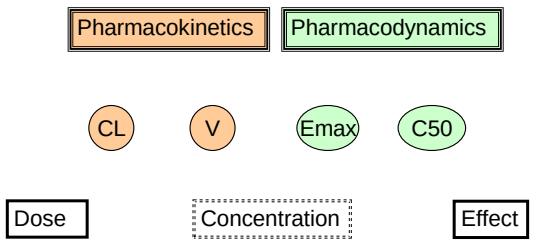
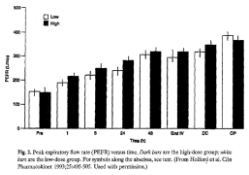
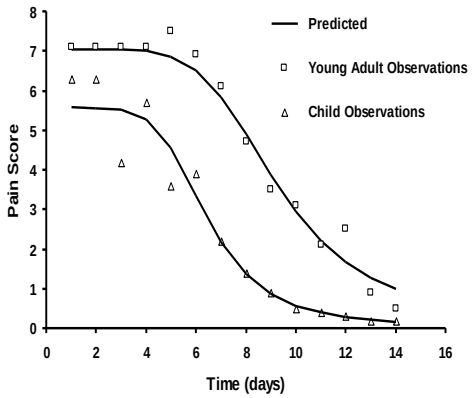
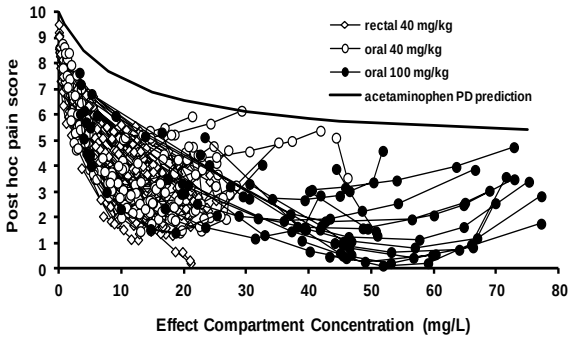
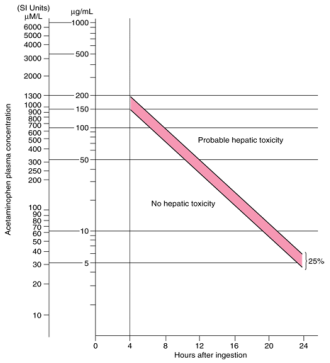
Slide 1	# Children are small adults and babies are young children **Nick Holford** Dept Pharmacology & Clinical Pharmacology **Brian Anderson** Dept Anaesthesia & Starship Hospital University of Auckland, New Zealand	
Slide 2	# Objectives - Appreciate how clinical pharmacology has helped medical practice - Review examples of real research projects - Recognize the challenges of getting doctors to use science in their daily practice 	
Slide 3	# Clinical Pharmacology  	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 (C50).

Slide 4	**First Target Concentration Controlled Clinical Trial** 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 	A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital. It showed that the target concentration is 10 mg/L. Higher concentrations had little extra benefit but substantially more toxicity e.g. nausea and vomiting. The primary objective of this study was to determine which target concentration was safe and effective when starting treatment with theophylline.
Slide 5	**What Was The Clinical problem?** ● Severe asthma and COPD are very common causes of hospital admission. ● Intravenous theophylline was the standard emergency treatment. ● But what was the right starting dose? ● The target concentration approach was being discussed by clinical pharmacologists but 'real doctors' had no idea what it was about. 	COPD = Chronic Obstructive Pulmonary Disease Theophylline is administered using an intravenous formulation of aminophylline which contains 80% theophylline by weight.
Slide 6	**Target Concentration Controlled Trial** ● Patients were randomized to a target conc of 10 or 20 mg/L. ● Laboratory scaled the actual measurements e.g. if the target was 10 mg/L and the actual conc was 10 mg/L it was reported as 15 mg/L. ● Only the lab knew the actual value. Scaled values were reported to doctors. This maintained the double blind feature of the trial. ● Doctors used the reported theophylline concentrations to try to target 15 mg/L by changing IV infusion rate. 	

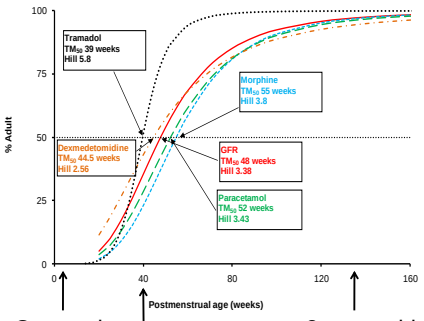
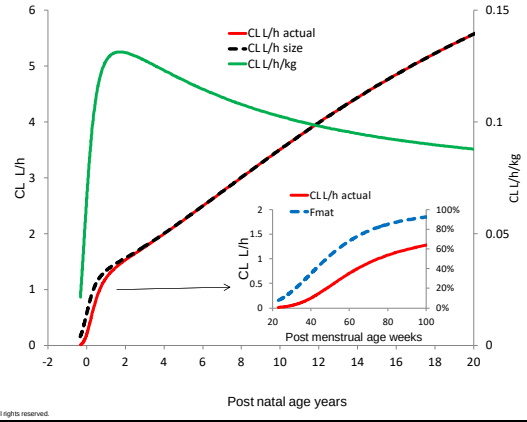
Slide 7	**The Outcome of the Trial** ● Trial showed 10 mg/L was safer than 20 mg/L » 20 mg/L group included vomiting, arrhythmias and convulsions » Little difference in effects on peak expiratory flow rate ● Conclusion: Target concentration is 10 mg/L ● Doctors had a clear idea of how to start and adjust doses for individualized safe and effective treatment ● Research example for clinical pharmacologists (Sheiner 1997)  CLINICAL PHARMACOLOGY & THERAPEUTICS COMMENTARY Learning versus confirming in clinical drug development Lewis B. Sheiner, MD ©NHG Holford, 2017 all rights reserved.	Holford N, Black P, Couch R, Kennedy J, Briant R. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? A randomised concentration-controlled trial. Clin Pharmacokinet. 1993;25(6):495-505. Holford N, Hashimoto Y, Sheiner LB. Time and theophylline concentration help explain the recovery of peak flow following acute airways obstruction. Population analysis of a randomised concentration controlled trial. Clin Pharmacokinet. 1993;25(6):506-15. Sheiner LB. Learning versus confirming in clinical drug development. Clinical Pharmacology & Therapeutics. 1997;61(3):275-91. Professor Sheiner is probably the most important figure in the development of rational clinical pharmacology – especially for bringing a quantitative approach to decisions about the development and clinical use of medicines. He trained many clinical pharmacologists who use his ideas every day in clinical practice, research and teaching e.g. Professor Park (Seoul, Korea), Professor Karlsson (Uppsala, Sweden), Professor Holford (Auckland, New Zealand)
Slide 8	 ©NHG Holford, 2017 all rights reserved.	Nick Holford (left) and Brian Anderson (right) at Seoul Hilton, Korea, 2012

Slide 9	**Paediatric Clinical Research** • Brian Anderson, consultant intensive care physician at StarShip Hospital, Auckland, New Zealand » Mid-life crisis so decided to do a PhD • Studies of pharmacokinetics and pharmacodynamics of paracetamol in children after tonsillectomy • Pharmacodynamic study used doses of 100 mg/kg compared to traditional doses of 40 mg/kg by the rectal route to establish the maximum pain relief (Emax) and potency (C50) 	Anderson BJ, Woollard GA, Holford NH. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. Eur J Clin Pharmacol. 2001;57(8):559-69.
Slide 10	**How Does Paracetamol Work?**  • POX site of Prostaglandin H2 synthetase (PGHS) enzyme • Metabolite (N-arachidonoylphenolamine, AM404) is endogenous cannabinoid • CB(1) receptor antagonist completely prevents the analgesic activity of paracetamol 	Ottani A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur. J. Pharmacol 2006 531 (1-3): 280
Slide 11	**Tonsillectomy Pain Resolution**  	Anderson BJ, Woollard GA, Holford NH. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. Eur J Clin Pharmacol. 2001;57(8):559-69.

Slide 12	**Paracetamol Pharmacodynamics**  	Note large placebo response (difference between predicted paracetamol effect (acetaminophen PD prediction)) and pain score with different doses and routes.
Slide 13	**Paracetamol Analgesia and Toxicity** • **5 mg/L** **1.7 pain units** • **10 mg/L** **2.6 pain units** • **20 mg/L** **3.4 pain units** • **30 mg/L** **4.2 pain units** • **Paracetamol 100 mg/kg** **11/20 vomited** • **Paracetamol 40 mg/kg** **3/12 vomited** » **Vomiting more frequent with high dose (Chi square, p=0.037)** » **Vomiting with high dose similar to morphine** 	. Anderson BJ, Woollard GA, Holford NH. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. Eur J Clin Pharmacol. 2001;57(8):559-69.
Slide 14	**Paracetamol Target Concentration** • Recommended target concentration is 10 mg/L • This concentration affords reasonable analgesia • The target concentration is easily achieved in most individuals using the recommended dosage schedule. • While higher doses could achieve greater analgesia, chronic use of higher doses is associated with an increased incidence of hepatotoxicity. » Note: The adverse effects on the liver short term use of higher doses e.g. for a target of 20 mg/L are unknown. » To be safe: “First do not harm”/”Primum non nocere” 	

Slide 15	**Pharmacokinetic Model for Children** ● Results from the pain relief study were combined with other studies in children and adults ● Pharmacokinetic model showed how concentration depends on size (weight) and maturation (age) » Anderson et al. 2000, Anderson & Holford 2011 	Anderson BJ, Woollard GA, Holford NH. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. Br J Clin Pharmacol. 2000;50(2):125-34. The paracetamol model was updated again in 2011: Anderson BJ, Holford NHG. Tips and traps analyzing pediatric PK data. Pediatric Anesthesia. 2011;21(3):222-37.
Slide 16	**Application of PK to Clinical Practice** ● Paracetamol accidental overdose is common in infants and children ● Guidelines for treatment in adults starts by measuring paracetamol concentration at 4 hours after ingestion » 4 hours is a long time to wait for children (and adults!) ● Auckland pharmacokinetic model was used to simulate concs after overdose with liquid ("elixir") formulations usually taken by children.  	Anderson BJ, Holford NH, Armishaw JC, Aicken R. Predicting concentrations in children presenting with acetaminophen overdose. J Pediatrics. 1999;135(3):290-5.
Slide 17	**Accidental Ingestion in Children Recommendations** ● Measure concentration if ingestion > 200 mg/kg of elixir (or if dose unknown) ● Obtain sample at two hours ● If 2 h level is > 150 mg/L, then a second level should be measured at 4 hours ● Start N-acetyl-cysteine if plasma conc. > 150 mg/L (4 h) 	

Slide 18	**International Recognition**  THE JOURNAL OF PEDIATRICS September 1999 Volume 135 Number 3 EDITORIALS Acetaminophen overdose? A quick answer Blood sample at 2 hours after ingestion Less stress; shorter time in hospital 	Rumack BH. Acetaminophen overdose? A quick answer. J Pediatr. 1999;135(3):269-70.
Slide 19	**International Collaborations** ● Paracetamol work led to fame in the paediatric world ● Invited to work on data collected by other groups who were impressed by our PKPD approach ● Morphine, Ketamine, Clonidine, Dexmedetomidine, Tramadol… 	
Slide 20	**Morphine**  ● Dutch group – infants and children ● American group – premature neonates ● PK model » Allometric size » Maturation based on post-menstrual age ● Predictions compared to literature values from neonates to elderly » Theory based allometry and maturation was the only method that predicted acceptable doses across human age range 	Anand KJ, Anderson BJ, Holford NH, Hall RW, Young T, Shephard B, et al. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. Br J Anaesth. 2008;101(5):680-9. Holford NH, Ma SC, Anderson BJ. Prediction of morphine dose in humans. Paediatr Anaesth. 2012;22(3):209-22.

Slide 21	General Principles Learned from Paracetamol Studies in Children ©NHG Holford, 2017 all rights reserved.	
Slide 22	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 ©NHG Holford, 2017 all rights reserved.	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.
Slide 23	Weight and Age Explain Higher mg/kg Doses in Young Children  ©NHG Holford, 2017 all rights reserved.	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. Clinically used maintenance doses are commonly expressed per kg in clinical practice and are higher around 2 years of age than in babies and adults.

Slide 24

Practical Application to Dosing

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 25

PK Standard

- Theory based allometry and maturation now used widely
- Standardized PK parameters from over 50 medicines

Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32.
Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. 2013;102(9):2941-52.

Slide 26

Back to the target …

Slide 27

A High Clinical Need

- Busulfan is used to knock-out bone marrow in children and adults prior to bone marrow transplant
- High mortality (30%) due to drug toxicity or graft failure
- FDA product label recommends using AUC to individualize subsequent doses
- Auckland Hospital asks “How to calculate AUC for busulfan?”

Slide 28

AUC Dose Adjustment

from Busulfex label (PDL 2006)

Dose Adjustment Based on Therapeutic Drug Monitoring

Instructions for measuring the AUC of busulfan at dose 1 (see Blood Sample Collection for AUC Determination), and the formula for adjustment of subsequent doses to achieve the desired target AUC (1125 µM•min), are provided below.

Adjusted dose (mg) = Actual Dose (mg) x Target AUC (µM•min)/Actual AUC (µM•min)

For example, if a patient received a dose of 11 mg busulfan and if the corresponding AUC measured was 800 uM•min. for a target AUC of 1125 µM•min, the target mg dose would be:

Mg dose = 11 mg x 1125 µM•min / 800 µM•min = 15.5 mg

Busulfex dose adjustment may be made using this formula and instructions below.

Blood Sample Collection for AUC Determination:

Calculate the AUC (µM•min) based on blood samples collected at the following time points:

For dose 1: 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration). Actual sampling times should be recorded.

For doses other than dose 1: Pre-infusion (baseline), 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration).

AUC calculations based on fewer than the three specified samples may result in inaccurate AUC determinations.

For each scheduled blood sample, collect one to three mL of blood into heparinized (Na or Li heparin) Vacutainer® tubes. The blood samples should be placed on wet ice immediately after collection and should be centrifuged (at 4°C) within one hour. The plasma, harvested into appropriate cryovial storage tubes, is to be frozen immediately at -20°C. All plasma samples are to be sent in a frozen state (i.e., on dry ice) to the assay laboratory for the determination of plasma busulfan concentrations.

Calculation of AUC:

BUSULFEX AUC calculations may be made using the following instructions and appropriate standard pharmacokinetic formula:

Dose 1 $AUC_{Infinity}$ Calculation: $AUC_{Infinity} = AUC_{0-2hr} + AUC_{Extrapolated}$

where AUC_{0-2hr} is to be estimated using the linear trapezoidal rule and AUC extrapolated can be computed by taking the ratio of the busulfan concentration at Hour 6 and the terminal elimination rate constant, λ_z. The λ_z must be calculated from the terminal elimination phase of the busulfan concentration vs. time curve. A "0" pre-dose busulfan concentration should be assumed, and used in the calculation of AUC.

If the AUC is assessed subsequent to Dose 1, steady-state AUC_{ss} (AUC_{0-6h}) is to be estimated from the trough, 2 hr, 4 hr and 6 hr concentrations using the linear trapezoidal rule.

Instructions for Drug Administration and Blood Sample Collection for Therapeutic Drug Monitoring:

An administration set with minimal residual hold up (priming) volume (1-3 mL) should be used for drug infusion to ensure accurate delivery of the entire prescribed dose and to ensure accurate collection of blood samples for therapeutic drug monitoring and dose adjustment.

Prime the administration set tubing with drug solution to allow accurate documentation of the start time of BUSULFEX infusion. Collect the blood sample from a peripheral IV line to avoid contamination with infusing drug. If the blood sample is taken directly from the existing central venous catheter (CVC), DO NOT COLLECT THE BLOOD SAMPLE WHILE THE DRUG IS INFUSING to ensure that the end of infusion sample is not contaminated with any residual drug. At the end of infusion (2 hr), disconnect the administration tubing and flush the CVC line with 5 cc of normal saline prior to the collection of the end of infusion sample from the CVC port. Collect the blood samples from a different port than that used for the BUSULFEX infusion. When recording the BUSULFEX infusion stop time, do not include the time required to flush the indwelling catheter line. Discard the administration tubing at the end of the two-hour infusion.

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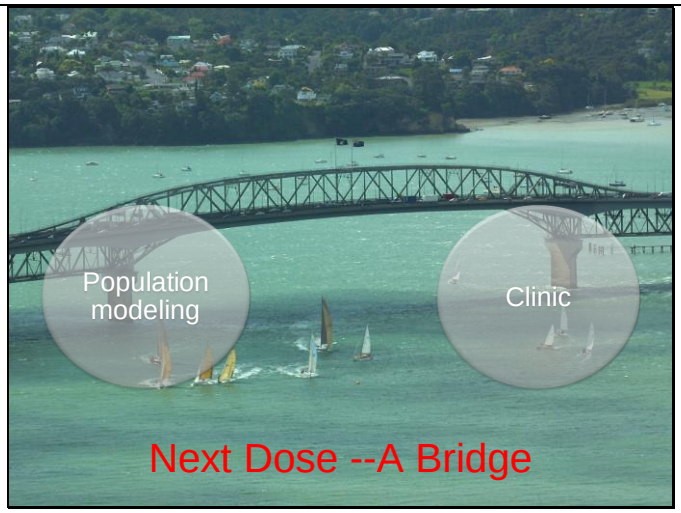
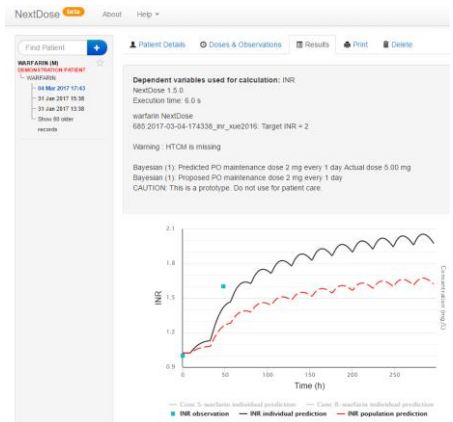
Busulfan Collaboration

- American national lab for measuring busulfan asks for assistance in PK analysis of concs from 1610 patients
- Allometric size, maturation and normal fat mass used to predict initial doses
- Initial dose predictions much better than FDA method (72% vs 57% acceptable)
- But still 28% with un-acceptable dose …

Slide 30	**Why Target Concentration Intervention is Necessary** • The acceptable exposure range for busulfan is based on a goal of 95% of patients lying within 80-125% of the target average steady state concentration (Css) (Holford & Buclin 2012) • With TCI the unpredictable variability for Css can be reduced to the within subject variability of 11.3% (McCune 2014) • This means that only 5% of patients will be under- or over-dosed if measured concentrations are used to predict future doses. A major improvement over initial dosing based on size and age. 	McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NH. 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. Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit. 2012;34(5):565-8.
Slide 31	 	
Slide 32	**TCI with NextDose** • Web based dose calculator developed with Auckland medical student (now a surgical registrar) • Uses measured busulfan concentrations and population PK model • Recommended doses available within seconds of entering concentration measurements • In routine use at Auckland City and Starship hospitals in New Zealand 	

Slide 33	NextDose  dev.nextdose.org	
Slide 34