Babies, Children, Adults Are All One Species

Integrated Rational Dosing

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Presented at FDA, White Oak, Thursday 14 Sep 2017.
Seminar on Dose Selection in Children.
Participants were asked before this presentation:
1.) In children over 2 years of age, exposures can be reliably predicted and dosing can be derived based on adult PK data: (multiple choice)
Responses
YES 24 31.58%
NO 52 68.42%

The same question was asked after the panel discussion and showed many of those present had changed their mind:
YES 37 72.55%
NO 14 27.45%

Body Size is the most important quantitative determinant of drug dose

- The human body weight range varies from about 500 g to over 250 kg due to both biological variability and changes over the lifespan.
- This more than 500 fold range in size is directly translatable through volume of distribution into drug loading dose differences
- Because of allometrically predictable relationships between weight and clearance the corresponding range of maintenance dose rates is only about 100 fold

Theory Based Allometry

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


The fundamental assumption of West’s allometric theory is that all cells are similar in size and have similar energy requirements. The structure of the energy delivery system e.g. blood vessels in humans, requires a certain mass e.g. bones in humans, to support the delivery system as well as the target cells. The mass overhead from these delivery and support systems increases total body mass without a linear increase in function. The allometric exponent value of ¾ describes this non-linear relationship for clearance. In contrast to functional processes such as clearance, allometric theory predicts a linear relationship between mass and structural properties such as volume of distribution. The allometric exponent for volume of distribution is 1.

Photo shows Nick Holford (41 y 80 kg) and Sam Holford (1 y 8 kg) on Fox Glacier, NZ 1987

Allometric Size Matches Observations
18 Orders of Magnitude


The relationship between weight and clearance is non-linear. It is predictable from theory based allometry. Allometric size is scaled in this figure relative to a value of 1 at a weight of 0.5 kg. With weight varying 500 fold from 0.5 kg to 250 kg the equivalent allometric size varies by a factor of just over 100.
Allometric Size and Body Composition

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…

How Old is a Baby?
- 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

The age of a baby may be described using several kinds of “age”:
- Post-natal age (PNA). This is the age (e.g., days) since birth. It does not account for in utero maturation of body structure and function.
- Post-menstrual age (PMA). This is the age (e.g., weeks) since the mother’s last menstrual period. On average it is 2 weeks longer than biological age.
- Post-conception age (PCA). This is the age (e.g., weeks) since conception. This is the best description of biological age but it is not widely recorded because the date of conception is often difficult to identify.
- Gestational age (GA). Defined by the PMA at birth. GA does not change with time.
  - Post menstrual age is the recommended way to describe biological age. This recommendation is pragmatic rather than theoretically correct.
Clearance Maturation

Maturation is complete by 2 years of age – then weight is the sole predictive factor for drug clearance.

Post-menstrual age is the recommended way to describe the biological age in weeks after conception. It is based on the mother’s recall of the date of the last menstrual period. It is therefore typically biased by overestimating the age since conception by 2 weeks.

Clearance increases with weight and age (red line). Allometric size predicts increasing clearance per kg with lower weights (green line). Below 2 years of age immaturity of drug clearance has a major effect on clearance (see inset) so clearance per kg decreases. This leads to a peak in clearance when expressed per kg around 2 years of age. Maintenance doses are commonly expressed per kg in clinical practice and are also higher around 2 years of age than in babies and adults.

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 size model which may be re-arranged:

\[
\frac{W}{W_{\text{Std}}}^{1/4} = \left(W\right)^{1/4} \frac{1}{W_{\text{Std}}}^{1/4}
\]

The expression \(\frac{1}{W_{\text{Std}}}^{1/4}\) 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 Parameter Estimation

<table>
<thead>
<tr>
<th></th>
<th>CL (%)</th>
<th>V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centred on 1 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1.55</td>
<td>1.13</td>
</tr>
<tr>
<td>Median</td>
<td>1.40</td>
<td>0.80</td>
</tr>
<tr>
<td>RSE</td>
<td>0.43</td>
<td>2.26</td>
</tr>
<tr>
<td>2.5 percentile</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>97.5 percentile</td>
<td>113</td>
<td>108</td>
</tr>
<tr>
<td>Centred on 20 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1.68</td>
<td>1.13</td>
</tr>
<tr>
<td>Median</td>
<td>1.33</td>
<td>1.15</td>
</tr>
<tr>
<td>RSE</td>
<td>0.42</td>
<td>3.26</td>
</tr>
<tr>
<td>2.5 percentile</td>
<td>91</td>
<td>95</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

Analyzed using individual PMA and weight to describe differences in clearance and volume.

Don’t Use Categories!

<table>
<thead>
<tr>
<th></th>
<th>CL (%)</th>
<th>V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>3.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Median</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td>RSE</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>2.5 percentile</td>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>97.5 percentile</td>
<td>125</td>
<td>119</td>
</tr>
</tbody>
</table>

The Compromise between Science and Clinical Practice

- Biology and pharmacology are strong sciences
  - Do the science first then make it practical for clinical use
  - Compromise should be made transparent to clinicians
- Clinical practice is often a compromise because of:
  - Lack of computational tools
  - Limited formulation flexibility
Weight is combined with post-natal age (PNA) and post-menstrual age (PMA) to predict the typical dose as a % of the adult dose. The coloured areas of the table show the fraction of adult maintenance dose that would be expected for infants and children. The fractions are based on the theoretical size and maturation model for typical drug clearance with some approximation to make the numbers easier to remember. The ‘rule of PMA+PNA’ has an acceptable error for clinical dose prediction. Although maturation is best described by a non-linear relationship it is quite well approximated by a linear function of PMA.

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**Rules of PNA and PMA**

<table>
<thead>
<tr>
<th>Typical Weight Kg</th>
<th>PMA or PNA</th>
<th>Fraction Adult Dose</th>
<th>Rule of PMA+PNA Error</th>
<th>true’ % Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 weeks</td>
<td>1/300</td>
<td>10%</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>30 weeks</td>
<td>1/120</td>
<td>1%</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>Full Term</td>
<td>1/30</td>
<td>1%</td>
<td>3.3</td>
</tr>
<tr>
<td>6</td>
<td>3 mo</td>
<td>1/10</td>
<td>6%</td>
<td>9.3</td>
</tr>
<tr>
<td>7</td>
<td>6 mo</td>
<td>1/6</td>
<td>24%</td>
<td>13.4</td>
</tr>
<tr>
<td>9</td>
<td>1 year</td>
<td>1/5</td>
<td>3%</td>
<td>19.5</td>
</tr>
<tr>
<td>12</td>
<td>2 years</td>
<td>1/4</td>
<td>-4%</td>
<td>26.1</td>
</tr>
<tr>
<td>19</td>
<td>5 years</td>
<td>1/3</td>
<td>-11%</td>
<td>37.4</td>
</tr>
<tr>
<td>34</td>
<td>10 years</td>
<td>1/2</td>
<td>-14%</td>
<td>58.5</td>
</tr>
<tr>
<td>50</td>
<td>15 years</td>
<td>3/4</td>
<td>-3%</td>
<td>77.4</td>
</tr>
<tr>
<td>70</td>
<td>Adult</td>
<td>1</td>
<td></td>
<td>100.0</td>
</tr>
</tbody>
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**First Pick A Target**

- **Therapeutic Drug Monitoring**
  - TDM Therapeutic Range
  - Sub-optimal at borders of the range

- **Target Concentration Intervention**
  - TCI Single Target
  - Optimal – do the best you can

Therapeutic drug monitoring is a traditional concept associated with empirical ‘seat of the pants’ dose adjustment determined by a measurement being outside a ‘therapeutic range’. The therapeutic range is hard to identify and is often mistakenly justified because it seems to be similar to the normal reference range for endogenous substances. A concentration at the bottom of the range has a very different meaning (close to being ineffective) from one at the top (close to being toxic) but TDM proponents usually ignore this and are happy to do nothing as long as the concentration is ‘within range’.

Target concentration intervention is a science-based method that uses pharmacokinetic and pharmacodynamic principles to identify how patients are different and uses PK guided dose individualization to achieve a precise therapeutic target. It has been shown to improve clinical outcome as well as being a cost-effective use of health resources.

Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with

The most important parameter determining a regular maintenance dose rate is clearance. It is important to check proposed methods for predicting clearance to see how well they match with reality. However some methods of performing this check may not be appropriate as illustrated by this paper from Dr Mahmood at the US FDA.

### Morphine

**External evaluation**

- **Patients:** 257 human morphine ‘observed’ CL
- **Age:** 24 PMA week to 91 year
- **Target:** 10 mcg/L

- **Approach**
  - Acceptable: if dose <= 25% ideal
  - Unacceptable: if => than 100%

### Table 1: Empirical equations of allometric models for morphine clearance

<table>
<thead>
<tr>
<th>Model</th>
<th>N</th>
<th>Preterm</th>
<th>Infant</th>
<th>Child</th>
<th>Adult</th>
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</thead>
<tbody>
<tr>
<td>Reich</td>
<td>83</td>
<td>35</td>
<td>26</td>
<td>23</td>
<td>90</td>
</tr>
<tr>
<td>Holford</td>
<td>23</td>
<td>12</td>
<td>-</td>
<td>-25</td>
<td>-25</td>
</tr>
<tr>
<td>Knibbe</td>
<td>10d</td>
<td>37</td>
<td>33</td>
<td>-4</td>
<td>24</td>
</tr>
<tr>
<td>Wang</td>
<td>-</td>
<td>31</td>
<td>74</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mahmood</td>
<td>-</td>
<td>21</td>
<td>149</td>
<td>-16</td>
<td>-11</td>
</tr>
</tbody>
</table>

**Textbook**

<table>
<thead>
<tr>
<th></th>
<th>mg/kg</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reich</td>
<td>18</td>
<td>68</td>
</tr>
<tr>
<td>Holford</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Knibbe</td>
<td>31</td>
<td>74</td>
</tr>
<tr>
<td>Mahmood</td>
<td>21</td>
<td>149</td>
</tr>
</tbody>
</table>

### Figures

- Only theory based allometry + maturational predicted adult dose (better than clinical textbook?)
- All empirical allometric models unacceptable!

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**Why Estimated Allometric Exponents are A Bad Idea without Good Design**

**Estimation of exponents is imprecise**

<table>
<thead>
<tr>
<th>Weight Distribution</th>
<th>PKCS</th>
<th>ANCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-normal median 74kg, PKCS</td>
<td>0.40</td>
<td>1.01</td>
</tr>
<tr>
<td>Log-normal median 74kg, ANCS</td>
<td>0.40</td>
<td>0.06</td>
</tr>
<tr>
<td>Distribution 4.1-80kg, PKCS</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Distribution 4.1-80kg, ANCS</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

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**References**