Dosing in Children

How to Reach the Target Effect

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First Pick A Target
Target Concentration Intervention

» Not An Imprecise Range!
» Single Target
» Optimal – do the best you can

Therapeutic drug monitoring (TDM) has become something that represents tedium. In part this is because it is mainly about measuring drug concentrations and not about using them to improve therapy. Target concentration intervention is about picking a therapeutic target concentration and doing everything possible to achieve it (Holford NH. Target concentration intervention: beyond Y2K. Br J Clin Pharmacol. 1999;48(1):9-13).

The important concept is to pick an exact target – not an imprecise range.
Target Effect and Target Concentration

$$\text{Target Conc} = \frac{\text{Target Effect} \times EC50}{(E_{\text{max}} - \text{Target Effect})}$$

Ideal dose prediction requires individual estimates of $E_{\text{max}}, EC50, V \text{ and } CL$

The principles of target concentration defined dosing are quite simple. The target effect leads to the target concentration which in turn allows the appropriate loading and maintenance dose to be calculated.

The right dose in an individual patient depends upon being able to make a good prediction of the individual values of $E_{\text{max}}, EC50, CL \text{ and } V$. These are the cardinal 4 parameters that define rational therapeutics.

How to Find the Target?


Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
A Randomised Concentration-Controlled Trial

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• Randomized concentration controlled trials are the gold standard

Check to See If You Can Hit the Target

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Evaluation of a morphine maturation model for the prediction of morphine clearance in children: how accurate is the predictive performance of the model?


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.
How Not to Do The Check

AIMS

Recently, a maturation model that incorporates a sigmoidal CL\textsubscript{STD} type model has been proposed for the estimation of morphine clearance in preterm infants. The primary objective of this report is to evaluate the predictive performance of the morphine maturation model for the prediction of morphine clearance in children of different ages. The secondary objective of this report is to evaluate the predictive performance of exponent 0.75 on bodyweight in the absence of the sigmoidal part of the morphine maturation model.

METHODS

In order to evaluate the predictive performance of the morphine maturation model, the clearance values of morphine for individual children (preterm infants, 23 - 32 weeks postmenstrual age) were obtained from the literature. The predicted clearance of morphine in an individual child obtained from the maturation model was then compared with the observed clearance in that individual child.

RESULTS

The morphine maturation model predicts the clearance in neonates. Infants and young children is poor and the inclusion of the sigmoidal part in the model only helps in resolving the underestimation. The observed clearance values at the 50th postmenstrual age (55 weeks PMA) is 75 L/h/70 kg bodyweight. Furthermore, the excellent benefit of the sigmoidal CL\textsubscript{STD} part of the model disappears by -1 year of age.

A theory based allometric model with sigmoidal maturation (Anand et al. 2008) was evaluated with these claims about its performance:

1. “substantial error due to exponent 0.75”
2. “not of any practical value for prediction of morphine clearance”

Mahmood made two negative assertions about a model for predicting clearance of morphine based on size and maturation. He said that the use of a theory based allometric exponent of ¾ caused a substantial error. Furthermore he indicated that the model was unlikely to be of any practical value for predicting morphine clearance in clinical practice.

How Was Clearance Predicted in Anand 2008?

Anand et al. implemented a model for predicting clearance that was similar to that proposed by Tod, Julien and Pons. It has 3 components – size, maturation and organ function.

Morphine Clearance (Anand 2008)

449 Preterm neonates
23-32 weeks PMA
184 Full term infants
PMA 23 -189 weeks

The influence of size and maturation is shown in this graph. Size adjusted values of morphine clearance are plotted as a function of post-menstrual age. This reveals the shape of the maturation function used to make the predictions. The mature standard value of morphine clearance is very similar to adult values. Half of the adult value is reached around 55 weeks of post-menstrual age.
Evaluation with Naive Prediction Error

1. Used naïve (Sheiner 1984) prediction error (PE)
   - PE = Predicted – (True + σ)
   - Inflates fixed effect prediction error with random between subject variability

2. Normalized PE to average clearance (30 L/h) in evaluation data set
   - Makes neonatal error negligible
     e.g. (0.2 - 0.1)/30 = 0.33%
   - Exaggerates adult error
     e.g. (200 - 100)/30 = 330%

3. Bioequivalence 80-125%
   - a conservative clinical ‘bias’ standard

4. BSV ‘precision’ is 48% (Anand 2008)
   - minimum possible with perfect prediction


External Evaluation Proposal

“Recently, a maturation model that incorporates a sigmoidal Emax type model [8] has been proposed for the estimation of morphine clearance in children. The authors, however, have not tested the predictive performance of their morphine model with data which were not included in the model building or outside the age range of the model.”

Mahmood 2011 (emphasis added)

Following this suggestion we have undertaken an external evaluation of morphine clearance predictions with the same neonate and child data used by Mahmood but extended to include older children and adults.

The predictive performance we have evaluated predictions in premature neonates, term neonate, infants, children and adults with numerous models and textbook standard of care

Mahmood used an external data set for evaluation of the morphine model predictions. We used the same external data set but added to it older children and adults to test the predictive performance outside the age range of the data used for the original model (as suggested by Mahmood).
Use What Is Known

• Don’t ignore what is already known

• Age and weight are well understood

• Maturation of kidneys and liver have been described

A population approach to evaluation of the predictions of morphine clearance showed that the theory based allometric model proposed by Anand et al. was somewhat better than standard empirical textbook recommendations. All the empirical models for prediction were unacceptable for some age group.


Standard growth charts are based on an idealized population of well nourished children which excludes premature infants.

In real clinical practice the age of a child is almost always known but weight may not be readily available. A prediction of weight can be made from post-menstrual age.


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 tramadol, mature earlier reaching 50% of adult value around the expected time of full term gestation.

Most drugs are given intermittently and often from a restricted range of dose sizes. The practically useful dose will usually need to be determined by considering how close it is to the ideal predicted dose. This requires some compromise between convenience of use and achievement of the desired target concentration. The example shown here is for paracetamol (acetaminophen) dosing. The dotted lines show the predicted dose needed to maintain a target concentration of 10 mg/L if given at a continuous rate over the dosing interval. The solid lines are suggested practical dose sizes with commonly used dosing intervals for neonates and children. The discrepancy between the dotted and solid lines indicates the compromise that has been made between practical use and a rational science-based prediction.


Calculation of an appropriate dose can be complex in neonates and children because of the rapid changes in age and weight. Other factors such as renal function may also need to be considered. A web-based dosing calculator that is accessible with most computers and web-enabled mobile devices (e.g., iPhone) is under development and will shortly be evaluated in a clinical trial compared to standard of care.


http://firstdose.org
Conclusion

• Pick your target not the dose!
  – Understand the egg and the chicken relationship

• A lot of variability in infants/children is predictable
  – Effects of weight and age are largely understood

• Age and weight are continuous variables
  – Don’t put your children into boxes until you have to

• Use a calculator
  – Every child is different

Theory Based Allometry
Scaling based on Fractal Geometry

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

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

Allometric Size Matches Observations
18 Orders of Magnitude


Which Size?

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

- Normal Fat Mass (NFM)
  - FFM + Ffat*(WT – FFM)
  - Derived from Duffull et al. 2004

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

Empirical Sigmoid 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

TM50=PMA at 50% maturation
Population Approach to Prediction Bias

\[ \text{Prediction Bias} = \frac{\text{Group Prediction} + \eta}{\text{Individual Observation}} \]

\[ \text{Individual Observation} = \frac{\text{Group Prediction} + \eta}{\text{Prediction Bias}} \]

Relative Bias % = 100 \times (\text{Prediction Bias} - 1)

e.g. If Group Prediction of Clearance is 15 L/h and the observed Individual Clearance is 10 L/h then

Prediction Bias = \frac{15}{10} = 1.5

Relative Bias % = 100 \times (1.5 - 1) = +50%

Prediction Bias Application

- Morphine clearance parameters from PK analysis are FIXED
- Bias of clearance (GBIAS) and variability of CL (GVBIAS) are estimated
- Clearance 'observations' from 257 individual estimates reported in the literature
- Target conc and maintenance dose rate allows the method to evaluate performance of recommended dosing protocols, e.g. mg/kg/h

\[
\begin{align*}
\text{IF } (\text{GAW}.LT.37) & \text{ THEN } \text{GRP}=1 ; \text{ premature neonate} \\
& \text{GBIAS}=B_{\text{PRE}} \\
& \text{GVBIAS}=B_{V_{\text{PRE}}} \\
\text{ELSE} & \\
& \text{AGEM}=\text{AGEY} \times 12 \\
& \text{IF } (\text{AGEM}.\text{LE}.1) & \text{ THEN } \text{GRP}=2 ; \text{ full term neonate} \\
& & \text{GBIAS}=B_{\text{N 0}} \\
& & \text{GVBIAS}=B_{V_{\text{N 0}}} \\
& \text{ELSE} & \\
& & \text{IF } (\text{AGEY}.\text{LE}.2) & \text{ THEN } \text{GRP}=3 ; \text{ infant} \\
& & & \text{GBIAS}=B_{\text{INF}} \\
& & & \text{GVBIAS}=B_{V_{\text{INF}}} \\
& \text{ELSE} & \\
& & & \text{IF } (\text{AGEY}.\text{LE}.20) & \text{ THEN } \text{GRP}=4 ; \text{ child} \\
& & & & \text{GBIAS}=B_{\text{CHI}} \\
& & & & \text{GVBIAS}=B_{V_{\text{CHI}}} \\
& \text{ELSE} & \\
& & & & \text{GRP}=5 ; \text{ adult} \\
& & & & \text{GBIAS}=B_{\text{A 0}} \\
& & & & \text{GVBIAS}=B_{V_{\text{A 0}}} \\
& \text{ENDIF} \\
& \text{ENDIF} \\
& \text{ENDIF} \\
\end{align*}
\]

\[
\begin{align*}
\text{FSIZE} &= (\text{WTKG} / 70)^{.75} \\
\text{FMAT} &= 1 / (1 + (\text{PMAW} / \text{TM50_CL})^{(\text{HILL_CL})}) \\
\text{IF } (\text{VENT}.\text{EQ}.1) & \text{ THEN } \text{FVENT}=\text{FDEV_CL} ; \text{ from NEOPAIN} \\
& \text{ELSE} \\
& \text{FVENT}=1 \\
& \text{ENDIF} \\
\text{GRPCL} &= \text{FVENT} \times \text{FMAT} \times \text{FSIZE} \times \text{CLSTD} \\
\text{GMDR} &= \text{GRPCL} \times \text{POPTC} \\
\text{MDR} &= \text{GMDR} / \text{GBIAS} \\
& \text{POPTC is target concentration} \\
\text{GCLB} &= \text{MDR} / \text{POPTC} \times 1000 / 60 \text{ L/h -> mL/min} \\
\text{CL} &= \text{GCLB} \times \exp(\text{PPV_CL} / \text{GVBIAS}) \\
\text{Y} &= \text{CL} \times (1 + \text{RUV}) ; \text{DV is observed CL}
\end{align*}
\]

Models for Morphine Clearance

Published Morphine Studies

1. BOUWMEESTER 2004
   - Neonates, infants
2. ANAND 2008
   - NEOPAIN (very premature)
   - + Bouwmeester (neonates, infants)
3. KNIBBE 2009
   - Premature
   - + Bouwmeester (neonates, infants)
4. ANAND 2010
   - NEOPAIN + Bouwmeester
   - Morphine salt correction
   - 2 molecules per morphine SO4 (Bush)
5. SIZEMAT1
   - Size, maturation, 1 CPT
6. SIZEMAT2
   - Size, maturation, 2 CPT
7. PWRLMAT2
   - CL exponent estimated
8. WTHILL
   - CL exponent HILL (wt)
9. PWRLpna10
   - Knibbe with NEOPAIN+Bouwmeester data
10. PWRLV
    - CL & V exponents, no maturation
11. BSA
    - Surface area (duBois & duBois or Boyd f(wt))