PHAR:8370 Integrated Pharmacotherapy: Respiratory

Therapeutic Drug Monitoring

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IOWA PHARMACY

Objectives

- List the criteria for when monitoring is appropriate.
- Describe the role of population estimates in concentration monitoring.

Objectives

- Estimate PK parameters in a specific patient and calculate drug concentrations expected at the time of sampling.
- Understand and know how to avoid common errors when using drug concentrations to individualize drug therapy.

Reading

- Herman RA: General Approaches to Clinical Pharmacokinetic Monitoring. In *Pharmacokinetics in Drug Discovery and Development*, by Ronald Schoenwald, pp 115-126, Boca Raton, FL: CRC Press LLC, 2002.
- Sawchuk RJ, Zaske DE: Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: Gentamicin in burn patients. *J Pharmacokin Biopharm* 1976;4:183-195.

Basic Pharmacokinetics

- **L** iberation
- **A** bsorption
- **D** istribution
- **M** etabolism
- **E** limination
- **T** herapeutic Drug Monitoring

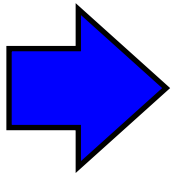
Therapeutic Drug Monitoring

Applied Pharmacokinetics

Drug Concentration

Pharmacokinetic Principles

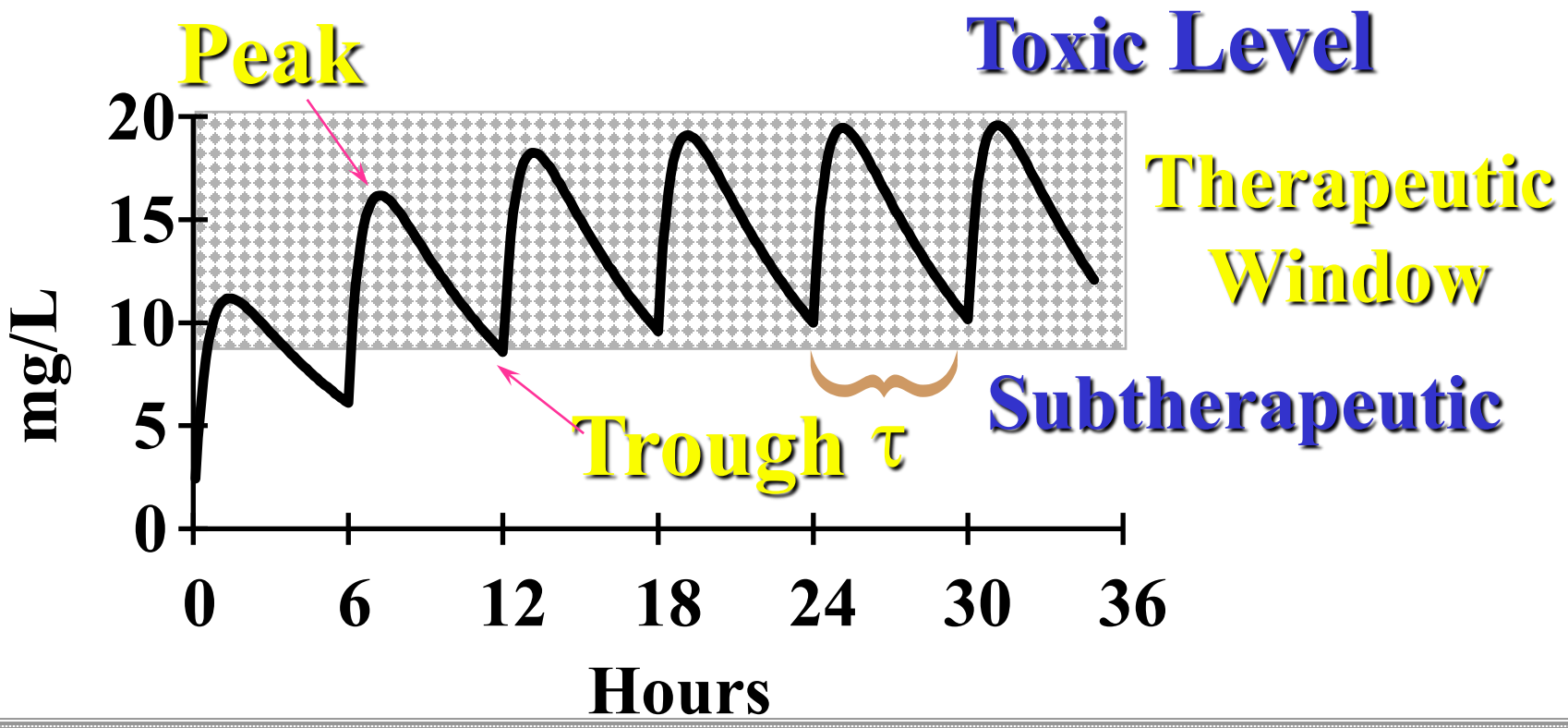
Clinical or Pharma-cological Response



To optimize drug therapy for the patient.

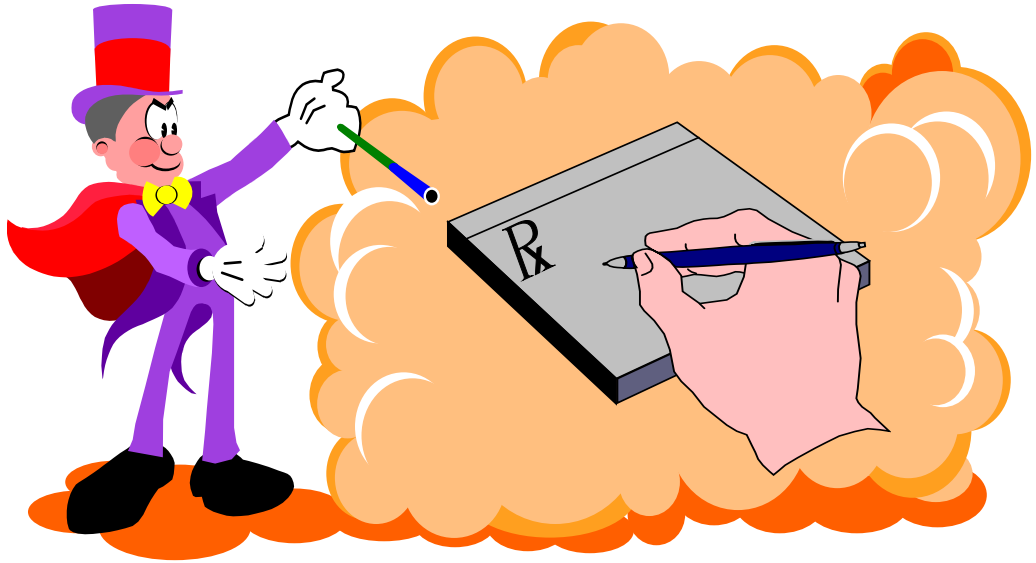
Blood Level Determinations

Steady State Concentration



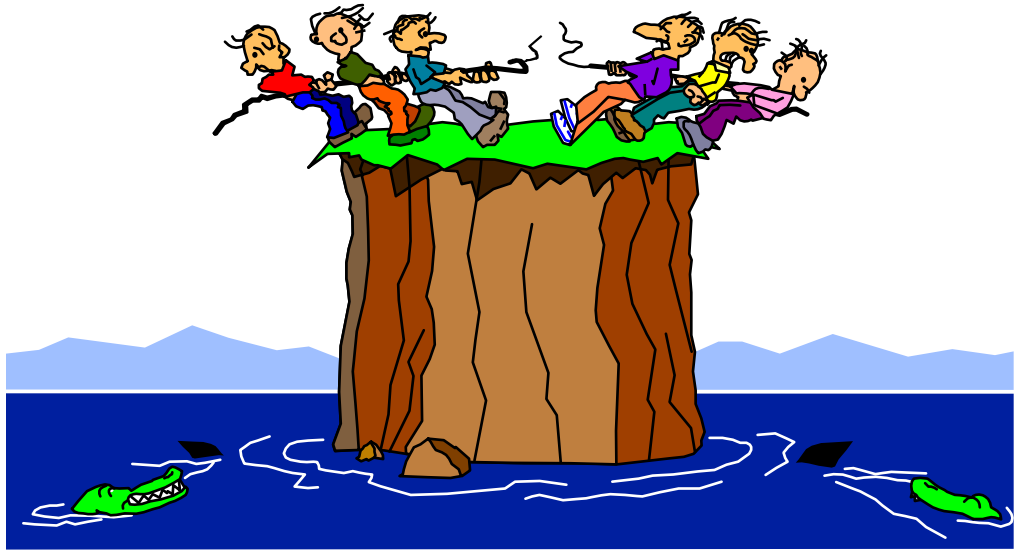
Blood Level Determinations

- Determine the best possible safe dosing regimen.



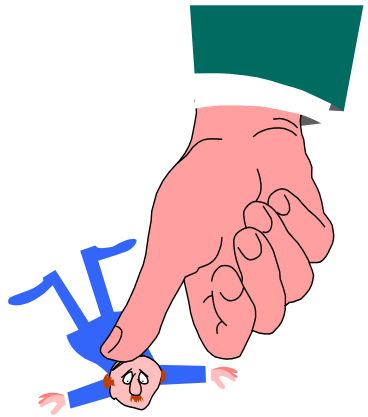
Blood Level Determinations

- Determine the best possible safe dosing regimen.
- **Maintain optimal therapy.**

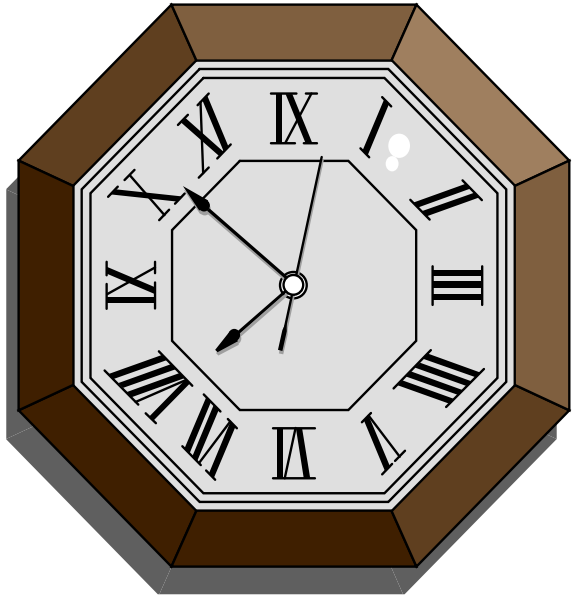


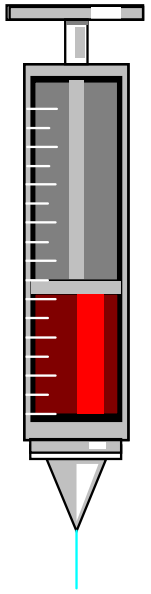
Blood Level Determinations

- Determine the best possible safe dosing regimen.
- Maintain optimal therapy.
- **Aid in the identification of patient non-compliance.**



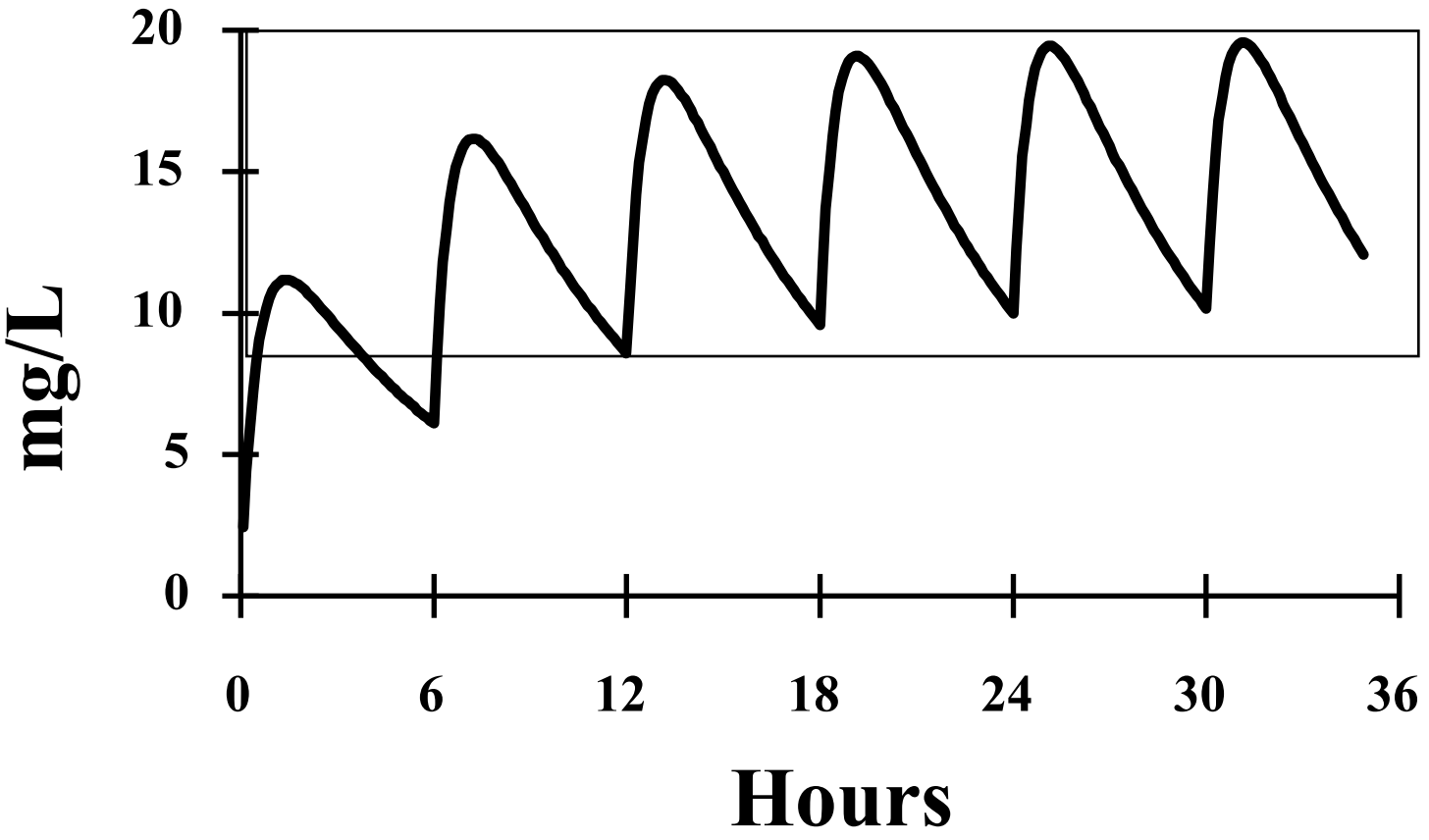
Drug Level Determinations



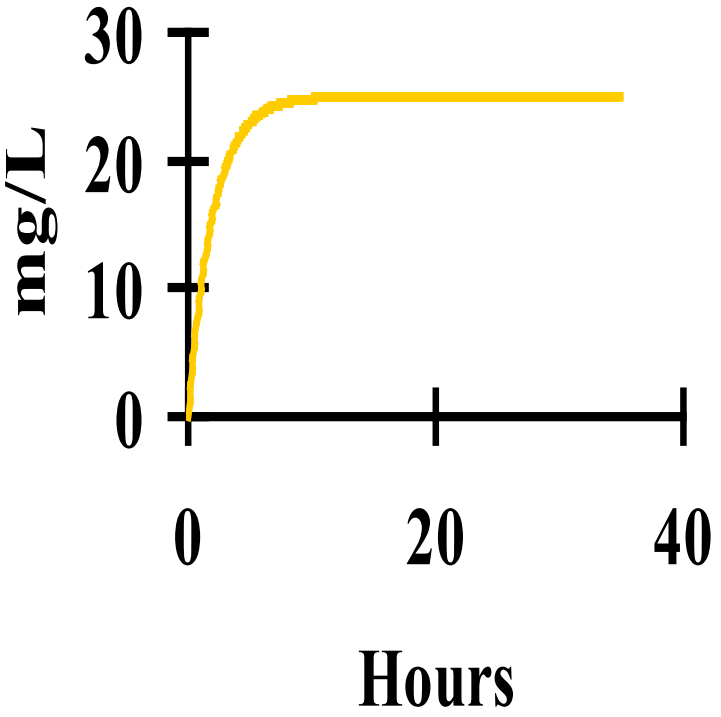


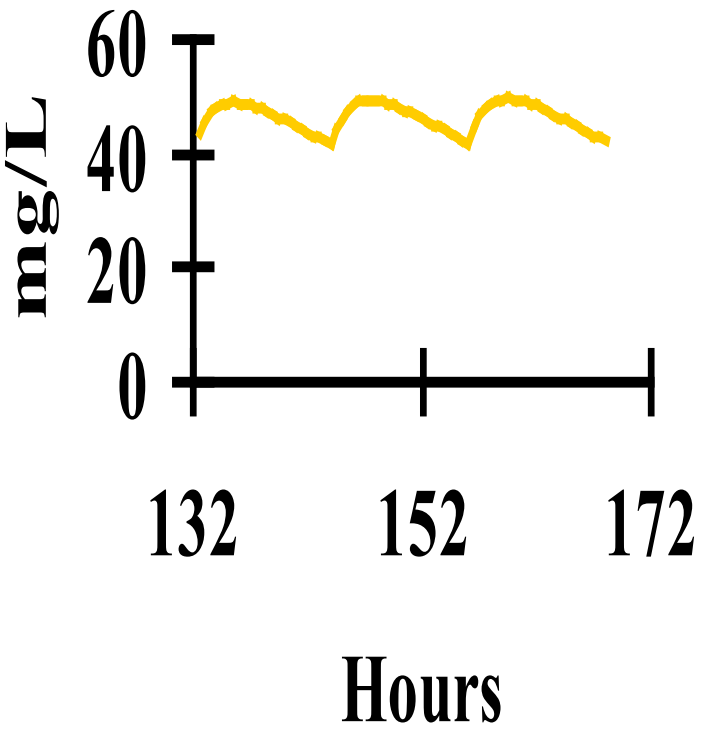
When do we draw levels?

Most often at steady state.

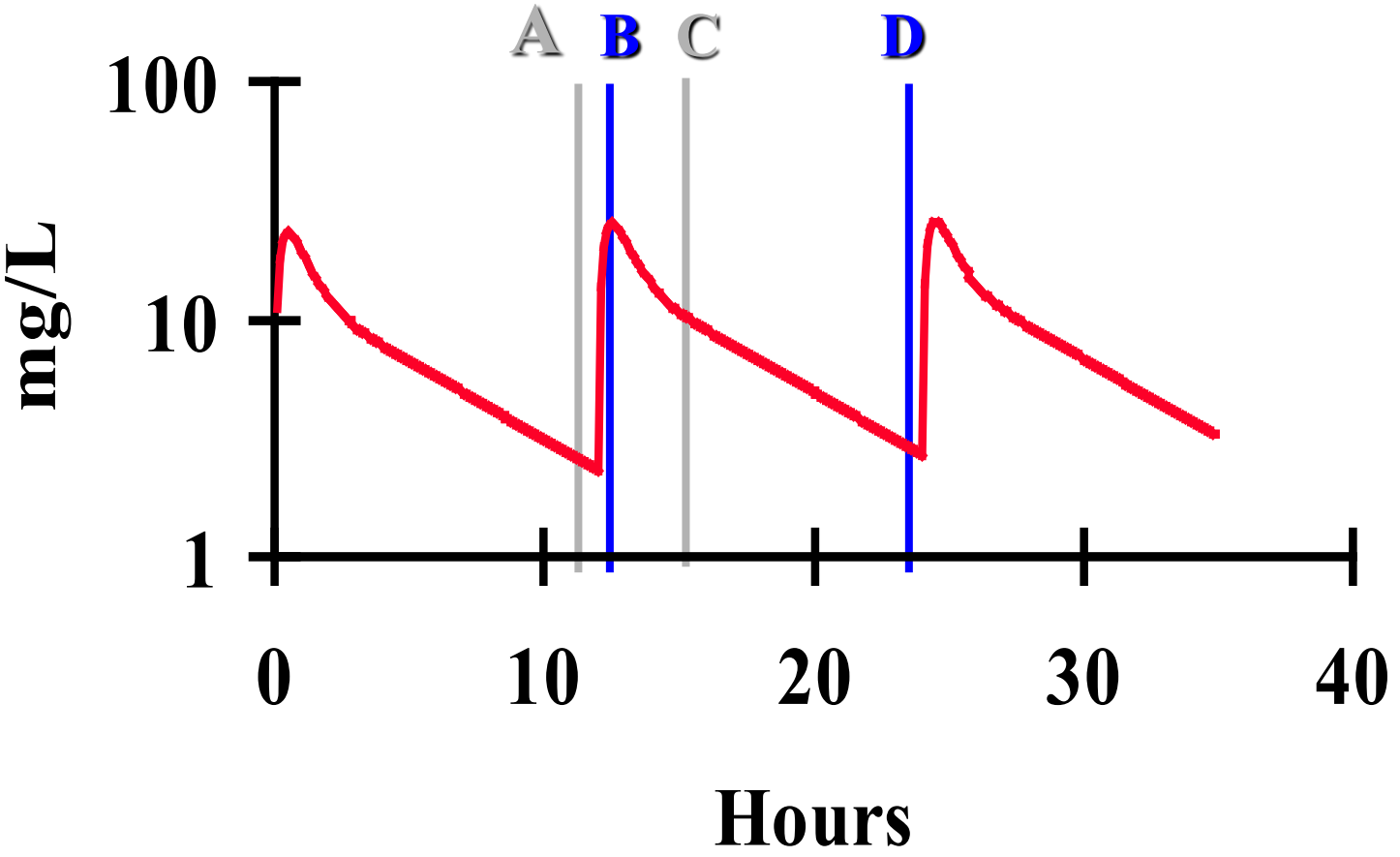


Sometimes a single level.

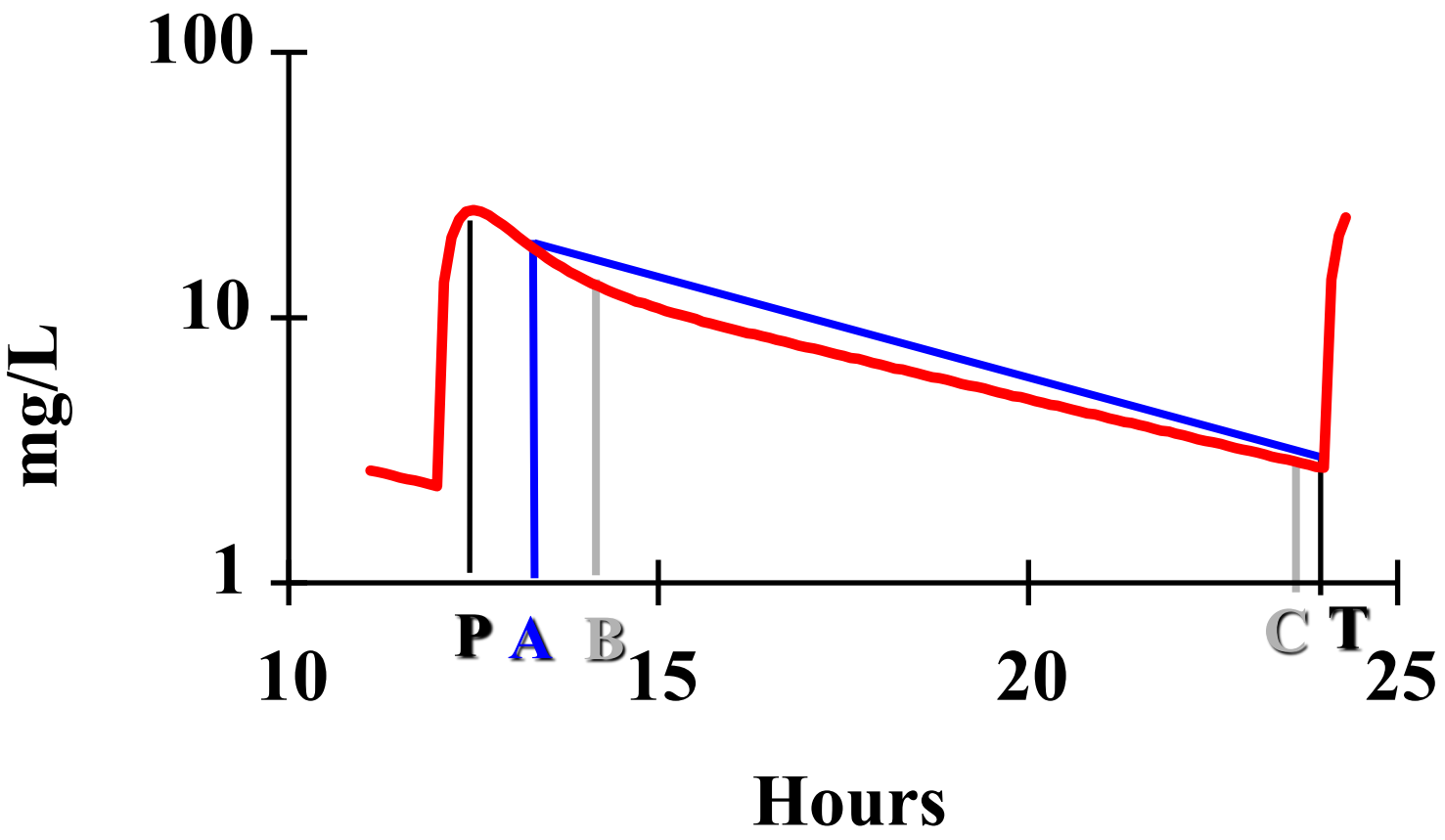




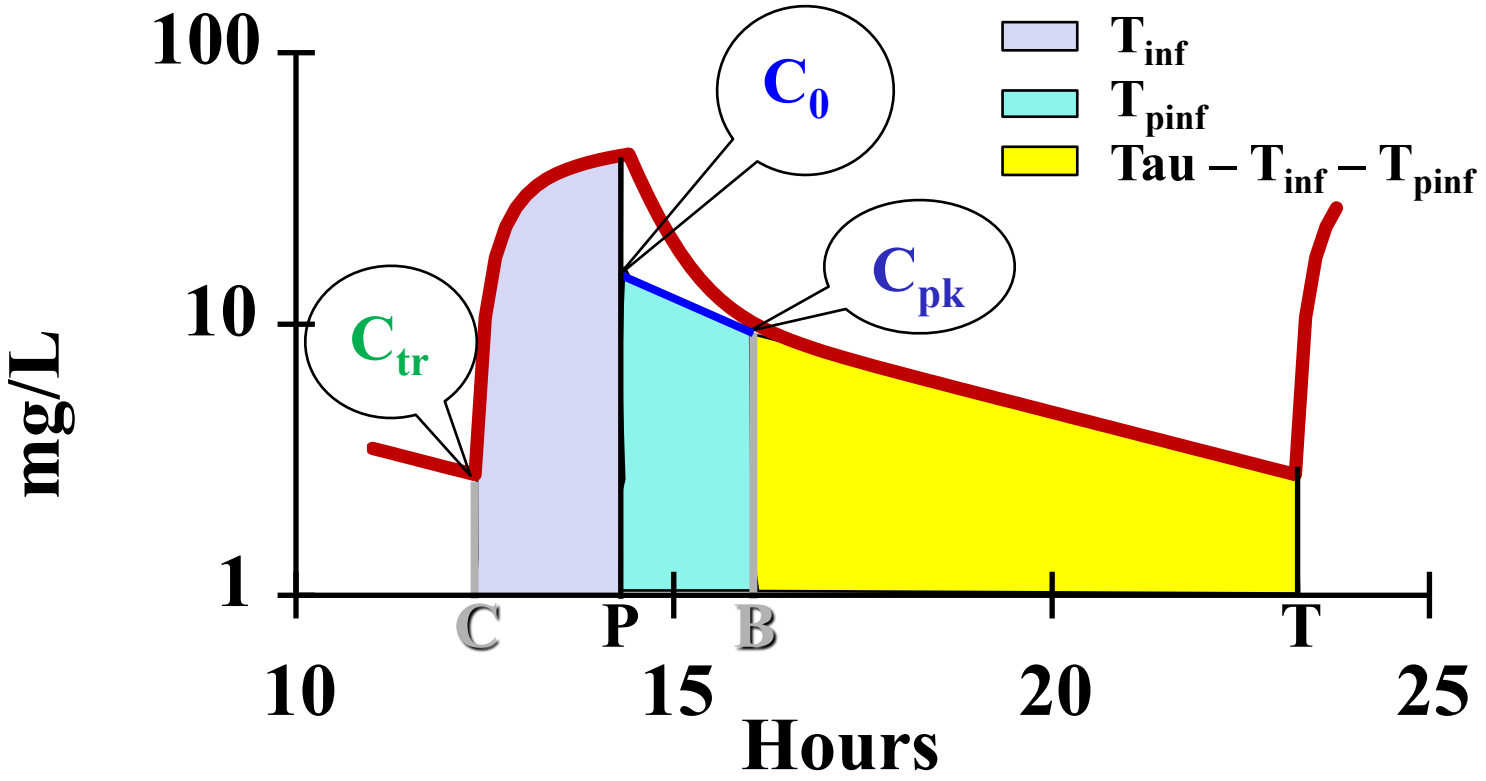
Often a peak and a trough.



When is the peak drawn?



Times & Concentrations

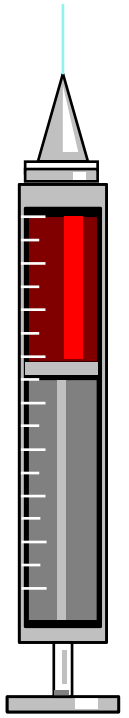


- C_0 is where the blue line intersects P
- C_{pk} is where the blue line intersects B
- T_{inf} is the time from C to P
- T_{pinf} is the time from P to B

- The peak (C_{pk}) is measured when distribution is complete (B)
- The trough (C_{tr}) is measured within 30 minutes of the administration (C)

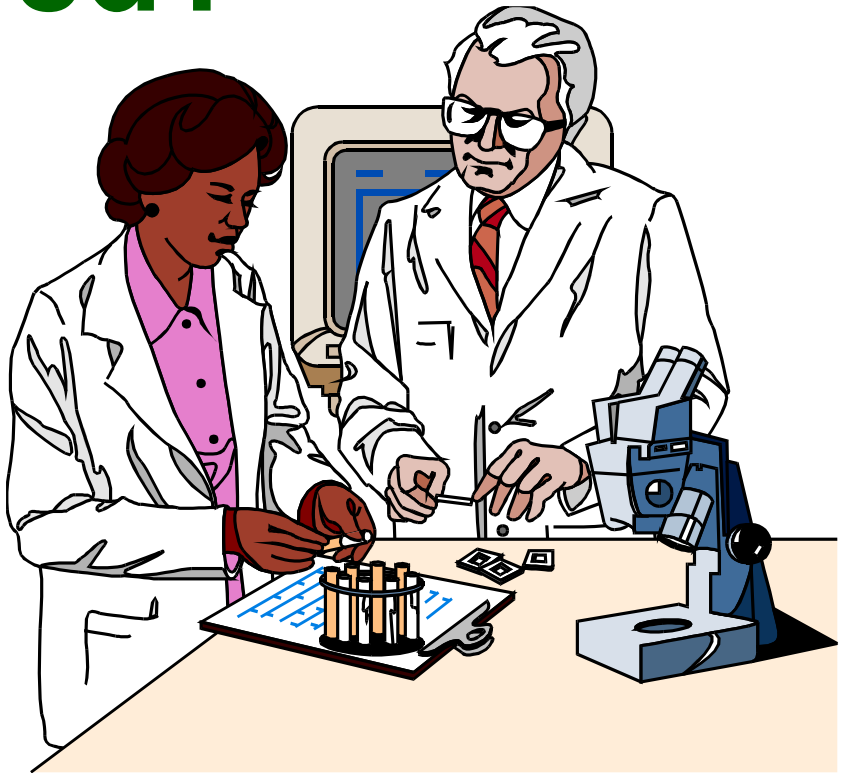
Optimum Peak Sampling Times

- **Gentamicin and Tobramycin**
  - Infuse over 30 minutes
  - Draw the peak 30 minutes after the infusion stops.
- **Vancomycin**
  - Dose ≤ 1.25 g infuse over 90 minutes
  - Dose 1.5 - 2 g infuse over 120 minutes
  - Draw the peak 60 minutes after the infusion stops.



How are drug concentrations measured?

(Chapter 3, pp 30-38)



- Sample Collection
  - Venous vs Arterial
  - Plasma vs Serum
- Assay Method
  - Microbiological
  - HPLC
  - GLC
  - Radio-immunoassay
  - Enzyme Meditated Immunoassy (EMIT)
- Units

Individualizing Drug Therapy

- **Steady state - single sample**
  - **Constant rate infusions**
  - **Extravascular Administration**

$$D_{new} = \frac{D_{current} \cdot C_{desired}}{C_{ss,measured}}$$

Note: D (dose) involves two components amount and interval: e.g.

- **Lidocaine 1 mg/Hr**
- **Theophylline SR 200 mg/12 Hr**

Individualizing Drug Therapy

- Steady state - single sample Example
  - Theophylline SR 200 mg Q12H
  - Steady state level came back 8 mg/L
  - Target concentration is 12 mg/L

$$D_{new} = \frac{D_{current} \cdot C_{desired}}{C_{ss,measured}} \qquad D_{Current} = \frac{200\ mg}{12\ Hr} \qquad \frac{C_{desired}}{C_{ss,measured}} = \frac{12\ mg/L}{8\ mg/L}$$

Theophylline Example

- You have 2 options:
  - Take the ratio times the amount (dose):
    - 200 mg * 12/8 = 300 mg (keeping the interval Q12H).
    - D_{new} = 300 mg Q12H
  - Take 1 over the ratio times the interval (denominator)
    - 12 Hr * 8/12 = 8 Hr and keep 200 mg dose
    - D_{new} = 200 mg Q8H

Individualizing Drug Therapy

- Intermittent infusions
  - Target Concentrations
  - Volume of distribution
  - Elimination rate
- Prospectively
  - Population Estimates
- Retrospectively
  - Blood Level Data

Vancomycin Example

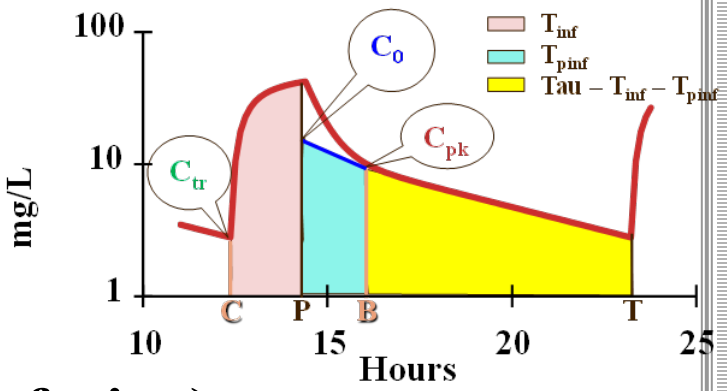
- Target Concentration
  - Peak 30-40 mg/L
  - Trough = 15 mg/L

- Volume of Distribution
  - 0.7 L/Kg
- Elimination Rate Constant
  - $K = (8.3*CrCl + 44)/10^4$

Sawchuk - Zaske Approach to Dosage Adjustment

1. **Calculate the elimination rate constant.**

$$k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln\left(C_1 / C_2\right)}{\tau - t_{pk}} = \frac{\ln\left(C_{pk} / C_{tr}\right)}{\tau - t_{inf} - t_{pi}}$$



2. **Calculate C_o (t_{pk} = elapsed time from start of infusion)**

$$C_0 = \frac{C_{pk}}{e^{-k_e\,(t_{pk} - t_{inf})}}$$

Sawchuk - Zaske Approach to Dosage Adjustment

3. **Calculate the half-life.**

$$t_{1/2} = \frac{\ln 2}{k_e}$$

4. **Calculate the volume of distribution.**

$$V_{ss} = \frac{R_0}{k_e} \cdot \frac{1 - e^{-k_e t_{\text{inf}}}}{(C_0 - C_{tr} \cdot e^{-k_e t_{\text{inf}}})}$$

Sawchuk - Zaske Approach to Dosage Adjustment

5. **Calculate the dosing interval.**

$$\tau = \frac{\ln\left(C_{Max,desired} / C_{Min,desired}\right)}{k_e} + t_{\inf}$$

6. **Calculate the new infusion rate.**

$$R_0 = C_{Max,desired} \cdot k_e \cdot V_{ss} \cdot \frac{\left(1 - e^{-k_e \tau}\right)}{\left(1 - e^{-k_e t_{\inf}}\right)}$$

Sawchuk - Zaske Approach to Dosage Adjustment

7. **Calculate the new peak.**

$$C_{ss,pk} = \frac{R_0}{V_{ss} \cdot k_e} \cdot \frac{\left(1 - e^{-k_e t_{\text{inf}}}\right)}{\left(1 - e^{-k_e \tau}\right)}$$

8. **Calculate the new trough.**

$$C_{ss,tr} = C_{ss,pk} \cdot e^{-k_e\left(\tau - t_{\text{inf}}\right)}$$

Common Errors

- **Single drug concentration:**
  - **When using the D_{New} equation to insure valid recommendations are made, the measured concentration should be obtained at steady state. Check to see that the concentration was measured at least 5 times the average elimination half-life for the drug.**
  - **The $D_{Current}$ can be adjusted by multiplying the dose by the concentration ratio, or dividing the interval by the ratio.**

Common Errors

- **Peak and Trough**
  - When calculating the rate of elimination (K_e) make sure the correct time is used in the denominator Equation 1.
  - The time term in the denominator exponent in equation 2 t_{pk} is elapsed time from the start of the infusion to when the peak is measured minus the length of the infusion (which is the time post infusion – t_{pinf}).

Common Errors

- **Peak and Trough**
  - Equation 4 there are two common errors:
    - R_0 is rate of input – dose in mg divided by the length of infusion (hr.)
    - Do not subtract the trough concentration from the C_0; you must multiply the exponent term times the trough then subtract this product from C_0.
  - Equation 5 when calculating a dosing interval do not use the calculated value, but choose a practical dosing interval, Q6H, Q8H, Q12H or Q24H.
    - Q16H and Q18H are not practical intervals.

Common Errors

- **Peak and Trough**
  - **When you calculate the new infusion rate (R_0):**
    - **Convert the rate to a dose in mg by multiplying by the length of the infusion.**
    - **Then round to a practical dose. E.g. aminoglycosides round to the nearest 10 mg increment and vancomycin round to the nearest 250 mg increment.**
  - **When calculating the peak and trough (Equations 7 & 8) use the practical dosing interval that you chose and use the practical R_0 that you chose as well.**

Case: BJ 67 YO WF

- **BJ is a 67 YO 5'5" woman with cellulitis from *Staph aureus*.**
  - **Her weight is 70 Kg (IBW = 57 Kg)**
  - **Her serum creatinine is 1.3 mg/dl.**
  - **Her measured CrCl was 44.7 ml/min.**
- **To give you a target peak of about 36 mg/L and trough of 15 mg/L:**
  - **What dose (mg) of vancomycin would you recommend for initiation of therapy?**
  - **And what dosing interval?**

Sawchuk-Zaske Approach

- Equation 1
  - Prospectively estimate K_e.
  - Normally you would need to first estimate CrCl from Cockcroft & Gault, but note that the measured CrCl was given to you, so use that.
- Equation 2
  - Determine the half-life (from K_e).

Sawchuk-Zaske Approach

- Equation 3
  - Prospectively C_0 is your target peak concentration (here 36 mg/dl) so no calculation is necessary.
- Equation 4
  - Prospectively estimate V_{ss} from the V_d,factor for vancomycin (here 0.7 L/Kg).

Sawchuk-Zaske Approach

- Equation 5
  - Now you can estimate the dosing interval from the target peak and trough and the calculated K_e.
  - You must select a practical Tau.
- Equation 6
  - Now use the practical Tau to determine the dose.
  - Equation 6 gives you R_0, the rate of infusion, so to get the dose you have to take the length of the infusion times R_0.
  - Remember to select a practical dose.

Sawchuk-Zaske Approach

- Equations 7 & 8
  - Verify that this practical dose and practical interval that you have chosen give you a steady state peak and trough near your targets.

Case: Vancomycin Retrospective

- RW is a 19 YO 5'6" woman with cellulitis from *Staph aureus*.
  - Her weight is 68 Kg
- She has been on vancomycin 1 Gm Q12H for 5 days.
  - Pk/Tr came back at 17.0 and 4.1 mg/L
  - The Pk was measured 60 minutes after the 90 minute infusion.
  - The skin grafts still show signs of cellulitis and the physician wants to increase the dose
- What dose (mg) of vancomycin and what dosing interval would you recommend to clear the infection?

Summary Observation

- Properly collected serum drug concentrations can be very useful to optimize drug therapy for those agents that have a narrow therapeutic window.
- They can be used to calculate patient specific PK parameters and then make dosage adjustments.
- However, it is essential the drug concentrations used to optimize therapy be properly obtained and that the pharmacokinetic equations used to individualize drug therapy be utilized correctly.