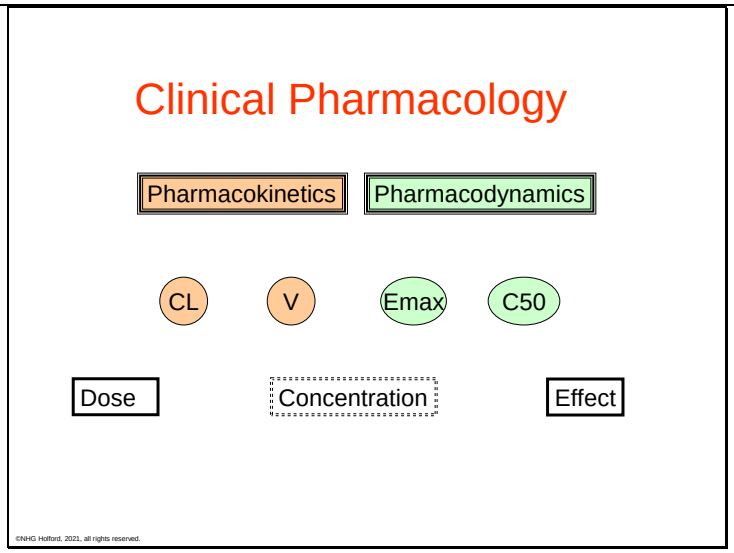
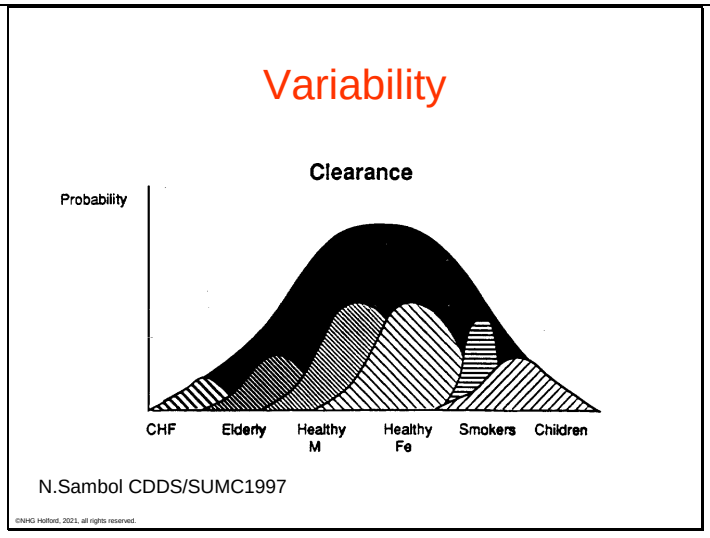
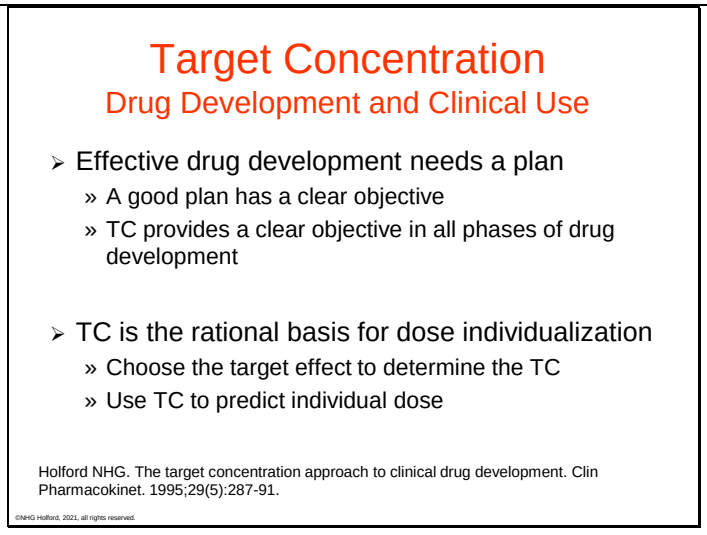
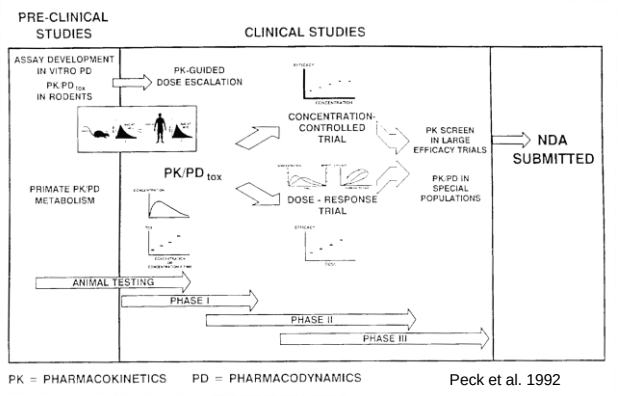
Slide 1	# PKPD Variability ## Quantifying Variability to aid Dose Individualization Nick Holford University of Auckland 	
Slide 2	# Objectives 1) Learn about the sources of variability in clinical pharmacology 2) Appreciate how a target concentration (TC) strategy is essential for rational drug development and clinical use 3) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM) 4) Understand how to make rational choices for dose individualization 	
Slide 3		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 4		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 5		
Slide 6		

Slide 7	**Target Concentration in Drug Development**  Peck et al. 1992 	The 1992 view was based on using PKPD for drug development but did not explicitly include how to use medicines in patients.
Slide 8	**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 PKPD to prediction of the right dose for a patient. If Emax and C50 and Target Effect are not known then the Target Conc may be estimated from: Typical Average Daily Dose Target Conc =---------- Typical Clearance
Slide 9	**TDM or TCI?** ➢ Therapeutic Drug Monitoring » TDM Therapeutic Range ☹ Imprecise » Sub-optimal at borders of the range Toxic Ineffective ▯ Target Concentration Intervention » TCI Single Target ☺ Accurate Ideal ! » Optimal – do the best you can 	

Slide 10	**Why TDM Cannot Work** ➢ TDM proposes a range of concentrations to judge if an individual is getting the right dose ➢ It is not reasonable to prescribe a range of doses in order to match the range of concentrations ➢ Therefore the therapeutic window cannot be used to get the right dose ➢ There is only one dose that can achieve the target concentration that will produce the target effect 	
Slide 11	**TCI vs TDM - Tacrolimus** ➢ TDM » Use of TDM had no effect in reducing renal transplant rejection – Thervet (2010): Fixed dose vs Genotype dosing (increased fraction within therapeutic window) – Anutrakulchai (2019): Fixed dose vs Genotype dosing (increased fraction within therapeutic window, more delayed graft function) TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were given dosing advice. 	Anutrakulchai S, Pongskul C, Kritmetapak K, Limwattananon C, Vannaprasaht S. Therapeutic concentration achievement and allograft survival comparing usage of conventional tacrolimus doses and CYP3A5 genotype-guided doses in renal transplantation patients. Br J Clin Pharmacol. 2019;85(9):1964-73. Thervet E, Loriot MA, Barbier S, Buchler M, Ficheux M, Choukroun G, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721-6.
Slide 12	**TCI vs TDM - Vancomycin** ➢ Three studies compared TCI with historical TDM ➢ All showed TCI achieved more exposure in the therapeutic window than TDM ➢ All showed reduced nephrotoxicity with TCI TCI = goal was to reach target AUC in every patient. Clinicians were given dosing advice using Bayesian estimation. TDM = goal was to reach target trough within therapeutic window in every patient. Clinicians may have been given dosing advice (varied by study). Truong et al. Int Med J (2012), Neely et al. Antimicrob Agents Chemo (2018), Meng et al. Pharmacotherapy (2019) 	Meng L, Wong T, Huang S, Mui E, Nguyen V, Espinosa G, et al. Conversion from Vancomycin Trough Concentration–Guided Dosing to Area Under the Curve–Guided Dosing Using Two Sample Measurements in Adults: Implementation at an Academic Medical Center. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019;39(4):433-42. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. Internal Medicine Journal. 2012;42(1):23-9. Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. Antimicrob Agents Chemother. 2018;62(2):e02042-17.

Slide 13	**TCI vs TDM - Mycophenolate** ➢ TCI » Use of TCI reduced renal transplant rejection – Hale 1998 (Phase 3): Randomized Concentration Controlled Trial. 3 Target AUCs. – Le Meur 2008 (APOMYGYRE): Fixed Dose vs Target AUC ➢ TDM » Use of TDM had no effect in reducing renal transplant rejection – van Gelder 2008 (FDCC): Fixed dose vs Therapeutic Window AUC – Gaston 2009 (OPTICEPT): Fixed dose vs Therapeutic Window Trough TCI = goal was to reach target in every patient. Clinicians were given dosing advice using Bayesian estimation. TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were not given dosing advice. 	Hale M, Nicholls A, Bullingham R, Hene R, Hoitsman A, Squifflet J, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther. 1998;64:672-83. 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. van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. Transplantation. 2008;86(8):1043-51. Gaston RS, Kaplan B, Shah T, Cibrik D, Shaw LM, Angelis M, et al. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticept trial. Am J Transplant. 2009;9(7):1607-19. Rousseau A, Laroche M-L, Venisse N, Loichot-Roselmac C, Turcant A, Hoizey G, et al. Cost-Effectiveness Analysis of Individualized Mycophenolate Mofetil Dosing in Kidney Transplant Patients in the APOMYGRE Trial. Transplantation. 2010;89(10):1255-62.
Slide 14	**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 15

Why does PKPD vary?

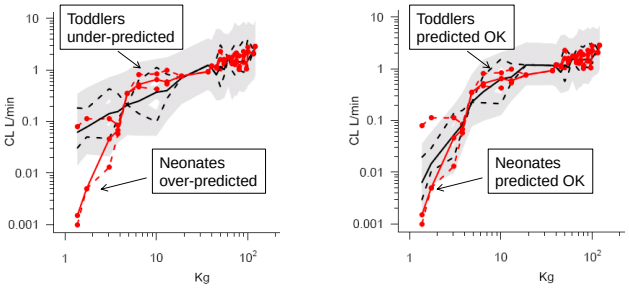
- Systematic (predictable)
  - » Body size
  - » Disease state (liver, kidney)
  - » Genotype
  - » etc...
- Random (not predictable)
  - » Between Subject Variability
  - » Within Subject Variability

Slide 16

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 17

Unexplained Clearance Variability

Drug	BSV_U %	WSV_U %	Source
Metoprolol	53	35	Lunn (1997)
Fenoterol	12	16	Bouillon (1996)
Riluzole	51	28	Bruno (1997)
Felodipine	34	33	Wade (1995)
Drug A	57	29	Karlsson (1993)
Drug B	35	19	Karlsson (1993)
Drug B	33	19	Jonsson (1996)
Moxonidine	22	15	Karlsson (1998)
Artemisinin	48	53	Sidhu (1998)
Average	**41**	**30**	

BSV_U=Between Subject **WSV_U=Within Subject**

BSVu=Between Subject Variability unexplained by predictable factors such as weight, etc.
WSVu=Within Subject Variability unexplained by predictable factors such as weight, etc.

% expresses an apparent co-efficient of variation

Slide 18	**Safe and Effective Variability** ➢ CLINICAL JUDGMENT Suppose medicine use is safe and effective if: 1. Individual Css is on average at the Target Conc – Aim for the optimum target 2. 90% of the time Css is within 80%-125% of Target Conc – 'therapeutic range' with optimum target ➢ STATISTICS Assume log-normal distribution for Css 90% of Css must lie within ± 1.64 x SD – Therefore SD must be 0.136 The Safe and Effective Variability (SEV) is 13.6% 	Css = Average steady state concentration SD = Standard Deviation SEV=Safe and Effect Variability around target concentration
Slide 19	**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 	CLcr = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio
Slide 20	**Identifying Variablility** ➢ PPVtotal = Population Parameter Variability total of predictable and unexplained sources ➢ PPVu=Population Parameter Variability that is unexplained ➢ BSVp=Between Subject Variability that is predictable ➢ BSVu=Between Subject Variability that is unpredictable ➢ WSVu=Within Subject Variability that is unpredictable ➢ SEV=Safe and Effect Variability around target concentration 	

Slide 21

Dosing Individualization Method Depends on SEV

Suppose PPV_{total}=0.7, BSV_u=0.4, WSV_u=0.3

$PPV_U=sqrt(BSV_u^2 + WSV_u^2)=0.5$ $BSV_P=sqrt(PPV_{total}^2 – BSV_u^2)=0.57$

SEV	Method Criteria	Example	Dosing Strategy
0.9	SEV>PPV_{total}	**0.9>0.7**	Population dosing
0.55	PPV_{total} > SEV SEV>PPV_u	0.7>0.55 **0.55>0.5**	Group dosing (WT, CLcr, etc) (BSV_P ⇨ 0)
0.35	PPV_u > SEV SEV>WSV_u	0.5>0.35 **0.35>0.3**	Individual response dosing (TCI) (BSV_U ⇨ 0)

Note: If SEV<WSV_u then medicine cannot be used safely

Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68

Slide 22

Safe and Effective Variability (SEV) Aminoglycosides

PPV_U	BSV_U	WSV_U
0.33	0.30	0.13

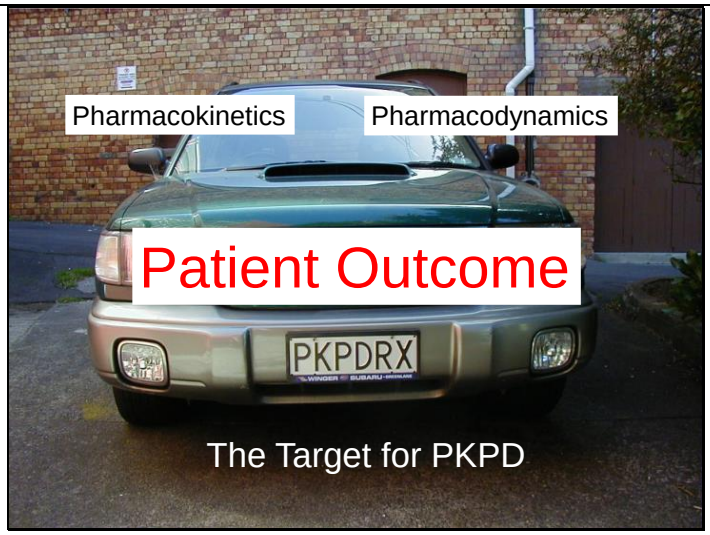
- Suggested Therapeutic Success Criterion
  90% of Concs Within 80%-125% of Target Css
  ∴ SEV is 0.136 (log normal SD)
- Unpredictable PPV_U is 0.33 and is > SEV
  ∴ Covariate (WT, CLcr) prediction alone will be inadequate
- Unpredictable WSV_U is 0.13 and is < SEV (just!)
  ∴ TCI can achieve safe and effective target

Matthews I, Kirkpatrick C, Holford NHG. Quantitative justification for target concentration intervention - Parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. British Journal of Clinical Pharmacology 2004;58(1):8-19

Slide 23

Which Way to Aim?

- Phase 2 Drug Development
  - » PK and PKPD relationships (Target Effect ⟶ Target Conc)
  - » Predictable and Unpredictable variability (PPV_T)
  - » Between (BSV_U) and within subject (WSV_U)
- Phase 3 Drug Development
  - » Safe and effective variability (SEV)
  - » The BIG difficulty is deciding on SEV !
- Clinical Use of Medicines
  - » Use quantitative criteria to decide on dosing method
    - » Covariate Dosing if PPV_T>SEV>PPV_U
    - » TCI Dosing if PPV_U>SEV>WSV_U

Slide 24		The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect
Slide 25	**Why TCI?** 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 ➢ How can a target concentration of 10 mg/L be achieved and maintained? 	
Slide 26	**Which Drugs for TCI?** 1. Effect is hard to measure (drug is working when the response is not observable) » Anti-arrhythmics e.g. lignocaine » Anti-convulsants e.g. phenytoin » Anti-coagulants e.g. warfarin 2. Big unpredictable variability (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 BP, 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 27

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 28

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
Ciclosporin**	150 ng/mL	17 L/h	245 L
Phenytoin	10 mg/L	Vmax=415 mg/d, Km= 4mg/L	45 L
Digoxin	2 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 29

Target Effects

Target Effects and Pharmacodynamic Parameters for Selected Medicines. Emax is the maximum effect due to the drug, EC50 is the concentration producing 50% of Emax. PEFR is peak expiratory flow rate.

Drug	Target Effect	Emax	EC50
Aminoglycosides	"cure"	?	?
Cyclosporine	"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

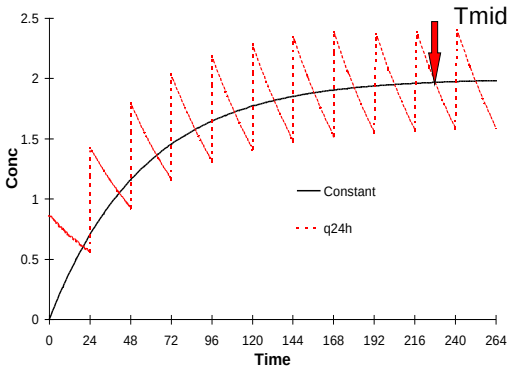
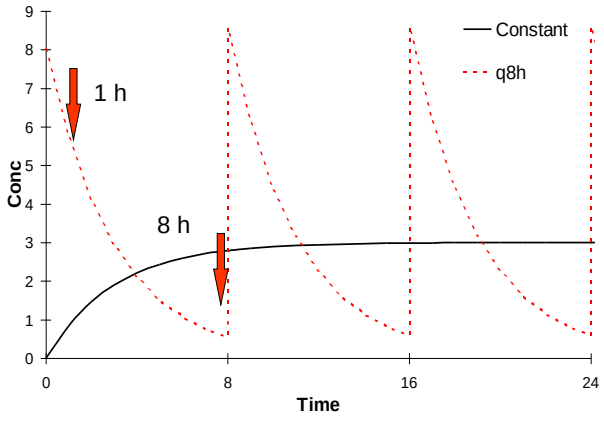
- Inhibition of prothrombin complex synthesis

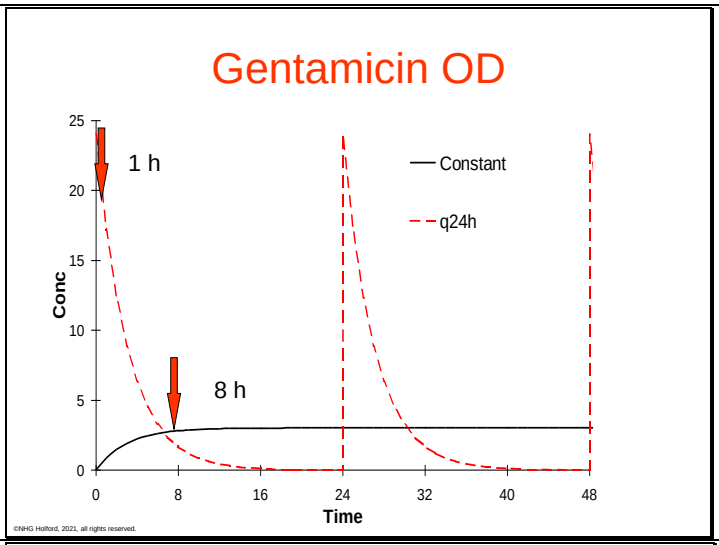
The pharmacodynamic parameters for medicines that use TCI are typically not well known. This is a reflection of the difficulty of measuring a clinical response that can be related to concentration.

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

Slide 30	**Determine Group V and CL** ➢ 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 31	**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 	
Slide 32	**When to Measure Concs?** Goal is to estimate PK e.g. CL ➢ Number of Samples » Most medicines 1 » Gentamicin 2 ➢ Timing of Sample » 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.

Slide 33	**When to Measure Concs?** Goal is to estimate PK e.g. CL ➢ Number of Samples » Most medicines 1 » Gentamicin 2 ➢ Timing of Sample » 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.
Slide 34	**Digoxin**  Tmid = middle of dosing interval 	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 35	**Gentamicin TDS**  	

Slide 36		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.
Slide 37