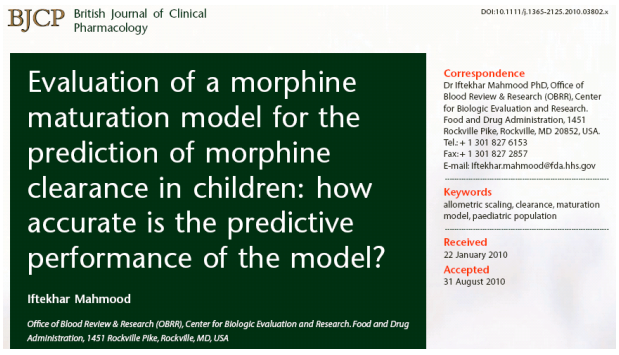
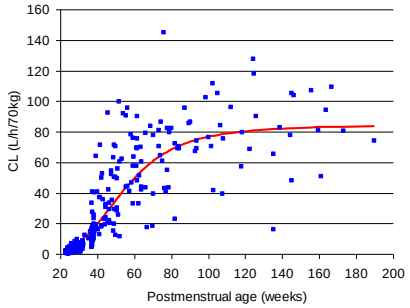
Slide 1	# Dosing in Children ## How to Reach the Target Effect Nick Holford University of Auckland Auckland, New Zealand	Holford NH, Ma SC, Anderson BJ. Prediction of morphine dose in humans. Paediatr Anaesth. 2011;10.1111/j.1460-9592.2011.03782.x.
Slide 2	## Acknowledgements • Brian Anderson, Starship Hospital, Auckland, New Zealand • Shu Chin Ma, University of Auckland, New Zealand • Sam Holford, University of Auckland, New Zealand ©NHG Holford, 2011, all rights reserved.	
Slide 3	## First Pick A Target Target Concentration Intervention » Not An Imprecise Range! » Single Target ☺ Accurate Ideal !  » **Optimal – do the best you can** ©NHG Holford, 2011, all rights reserved.	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.

Slide 4	**Target Effect and Target Concentration** **Target Conc**= Target Effect x EC50 / (Emax – Target Effect) **Target Conc** — **Dose Model** Initial Peak — Loading Dose=**Target Conc** x **Volume of Distribution** Average Steady State — Maintenance Dose Rate=**Target Conc** x **Clearance** Ideal dose prediction requires **individual** estimates of **Emax, EC50, V and CL** ©NHG Holford, 2011, all rights reserved.	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 Emax, EC50, CL and V. These are the cardinal 4 parameters that define rational therapeutics.
Slide 5	**How to Find the Target?** Clin. Pharmacokinet. 25 (6): 495-505, 1993 Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L? A Randomised Concentration-Controlled Trial *Nicholas Holford*[1], *Peter Black*[1], *Ron Couch*[2], *Julia Kennedy*[3] and *Robin Briant*[1] 1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand 2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand 3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand • Randomized concentration controlled trials are the gold standard ©NHG Holford, 2011, all rights reserved.	The target concentration can be evaluated by performing a clinical trial just like any other randomized trial based on dose. The target concentration controlled trial (RCCT) represents the highest standard of rational clinical pharmacology investigation. An RCCT does the best possible to determine how to individualize treatment short of actually using the therapeutic response to titrate the dose.
Slide 6	**Check to See If You Can Hit the Target**  BJCP British Journal of Clinical Pharmacology DOI:10.1111/j.1365-2125.2010.03802.x Evaluation of a morphine maturation model for the prediction of morphine clearance in children: how accurate is the predictive performance of the model? Iftekhar Mahmood Office of Blood Review & Research (OBRR), Center for Biologic Evaluation and Research. Food and Drug Administration, 1451 Rockville Pike, Rockville, MD, USA Correspondence Dr Iftekhar Mahmood PhD, Office of Blood Review & Research (OBRR), Center for Biologic Evaluation and Research. Food and Drug Administration, 1451 Rockville Pike, Rockville, MD 20852, USA. Tel.: + 1 301 827 6153 Fax: + 1 301 827 2857 E-mail: Iftekhar.mahmood@fda.hhs.gov Keywords allometric scaling, clearance, maturation model, paediatric population Received 22 January 2010 Accepted 31 August 2010 Mahmood I. Evaluation of a morphine maturation model for the prediction of morphine clearance in children: How accurate is the predictive performance of the model? Br J Clin Pharmac. 2011;71(1):88-94. ©NHG Holford, 2011, all rights reserved.	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.

Slide 7	**How Not to Do The Check** **AIMS** Recently, a maturation model that incorporates a sigmoidal E_{max} type model has been proposed for the estimation of morphine clearance in paediatric patients. 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 neonates to 5-year-old children; $n = 147$) were obtained from the literature. The predicted clearance of morphine in an individual child, obtained from the maturation model as well as from the fixed exponent 0.75 was compared with the observed clearance in that individual child. **RESULTS** The morphine maturation model's predictive power in neonates, infants and younger children is poor and the inclusion of the sigmoidal part in the model only helps in reducing the substantial error introduced in the prediction due to the application of exponent 0.75 on bodyweight. Furthermore, the real benefit of the sigmoidal E_{max} part of the model disappears by 1 year of age. **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. A theory based allometric model with sigmoid 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" Anand KJS, Anderson BJ, Holford NHG, Hall RW, Young T, Barton BA. Morphine Pharmacokinetics and Pharmacodynamics in Preterm Neonates: Secondary Results from the NEOPAIN Multicenter Trial 2008. ©NHG Holford, 2011, all rights reserved.	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.
Slide 8	**How Was Clearance Predicted in Anand 2008?** Organ Function $$CL_{PREDICTED} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}}\right)^{3/4} \cdot MF \cdot OF$$ Size Maturation $CL_{PREDICTED}$=Group CL CL_{STD}=Population standard CL WT =Total Body Weight WT_{STD}=Standard weight e.g. 70 kg Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008;47(4):231-43. ©NHG Holford, 2011, all rights reserved.	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.
Slide 9	**Morphine Clearance (Anand 2008)**  449 Preterm neonates 23-32 weeks PMA 184 Full term infants PMA 23 -189 weeks CL_{STD}= 84 L/h/70kg TM_{50} = 55 weeks PMA Hill = 3.8 Anand KJS, Anderson BJ, Holford NHG, Hall RW, Young T, Barton BA. Morphine Pharmacokinetics and Pharmacodynamics in Preterm Neonates: Secondary Results from the NEOPAIN Multicenter Trial 2008. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth. 2004;92(2):208-17. ©NHG Holford, 2011, all rights reserved.	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.

Slide 10	**Evaluation with Naive Prediction Error** The bias of the methods was measured by calculating the mean predictive error (MPE) according to the following equations [20]: $$MPE = \frac{\sum(\text{predicted-observed})}{n} \quad (4)$$ where n is the number of observations. MPE was expressed as percent of mean using Equation 4: $$\%MPE = \frac{(MPE \times 100)}{\text{mean observed CL}} \quad (5)$$ Acceptable limits for bias and precision are generally ≤5%, and ≤15%, respectively [21]. Due to high variability in the morphine clearance values in children, in this study, bias and precision limits were set as 10% and 25%, respectively. 1. Used naïve (Sheiner 1984) prediction error (PE) • PE = Predicted – (True + η) • 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 Mahmood I. Evaluation of a morphine maturation model for the prediction of morphine clearance in children: How accurate is the predictive performance of the model? Br J Clin Pharmac. 2011;71(1):88-94. ©NHG Holford, 2011, all rights reserved.	Mahmood tried to evaluate the Anand model for morphine clearance using an approach that can be called the Naïve Prediction Error method. This is based on a term introduced by Sheiner to describe the naïve approach to analysing data when between individual differences are ignored. Because between individual differences are quite large (Anand et al. estimated a co-efficient of variation of 48% for clearance) the mean prediction error reported by Mahmood is a gross exaggeration of the prediction error of a model using size and maturation. Furthermore, the relative prediction error was computed in relation to the mean observed clearance which underestimates the error in neonates and exaggerates it in adults. Mahmood also proposed unrealistic goals for acceptable bias and imprecision of the prediction. Sheiner LB. The population approach to pharmacokinetic data analysis: rationale and standard data analysis methods. Drug Metab Rev. 1984;15(1-2):153-71.
Slide 11	**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 ©NHG Holford, 2011, all rights reserved.	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).

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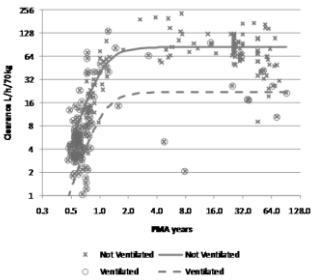
Morphine Dose Rate Relative Bias

External evaluation for Target Concentration



- 257 human morphine 'observed' CL
- 24 PMA week to 91 year
- **Acceptable if dose <= 25% ideal**
- **Unacceptable if >= than 100%**

Model	Data	Premature	Neonate	Infant	Child	Adult
	N	83	35	26	23	90
Textbook mg/kg	Reich	-18	68	31	-11	21
CL^3/4 MF,ventilated	Holford	-23	12	-32	-25	-1
CL^PWR PNA 10 d	Knibbe	37	33	-4	24	224
CL^(f(WT)) Ventilated	Wang	-31	74	6	6	106
CL^PWR, V^PWR Ventilated	Mahmood	-31	149	-16	-11	101

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

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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.

Reich A, Beland B, Van Aken H. Intravenous narcotics and analgesic agents. In: Pediatric Anesthesia, eds. Bissonnette B, Dalens B, London McGraw-Hill, 2002.
Holford NHG, Ma S, Anderson BJ. Prediction of morphine dose in humans. Submitted. 2011.
Wang C, Peeters MYM, Allegaert K, Tibboel D, Danhof M, Knibbe CAJ. Scaling clearance of propofol from preterm neonates to adults using an allometric model with a bodyweight-dependent maturational exponent [www.page-meeting.org/?abstract=1818]. PAGE 2010; 19.
Knibbe CA, Krekels EH, van den Anker JN, DeJongh J, Santen GW, van Dijk M, Simons SH, van Lingen RA, Jacqz-Aigrain EM, Danhof M, Tibboel D. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. Clin Pharmacokinet 2009; 48: 371-85.
Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol 2006; 61: 545-57.

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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

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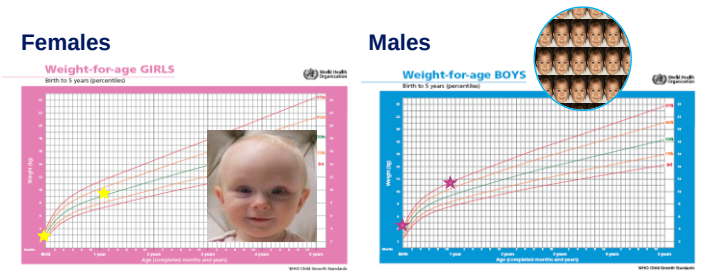
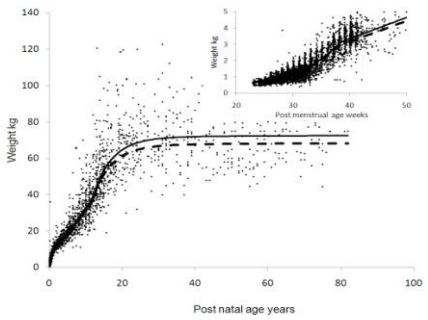
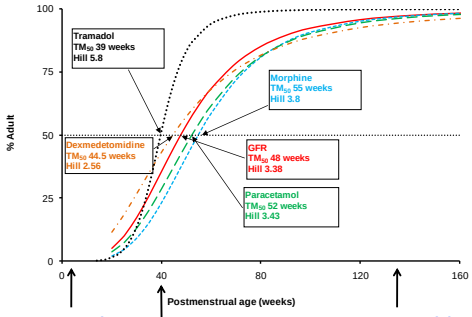
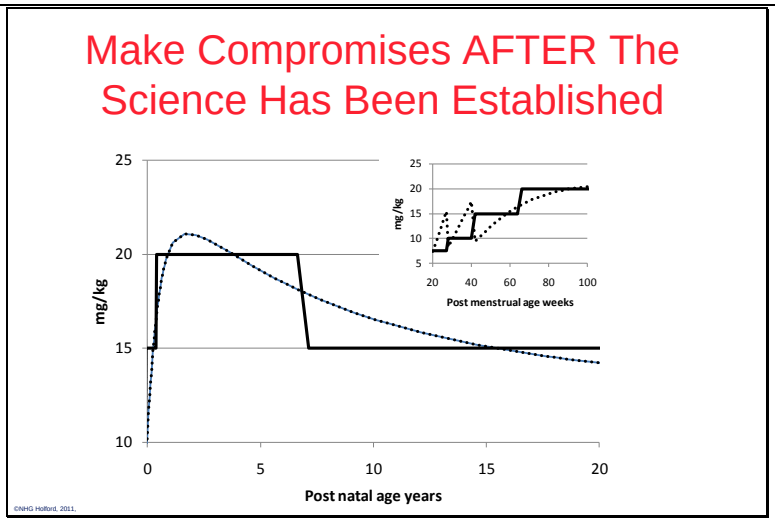
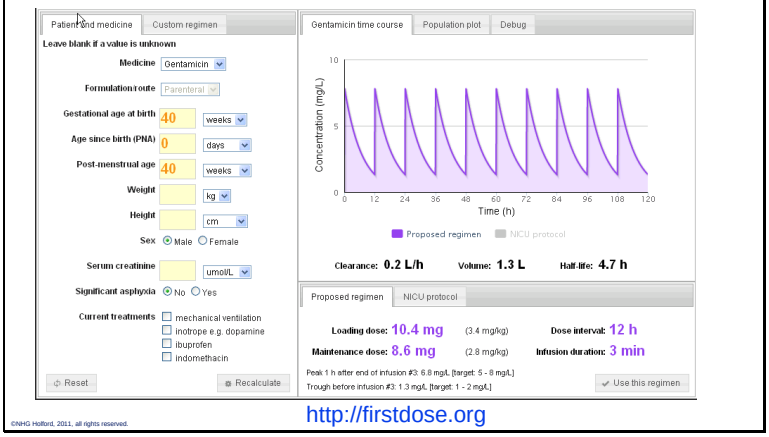
Slide 14	**WHO Chart 0-5 postnatal age**  7551 Observations Based on observations of 882 infants & 6669 children from an idealized population across 6 countries 1997 -2003. Premature infants excluded. ©NHG Holford, 2011, all rights reserved.	Standard growth charts are based on an idealized population of well nourished children which excludes premature infants.
Slide 15	**Predicting Weights from Age**  Observed weights (dots) Predicted weights: Females (dashed line) & Males (solid line) ©NHG Holford, 2011, all rights reserved.	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. Sumpter AL, Holford NHG. Predicting weight using postmenstrual age – neonates to adults. Pediatric Anesthesia. 2011;21(3):309-15.
Slide 16	**Clearance Maturation**  Conception Full Term 2 years old Maturation is predictable – complete by 2 years of age – – then Size is the main predictor of drug clearance ©NHG Holford, 2011, all rights reserved.	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. Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76

Slide 17		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 a rational science based prediction. For details see: Holford N. Dosing in children. Clin Pharmacol Ther. 2010;87(3):367-70.
Slide 18	 http://firstdose.org	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 (eg. iPhone) is under development and will shortly be evaluated in a clinical trial compared to standard of care. Anderson BA, Herbert CH, N.H.G., Holford SD. What is needed for a dosing calculator? PAGE PAGANZ 2011 (2011) Abstr 1147 [wwwpage-meetingorg/?abstract=1147]. 2011.

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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

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Back Up Slides

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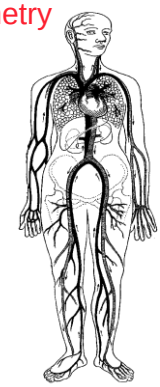
Theory Based Allometry
Scaling based on Fractal Geometry

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



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

West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999;284(5420):1677-9.

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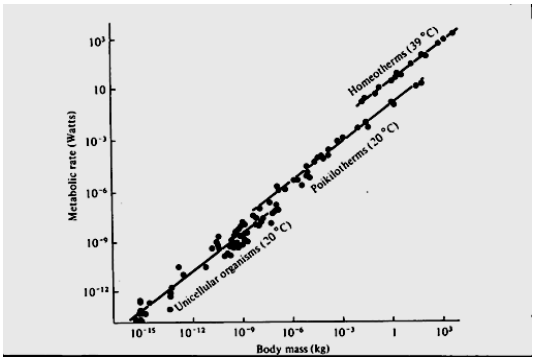
Allometric Size Matches Observations 18 Orders of Magnitude



Peters R. The ecological implications of body size. Cambridge: Cambridge University Press; 1983.

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Which Size?

- Normal Fat Mass (NFM)
  - FFM + Ffat*(WT – FFM)
  - *Derived from Duffull et al. 2004*
- Fat Free Mass (FFM)
  - weight, height and sex
  - *Janmahasatian 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

$$CL_{PREDICTED} = CL_{STD} \cdot \left(\frac{NFM}{NFM_{STD}} \right)^{3/4}$$

Duffull SB, Dooley MJ, Green B, Poole SG, Kirkpatrick CM. A standard weight descriptor for dose adjustment in the obese patient. Clin Pharmacokinet. 2004;43(15):1167-78.
Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.

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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

$$CL_{PREDICTED} = \frac{CL_{STD}}{1 + \left(\frac{PMA}{TM50} \right)^{-Hill}}$$

TM50=PMA at 50% maturation

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Population Approach to Prediction Bias

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

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

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

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

Prediction Bias = 15/10=1.5

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

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Prediction Bias Application

```
IF (GAW.LT.37) THEN
   GRP=1 ; premature neonate
   GBIAS=B_PRE
   GVBIAS=BV_PRE
ELSE
   AGEM=AGEY*12
   IF (AGEM.LE.1) THEN
      GRP=2 ; full term neonate
      GBIAS=B_NEO
      GVBIAS=BV_NEO
   ELSE
      IF (AGEY.LT.2) THEN
         GRP=3 ; infant
         GBIAS=B_INF
         GVBIAS=BV_INF
      ELSE
         IF (AGEY.LT.20) THEN
            GRP=4 ; child
            GBIAS=B_CHI
            GVBIAS=BV_CHI
         ELSE
            GRP=5 ; adult
            GBIAS=B_ADU
            GVBIAS=BV_ADU
         ENDIF
      ENDIF
   ENDIF
ENDIF
```

- 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

```
;Size model
FSIZE=(WTKG/70)**.75
;Maturation model
FMAT=1/(1+(PMAW/TM50_CL)**(-HILL_CL))
;Mechanical ventilation effect
IF (VENT.EQ.1) THEN
   FVENT=FDEV_CL ; from NEOPAIN
ELSE
   FVENT=1
ENDIF

GRPCL=FVENT*FMAT*FSIZE*CLSTD

; Maintenance dose rate
GMDR=GRPCL*POPTC
MDR=GMDR/GBIAS

;POPTC is target concentration

GCLB=MDR/POPTC*1000/60  ; L/h -> mL/min
CL=GCLB*EXP(PPV_CL/GVBIAS)

Y= CL * (1 + RUV) ; DV is observed CL
```

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Models for Morphine Clearance

Published MorphineStudies
MDV for BLQ

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 S04 (blush)

NEOPAIN + Bouwmeester
Beal M3 for BLQ

5. SIZEMAT1
   - Size, maturation, 1 CPT
6. SIZEMAT2
   - Size, maturation, 2 CPT
7. PWRCLMAT2
   - CL exponent estimated
8. WTHILL
   - CL exponent Hill f(wt)
9. PWRCLpna10
   - Knibbe with NEOPAIN+Bouwmeester data
10. PWRCLV
    - CL & V exponents, no maturation
11. BSA
    - Surface area (duBois & duBois or Boyd f(wt))

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