Clinical Pharmacokinetics

Vancomycin Pharmacokinetics

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REAL WORLD | REAL EXCELLENCE | REAL IMPACT

Objectives

- Describe the pharmacological properties and clinical indications of vancomycin.
- Describe the absorption, distribution and elimination of vancomycin.

Objectives

- Define the therapeutic range of vancomycin and be able to explain the monitoring controversy.
- Recommend appropriate sampling times and monitoring parameters for a given patient's demographic characteristics and clinical setting.

Objectives

- Given a patient's demographic characteristics without concentration-time data, calculate the appropriate initial dosage regimen.
- Given a patient's demographic characteristics and vancomycin concentration-time data, calculate a dosage regimen to achieve a desired peak and trough concentration.

Vancomycin

(Chapter 15, p 328)

- Glycopeptide Antibiotic
- Mechanism of Action
  - Dose independent killing by irreversible binding to the cell wall.
- Spectrum of Activity
  - Primarily gram + organisms.

Basic Pharmacokinetics

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

Liberation and Absorption

(Chapter 15, p 329)

- No special release dosage forms available

- Oral Absorption

- Parenteral Absorption

Distribution

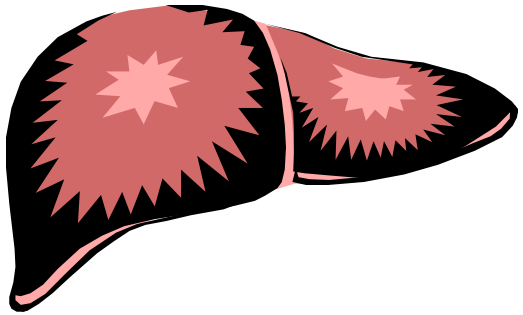
(Chapter 15, p 330)

- Fairly rapid, but measurable distribution
- Protein Binding 30-55%
- Tissue penetration – good into most tissues.
- Reasonable lipid solubility
  - Distribution into adipose tissue
  - No penetration into normal CSF

Metabolism

- 80-100 % is excreted unchanged.

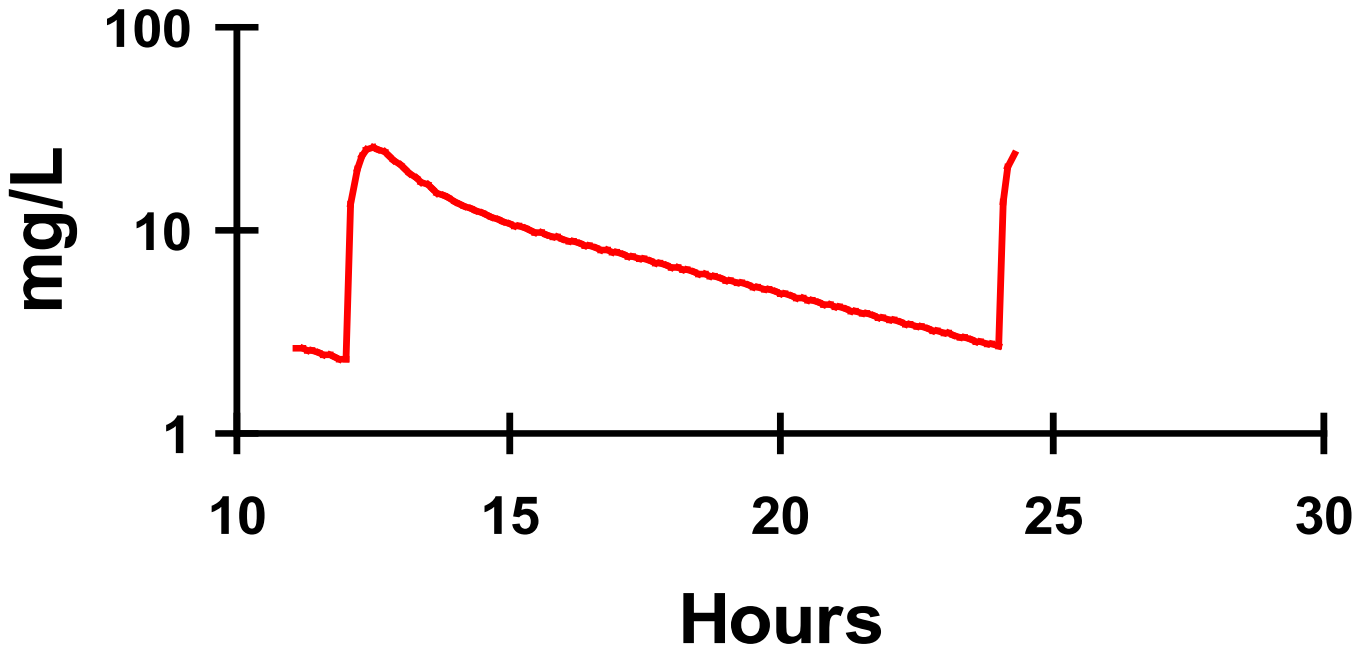
Kirby and Divelbiss, *Antibiot Ann* 1957,107-117.



Elimination

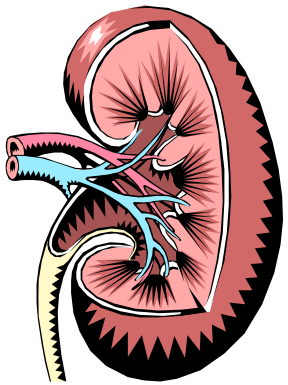
(Chapter 15, p 330)

Tri-exponential Disposition



Distribution and Elimination

- **Volume of Distribution**
  - Central Compartment $V_c = 0.15$ L/Kg
  - Steady State $V_{ss} = 0.5 - 0.9$ L/Kg
- **Elimination Half-Lives**
  - $\alpha = 7$ minutes
  - $\beta = 0.4$ hours
  - $\gamma = 3\text{-}9$ hours



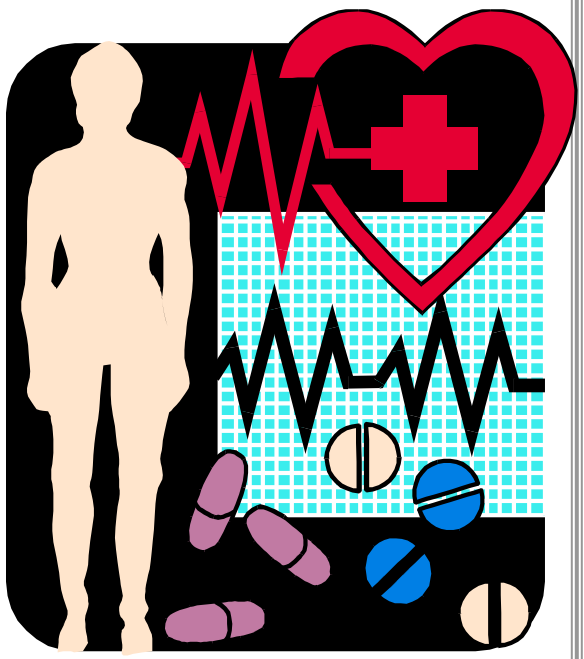
Matzke, Zhanel and Guay: *Clin Pharmacokinet* 1986; **11**:275-282

Therapeutic Drug Monitoring

- **Why do we do it?**
  - **To improve efficacy.**

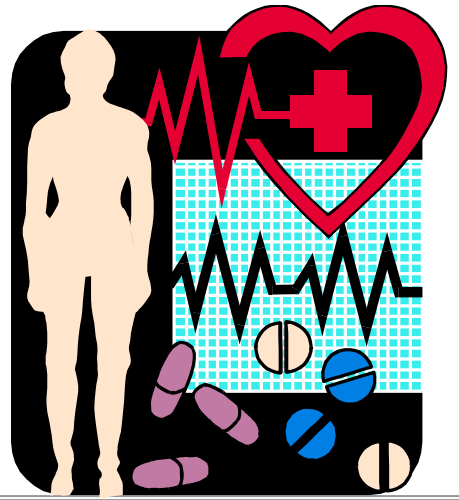
    (Chapter 15, pp 333-335)
  - **To improve safety.**

    (Chapter 15, pp 335-336)
- **Should we monitor?**



Therapeutic Drug Monitoring

- What do we monitor?
  - Things which influence its distribution.
  - Things which influence its elimination.
  - Drug levels of vancomycin.

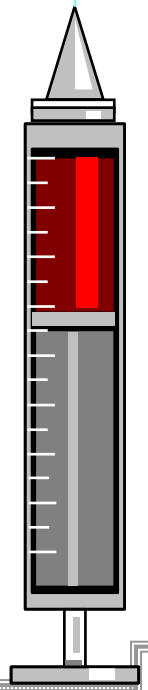


Therapeutic Drug Monitoring

- How do we measure it? *(Chapter 15, p 337)*
  - Plasma or serum?
  - FPI® – Fluorescence Polarization Immunoassay
  - EMIT®- Enzyme Multiplied Immunoassay
- When do we do it? *(Chapter 15, p 336)*
  - When we reach steady state.
  - When distribution is complete.

Optimum Sampling Times

- **Vancomycin**
  - **Trough within 30 minutes of a scheduled dose.**
    - **Dose ≤ 1.25 g infuse over 90 minutes.**
    - **Dose 1.5-2 g infuse over 120 minutes.**
  - **Peak 60 minutes after the infusion stops.**



Predicting Steady Levels

- Target concentrations.
- Volume of distribution.
- Rate of elimination.

Target Concentrations

- **Vancomycin**
  - **Peak** 30-40 mg/L
  - **Trough** 10-20 mg/L

Prospectively

Population Pharmacokinetic Estimates

$$CrCl = \frac{(140 - Age) \cdot CrClWt}{72 \cdot SrCr}(0.85 + Sex \cdot 0.15)$$

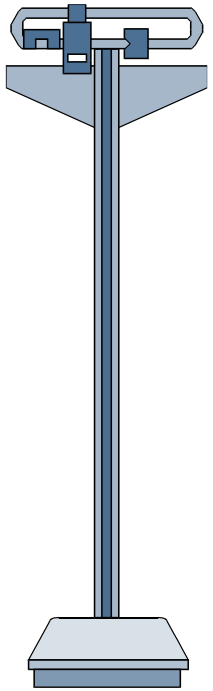
Cockcroft & Gault:
Nephron 1976;6:31-41.

$$Est.\ k_e = \frac{8.3 \cdot CrCl + 44}{10000}$$

Matzke and coworkers:
Antimicrob Agents Chemother
1984; 25:433-437.

$$Est.\ V_{ss} = 0.7L/Kg \cdot \text{ActWT}$$

Dosing Weight



IBW (males) =

50 Kg + 2.3 Kg/inch over 5 feet

IBW (females) =

45.5 Kg + 2.3 Kg/inch over 5 feet

If ActBW is ≥ 30% over IBW, then

AdjWT = (ActBW - IBW)(0.4) + IBW

Individualizing Drug Therapy

- **Steady state - single sample (TR Only)**

$$\left(Dose/Tau\right)_{new} =$$

$$\left(Dose/Tau\right)_{current} * C_{desired}/C_{ss,measured}$$

$C_{desired}$ – Should target 15 mg/L

Sawchuk - Zaske Approach to Dosage Adjustment

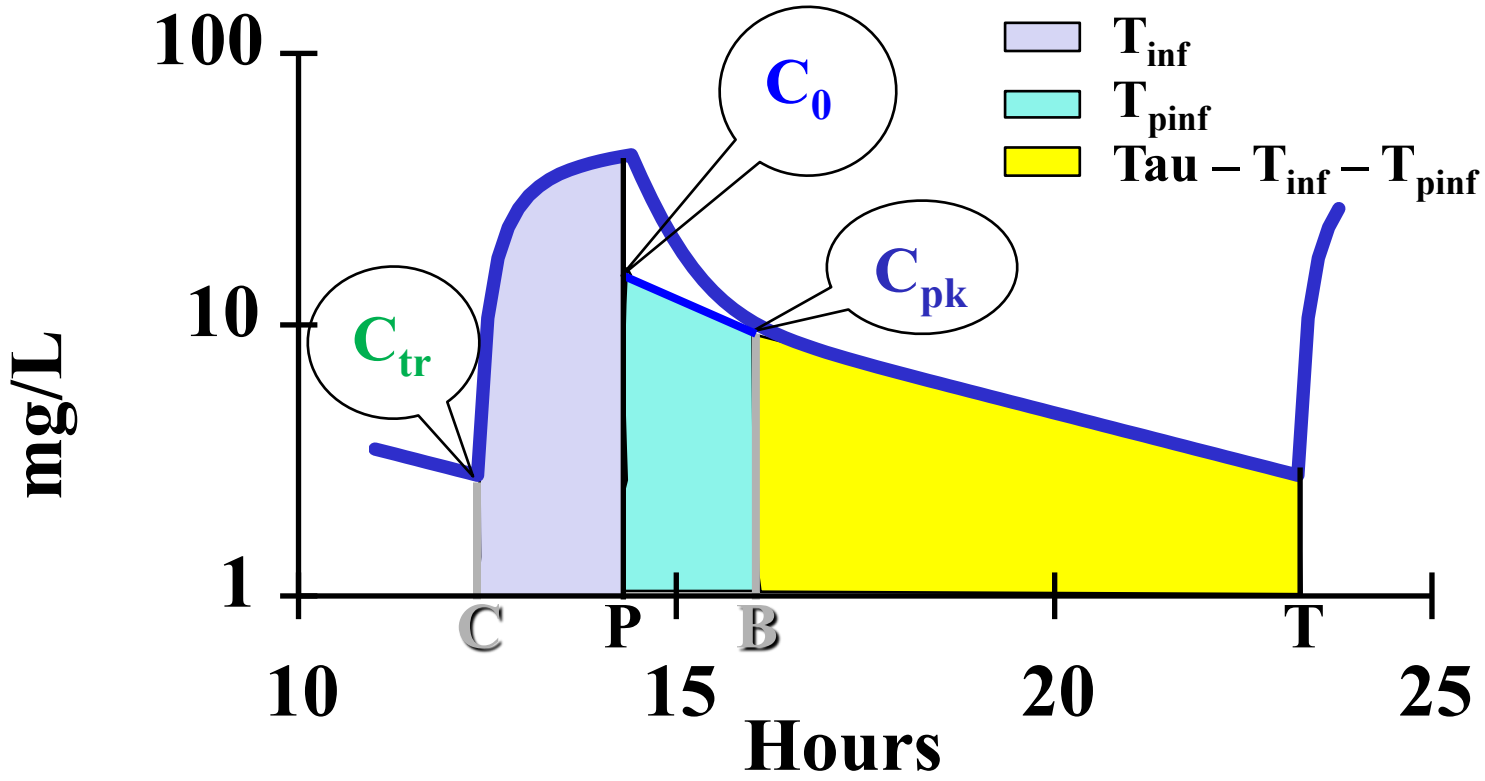
1. Calculate the elimination rate constant.

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

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

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

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)

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.

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

Sawchuk - Zaske Approach to Dosage Adjustment

5. Calculate the dosing interval.

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

- Practical
- Estimate

6. Calculate the new infusion rate.

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

Target Peak (36 mg/L)

Sawchuk - Zaske Approach to Dosage Adjustment

7. Calculate the new peak.

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

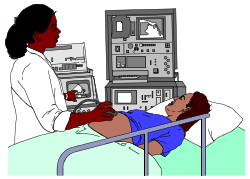
8. Calculate the new trough.

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

Special Populations

(Chapter 15, pp 330-332)

- **Premature Infants**
  - **Usually will require a lower dose, 10 mg/Kg/day in divided doses instead of 30 mg/Kg/day, until gestational age is > 40 weeks.**



- **Dialysis Patients**
  - **For the most part it is not dialyzed (< 10%)**
  - **However, use of high flux membranes can result in 20-40% being dialyzed.**

Special Populations

- Critically Ill Patients
  - Multi-system organ failure
  - Burn patients

Burn Patients

Steady State Volume of Distribution

	Measured	Predicted
Mean	56.1 L (0.7 L/Kg)	68.5 L (0.9 L/Kg)
S.D.	25.9 L	18.5 L
Minimum	4.9 L	9.6 L
Maximum	213.9 L	92.5 L

n = 142 P < 0.05

Burn Patients

Elimination Half-Life

	Measured	Predicted
Mean	5.7 Hours	8.8 Hours
S.D.	2.9	4.9
Minimum	0.9	3.9
Maximum	20.3	50.5

n = 142 P < 0.05

Burn Patients

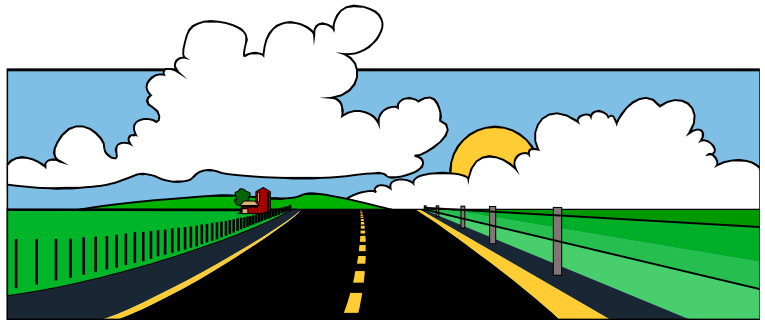
Vancomycin Clearance (ml/min/1.73 m^2)

	Measured	Predicted
Mean	110.3	92.2
S.D.	39.4	33.4
Minimum	30.7	14.6
Maximum	308.2	187.1

n = 142 P < 0.05

Summary

- **Routine monitoring controversy.**
  - **PK & TR not routinely recommended. TR is almost always sufficient.**
    - **Last two readings on the handout.**
- **Prospective dosing.**
  - **Many institutions still require.**
- **Selective monitoring.**
  - **For patients who already have renal failure, are at high risk for renal failure, are concurrently on another renal toxic drug or they are hypermetabolic (e.g. burns).**



Case 1

A 65 Y.O. male with a Sr.Cr. of 1.4 mg/dl develops a cellulitis. The Gram stain shows a Gram + cocci. The physician suspects *Staph. aureus* and wants to start vancomycin. The patient is 5' 4" and weighs 86 Kg. What would be the appropriate dose to use?

Case 2

The above patient was given 1000 mg Q24H and the trough right before the fifth dose was 11.4 mg/dL. What new dose would you recommend?

Case 3

A 52 year old black female patient, 5'7" and 79 Kg and with a SrCr = 1.3 mg/dL was given 1000 mg Q12H and the trough right before the fifth dose was 17.3 mg/dL. What new dose would you recommend?

Case 4

- A 5’ 5” 88 Kg. 72 Y.O. Hispanic female patient has been on vancomycin 750 mg Q12H for 3 days. A single trough level came back at 6.6 mg/dl. What new dose would you recommend?

Case 5

A 5' 6" 68 Kg. 19 Y.O. female burn victim has been on vancomycin 1 Gm Q12H for 5 days. Levels are done and come back with a Pk/Tr = 17/4.1 mg/dl. The skin grafts still show signs of cellulitis and the physician wants to increase the dose. What would you recommend? (The Pk was 60 minutes after a 90 minute infusion.)