Children are not small adults

Adults are BIG children &
Children are OLD babies

Brian J Anderson

University of Auckland
New Zealand
Example for colinearity in a pediatric covariate data set
(n=40; age range 12 days to 2 years)
(Meibohm B. The AAPS Journal 2005)
The Major PK Covariates in Children

• SIZE
• AGE
• Organ Function
• Body Composition
• Drug interactions
• Pharmacogenetics
• Environmental factors
• Circadian rhythms

Require a mechanistic approach
CLEARANCE: A Mechanism Based Model

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

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

Scaling Size in Humans
Percent differences in clearance determined by the surface area and per kilogram models when compared with the allometric 3/4 power model.
Predictions Match Observations
18 Orders of Magnitude

Theoretical Foundation for Allometric Scaling: Fractal Geometry

Allometric Theory

\[
\begin{align*}
\text{CL} & = \text{CL}_{\text{std}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{std}}}\right)^{3/4} \\
\text{V} & = \text{V}_{\text{std}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{std}}}\right)^{4/4} \\
\text{T} & = \text{T}_{\text{std}} \times \left(\frac{\text{WT}}{\text{WT}_{\text{std}}}\right)^{1/4}
\end{align*}
\]


**NOTE** Surface area model can be approximated by exponent of 2/3
Why Estimated Allometric Coefficients are Usually Unreliable

Table 4  Imprecision of estimates of allometric coefficient for clearance (true value 0.75)

<table>
<thead>
<tr>
<th>Weight distribution</th>
<th>5%CI</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log normal median 70 kg, 20%CV</td>
<td>0.48</td>
<td>1.01</td>
</tr>
<tr>
<td>Log normal median 70 kg, 50%CV</td>
<td>0.64</td>
<td>0.86</td>
</tr>
<tr>
<td>Uniform 0–140 kg</td>
<td>0.69</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Estimation was performed using NONMEM V 1.1 with the FOCE interaction method. Empirical confidence interval (CI) and CV (standard deviation/average) from parametric bootstrap distribution of 1000 replications. One hundred subjects were drawn from each weight distribution for each replication.

### 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>95% confidence interval</th>
<th>CV</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>270</td>
<td>2–88 years</td>
<td>Range 12–100</td>
<td>0.76</td>
<td>0.38, 0.84</td>
<td>19.7%</td>
<td>(66)</td>
</tr>
<tr>
<td>Propofol</td>
<td>22</td>
<td>3–17 months</td>
<td>Range 8.3–12.5</td>
<td>0.61</td>
<td>0.38, 0.84</td>
<td>19.7%</td>
<td>(150)</td>
</tr>
<tr>
<td>Busulfan</td>
<td>24</td>
<td>3 months–16 years</td>
<td>Mean 23.8</td>
<td>0.74</td>
<td>0.59, 0.90</td>
<td>10.7%</td>
<td>(45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 7.1–62.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>322</td>
<td>18.4 SD 17.3 years</td>
<td>3 data sets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(a) 29.5 SD 15.2 years</td>
<td>(a) 54.4 SD 16.7</td>
<td>0.63</td>
<td>0.58, 0.67</td>
<td>3.7%</td>
<td>(63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) 6.05 SD 3.95 years</td>
<td>(b) 22.9 SD 11.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(c) 1.33 SD 0.62 years</td>
<td>(c) 11.8 SD 2.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>39</td>
<td>6 months–7 years</td>
<td>Mean 16.3</td>
<td>0.87</td>
<td>0.64, 1.10</td>
<td>13.3%</td>
<td>(151)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 8–43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>89</td>
<td>1 week–14 years</td>
<td>Range 3–59</td>
<td>0.53</td>
<td>0.47, 0.59</td>
<td>5.8%</td>
<td>(34)</td>
</tr>
<tr>
<td>Sulfadoxine</td>
<td>89</td>
<td>1 week–14 years</td>
<td>Range 3–59</td>
<td>0.64</td>
<td>0.58, 0.70</td>
<td>4.8%</td>
<td>(34)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>49</td>
<td>6 months–17 years</td>
<td>Mean 30.56</td>
<td>0.88</td>
<td></td>
<td></td>
<td>(152)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 7.46–80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>225</td>
<td>0.1–14 years</td>
<td>Mean 31.3</td>
<td>0.72</td>
<td>0.66, 0.77</td>
<td>4.2%</td>
<td>(153)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 4–74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotolol</td>
<td>76</td>
<td>0.03–17 years</td>
<td>Mean 16 (SD 17.1)</td>
<td>0.58</td>
<td>0.42, 0.74</td>
<td>14.4%</td>
<td>(154)</td>
</tr>
</tbody>
</table>

Size and Body Composition

- Fat Free Mass (FFM)
  - weight, height and sex
  - Janmahasatian et al. 2005

- Predicted Normal Weight (PNWT)
  - FFM + Ffat*(WT – FFM)
  - Duffull et al. 2004

\[
CL_{GRP} = CL_{STD} \cdot \left( \frac{PNWT}{WT_{STD}} \right)^{3/4} \cdot MF \cdot OF
\]

Hypothetical Drug

Clearance (L/h/70kg)

Age (years)

Clearance (L/h/kg)

allometric 3/4 power (l/h/70kg)

per kilogram (l/h/kg)

Anderson BJ. Pediatr Anest 2002;12; 205
Maturation in Humans
N-acetyltransferase Activity Maturation With Age

Isoniazid acetylation metabolic ratio (MR) was studied in 61 children with tuberculosis after administration of isoniazid. MR was calculated as the molar acetylisoniazid 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 0.48 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

Mature after 1 year or 4 years?

How to Describe Clearance Changes with Age?

• 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 true age
- Post-conception age (PCA)
  - The biologically obvious age but not widely recorded
Maturation Models

- **Linear increase (Linvall & Reith 2005)**
  - OK for small age ranges e.g. premature neonates

- **Exponential increase (Anderson 2000)**
  - 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

\[
MF = \frac{PMA_{HillCL}}{PMA_{HillCL} + TM_{50}^{HillCL}}
\]
Allometry + Sigmoid Emax

\[ F_{PMA} = \frac{PMA^{HillCL}}{PMA^{HillCL} + TM_{50}^{HillCL}} \]

\[ CL_{WT, PMA} = CL_{STD} \cdot \frac{Wt}{Wt_{STD}}^{3/4} \cdot F_{PMA} \]
Glomerular Filtration Rate
Derived from Acyclovir in Neonates

CL_{\text{max}}^* = 7.1 \text{ L/h/1.73 M}^2
TM_{50} = 53.6 \text{ weeks PCA}
Hill = 6.17

79 subjects
0 to 2 years PNA

*=Fixed at
‘normal adult value’

BSA model

Levetiracetam

- Antiepileptic drug
- Majority (66%) excreted unchanged in the urine
- Expect maturation of renal function to have influence
- $T_{M50} = 49$ weeks
- Hill coefficient 2.5
- Allometric exponents estimated

GFR Growth Curves


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

928 patients
22 weeks PCA to 32 y
Renal and Metabolic Maturation

Propofol
TM₅₀ 38.5 weeks
Hill 4.6

GFR
TM₅₀ 47.6 weeks
Hill 3.4

Morphine
TM₅₀ 54.2 weeks
Hill 3.92

Dexmedetomidine
TM₅₀ 46.5 weeks
Hill 2.78

Paracetamol
TM₅₀ 52.2 weeks
Hill 3.4

Propofol Metabolism
Glucuronide
CYP2B6, CYP2C9 or CYP2A6

Accounting for Asymmetry

A

\[ MF = \frac{1}{\left(1 + \delta \cdot \left[ \frac{PMA}{TM_{50}} \right]^{-Hill} \right)^{1/\delta}} \]

B

\[ MF = \frac{1}{\left(1 + \left[ \frac{PMA}{TM_{50}} \right]^{-Hill} \right)} \]


IF (PMA GT 44) THEN
    HILL = HILLA
ELSE
    HILL = HILLB
ENDIF
Impact of Gender

- P-glycoprotein expression, CYP3A4

- Renal Function (Cockcroft and Gault)
  - Cockcroft DW. Nephron 16:31-41
Body composition changes

- 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).
- Neonates have low body fat and muscle content and so less propofol is apportioned to these tissues. Delayed awakening occurs because CNS concentration remains higher than that observed in older children as a consequence of reduced redistribution.
Time for an Aphorism Change

Children are not Small Adults

Adults are BIG Children

Children are OLD Babies

THE END