Tips and Traps In Pediatric PKPD

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PK = Pharmacokinetics: What the body does to the drug
PD=Pharmacodynamics: What the drug does to the body
Rx=Treatment: What the prescribed and patient need to know.

Where are we going?

Clinical Pharmacology

PKPDRX

Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (EC50).
Principles and Tips
Why does PKPD vary?

- **Systematic (predictable)**
  - Body size
  - Maturation
  - Disease state (liver, kidney)
  - Genotype, etc…

- **Random (not predictable)**
  - Between Subject Variability
  - Within Subject Variability

Covariates Do Not Explain All Variability

Three Ways to Dose

- **Population**
  - Same dose for everyone
    - The dream dosing method!

- **Group (Covariate guided)**
  - Same dose for similar group
    - e.g. same weight, CLcr, genotype

- **Individual**
  - Dose determined by individual response
    - e.g. BP, INR, blood conc
The Problem of Weight and Age

How can effects of weight and age be separated from effects of obesity?


A Principle Based Model for Clearance

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

Size Maturation

Organ Function

$CL_{PREDICTED} = $ Group $CL$

$CL_{STD} = $ Population standard $CL$

$WT = $ Total Body Weight

$WT_{STD} = $ Standard weight e.g. 70 kg


Theory Based Allometry

Scaling based on Fractal Geometry

$CL_{PREDICTED} = \alpha \left( \frac{WT}{WT_{STD}} \right)^{3/4}$

Note allometry is based on using mass alone to predict differences in structure and function.

Allometric Size Matches Observations
18 Orders of Magnitude


Why CL per kg is higher in children

Size Alone
Size and Maturation
Explained by allometric scaling and maturation!

Age-related clearance changes for a hypothetical drug. All three models show an increase in clearance over the first year of life owing to maturation of metabolic pathways. Clearance expressed using the per kilogram model then decreases with age after 1 year to reach adult levels in adolescence. This course is not evident with the allometric 3/4 power and surface area models.

Which Age for 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

Fmat = \frac{1}{1 + \left( \frac{PMA}{TM50} \right)^{0.67}}

CL_{PREDICTED_{PMA}} = CL_{ATM} \cdot Fmat

TM50=PMA at 50% maturation

Maturation is predictable — complete by 2 years of Age —

Size is then the main predictor of drug clearance

Maturation of renal and metabolic function follows a common trajectory. Some drugs, especially those which are glucuronidated, follow a similar maturation pattern to glomerular filtration rate. Others, such as propofol, mature earlier reaching 50% of adult value around the expected time of full term gestation.


Maturation and Birth

Birth effect on GFR and metabolism is detectable but relatively small

Exponential and sigmoid emax models for influence of time since birth give similar results. The birth effect has a much shorter time to half-maximum effect (~ 6 weeks) compared with maturation (~ 35 weeks).

How Does Fat Affect Size?

• Normal Fat Mass (NFM)
  - FFM + Ffat*(WT – FFM)
  - Anderson & Holford 2008; Derived from Duffull et al. 2004

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

• Ffat
  - Fraction of fat mass accounting for PK parameter
  - Ffat = 0 means NFM is FFM
  - Ffat = 1 means NFM is Total WT

\[ CL_{NFM} = CL_{ZDO} \left( \frac{NFM}{NFM_{STD}} \right)^{2/4} \]
**Fat Free Mass**

**Semi-Mechanistic Model**

\[
\text{if (sex = FEMALE)} \\
\text{WHSmax} = 37.99 \text{ kg/m}^2 \\
\text{WHS50} = 35.98 \text{ kg/m}^2 \\
\text{else} \\
\text{WHSmax} = 42.92 \text{ kg/m}^2 \\
\text{WHS50} = 30.93 \text{ kg/m}^2
\]

\[
\text{FFM} = \frac{\text{WHSmax} \cdot \text{HTm}^2 \cdot \text{WTkg}}{\text{WHS50} \cdot \text{HTm}^2 + \text{WTkg}}
\]

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**Age and Fraction of Adult FFM**

**Very Premature Neonates to Adults**

Fat free mass observations from 1953 individuals and means from literature studies. Post-menstrual age (PMA) ranged from 24 weeks to 30 years.

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**GFR, Age and Size**

- 1264 GFR observations in 928 subjects. 391 had FFM calculable.
- Allometric ¾ for Size based on NFM, FFM, or Total WT.
- Sigmoid hyperbolic for Maturation (Post Menstrual Age).
- NONMEM Objective Function
  1. Allo NFM = 4750.1
  2. Allo FFM = 4755.1
  3. Allo Total WT = 4793.0
  4. Linear FFM = 5003.9
  5. Linear Total WT = 5030.4

GFR is predicted better by NFM than TBW. Allometric scaling superior to linear scaling.
### Normal Fat Mass

<table>
<thead>
<tr>
<th>Source</th>
<th>Flat Clearance</th>
<th>Flat Volume</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>0.621</td>
<td></td>
<td>928 neonates to adults</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0</td>
<td>0</td>
<td>56 Singaporean adults</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0</td>
<td></td>
<td>456 Singaporean adults</td>
</tr>
<tr>
<td>Osteoporosis drug</td>
<td>-0.37</td>
<td>-0.23</td>
<td>4014 adult women</td>
</tr>
<tr>
<td>Parent / metabolite</td>
<td>-0.76 / -0.82</td>
<td>-0.51 / -0.48</td>
<td>91 adults</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.27</td>
<td>0</td>
<td>195 adults</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1</td>
<td>1</td>
<td>56 children</td>
</tr>
<tr>
<td>Propofol</td>
<td>1</td>
<td>0</td>
<td>514 neonates to adults</td>
</tr>
</tbody>
</table>

### Principles Summary

- Life involves connected but separate processes
- Theory based allometry plus a model for maturation allow size and age to be separated from body composition
- Normal free mass model demonstrates that the influence of body composition on clearance is drug specific

### Pitfalls and Traps
Power Function Models

- Empirical power function models should be avoided if possible
  - Difficult to explain what the power parameter means

\[ \text{Conc} = \text{Conc}_{\text{STD}} \left( \frac{Hct}{45} \right)^{0.05} \]

- Simpler empirical models (linear, exponential) are easier

\[ \text{Conc} = \text{Conc}_{\text{STD}} \left( 1 + 0.03 \cdot (Hct - 45) \right) \]

Both these models had the same objective function value

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Estimation of Allometric Exponent

<table>
<thead>
<tr>
<th>Weight distribution</th>
<th>5% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log normal mean 70 kg, 20% CV</td>
<td>0.40</td>
<td>1.00</td>
</tr>
<tr>
<td>Log normal mean 70 kg, 90% CV</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Uniform 1-140 kg</td>
<td>0.00</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Don’t do it unless you know you can account for all other size associated factors and have the right distribution of weights!

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Standard Weight for Allometric Models

Concern is expressed sometimes that scaling parameter values estimated in neonates and children in terms of an adult size standard of 70 kg may bias the estimates or affect the precision of estimation. There is no basis for this concern. This can be seen by inspection of the allometric covariate model which may be re-arranged:

\[ F_{\text{size}} = \left( \frac{W}{70} \right)^{1/4} \cdot \left( \frac{1}{70} \right)^{1/4} \]

The expression

\[ \left( \frac{1}{70} \right)^{1/4} \]

is simply a constant that is determined by whatever weight is chosen for standardization. The precision of a parameter estimate will not be changed by multiplying the parameter value by an ad hoc constant.
Weight Used For Standardization Does Not Affect Allometric Scaling!

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Cl (%)</th>
<th>V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>1.08</td>
<td>1.03</td>
</tr>
<tr>
<td>Median</td>
<td>1.46</td>
<td>0.98</td>
</tr>
<tr>
<td>2.5 percentile</td>
<td>5.02</td>
<td>3.29</td>
</tr>
<tr>
<td>50th percentile</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>Centered on 70 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>1.56</td>
<td>1.12</td>
</tr>
<tr>
<td>Median</td>
<td>1.46</td>
<td>1.00</td>
</tr>
<tr>
<td>RSE</td>
<td>5.42</td>
<td>2.19</td>
</tr>
<tr>
<td>2.5 percentile</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>97.5 percentile</td>
<td>113</td>
<td>108</td>
</tr>
</tbody>
</table>

Use of Age Categories for PK Study Analysis

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cl (%)</th>
<th>V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Median</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td>RSE</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>2.5 percentile</td>
<td>62</td>
<td>96</td>
</tr>
<tr>
<td>97.5 percentile</td>
<td>135</td>
<td>110</td>
</tr>
</tbody>
</table>

Don’t Use Categories!

Allometry and Everything Else

Size is Not Everything
- Attempts to describe all differences using weight alone will fail if other factors are ignored (even if correlated with weight)
  - Don’t ignore species
  - Don’t ignore age
  - Don’t ignore genotype
  - Don’t ignore disease state
  - Etc...

Allometry is about Mass
- Statements such as “allometry does not work” typically come from people who do not understand that allometry does not involve
  - Species
  - Age
  - Genotype
  - Disease state
  - Etc…
Predictable Variability
Size and Maturation

\( \frac{3}{4} \) Allometry Alone explains 67% of CL variability

\( \frac{3}{4} \) Allometry + Maturation explains 80% of CL variability

Toddlers
Under-predicted

Neonates
Over-predicted


Model Evaluation

- Standard “Goodness of Fit” plots are of little value
- NPDE is often over-sensitive and rejects acceptable models
- Common sense and parameter plausibility are essential
- VPCs are insensitive but will identify important problems
- Gold standard is external evaluation

Paediatric Clinical Pharmacology in BJCP

"However, medications for children are more usually quoted for surface area to body mass than adults. Rate of distribution or metabolism of a drug correlates with heat loss which, in turn, is considered generally as being proportional to surface area. Thus, surface area is accepted widely as being the best criterion when calculating drug doses in children."

Downing HJ, Pirmohamed M, Beresford MW, Smyth RL. Paediatric use of Mycophenolate Mofetil. Br J Clin Pharmacol 2012: Accepted. Announced online 23 April 2012 (possibly submitted 1 April 2012?)
Does this make sense?

\[
CL = 0.234 \text{ L min}^{-1} \text{ Kg}^{0.75}
\]

\[
= 0.234 \left( \frac{70}{70} \right)^{0.75} = 5.7 \text{ L min} = 340 \text{ L h/70 kg}
\]

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Evaluation of Predictions

Conclusions: The morphine maturation model has a poor predictive power of morphine clearance in preterm and term neonates, infants and very young children and may not be of any practical value for the prediction of morphine clearance in this age group.


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External Evaluation of Size and Maturation Models

A population approach to evaluation of the predictions of morphine clearance showed that the theory based allometric model combined with sigmoid maturation using post-menstrual age was better than standard empirical textbook recommendations. All the empirical models for prediction were unacceptable for some age group.


Knibbe CA, Krekels EH, van den Anker JN,


Do the Science First Then Tell the Doctors What to Do

Clearance determines maintenance dose. However, clearance changes with age as a continuous variable and a comprehensive analysis encompasses all ages.

Dose, based on clearance, also follows a continuum. Dose compromise is reached when discrete age bands are used based on clearance changes over the entire age range.

Dashed lines are suggested doses in mg/kg for 3 age groups: 0.05-0.5 y PNA 15 mg/kg q6 h, 0.5-7 y PNA 20 mg/kg q6h, >10 y 15 mg/kg q6h

The target is to maintain a target concentration of 10 mg/L for the relief of postoperative pain.

Note that mg/kg dosing is a practical approximation using age categories. It does not assume that clearance is linearly related to body weight.

Pitfalls Summary

• Test alternative explanations
• Think of biology before statistics
• Don’t believe it just because you read it in the BJCP
• Clinical compromises need to be based on a scientific foundation