Slide 1

Environmental Variability

Body Size, Body Composition, Maturation and Organ Function

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland

Slide 2

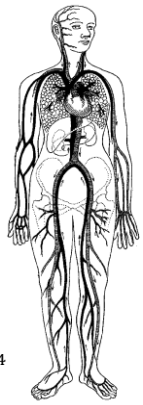
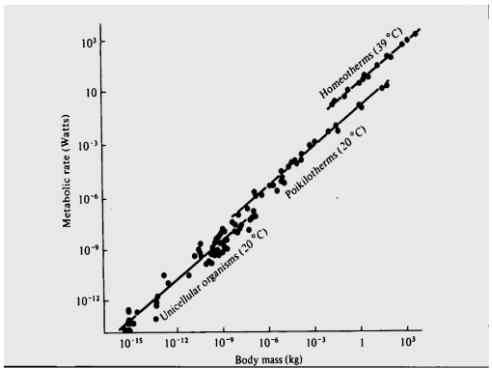
Objectives

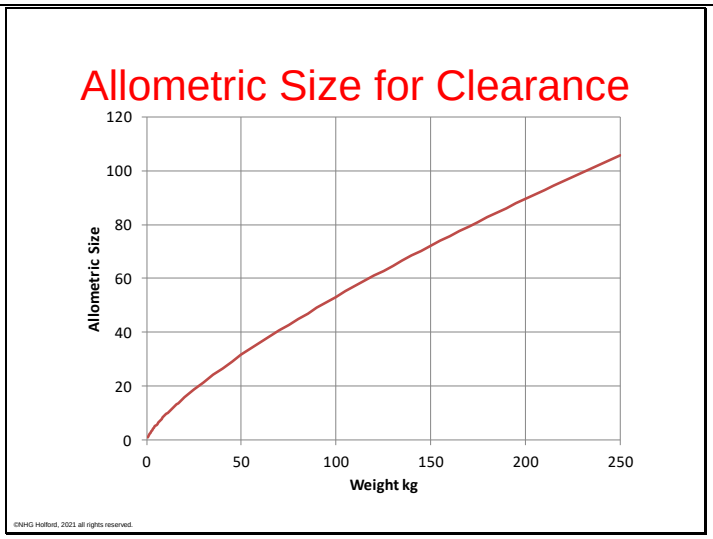
- Understand the major sources of variability affecting the response to medicines
- Appreciate the relative contributions of body size, body composition, maturation and organ function to variability
- Learn the principles of dose individualization based on predictable sources of variability

Slide 3

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 beween weight and clearance the corresponding range of **maintenance dose rates** is only about **100 fold**

Slide 4	**Theoretical Foundation for Allometric Scaling**    $$CL_{CHILD} = CL_{ADULT} \times \left(\frac{WT_{CHILD}}{WT_{ADULT}}\right)^{3/4}$$ 	West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999;284(5420):1677-9. 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
Slide 5	**Allometric Size Matches Observations 18 Orders of Magnitude**  	Peters R. The ecological implications of body size. Cambridge: Cambridge University Press; 1983.

Slide 6		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.
Slide 7	**Body Composition** ➢ Simplest view of body composition is to distinguish between fat free mass and fat mass ➢ Fat mass is typically around 22% of total body weight (men) and 28% (women) ➢ Fat free mass is predictable from total body weight, height and sex (Janmahasatian 2005) ➢ Drug clearance and volume of distribution is 'driven' mainly by fat free mass but also by fat mass. The fraction of fat mass predicting drug elimination and distribution varies from drug to drug. 	http://en.wikipedia.org/wiki/Body_fat_percentage The fraction of fat mass predicting drug elimination and distribution varies from drug to drug e.g. 0 for warfarin clearance and volume (Xue et al 2017), 0.509 for busulfan clearance and 0.203 for busulfan volume (McCune et al. 2014) and 1 for propofol clearance and volume (Cortinez et al. 2010). These fractions are multiplied by fat mass to predict the equivalent fat free mass determining either clearance or volume. The resulting sum of fat free mass and fraction of fat mass is called normal fat mass. Normal fat mass is used in allometric scaling to combine body mass and body composition (Holford et al 2017). If fat mass is a partial determinant of normal fat mass then this can be described by the fraction of fat mass (Ffat) that is equivalent to fat free mass in its contribution to normal fat mass. Suppose you want to calculate clearance (CL) with total body mass TBM and fat free mass FFM. The values of TBM and FFM will determine FATM=TBM-FFM. Standard normal fat mass (NFMstd) may be defined using an FFM of 56.1 kg which is expected for a male with TBM of 70 kg and height of 1.76 M. If the normal fat mass is the same as total body mass then Ffat is equivalent to a value of 1: CL=CLstd x (TBM/TBMstd)^(3/4); CLstd is for total body mass of 70 kg If the normal fat mass is the same as fat free mass then Ffat is equivalent to a value of 0:

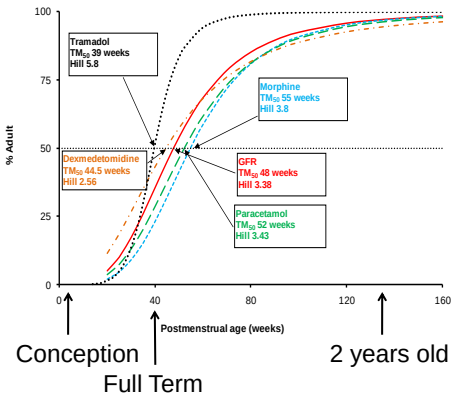
		CL=CLstd x (FFM/FFMstd)^(3/4); CLstd is for fat free mass of 50 kg If the normal fat mass is the same as fat free mass plus a fat free mass equivalent fraction (Ffat) of fat mass then: CL=CLstd x ((FFM + FATM x Ffat)/(FFMstd + FATMstd x Ffat))^(3/4); CLstd is for fat free mass of 50 kg and fat mass of 15 kg. Note that the standard mass used to calculate allometric size is the normal fat mass for a standard person (NFMstd). Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65. Xue L, Holford N, Ding XL, Shen ZY, Huang CR, Zhang H, et al. Theory-based pharmacokinetics and pharmacodynamics of S- and R-warfarin and effects on international normalized ratio: influence of body size, composition and genotype in cardiac surgery patients. Br J Clin Pharmacol. 2017;83(4):823-35. McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin Cancer Res. 2014;20(3):754-63. Cortinez LI, Anderson BJ, Penna A, Olivares L, Munoz HR, Holford NH, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth. 2010;105(4):448-56. Holford NHG, Anderson BJ. Allometric size: The scientific theory and extension to normal fat mass. Eur J Pharm Sci. 2017;109(Supplement):S59-S64.

Slide 8	**Renal Function** ➢ **Differences in renal function** can explain about a **10 fold difference in total drug clearance**. ➢ Glomerular Filtration Rate » 7 L/h in healthy young adult » 0.5 L/h in terminal renal failure ➢ There is always some non-renal clearance e.g. via the gut which adds 0.5 L/h to total clearance even in renal failure 	
Slide 9	**Prediction of Renal Function** ➢ **Serum Creatinine is Used to Calculate Creatinine Clearance (CLcr)** » Adults: – Cockcroft & Gault, MDRD and eGFR » Children and babies – Schwartz ➢ CLcr is approximately the same as glomerular filtration rate ➢ Renal function is calculated relative to normal CLcr for weight and age: $\text{Renal Function} = \frac{\text{Predicted CLcr}}{\text{Normal CLcr}}$ 	Cockcroft & Gault method is recommended for prediction of drug clearance. The formula is based on clearance concepts and uses weight, age and sex to predict creatinine production rate based on expected muscle mass. Schwartz methods developed for children and babies using height as a measure of body size. MDRD and eGFR methods developed for diagnosis of different categories of renal function. These are empirical formulae that do not include body size (Levey et al. 1999). Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New Equations to Estimate GFR in Children with CKD. J Am Soc Nephrol. 2009:ASN.2008030287. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461-70.

Slide 10	**Hepatic Function** ➢ **Difficult to predict hepatic drug clearance without administering the drug** ➢ "Liver Function Tests" » measure liver damage which is not the same as function » AST/ALT may be very high (1000s) in viral hepatitis with no changes in hepatic drug clearance » Albumin and INR changes in terminal hepatic failure are correlated with hepatic drug clearance ➢ Clinical Staging Systems » Child-Pugh system » Loosely correlated with hepatic drug clearance 	
Slide 11	**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.
Slide 12	**Maturation and Ageing** • **Maturation Of Drug Clearance** • Typical maturation is about 30% of adult values at full term delivery • Very premature neonates are around 10% of adult values • In neonates and infants age accounts for a 10 fold increase in glomerular filtration rate from 24 weeks post-menstrual age up to 1 year of post-natal age (Rhodin et al. 2009). • **Ageing and Drug Clearance** • Age in older adults has a minor (~ 25% lower) influence on drug clearance once weight and other factors such as renal function are accounted for. 	Rhodin, M. M., B. J. Anderson, A. M. Peters, M. G. Coulthard, B. Wilkins, M. Cole, E. Chatelut, A. Grubb, G. J. Veal, M. J. Keir and N. H. Holford (2009). "Human renal function maturation: a quantitative description using weight and postmenstrual age." Pediatr Nephrol **24(1): 67-76.**

Slide 13

Clearance Maturation



Conception

Full Term

2 years old

Maturation is complete by 2 years of age –

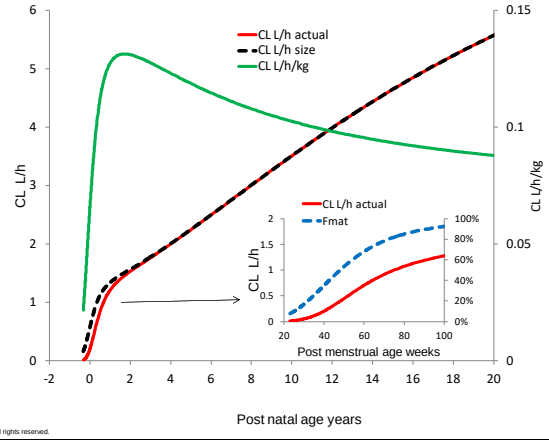
– then weight is the sole predictive factor for drug clearance

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.

This presentation was made by a clinical pharmacologist (Paolo Denti) with some helpful advice about using allometry and maturation concepts. https://www.rosaandco.com/webinars/2020/what-drives-policy-change

Slide 14

Weight and Age Explain Higher mg/kg Doses in Young Children



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.

Slide 15

Rules of PNA and PMA

Fraction of adult maintenance dose

Typical Weight Kg	PMA or PNA	Fraction Adult Dose	Rule of PMA+PNA Error	'true' % Adult Dose
1	25 weeks	1/300	10%	0.3
1	30 weeks	1/120	1%	0.8
3	Full Term	1/30	1%	3.3
6	3 mo	1/10	8%	9.3
7	6 mo	1/6	24%	13.4
9	1 year	1/5	3%	19.5
12	2 years	1/4	-4%	26.1
19	5 years	1/3	-11%	37.4
34	10 years	1/2	-14%	58.5
50	15 years	3/4	-3%	77.4
70	Adult	1		100.0

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.

Slide 16	**Body size, renal function and post-menstrual age are the most important determinants of drug dose** ➢ In comparison to these factors other covariates such as **genotype may pale into quantitative insignificance**. ➢ Quantitative pharmacology can help put the role of using covariates to predict drug dose into **a realistic perspective**. 	Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. The Lancet. Theken KN, Grosser T. Weight-adjusted aspirin for cardiovascular prevention. The Lancet. 2018;392(10145):361-2.
Slide 17	**Assessment Short Answer Question Examples** 1. Draw a graph of the relationship between body mass and clearance and body mass and volume of distribution over the human weight range. 2. What are the major determinants of between subject differences in clearance? Give approximate relative importance of the determinants in numerical terms. 3. Why are doses per kg typically larger in children when compared to adults? 	