Slide 1

Target Concentration Intervention

Dose Individualization using Monitoring of Patient Response

Nick Holford
University of Auckland

Slide 2

Objectives

1) Appreciate how a target concentration (TC) strategy is essential for rational clinical use of medicines
2) Understand when and why individual patient monitoring can be used for dose individualization
3) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM)

Slide 3

Target Concentration in Clinical Use of Medicines

Target Conc = Target Effect x C50 / (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, C50, V and CL**

The target concentration approach links pharmacokinetics (PK) with pharmacodynamics (PD) to predict the right dose for a patient.

Slide 4

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

Slide 5

Why does PKPD vary?

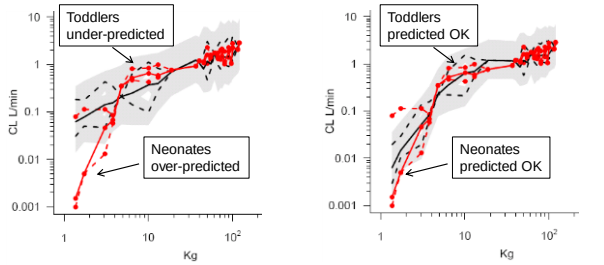
- Systematic (predictable)
  - » Body size
  - » Disease state (liver, kidney)
  - » Genotype
  - » etc...
- Random (not predictable)
  - » Between Subject Variability
  - » Within Subject Variability

Slide 6

Predictable Variability Size and Maturation

¾ Allometry Alone
explains 67% of CL variability

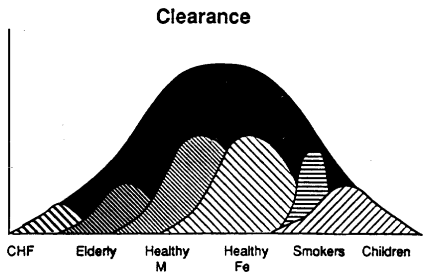
¾ Allometry + Maturation
explains 80% of CL variability



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.

Holford NHG. Target concentration intervention - can we hit the targets? 6th International Symposium on Measurement and Kinetics of In Vivo Drug Effects; Noordwijkerhout. LACDR; 2010.

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 7	**Differences Remain Even After Accounting for Obvious Features**  	Figure originally drawn by Dr N.Sambol CDDS/SUMC1997 It shows the frequency distribution of clearance (expressed per kg body weight) for a medicine eliminated largely by metabolism with the distribution of clearance in specific sub-populations. Despite the use of weight, sex, age, disease, concomitant medications there remains a substantial variability of clearance within each sub-population. This remaining variability is what TCI can reduce. The limiting variability for the benefit of TCI is within subject variability. Theophylline is metabolized by CYP1A2. This enzyme is induced by polycyclic hydrocarbons in cigarette smoke. Enzyme induction reduces variability because there is a maximum biological limit on the extent of enzyme induction. Note that the naïve per kg method of scaling leads to an apparent higher clearance in children but in fact the clearance in children is the same as adults when scaled based on allometric theory (Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.)
Slide 8	**Three Ways to Dose** • Population » Same dose for everyone – The dream dosing method! (often used in adults) • Group (Covariate guided) » Same dose for similar group – e.g. same weight, CLcr, genotype (usually used for children) • Individual » Dose determined by individual response – e.g. BP, INR, blood conc 	The population dosing method is most commonly used but usually just for convenience. This means that some patients are either under-dosed or over-dosed. The use of weight or renal function to adjust the dose is recommended for some medicines but probably not used as often as it should be. CLcr = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio Individual dosing based on response is widely used when the response is easily measured. But sometimes it is used e.g. with anti-HIV medicines, when the within subject variability is large and predictable individualization is not really possible. Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.

Slide 9

Which Drugs for TCI?

1. Usefulness is hard to measure (drug is working when the clinical outcome is not easily observable)
   - » Anti-arrhythmics e.g. lignocaine
   - » Anti-convulsants e.g. phenytoin
   - » Anti-coagulants e.g. warfarin
2. Big unpredictable variability (after using weight, renal function,etc) and small within subject variability
   - » Too much variability means either inadequate beneficial effect or too much adverse effect
   - » Observing patient response can predict future dose needs

The first reason for using TCI uses a response, such as blood pressure, as a substitute for being able to measure the clinical disease state that is being treated. When the medicine is working well or it is not working at all the clinical disease state may appear to be the same. It is assumed that trying to reach a typical response that is usually associated with benefit is better than giving everyone the same dose.

The second reason for using TCI is when group based dosing (e.g. using weight) is not enough to reduce the between subject variability so that the medicine can be used safely and effectively. TCI can only work however if the within subject variability (that cannot be influenced by TCI) is small enough so that dose individualization is really predictive for future use of the medicine in the same patient.

Slide 10

How?
Target Concentration Strategy

1. Choose Target Concentration
2. Determine V and CL using WT etc.
3. Calculate LD and MDR
4. Measure Response (e.g. INR)
   Revise Target Conc
5. Measure Concs
   Revise V and CL
6. Goto Step 3

The target concentration strategy is an algorithm for reaching the best individual dose. It starts with choosing a target concentration based on pharmacodynamic studies. A group value for volume (V) and or clearance (CL) can be determined before the medicine is given. These PK parameters are then used to calculate the initial loading dose (LD) and maintenance dose rate (MDR). A response is measured reflecting how the individual is different from the group of patients who are otherwise similar in weight, genotype, etc. If the response is a measure of drug effect e.g. INR, then it can be used to revise the target conc. If the response is a concentration then it can be used to revise V and CL. Most commonly the focus will be on CL so that a new individualized maintenance dose rate can be calculated.

Slide 11

Target Concentrations

Target Concentrations and Pharmacokinetic Parameters for Selected Medicines (70 kg standard individual). Css is the average steady state concentration.

Drug	Target Conc	Clearance	Volume of distribution
Aminoglycosides	Peak 20 mg/L* Css 3 mg/L	6 L/h	18 L
Tacrolimus**	7 mcg/L	20 L/h	100 L
Phenytoin	10 mg/L	Vmax=415 mg/d, Km= 4mg/L	45 L
Digoxin	1 ng/mL	9 L/h	500 L
Theophylline	10 mg/L	3 L/h	35 L

* 24 hour dosing ** whole blood

Target concentrations and PK parameters are known for most medicines which are helped by TCI.

Slide 12

Target Effects

Target Effects and Pharmacodynamic Parameters for Selected Medicines. Emax is the maximum effect due to the drug, C50 is the concentration producing 50% of Emax. PEFR is peak expiratory flow rate.

Drug	Target Effect	Emax	C50
Aminoglycosides	"cure"	?	?
Tacrolimus	"prevention of rejection"	?	?
Phenytoin	"prevention of seizures"	?	?
Digoxin	"control of atrial fibrillation"	?	?
Theophylline	"normal PEFR"	344 L/min	11 mg/L
Warfarin	INR 2-3	100% *	1.5 mg/L

- Inhibition of prothrombin complex synthesis

The pharmacodynamic parameters for medicines that use TCI are typically not well known. This is a reflection of the difficulty of measuring a clinical response that can be related to concentration.

Holford NHG, Black P, Briant R, Couch R, Kennedy J. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? A randomised concentration-controlled trial. *Clinical Pharmacokinetics* 1993; 25:495-505

Holford NHG, 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. *Clinical Pharmacokinetics* 1993; 25:506-515

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):1810-52.

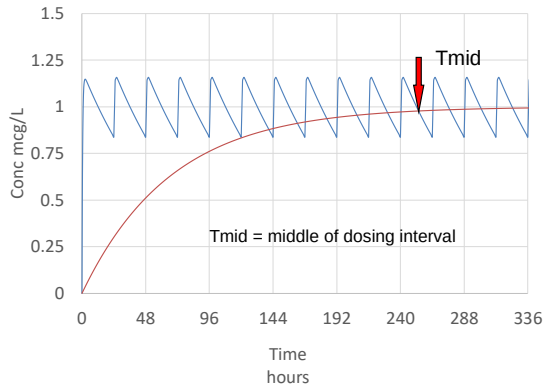
Slide 13

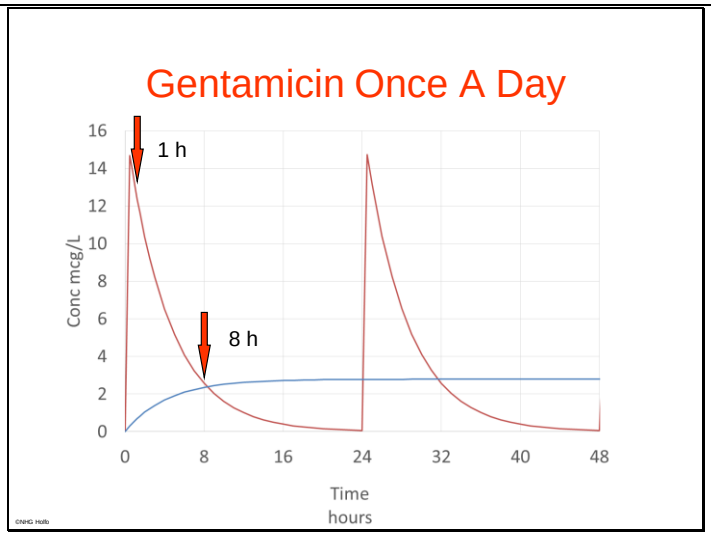
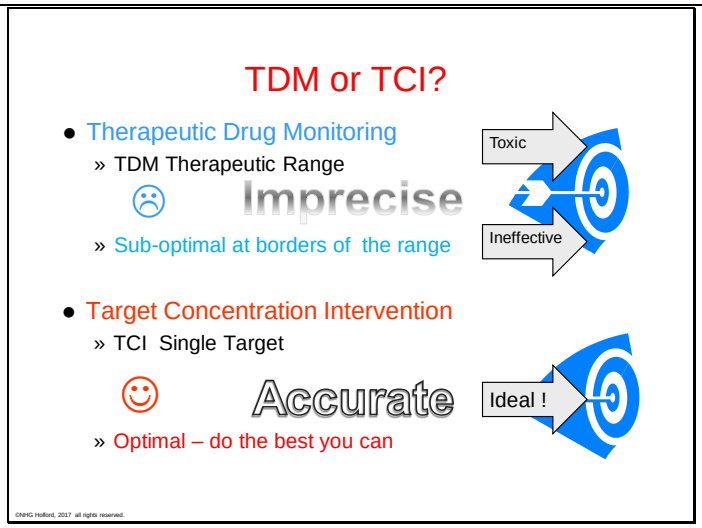
Determine Group V and CL
(predictable variability)

- Volume of Distribution
  - » size $V = V_{pop} \times WT/WT_{std}$
  - » body composition

- Clearance
  - » size $CL = Cl_{pop} \times (WT/WT_{std})^{3/4}$
  - » renal function
  - » hepatic function
  - » concomitant drugs

WT=patient weight
WTstd=standard weight e.g. 70 kg
Vpop, CLpop=population volume and clearance in a standard subject e.g. 70 kg.

Slide 14	**Calculate LD and MDR e.g. Gentamicin** ● LD = TC x V = 20 mg/L x 20 L = 400 mg ● MDR = TC x CL = 3 mg/L x 6 L/h = 18 mg/h = 400 mg/day 	
Slide 15	**When to Measure Concs?** Goal is to estimate PK e.g. CL ● Number of Samples » Most medicines 1 » Gentamicin 2 ● Timing of Sample - As soon as possible » Most medicines Middle of dosing interval » Gentamicin "peak" and "trough" 	A rational approach to measuring drug concentrations is based on using the measurement to predict pharmacokinetic parameters – most commonly clearance. The least informative time to measure concentrations is just before the next dose (the 'trough' concentration) unless this is paired with another 'peak' concentration. This is because clearance determines the average concentration. So measuring a concentration in the middle of the dosing interval will be closer to the average and therefore more useful for predicting clearance. Gentamicin concentrations vary widely in a dosing interval so two concentrations are needed to reliably estimate clearance. The sooner the sample is taken the sooner concentrations can be used to improve dosing.
Slide 16	**Digoxin**  	A concentration in the middle of the dosing interval (Ctmid) will be closer to the average steady state concentration (Css) then either a peak or trough concentration. Clearance is easily calculated from CL=DoseRate/Css which can be approximated by CL=DoseRate/CTmid.

Slide 17		Gentamicin concentrations with once a day dosing vary considerably. The trough concentration at 24 h is often unmeasurable because it is below the limit of quantitation. Concentrations are best measured 1h and 8 h after the dose. In this example a dose of 240 mg was given every 24 hours. V can be approximated from the first conc (C1 ~= 13 mg/L) assuming about 15% of the dose is eliminated in 1 hour. V=0.85*Dose/C1 e.g. 0.85*240 mg/13 mg/L=15.7 L Half-life can be estimated from C1 at time T1 (1 h) and the second conc (C2 ~= 2.5 mg/L) at time T2 (8 h): K=ln(C1/C2)/(T2-T1)=ln(13/8)/(8-1)=0.236 h-1 Thalf=ln(2)/K=2.94 h CL can then be calculated: CL=V*K=3.7 L/h
Slide 18		Therapeutic drug monitoring is a traditional concept associated with empirical ‘seat of the pants’ dose adjustment determine by a measurement being outside a ‘therapeutic range’. The therapeutic range is hard to identify and is often mistakenly justified because it seems to be similar to the normal reference range for endogenous substances. A concentration at the bottom of the range has a very different meaning (close to being ineffective) from one at the top (close to being toxic) but TDM proponents usually ignore this and are happy to do nothing as long as the concentration is ‘within range’. Target concentration intervention is a science based method that uses pharmacokinetic and pharmacodynamic principles to identify how patients are different and uses PK guided dose individualization to achieve a precise therapeutic target. It has been shown to improve clinical outcome as well as being a cost-effective use of health resources. Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl J Med. 1998;338(8):499-505. van Lent-Evers NAEM, MathÃ´t RAA, Geus WP, van Hout BA, Vinks AATMM. Impact of Goal-Oriented and Model-Based Clinical Pharmacokinetic Dosing of Aminoglycosides on Clinical Outcome: A Cost-Effectiveness Analysis. Ther Drug Monit. 1999;21(1):63-73. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure

		significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7(11):2496-503. Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.