition, maturation and organ function to variability
- Learn the principles of dose individualization based on predictable sources of variability
Historical Drug Development in Children

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

Drug Therapy in Pediatric Patients

• Inadequate research data currently exists for prescribers to ensure safe dosing for infants/children.
  → Two thirds of drugs used in pediatrics have never been tested in pediatric patients
  • Best Pharmaceuticals for Children Act (2002)
  • Pediatric Research Equity Act of 2003
• 20 % of drugs were ineffective for children (even though they were effective for adults)
• 30 % of drugs caused unanticipated side effects, some of which were potentially lethal
• 20 % of drugs required dosages different from those that had been extrapolated from dosages used in adults
• These laws were permanently reauthorized as part of the FDA Safety and Innovation Act (FDASIA) of 2012
Incidence of Adverse Drug Events

- Medication error rate: pediatric error rates approximately equal to adult error rates
- Errors in pediatrics are 3 times more likely to be associated with a potential ADE
- Neonatal ICU: patient group with highest error and potential ADE rate
- 74% of errors and 79% of potential ADEs occur in ordering phase

Reasons for Increased Risk

- Different and changing pharmacokinetic parameters
- Lack of pediatric formulations, dosage forms, guidelines
- Calculation errors
- Inconsistent measurement of preparations
- Problems with drug delivery systems

Pediatric and Neonatal Pharmacokinetics

- One size doesn’t fit all
  - Preterm neonates (<36 weeks’ gestation)
  - Full-term neonates (birth to 30 days)
  - Infants (1–12 months)
  - Toddlers (1–4 years)
  - Children (5–12 years)
  - Adolescents (>12 years)
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

• Pharmacokinetics

• Pharmacodynamics

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

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
**Concentration Effect Site**

\[ D+R \rightarrow DR \]

**Disease EFFECT**

(Emax model)

**Stimulus transduction**

**Elimination**

**EFFECT**

(Emax model)

**DOSE**

- Concentration
- Effect Site
- D\(^+\)R \(\rightarrow\) DR
- Stimulus transduction

**Formulation Route**

**Covariates**
- Size
- Age
- Gender
- Drug interactions
- Pharmacogenomics

**PHARMACOKINETICS**
- Biophase

**PHARMACODYNAMICS**
- Elimination
- Metabolites


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**Paediatric Differences**

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

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**Growth**

Separation of Size usually kg

**Maturation**

Sumpter A. Pediatr Anesth 2011
The Major PK Covariates in Children

- SIZE
- Maturation
- Organ Function
- Drug interactions
- Pharmacogenetics
- Environmental factors
- Circadian rhythms

Paracetamol clearance –weight or age?

Body size is primary covariate

- 500x weight difference (e.g. 0.5-250 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

Anderson BJ. Pediatr Anest 2002;12; 205
Sotolol clearance changes with age

Laer S. J Am Coll Cardiol 46:1322-30

Per kilogram model

Weight (kg)

% difference in clearance

-60
-50
-40
-30
-20
-10
0
10
20
0 20 40 60 80 100


Body Surface Area Model

- Nomogram required
  - $\text{BSA} = W(kg)^{0.425} \times H(cm)^{0.725} \times 0.007184$

- Original model from only 9 individuals
  - Du Bois D. Arch Intern Med 1916;17:863

- Works reasonably well 7-100 kg
  - Can be estimated using $Wt^{2/3}$
**Slide 25**

**Surface Area Model**


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**Slide 26**

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

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**Slide 27**

**Fractal Geometry**

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

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

\[ V = V_{std} \times \left( \frac{WT}{WT_{std}} \right)^{1} \]

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


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

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**Allometric Examples**


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**Clearance changes with weight**

**PAEDIATRIC DOSING**

- **Term**
  - 3.5 kg: 12%

- **3 mo**
  - 6.0 kg: 15%

- **6 mo**
  - 7.5 kg: 20%

- **1 yr**
  - 10 kg: 25%

- **3 yr**
  - 14 kg: 33%

- **7 yr**
  - 22 kg: 50%

- **10 yr**
  - 30 kg: 60%

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**CLEARANCE: A Mechanism Based Model**

\[
CL_{GRP} = CL_{STD} \left( \frac{WT}{WT_{STD}} \right)^{1/4} \]

- **CL_{GRP}**: Group clearance
- **CL_{STD}**: Population standard clearance
- **WT**: Total Body Weight
- **WT_{STD}**: Standard weight e.g. 70 kg


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**Evidence for Allometry in Humans**


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**Table 3** Examples that support the proposal that CL scales allometrically within humans

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Allometric coefficient</th>
<th>%</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>270</td>
<td>2–86 yrs</td>
<td>Range 12-100</td>
<td>0.67</td>
<td>96</td>
<td>(96)</td>
</tr>
<tr>
<td>Propofol</td>
<td>22</td>
<td>3–17 months</td>
<td>Range 3.5–12.5</td>
<td>0.64, 0.64</td>
<td>19.7%</td>
<td>(130)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>24</td>
<td>3 months–6 years</td>
<td>Mean 21.6</td>
<td>0.67, 0.67</td>
<td>27%</td>
<td>(65)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>52</td>
<td>18.4 ± 7.3 years</td>
<td>60.9–91.12 years</td>
<td>0.67, 0.67</td>
<td>37%</td>
<td>(65)</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>49</td>
<td>6 months–7 years</td>
<td>Mean 18.3</td>
<td>0.67, 1.00</td>
<td>15.3%</td>
<td>(131)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>39</td>
<td>1 week–4 years</td>
<td>Range 0–69</td>
<td>0.67, 0.67</td>
<td>21.4%</td>
<td>(131)</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>89</td>
<td>1 week–16 years</td>
<td>Range 0–69</td>
<td>0.67, 0.67</td>
<td>0.8%</td>
<td>(74)</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>49</td>
<td>6 months–17 years</td>
<td>Mean 18.3</td>
<td>0.67, 0.67</td>
<td>16%</td>
<td>(132)</td>
</tr>
<tr>
<td>Valproate</td>
<td>223</td>
<td>0.1–18 years</td>
<td>Range 3–19</td>
<td>0.67, 0.67</td>
<td>2.1%</td>
<td>(133)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>76</td>
<td>0.6–17 years</td>
<td>Mean 16 (SD 37.3)</td>
<td>0.42, 0.74</td>
<td>14%</td>
<td>(134)</td>
</tr>
</tbody>
</table>

**Maintenance Dose in Child**

\[ \text{CL}_{\text{CHILD}} = \text{CL}_{\text{ADULT}} \times \left( \frac{\text{weight}_{\text{CHILD}}}{\text{weight}_{\text{ADULT}}} \right)^{\frac{3}{4}} \]

**Clearance changes with weight**

**Hypothetical Drug**

Anderson BJ. Pediatr Anest 2002;12: 205
**Age and Maturation**

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

- **Size**
- **Maturation**
- **Organ Function**

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

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**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

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**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

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**Maturation Models**

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

\[
MF = \frac{PMA_{Hill}}{PMA_{50}} = \frac{PMA_{Hill}}{TM_{50}}
\]


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**Dexmedetomidine Maturation**

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

Potts A. Pediatr Anesth 2009

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**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


**Morphine infusion**
- target concentration 10 mcg/L

- Birth 5 mcg/kg/h
- 1 Month 8.5 mcg/kg/h
- 3 Months 13.5 mcg/kg/h
- 1 Year 18 mcg/kg/h
- 2 Year 16 mcg/kg/h

**Clearance changes with age**

**Allometric size model**

+ **Maturation model**

**ORGAN FUNCTION**

\[ CL_{GRP} = CL_{STD} \left( \frac{WT}{WT_{STD}} \right)^{1/4} \]

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

Ventilated premature neonates in NICU have reduced morphine clearance


A PKPD approach to determine dose

\[ TC = \frac{C_{\text{max}} \times TE}{E_{\text{max}} \times TE} \]  
\[ \text{Size} = \frac{\text{WT}}{\text{WT}_{\text{std}}} \]  
\[ \text{WT}_{\text{std}} = \text{Weight in a standard individual (e.g. 70 kg)} \]  
\[ \text{Maturation} = \frac{\text{PMA}^{\text{Hill}}}{{\text{PMA}^{\text{Hill}}} + \text{TM}_{\text{Hill}}} \]  
\[ \text{Hill}=\text{Steepness of the maturation function} \]  
\[ \text{OrganFunction} = \frac{\text{OF}_{\text{actual}}}{\text{OF}_{\text{normal}}} \]  
\[ \text{OF}_{\text{actual}} = \text{Current organ function in an individual e.g. GFR=3L/h} \]  
\[ \text{OF}_{\text{normal}} = \text{Predicted organ function in a healthy individual e.g. GFR=6 L/h} \]  
\[ \text{CL} = \text{CL}_{\text{std}} \times \text{Size} \times \text{Maturation} \times \text{OrganFunction} \]  
\[ \text{CL}_{\text{std}} = \text{CL in an individual with standard covariates (e.g. WT, GFR)} \]  
\[ \text{MDR} = \text{CL} \times TC \]  

ALTERED PHARMACOKINETICS

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

- Skin thickness
- ↑ intragastric pH
  - ↑ bioavailability acid-labile compounds e.g. Penicillin G
  - ↓ bioavailability weak acids e.g. pentobarbitone
- Delayed gastric emptying
  - Tmax delayed
- Reduced transport bile salts
  - ↓ entero-hepatic circulation opioids

Oral Absorption of Paracetamol

![Graph showing oral absorption of paracetamol for neonates and children](image)

Volume of distribution

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

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

![Graph showing body water composition from fetus to adult.](Fris-Hansen_B_Pediatrics_1971)

**Slide 53**

*Body Water*

![Graph showing age-related body water composition in different age groups.](Anderson_BJ_AICM_2002)

**Slide 54**

*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
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**CYP2C9 Maturation (Phase I)**

Koukouritaki SB. J Pharmacol Exp Ther 2004

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**Renal and Metabolic Maturation**


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Slide 60

**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 2 years
  - Liver
    - 20-50% of size predicted value at birth
    - ‘Adult’ function within 1-2 years
**Relative Bioavailability**
How much drug available?

Varies with age

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

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**The Major PK Covariates in Children**

- SIZE
- Maturation
- Disease
- Drug interactions
- Pharmacogenetics
- Environmental factors
- Circadian rhythms

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

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**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

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**Formulations & Delivery**
- Children prefer liquid formulations
- IV may need lots of diluent
- Exact dose may be hard to give
- Use of IV formulations orally
- Taste
Formulation time-concentration profile

- **Paracetamol suppository**
- **Paracetamol elixir**
- **Diclofenac suppository**
- **Diclofenac enteric-coated tablet**

Van der Marel Paediatr Anaesth 2004;14:443-51

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**Altered Pharmacodynamics**

- Bronchodilators *(sm muscle ↓)*
- Warfarin *(sensitivity ↑)*
- Cyclosporin *(immunosuppression ↑)*
- Midazolam *(GABA_A receptor ↑)*
- Calcium and neonatal heart
- Gastric prokinetics *(↓ sensitivity)*

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**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

Fishbain DA. Pain Med 2004:5:81
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

Dosing During Breast Feeding

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

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


Determining Clearance in Children

• Size and Age important covariates
• Other Covariates
  – disease, drug interaction, PD, pharmacogenetics

Reading Material

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