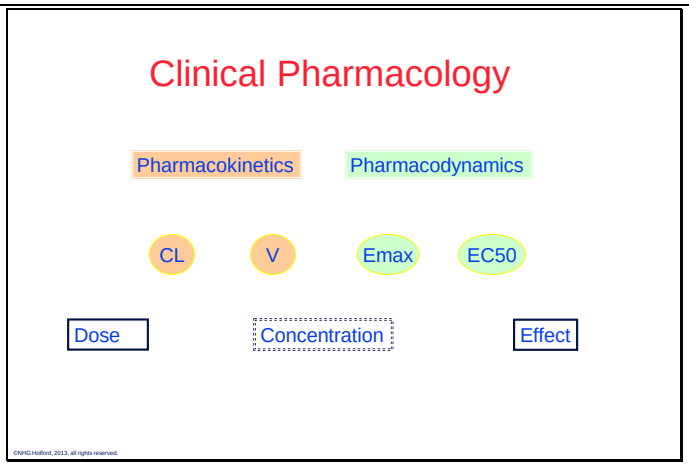
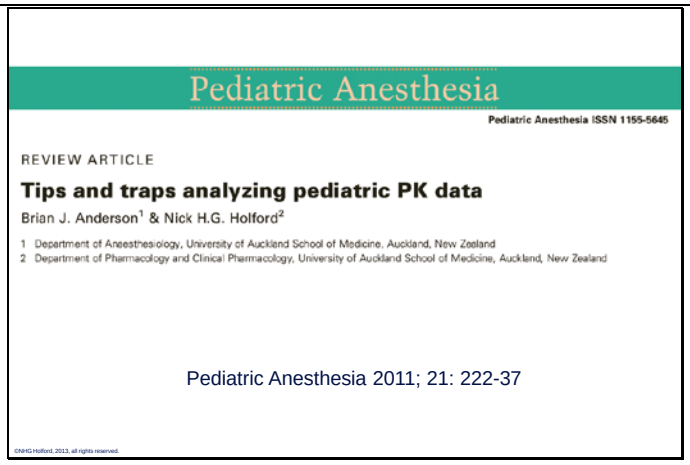
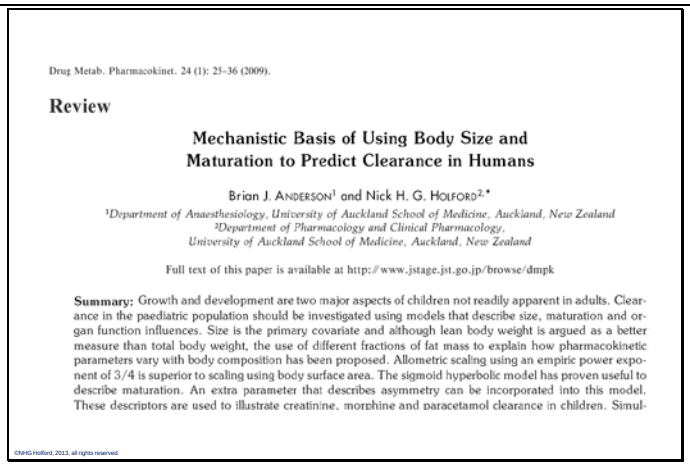
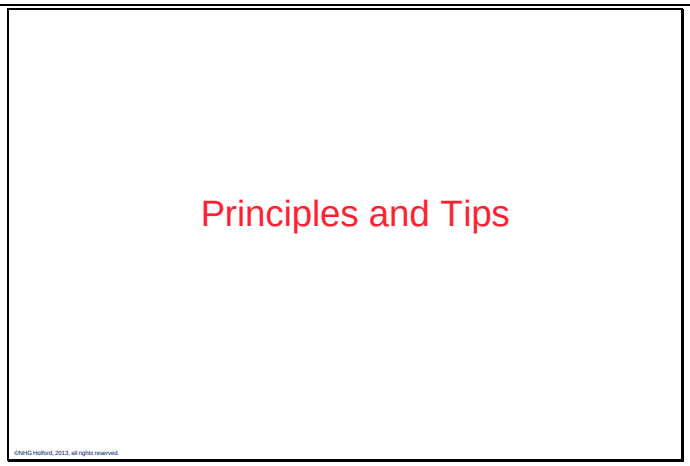
Slide 1	# Tips and Traps In Pediatric PKPD Nick Holford University of Auckland Brian Anderson Starship Hospital, Auckland	Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. 2013;102(9):2941-52. Anderson BJ, Holford NH. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child. 2013;98(9):737-44.
Slide 2		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.
Slide 3		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 science linking dose and concentration is pharmacokinetics. 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).

Slide 4		Anderson BJ, Holford NHG. Tips and traps analyzing pediatric PK data. Pediatric Anesthesia 2011; 21: 222-37.
Slide 5		
Slide 6		

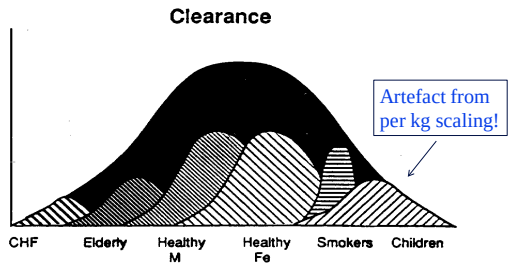
Slide 7

Why does PKPD vary?

- Systematic (predictable)
  - Body size
  - Maturation
  - Disease state (liver, kidney)
  - Genotype, etc…
- Random (not predictable)
  - Between Subject Variability
  - Within Subject Variability

Slide 8

Covariates Do Not Explain All Variability

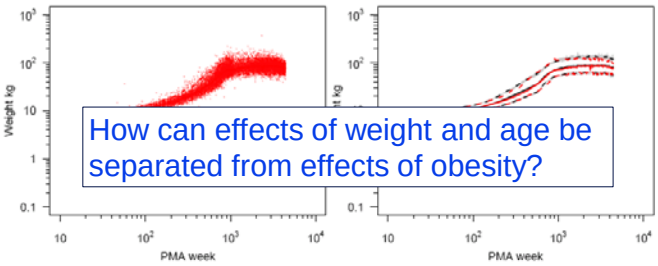
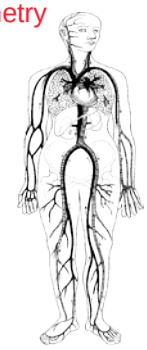


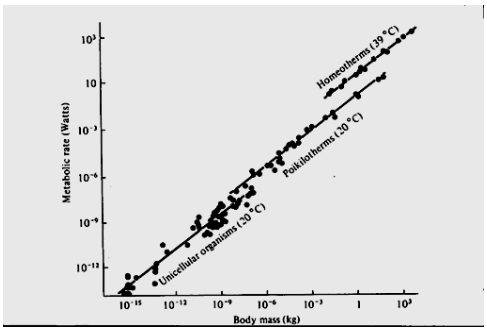
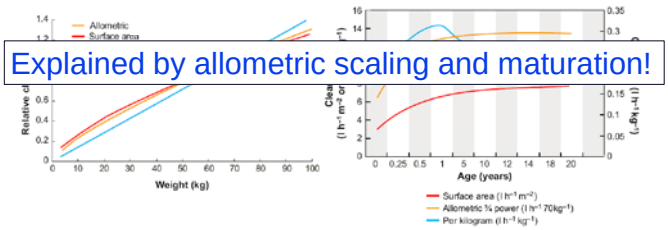
N.Sambol CDDS/SUMC1997

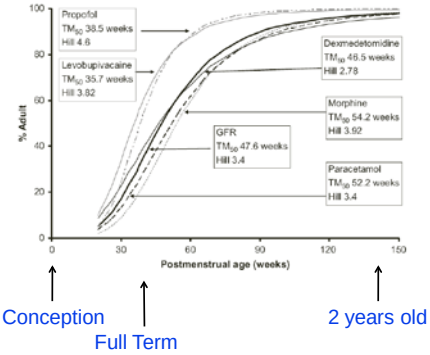
Slide 9

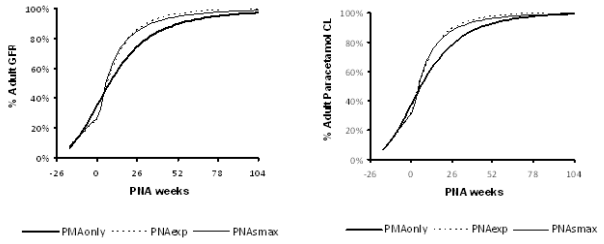
Three Ways to Dose

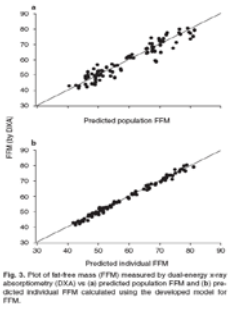
- Population
  - Same dose for everyone
    - The dream dosing method!
- Group (Covariate guided)
  - Same dose for similar group
    - e.g. same weight, CLcr, genotype
- Individual
  - Dose determined by individual response
    - e.g. BP, INR, blood conc

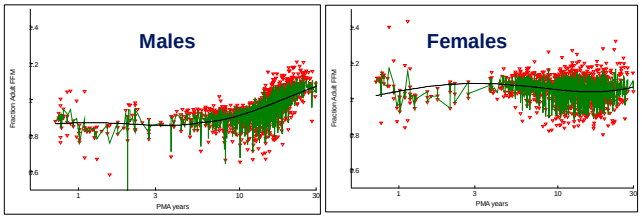
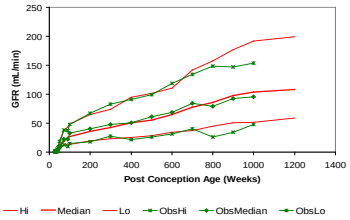
Slide 10	**The Problem of Weight and Age**  Data from Sumpter AL, Holford NHG. Predicting weight using postmenstrual age – neonates to adults. Pediatric Anesthesia. 2011;21(3):309-15. and CDC/NHANES database 	Sumpter AL, Holford NHG. Predicting weight using postmenstrual age – neonates to adults. Pediatric Anesthesia. 2011;21(3):309-15.
Slide 11	**A Principle Based Model for Clearance** 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. 	Model for predicting clearance proposed by Tod, Julien and Pons. It has 3 components – size, maturation and organ function. Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008;47(4):231-43.
Slide 12	**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. 	

Slide 13	**Allometric Size Matches Observations 18 Orders of Magnitude**  Peters R. The ecological implications of body size. Cambridge: Cambridge University Press; 1983. 	
Slide 14	**Why CL per kg is higher in children** Size Alone Size and Maturation  Explained by allometric scaling and maturation! Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48: 303-32. 	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.
Slide 15	**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 $$Fmat = \frac{1}{1+\left(\frac{PMA}{TM50}\right)^{-Hill}}$$ $$CL_{PREDICTED_{NFM,PMA}} = CL_{NFM} \cdot Fmat$$ TM50=PMA at 50% maturation 	Sigmoid maturation model first proposed by Tod M, Lokiec F, Bidault R, De Bony F, Petitjean O, Aujard Y. Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. Antimicrob Agents Chemother. 2001;45(1):150-7.

Slide 16	**Clearance 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. 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 Anderson BJ, Holford NHG. Tips and traps analyzing pediatric PK data. Pediatric Anesthesia 2011; 21: 222-37.
Slide 17	**Maturation or Birth** • Impractical to study PK *in utero* • All studies are after birth – Are changes due to: • Ongoing maturation *ex utero*? • Processes triggered by birth and exposure to extra-uterine life? 	
Slide 18	**Maturation AND Birth** • Both processes can be described using PMA for maturation and PNA for extra-uterine processes • PMA model $Fmat = \frac{1}{1+\left[PMA/TM_{50}\right]^{-Hill}}$ Sigmoid • PNA Models $F_{birth} = \frac{1+FB_{max}\cdot\left(1-\exp\left[-PNA\cdot\ln(2)/TB_{50}\right]\right)}{1+FB_{max}}$ Exponential $F_{birth} = \frac{1+FB_{max}/\left(1+\left[PNA/TB_{50}\right]^{-FB_{Hill}}\right)}{1+FB_{max}}$ Sigmoid 	

Slide 19	**Maturation and Birth**  Birth effect on GFR and metabolism is detectable but relatively small 	Anderson BJ, Holford NHG. Tips and traps analyzing pediatric PK data. Pediatric Anesthesia 2011; 21: 222-37.
Slide 20	**GFR Maturation and Birth** PNA Model / OBJ / GFRstd (ml/min/70kg) / TM_{50} (weeks) / TB_{50} (days) Base — 4750.129 — **121** — **47.7** — - 90%CI — 117, 125 — 45.1, 50.5 — - SE% — 1.8 — 2.7 — - Sigmoid Emax — 4688.6 — **122** — **35.3** — **5.9** 90%CI — 118, 126 — 31.1, 43.3 — 3.21, 7.7 SE% — 1.8 — 8.9 — 22.2 Exponential — 4687.6 — **122** — **34.4** — **7.25** 90%CI — 118, 126 — 30.0, 41.7 — 3.38, 11.2 SE% — 1.7 — 9.6 — 32.1 	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).
Slide 21	**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 – *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 $CL_{NFM} = CL_{STD} \cdot \left(\frac{NFM}{NFM_{STD}} \right)^{3/4}$ Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32. 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. 	

Slide 22	**Fat Free Mass**
	Semi-Mechanistic Model
	 
	Fig. 3. Plot of fat-free mass (FFM) measured by dual-energy x-ray absorptiometry (DXA) vs (a) predicted population FFM and (b) predicted individual FFM calculated using the developed model for FFM.
	if (sex = FEMALE)
	$WHSmax = 37.99\ kg/m^2$
	$WHS50 = 35.98\ kg/m^2$
	else
	$WHSmax = 42.92\ kg/m^2$
	$WHS50 = 30.93\ kg/m^2$
	$FFM = \frac{WHSmax \cdot HTm^2 \cdot WTkg}{WHS50 \cdot HTm^2 + WTkg}$
	Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65
	©NHG Holford, 2013, all rights reserved.
		Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65

Slide 23	**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  ©NHG Holford, 2013, all rights reserved.	Sumpter A, Holford NHG. A model for fat free mass in humans from very premature neonates to young adults. PAGANZ http://wwwpaganzorg/abstract/1296 2012; Accessed 19 April 2012. Data from Al-Sallami H, Goulding A, Taylor RW, Grant AM, Williams SM, Duffull SB. A semi-mechanistic model for estimating fat free mass in children [www.page-meeting.org/?abstract=2063]. 20. 2011 and extracted from published reports of FFM. To account for observations reported as means they were weighted by 1/sqrt(Nsubjects) contributing to the observation
Slide 24	**GFR, Age and Size**  GFR is predicted better by NFM than TBW Allometric scaling superior to linear scaling • 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) • FFM for body composition using Janmahsatian 2005 • 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 ©NHG Holford, 2013, all rights reserved.	

Slide 25

Normal Fat Mass

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

Slide 26

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

Slide 27

Pitfalls and Traps

Slide 28

Power Function Models

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

$$Conc = Conc_{STD} \cdot \left(\frac{Hct}{45}\right)^{0.93}$$

  - Simpler empirical models (linear, exponential) are easier

$$Conc = Conc_{STD} \cdot (1 + 0.03 \cdot (Hct - 45))$$

Both these models had the same objective function value

Slide 29

Estimation of Allometric Exponent

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

Weight distribution	5%CI	95%CI
Log normal median 70 kg, 20%CV	0.48	1.01
Log normal median 70 kg, 50%CV	0.64	0.86
Uniform 0–140 kg	0.69	0.81

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.

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

Slide 30

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:

$$Fsize = (W)^{3/4} \cdot \left(1/70\right)^{3/4}$$

The expression

$$\left(1/70\right)^{3/4}$$

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.

Slide 31

Weight Used For Standardization Does Not Affect Allometric Scaling!

	CL (%)	V (%)
Centered on 1 kg		
Bias		
Average	1.55	1.13
Median	1.40	0.80
RSE	5.43	3.26
2.5 percentile	91	96
97.5 percentile	113	108
Centered on 20 kg		
Bias		
Average	1.56	1.13
Median	1.33	1.15
RSE	5.42	3.25
2.5 percentile	91	96
97.5 percentile	113	108

	CL (%)	V (%)
Centered on 70 kg		
Bias		
Average	1.56	1.12
Median	1.40	1.00
RSE	5.42	3.27
2.5 percentile	91	96
97.5 percentile	113	108

Slide 32

Use of Age Categories for PK Study Analysis

	CL (%)	V (%)
Bias		
Average	3.6	2.2
Median	2.4	2.0
RSE	13	8
2.5 percentile	82	86
97.5 percentile	135	119

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

Don't Use Categories!

	CLP	VP	CLN	VN	CLI	VI	CLC	VC
Bias								
Average	5.1	3.8	4.4	7.4	−12	0.5	6.9	18
Median	2.7	2.9	4.1	6.4	−12	−0.3	6.3	16
RSE	22	15	13	14	13	18	13	22
2.5 percentile	69	77	81	84	62	66	83	80
97.5 percentile	152	136	130	136	114	137	135	163

Slide 33

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 …

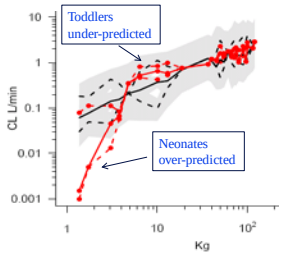
Allometry is about Mass

- 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…

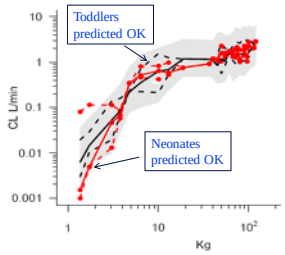
Slide 34

Predictable Variability Size and Maturation

¾ Allometry Alone
explains 67% of CL variability



¾ Allometry + Maturation
explains 80% of CL variability



Original data from Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010 Apr 1;49(4):269-75.

Slide 35

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

Slide 36

Paediatric Clinical Pharmacology in BJCP

"However, medications for children are more usually quoted for

Out of date ideas still appearing in the literature!

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?)

Slide 37

Does this make sense?

Parameters (units)	Model 1 - Infants, toddlers and adults mean	Bootstrap mean (CV%)
Fixed effects		
CL (L/min)	-	-
CL (L min^{-1} Kg$^{0.75}$)	0.234	0.232 (9.6)

$$CL = 0.234\,\text{L min}^{-1}\,\text{Kg}^{0.75}$$

$$= 0.234 \cdot \left(\frac{70}{1}\right)^{0.75} = 5.7\,\text{L/min} = 340\,\text{L/h/70 kg}$$

Cella M, Knibbe C, de Wildt SN, Van Gerven J, Danhof M, Della Pasqua O. Scaling of pharmacokinetics across paediatric populations: the lack of interpolative power of allometric models. Br J Clin Pharmacol 2012; doi: 10.1111/1365-2125.2012.04206.x.

Slide 38

Evaluation of Predictions

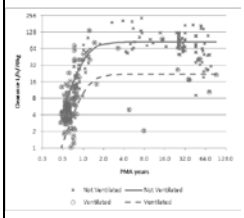
Conclusions: The morphine maturation model has a poor predictive power of morphine clearance
in preterm and term neonates, infants and very young children and may not be of any practical value for the prediction of morphine clearance in this age group.

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: 88-94.

Slide 39

External Evaluation of Size and Maturation Models

Holford NHG, Ma S, Anderson BJ. Prediction of morphine dose in humans. Pediatric Anesthesia. 2011



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

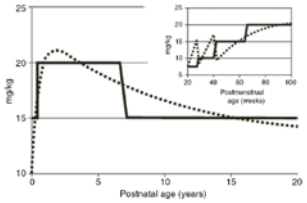
Model	Age Group	Premature	Neonate	Infant	Child	Adult
	N	83	35	26	23	90
CL^3/4 MF,ventilated	Holford	-23	12	-32	-25	-1
CL^PWR PNA 10 d	Knibbe	37	33	-4	24	224
CL^(f(WT)) Ventilated	Wang	-31	74	6	6	106
CL^PWR, V^PWR Ventilated	Mahmood	-31	149	-16	-11	101

Only **theory based allometry** + **maturation** predicts adult dose
All **empirical** allometric models **unacceptable**

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.

Holford NH, Ma SC, Anderson BJ. Prediction of morphine dose in humans. Paediatr Anaesth. 2012;22(3):209-22.

Reich A, Beland B, Van Aken H. Intravenous narcotics and analgesic agents. In: Pediatric Anesthesia, eds. Bissonnette B, Dalens B, London McGraw-Hill, 2002.
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.
Slide 40	**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^{-1} 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.
Slide 41	**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 	