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PKPD Variability

Quantifying Variability to aid Dose Individualization

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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

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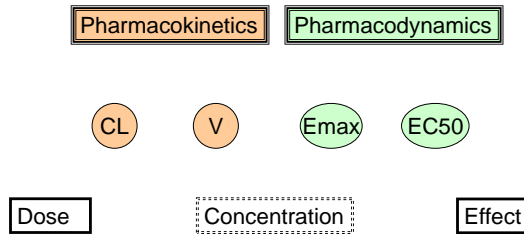
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PK = Pharmacokinetics: What the body does to the drug
PD=Pharmacodynamics: What the drug does to the body
Rx=Treatment: What the prescribed and patient need to know.

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Clinical Pharmacology

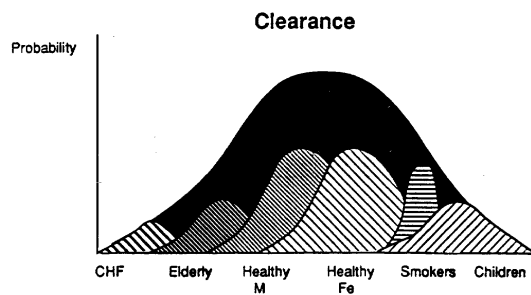


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Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is 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).

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Variability



N.Sambol CDDS/SUMC1997

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Target Concentration Drug Development and Clinical Use

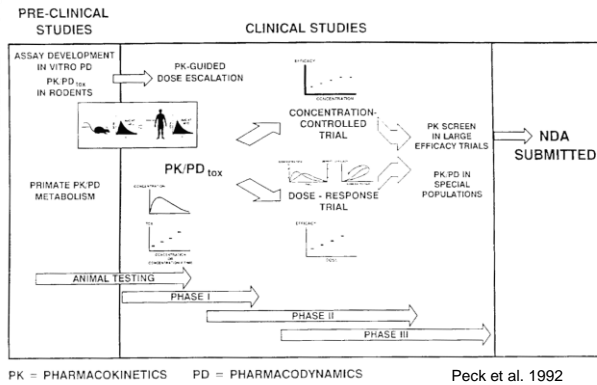
- Effective drug development needs a plan
 - » A good plan has a clear objective
 - » TC provides a clear objective in all phases of drug development
- TC is the rational basis for dose individualization
 - » Choose the target effect to determine the TC
 - » Use TC to predict individual dose

Holford NHG. The target concentration approach to clinical drug development. Clin Pharmacokinet. 1995;29(5):287-91.

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Target Concentration in Drug Development



The 1992 view was based on using PKPD for drug development but did not explicitly include how to use medicines in patients.

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Target Concentration in Clinical Use of Medicines

$$\text{Target Conc} = \text{Target Effect} \times \text{EC50} / (\text{Emax} - \text{Target Effect})$$

Target Conc	Dose Model
Initial Peak	Loading Dose = Target Conc x Volume of Distribution
Average Steady State	Maintenance Dose Rate = Target Conc x Clearance

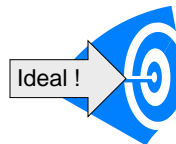
Ideal dose prediction requires **individual** estimates of **Emax, EC50, V and CL**

The target concentration approach links PKPD to prediction of the right dose for a patient.

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TDM or TCI?

- **Therapeutic Drug Monitoring**
 - » TDM Therapeutic Range
 - ☹ **Imprecise**
 - » Sub-optimal at borders of the range
- **Target Concentration Intervention**
 - » TCI Single Target
 - 😊 **Accurate**
 - » Optimal – do the best you can



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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

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- Randomized concentration controlled trials are the gold standard

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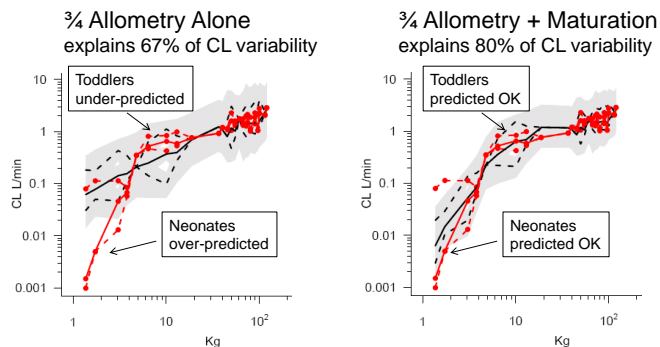
Why does PKPD vary?

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

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Predictable Variability Size and Maturation



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.

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<p>Slide 13</p>	<h2 style="text-align: center;">Unexplained Clearance Variability</h2> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Drug</th> <th style="text-align: center;">BSV_U %</th> <th style="text-align: center;">WSV_U %</th> <th style="text-align: left;">Source</th> </tr> </thead> <tbody> <tr><td>Metoprolol</td><td style="text-align: center;">53</td><td style="text-align: center;">35</td><td>Lunn (1997)</td></tr> <tr><td>Fenoterol</td><td style="text-align: center;">12</td><td style="text-align: center;">16</td><td>Bouillon (1996)</td></tr> <tr><td>Riluzole</td><td style="text-align: center;">51</td><td style="text-align: center;">28</td><td>Bruno (1997)</td></tr> <tr><td>Felodipine</td><td style="text-align: center;">34</td><td style="text-align: center;">33</td><td>Wade (1995)</td></tr> <tr><td>Drug A</td><td style="text-align: center;">57</td><td style="text-align: center;">29</td><td>Karlsson (1993)</td></tr> <tr><td>Drug B</td><td style="text-align: center;">35</td><td style="text-align: center;">19</td><td>Karlsson (1993)</td></tr> <tr><td>Drug B</td><td style="text-align: center;">33</td><td style="text-align: center;">19</td><td>Jonsson (1996)</td></tr> <tr><td>Moxonidine</td><td style="text-align: center;">22</td><td style="text-align: center;">15</td><td>Karlsson (1998)</td></tr> <tr><td>Artemisinin</td><td style="text-align: center;">48</td><td style="text-align: center;">53</td><td>Sidhu (1998)</td></tr> <tr> <td>Average</td> <td style="text-align: center;">41</td> <td style="text-align: center;">30</td> <td></td> </tr> </tbody> </table> <p style="margin-top: 10px;"> BSV_U=Between Subject WSV_U=Within Subject </p> <p style="font-size: small; margin-top: 5px;">©NHG Hoford, 2011, all rights reserved.</p>	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		<p>BSV_U=Between Subject Variability unexplained by predictable factors such as weight, etc. WSV_U=Within Subject Variability unexplained by predictable factors such as weight, etc.</p> <p>% expresses an apparent co-efficient of variation</p>
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<p>Slide 14</p>	<h2 style="text-align: center;">Safe and Effective Variability</h2> <ul style="list-style-type: none"> ● CLINICAL JUDGMENT <p>Suppose medicine use is safe and effective if:</p> <ol style="list-style-type: none"> 1. Individual C_{ss} is on average at the Target Conc <ul style="list-style-type: none"> - Aim for the optimum target 2. 90% of the time C_{ss} is within 80%-125% of Target Conc <ul style="list-style-type: none"> - 'therapeutic range' with optimum target ● STATISTICS <p>Assume log-normal distribution for C_{ss} 90% of C_{ss} must lie within 1.64 x SD - Therefore SD must be 0.136</p> <p style="margin-top: 10px; color: green;">The Safe and Effective Variability (SEV) is 13.6%</p> <p style="font-size: small; margin-top: 5px;">©NHG Hoford, 2011, all rights reserved.</p>	<p>C_{ss} = Average steady state concentration SD = Standard Deviation SEV=Safe and Effect Variability around target concentration</p>																																												
<p>Slide 15</p>	<h2 style="text-align: center;">Three Ways to Dose</h2> <ul style="list-style-type: none"> ● Population <ul style="list-style-type: none"> » Same dose for everyone <ul style="list-style-type: none"> - The dream dosing method! ● Group (Covariate guided) <ul style="list-style-type: none"> » Same dose for similar group <ul style="list-style-type: none"> - e.g. same weight, CL_{cr}, genotype ● Individual <ul style="list-style-type: none"> » Dose determined by individual response <ul style="list-style-type: none"> - e.g. BP, INR, blood conc <p style="font-size: small; margin-top: 5px;">©NHG Hoford, 2011, all rights reserved.</p>	<p>CL_{cr} = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio</p>																																												

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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	$PPV_{total} < SEV$	$0.7 < 0.9$	Population dosing
0.6	$PPV_{total} > SEV$ $PPV_u < SEV$	$0.7 > 0.6$ $0.5 < 0.6$	Group dosing (WT, CLcr, etc) ($BSV_p \rightarrow 0$)
0.35	$PPV_u > SEV$ $WSV_u < SEV$	$0.5 > 0.35$ $0.3 < 0.35$	Individual response dosing (TCI) ($BSV_u \rightarrow 0$)

Note: If $WSV_u > SEV$ then medicine cannot be used safely

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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

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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 C_{ss}
 - 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

Mathews 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

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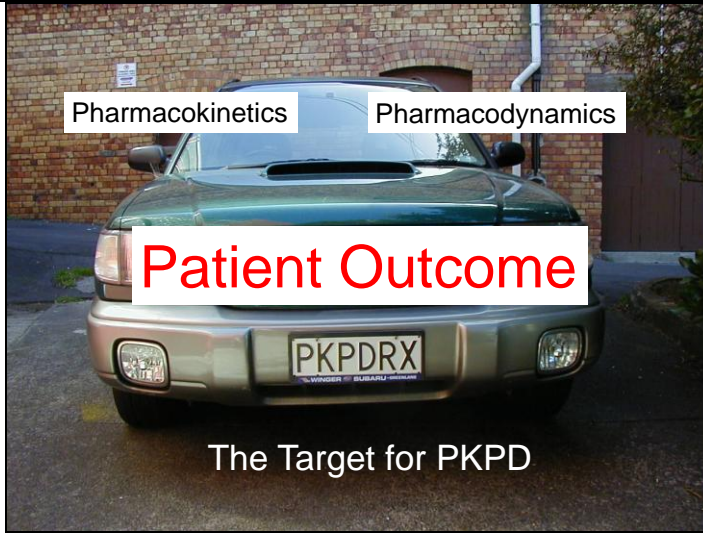
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Which Way to Aim?

- 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 $PPV_u > SEV > WSV_u$

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The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect

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Why TCI?

Clin. Pharmacokinet. 25 (6): 495-505, 1993

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- How can a target concentration of 10 mg/L be achieved and maintained?

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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

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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.

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How? Target Concentration Strategy

- Pick Target Concentration
- Determine Typical V and CL
- Calculate LD and MDR
- Measure Effects
 - Revise Target Conc
- Measure Concs
 - Revise V and CL
- Goto Step 3

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LD = Loading Dose
MDR = Maintenance Dose Rate

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Pick Target Concentration

Target Concentrations and Pharmacokinetic Parameters for Selected Drugs (70 kg standard individual). C_{ss} is the average steady state concentration.

Drug	Target Conc	Clearance	Volume of distribution
Aminoglycosides	Peak 8 mg/L C _{ss} 3 mg/L	6 L/h	18 L
Cyclosporine **	150 ng/mL	17 L/h	245 L
Phenytoin	10 mg/L	V _{max} =415 mg/d, K _m =4mg/L	45 L
Digoxin	2 ng/mL	9 L/h	500 L
Theophylline	10 mg/L	3 L/h	35 L

* 8 hourly dosing ** whole blood

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Target Effects

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

Drug	Target Effect	E _{max}	EC ₅₀
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

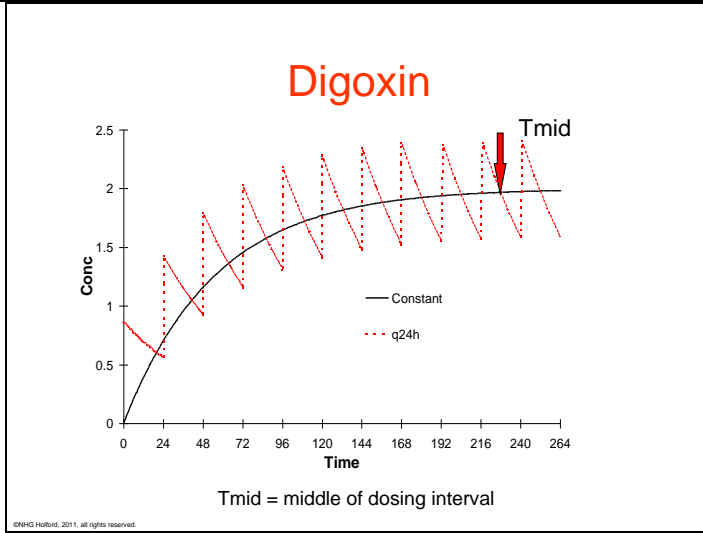
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The pharmacodynamic parameters for medicines that use TCI are typically not well known. This is a reflection of the difficulty of measuring a clinical response that can be related to concentration.

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

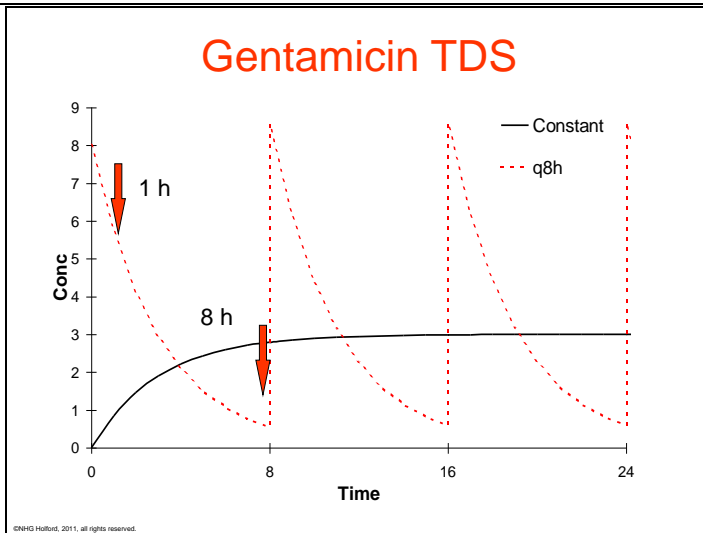
<p>Slide 25</p>	<p style="text-align: center;">Determine Group V and CL</p> <ul style="list-style-type: none"> ● Volume of Distribution <ul style="list-style-type: none"> » size $V = V_{pop} \times WT/WT_{std}$ » body composition ● Clearance <ul style="list-style-type: none"> » size $CL = Cl_{pop} \times (WT/WT_{std})^{3/4}$ » renal function » hepatic function » concomitant drugs <p><small>©NHG Hartford, 2011, all rights reserved.</small></p>	<p>WT=patient weight WTstd=standard weight e.g. 70 kg Vpop, CLpop=population volume and clearance in a standard subject e.g. 70 kg.</p>
<p>Slide 26</p>	<p style="text-align: center;">When to Measure Concs?</p> <p style="text-align: center;">Goal is to estimate PK e.g. CL</p> <ul style="list-style-type: none"> ● Number of Samples <ul style="list-style-type: none"> » Most medicines 1 » Gentamicin 2 ● Timing of Sample <ul style="list-style-type: none"> » Most medicines Middle of dosing interval » Gentamicin "peak" and "trough" <p><small>©NHG Hartford, 2011, all rights reserved.</small></p>	<p>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.</p>
<p>Slide 27</p>	<p style="text-align: center;">When to Measure Concs?</p> <p style="text-align: center;">Goal is to estimate PK e.g. CL</p> <ul style="list-style-type: none"> ● Number of Samples <ul style="list-style-type: none"> » Most medicines 1 » Gentamicin 2 ● Timing of Sample <ul style="list-style-type: none"> » Most medicines Middle of dosing interval » Gentamicin "peak" and "trough" <p><small>©NHG Hartford, 2011, all rights reserved.</small></p>	<p>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.</p>

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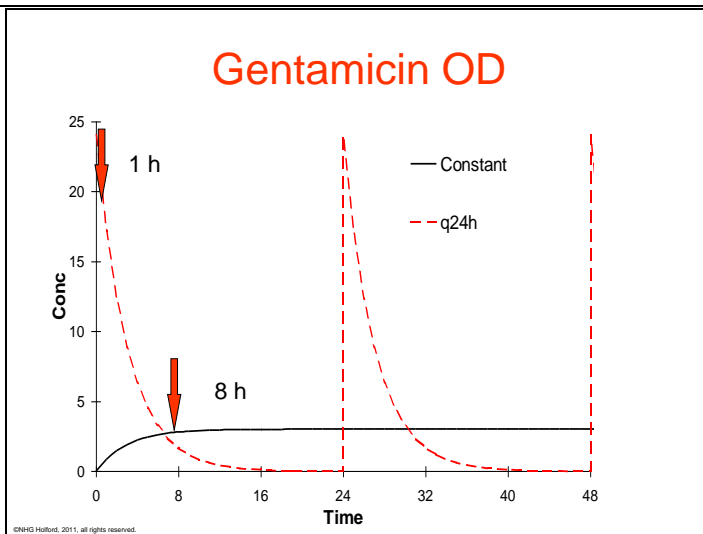


A concentration in the middle of the dosing interval (C_{tmid}) will be closer to the average steady state concentration (C_{ss}) than either a peak or trough concentration. Clearance is easily calculated from $CL = \text{DoseRate} / C_{ss}$ which can be approximated by $CL = \text{DoseRate} / C_{tmid}$.

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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.

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