

Therapeutic Drug Monitoring of Aminoglycosides

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Objectives

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- Participants will be able to develop a therapeutic drug monitoring plan for aminoglycosides with or without serum concentration time data.
- Participants will be able to make appropriate decisions as to the need for therapeutic drug monitoring
- Participants will be able to identify situations appropriate for series or peak/trough pharmacokinetic monitoring situations.
- Participants will be able to identify an appropriated schedule and time for aminoglycoside therapy.
- Participants will be able to identify appropriate peak and trough concentrations for conventional and single daily dosing strategies.
- Participants will be able to develop a plan to monitor the patient for successful resolution of infection or the development of adverse drug reactions to the aminoglycoside.

Conventional vs Single Daily Dose for Aminoglycosides

- ♦ **Gentamicin or Tobramycin**
 - Conventional ~1.5 mg/Kg Q8H or ~5 mg/Kg/day
 - SDD ~7 mg/Kg as one dose every 24 Hrs
- ♦ **Amikacin**
 - Conventional ~5 mg/Kg Q8H or 7.5 mg/Kg Q12H
 - SDD 15 mg/Kg as one dose every 24 Hrs

Data Poor or Rich Environment

What to do when:

No data	Poor
Population data	↕
Patient specific trough/peak data	
Patient specific series PK data	

Evaluating Aminoglycoside Dose & Interval without ASCTD

- ♦ **Parameters required for evaluation:**
 - Age
 - Height in inches
 - Weight
 - Serum creatinine

Evaluating Aminoglycoside Dose & Interval without ASCTD

- ♦ **Patient weight:**
 - Actual body weight (ABW)
 - Lean body weight (LBW) in Kg
 - Males = $50 + 2.3$ (# inches over 5 feet)
 - Female = $45 + 2.3$ (# inches over 5 feet)
 - Note if $LBW > ABW$ use ABW
 - Dosing body weight (DBW)
 - For patients $>30\%$ over LBW
 - $DBW = LBW + 0.4 (ABW - LBW)$

Evaluating Aminoglycoside Dose & Interval without ASCTD

- ♦ Calculated Creatinine Clearance(Crcl) in ml/min
 - Method of Cockcroft and Gault
 - Male = $((140 - \text{Age}) * \text{LBW}) / (72 * \text{Scr})$
 - Female = 0.85 (Male)
- ♦ Transform Crcl into Kd using Detli method
 - $K_d (\text{Hr}^{-1}) = 0.0024 (\text{Crcl}) + 0.01$
- ♦ Transform Estimated Kd into T1/2
 - $T_{1/2}(\text{Hrs}) = 0.693 / K_d$

Initial Evaluation for Conventional Aminoglycoside Therapy

- ♦ Peak concentrations should be ~ 10 x MIC of the likely bacterial pathogen
- ♦ Troughs should be as low as possible given the circumstances surrounding the patient
- ♦ Dose should be evaluated on a mg/kg/day basis and mg/kg per dose basis using the appropriate body weight parameter
- ♦ Dosing interval should be ~ 2 to 3 T1/2's plus the hour for drug infusion
- ♦ Try to limit total course of therapy to ≤ 5 days to reduce risk of nephrotoxicity or ototoxicity

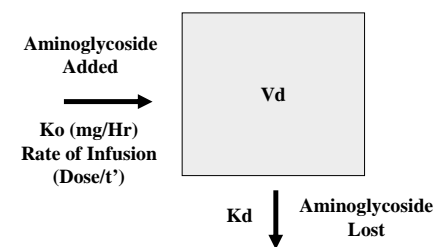
The Sawchuk-Zaske Method

- ♦ One Compartment Modeling of Aminoglycoside Serum Concentration Time Data
- ♦ Method Originated at University of Minnesota, College of Pharmacy & Used World Wide
- ♦ Resource:
http://www.courses.ahc.umn.edu/pharmacy/6124/tutorials/glycoside_kinetics/kinetics1.htm

Reference Parameters

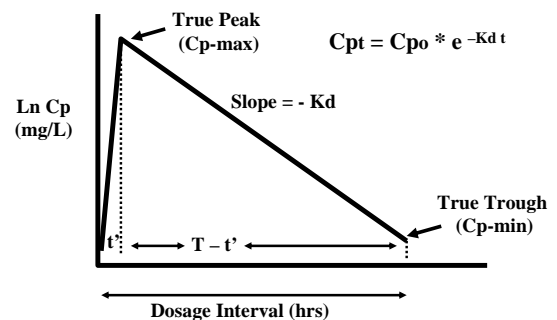
- ♦ t = Separation time between two points (Hours)
- ♦ t' = Time of infusion (Hour)
- ♦ K_0 = Rate of infusion (mg/Hr)
- ♦ T = Dosage interval (Hours)
- ♦ V_d = Distribution Volume (L or L/Kg)
- ♦ $T_{1/2}$ = Half-life (Hrs)
- ♦ K_d = Elimination rate constant (Hr^{-1})
- ♦ $C_{p_{\max}}$ = Peak concentration (mg/L or mcg/ml)
- ♦ $C_{p_{\min}}$ = Trough concentration (mg/L or mcg/ml)
- ♦ C_{p_0} = Reference concentration (mg/L or mcg/ml)
- ♦ C_{p_t} = Concentration of drug separated by t from C_{p_0}

One Compartment Model

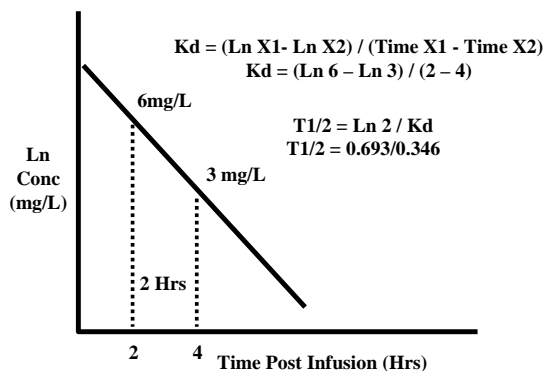


Assumption there are no other compartments & that all aminoglycoside distribution occurs during infusion

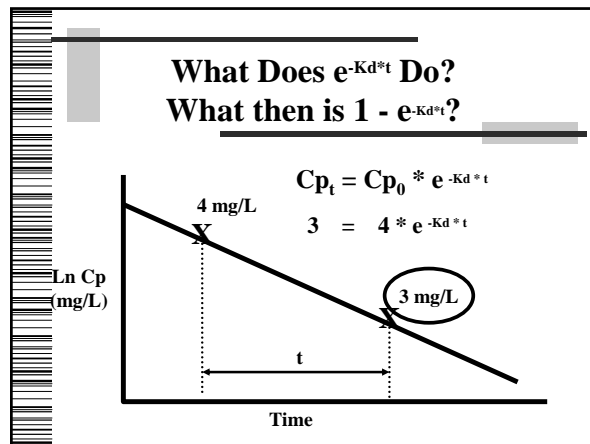
Resulting Serum Concentration Time Curve with One Compartment Modeling



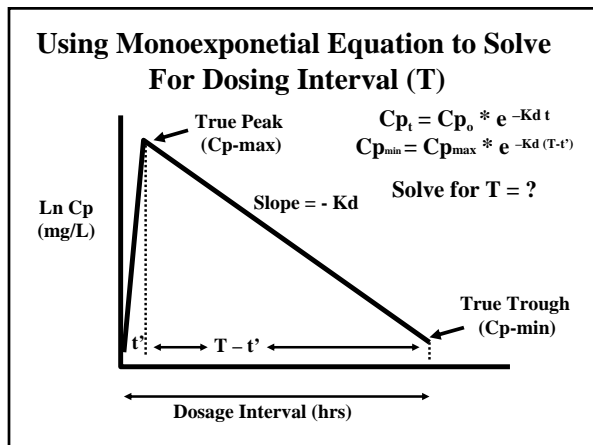
Elimination Constant (Kd) & Half Life (T1/2)



What Does $e^{-K_d \cdot t}$ Do? What then is $1 - e^{-K_d \cdot t}$?



Using Monoexponential Equation to Solve For Dosing Interval (T)



Why the Complicated Formula???

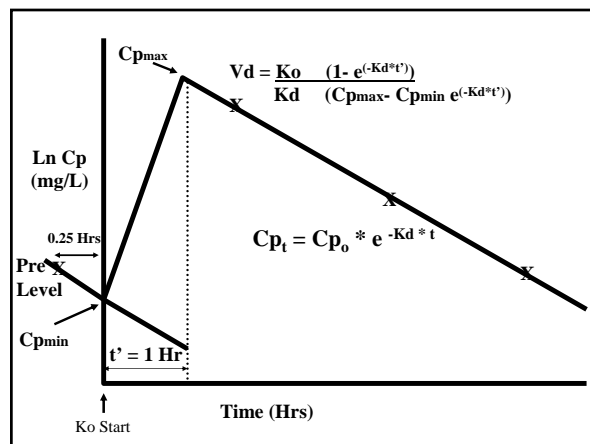
$$V_d = \frac{K_o}{K_d} \frac{(1 - e^{-K_d \cdot t'})}{(C_{p_{max}} - C_{p_{min}} e^{-K_d \cdot t'})}$$

or

$$V_d = \text{Dose} / C_p \text{ or Change in } C_p$$

Calculation of V_d

- Aminoglycoside does not enter the body as bolus but rather in a "zero order" process, an infusion rate (mg/Hr)
- Aminoglycoside is eliminated in a "first order" process, a constant percent per unit of time (50%/T1/2)



In the Calculation of V_d Note:

K_d by nature has a negative value but in the term $e^{(-k_d \cdot t)}$ you do not multiply $-K_d$ by a negative sign making the value positive

and

In the term K_o/K_d , K_d here must be a positive value or you calculate a $-V_d$

Aminoglycoside (AG) Pharmacokinetic Parameters

- ♦ V_d is dose sensitive in that if the patient received less drug, V_d will be overestimated & if patient receives more, V_d will be smaller
- ♦ Value of V_d may be result of blood loss, fluid or blood products being administered, 3rd spacing or drug inactivation
- ♦ Value of AG PK parameters may be a function of assay method used
- ♦ Half-life is dose independent if being evaluated ≥ 2 real post infusion values

Therapeutic Drug Monitoring (TDM) of Aminoglycosides

- ♦ Does the patient require an aminoglycoside?
- ♦ Are levels required?
- ♦ Do you have actual serum concentration time data or are you going to use population data?
- ♦ Is the patient at steady state (i.e. $\sim 3-5 T_{1/2}$'s into therapy with scheduled doses given on time)?
 - Steady state assumes patient's underlying fluid status and renal function remain status quo

Initial Evaluation of Aminoglycoside Dose & Interval

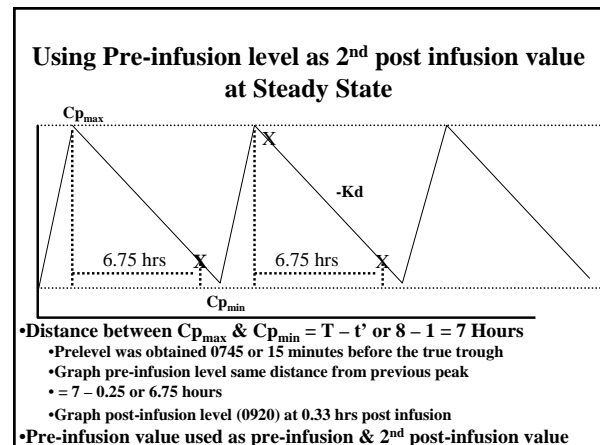
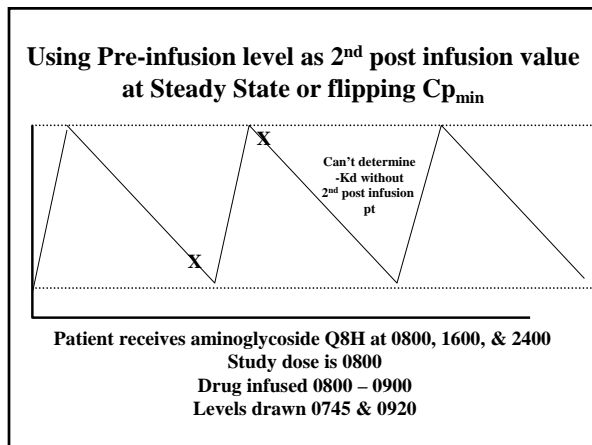
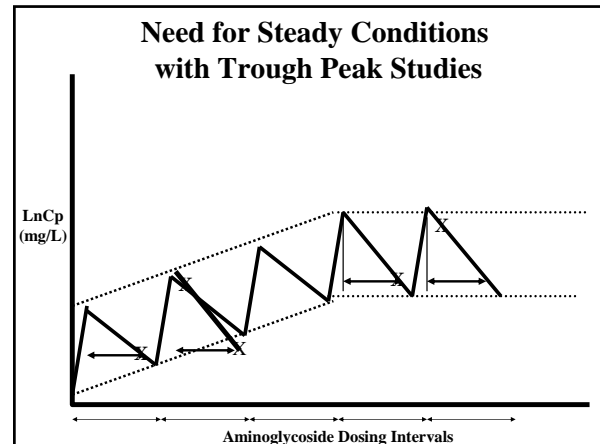
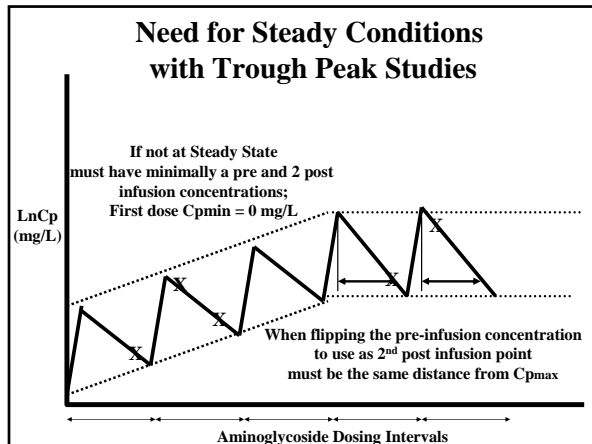
- ♦ Aminoglycoside serum concentration time data (ASCTD) available
- ♦ No ASCT data available
 - Far more common situation
 - General rule for conventional aminoglycoside therapy (Assume adult with normal renal function)
 - Daily dose for gentamicin or tobramycin ~ 5 mg/kg/d
 - Amount per dose ~ 1.5 mg / kg or Single Daily Dose
 - Daily dose for amikacin ~ 15 mg/kg/d
 - Amount per dose ~ 5 to 7.5 mg / kg or Single Daily Dose

Setting up Levels for TDM

- ♦ General requirements are that patient's renal function and fluid status be stable
- ♦ Trough / Peak Option
 - Patient must be at steady state
 - Received drug for 3-5 $T_{1/2}$'s
 - If $t_{1/2}$ is short in relation to doing interval, the likelihood of having measurable trough is low
 - Nurse has administered drug on time and on schedule during the 3 to 5 $T_{1/2}$ period
 - Note: If patient seriously ill with impaired renal function, clinician may not be able to wait for steady state

Setting up Levels for TDM

- ♦ Pharmacokinetic Series Option
 - Patient does not have to be at steady state
 - Need to obtain trough level if not the first dose
 - Need a minimum of 2-3 levels post antibiotic infusion spaced over a period of $\geq 1.5 T_{1/2}$'s



Aminoglycoside Monitoring

Part II

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Example I

- 28 year old female, 6' tall and weighs 75 Kg is admitted for treatment of pyelonephritis.
- Patient is started on gentamicin 400 mg QD and ampicillin 500 mg Q6H.
- Cultures of blood and urine are pending.
- Patient has no significant prior medical history reports no drug allergies.
- She is not pregnant or breast feeding.
- Pharmacy receives a pharmacokinetic consult, what should be done for this patient?

Example II

- ♦ 50 year old male (6' tall weight 85Kg) admitted for elective abdominal surgery eight days ago spikes temperature. Patient has no allergies and the serum creatinine has been 1.2 mg/dl.
- ♦ Patient is placed on ampicillin/sulbactam 3 Gm Q6H & gentamicin 140 mg Q8H.
- ♦ Prior to the 4th gentamicin dose, the night RPh orders a trough and peak gentamicin levels.
- ♦ Physician calls the DCP asking what should be done with the gentamicin dose.

Example III

- ♦ 24 year old male (5' 10" tall & weighs 105Kg) involved in a MVA suffers multiple injuries.
- ♦ The patient is started on piperacillin/tazobactam 3.375 Gm Q6H & gentamicin 100 mg Q12H.
- ♦ Patient has positive blood & sputum cultures for *P. aeruginosa*. Serum creatinine is 1 mg/dl.
- ♦ The physician contacts you wanting a pharmacokinetic study ASAP. You find out the last dose was just given twenty minutes ago and proceed to obtain two post infusion levels, how should these data be evaluated?

Critical Evaluation of Calculated Parameters

- ♦ **LBW**
 - Para or Quadraplegic patient or where LBW > ABW
- ♦ **Creatinine Clearance (CrCl) this is an estimate**
 - Elderly
 - Para or Quadraplegic patient
 - Nutritionally starved patients
 - CrCl not likely a linear function < 30 ml/min
- ♦ **Caution**
 - Dehydration or Overhydration
 - Bleeding
 - Going into or coming out of acute renal failure

Critical Evaluation

- ♦ **Result real vs artifact (most often the problem)**
 - **Volume is a dose sensitive parameter**
 - Preparation, administration or serum level handling error
 - Less drug than thought increases volume
 - More drug than thought reduces volume
 - Obese vs wasting, para/quadriplegic, 3rd spacing (pleural effusion, ascites etc) or overhydration (anasarca)
 - Stable fluid status vs massive IV fluids &/or blood products
 - May be a function of assay used
 - **Half-life is a dose independent parameter**
 - Method used trough/peak vs series pharmacokinetics
 - Young vs old, NRF vs ARF
 - Beta-lactam inactivation

Problem Set

Patient is a 40 year old female (5'10" tall, 69.5 Kg) who underwent intra-abdominal surgery for a ruptured appendix. She is placed on gentamicin 100 mg over an hour every eight hours and ampicillin/sulbactam 3 Gm every six hours. She has no allergies, not pregnant, or breast feeding. She has normal liver and renal function (serum creatinine 0.9 mg/dl).

Suppose you are given three options to optimize gentamicin dose:

- 1) Use demographic and laboratory information above to estimate Kd, T1/2, Dose, and Interval.
- 2) Trough and peak study off 2nd dose
- 3) Trough and peak study 2nd day

Aminoglycoside Parameter Estimates

$$\text{LBW} = 45 + 2.3 (10) = 68 \text{ Kg}$$

$$\text{LBW} \sim \text{ABW}$$

$$\text{CrCl} = 0.85 [((140-40) * 68)/(72 * 0.9)] = 89.2 \text{ ml/min}$$

$$\text{Kd} = (0.0024 * 89.2) + 0.01 = 0.224 \text{ /Hr}$$

$$\text{T1/2} = 0.693/0.224 = 3.09 \text{ Hrs}$$

$$\text{Dosing Interval} \sim 2-3 \text{ T1/2's} + t'$$

$$\text{Gentamicin dose} \sim 1.5 \text{ mg/Kg or } \sim 4.5 \text{ mg/Kg/Day}$$

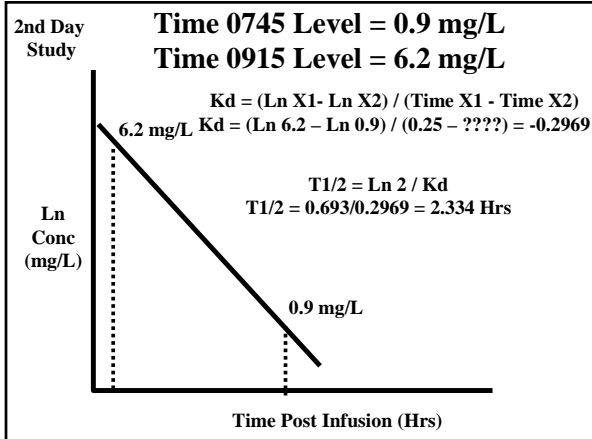
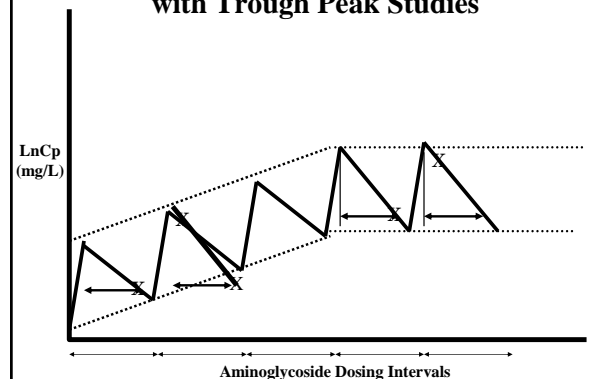
Serum Sampling Options

- ♦ 2nd Dose
 - 100mg infused 0800-0900
 - Pre level 0745
 - Post level 0915

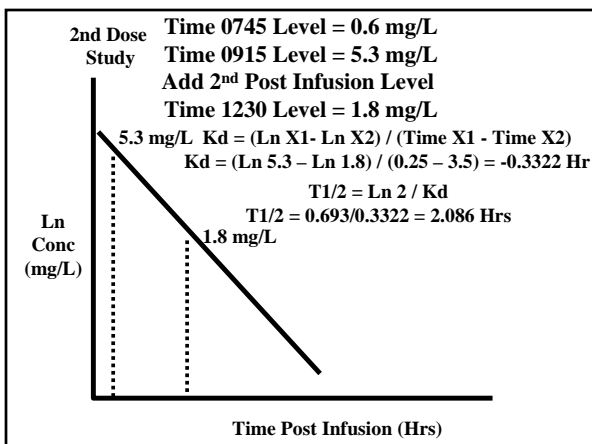
versus

- ♦ 2nd Day
 - 100mg infused 0800-0900
 - Pre level 0745
 - Post level 0915
- ♦ What can be done with these data?

Need for Steady Conditions with Trough Peak Studies



How Could the 2nd Dose Study be Fixed?



Volume of Distribution

- ♦ Correct pre level for start of infusion
 $C_{p_{\min}} = 0.6 e^{(-0.3322 \times 0.25)} = 0.5521 \text{ mg/L}$
 - Trough in non-steady state conditions is used only in calculation of V_d .
 - Trough in non-steady state conditions cannot be used as a post infusion point
- ♦ Correct 1st post level for true peak
 $C_{p_{15 \text{ min post}}} = C_{p_{\max}} e^{(-0.3322 \times 0.25)}$
 $5.3 / e^{(-0.3322 \times 0.25)} = C_{p_{\max}} = 5.76 \text{ mg/L}$
- ♦ Could make corrections for peak and trough using graph

$$Vd = \frac{K_0}{K_d} \frac{(1 - e^{(-K_d \cdot t')})}{(C_{pmax} - C_{pmin} e^{(-K_d \cdot t')})}$$

$$K_0 = \text{Dose} / t' = 100\text{mg} / 1 \text{ hr} = 100 \text{ mg/hr}$$

$$K_d = -0.3322 / \text{Hrs}$$

$$C_{pmax} = 5.76 \text{ mg/L}$$

$$C_{pmin} = 0.56 \text{ mg/L}$$

$$Vd = \frac{100 \text{ mg}}{0.3322 \text{ Hr}} \frac{(1 - e^{(-0.3322 \cdot 1.0)})}{(5.76 - 0.56 e^{(-0.3322 \cdot 1.0)})}$$

$$Vd = 15.87 \text{ L}$$

Note: K_d by nature has a negative value but in the term $e^{(-K_d \cdot t')}$ You do not multiply $-K_d$ by a negative sign making the value positive also in the term K_0/K_d , K_d here must be a positive value or you calculate a - V_d

Desired Cpmax & Cpmin: Resultant Dose & Dosing Interval

$$T = \frac{-1}{K_d} \frac{\ln C_{pmin}}{\ln C_{pmax}} + t'$$

$$C_{pmax} = \frac{K_0}{K_d Vd} \frac{(1 - e^{(-K_d \cdot t')})}{(1 - e^{(-K_d \cdot T)})}$$

$$C_{pmin} = C_{pmax} * e^{(-K_d \cdot (T - t'))}$$

Adjustment of C_{pmax} & C_{pmin} at Steady State

- Your patient is a 54 yr old (5 foot 2 inch) female (58 Kg) who is being treated for pyelonephritis. Serum creatinine 1.1 mg/dl.
- You have just completed a pre/post study at steady state. Gentamicin 80 mg is infused over an hour every eight hours. The extrapolated peak and trough are 6.2 mg/L and 0.8 mg/L, respectively. If the dose were increased to 120 mg Q8H, What are the new trough and peak concentrations?

Pre / Post Study with Wrong Dose What Happens

