Vancomycin

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Introduction

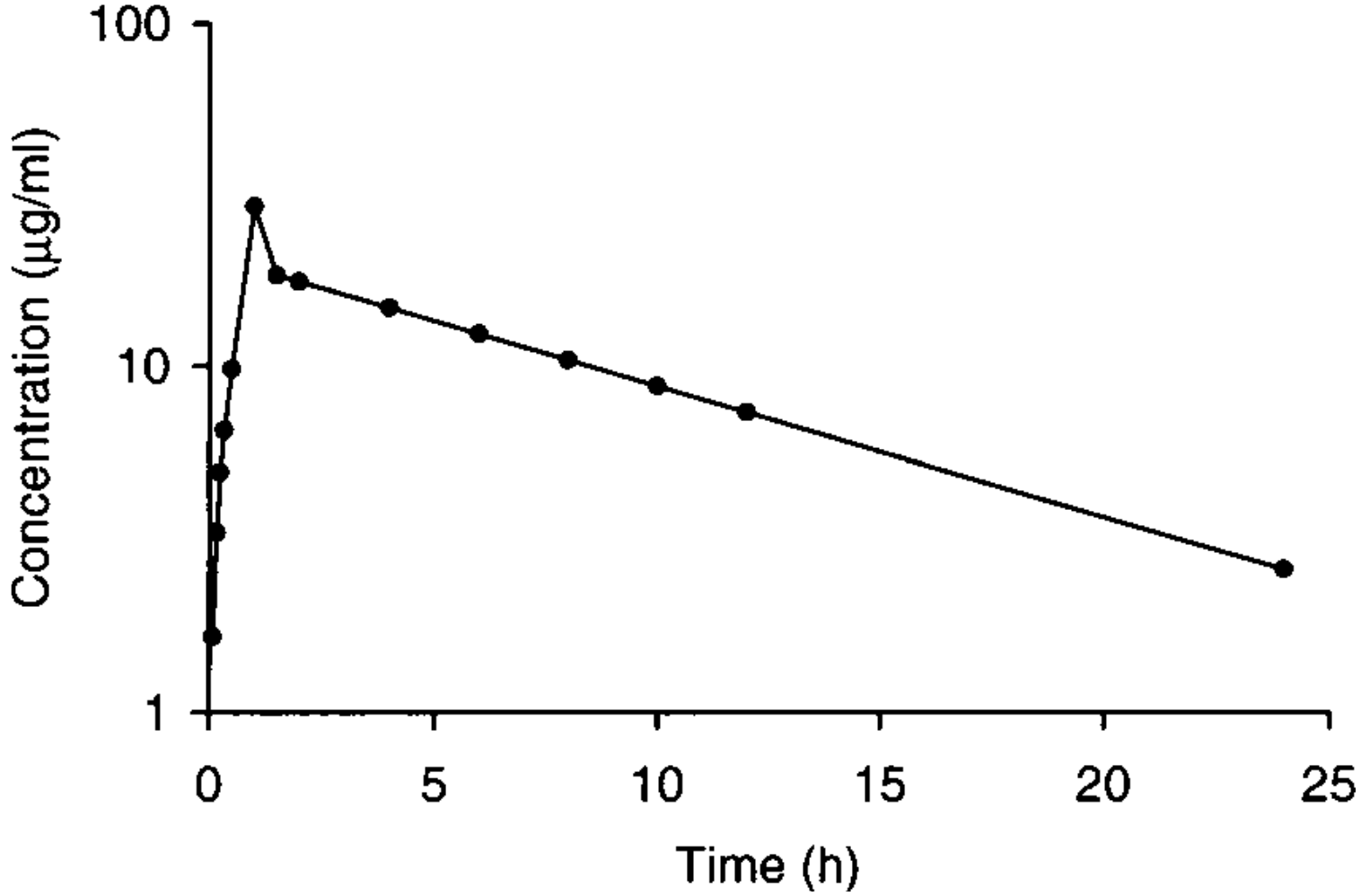
- Vancomycin is a glycopeptide antibiotic
- Vancomycin is bactericidal and exhibits time-dependent or concentration independent bacterial killing.
- Antibiotics with time-dependent killing kill bacteria most effectively when drug concentrations are a multiple (usually three to five times) of the minimum inhibitory concentration (MIC) for the bacteria.

Introduction

- Vancomycin is administered as a short-term (1-1.5hour) intravenous infusion

- Even with a 1-hour infusion time, vancomycin serum concentrations exhibit a distribution phase so that drug in the blood and in the tissues are not yet in equilibrium.

- Because of this, a **1/2–1 hour** waiting period is allowed for distribution to finish before maximum or “peak” concentrations are measured. A peak vancomycin concentration is obtained after **1.5** hr. or **2 hr**.



Concentration/time plot for vancomycin 1000 mg given as a 1-hour infusion

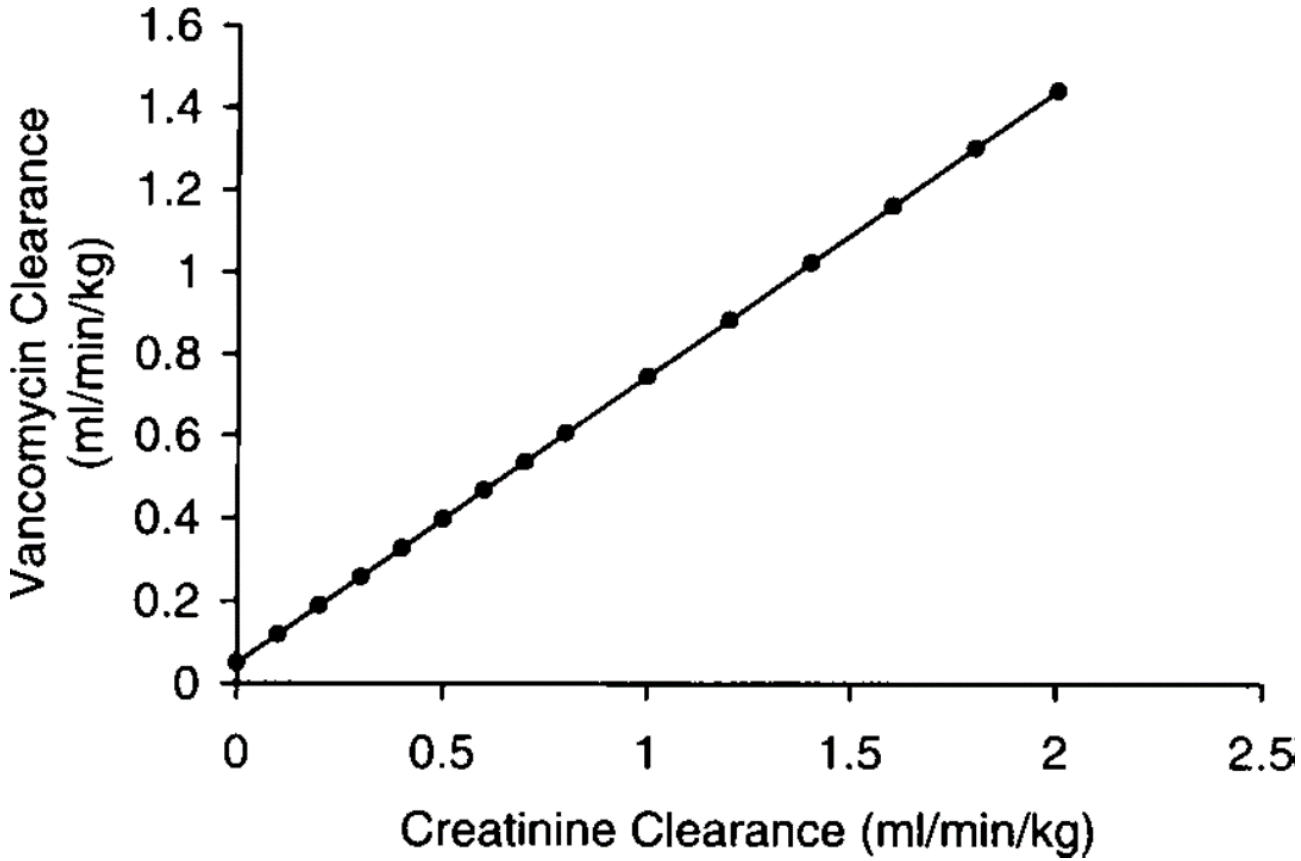
Basic Clinical Pharmacokinetic Parameters

TABLE 5-1 Disease States and Conditions That Alter Vancomycin Pharmacokinetics

DISEASE STATE/CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal function	8 hours (range: 7–9 hours)	0.7 L/kg (range: 0.5–1.0 L/kg)	Usual dose 30 mg/kg/d in 2 divided doses
Adult, renal failure	130 hours (range: 120–140 hours)	0.7 L/kg (range: 0.5–1.0 L/kg)	Underhydration or overhydration does not effect the volume of distribution as much as with aminoglycosides
Burns	4 hour	0.7 L/kg	Because of shorter half-life, some patients may need every 6–8-hour dosage interval to maintain therapeutic trough concentrations
Obesity (>30% over IBW) with normal renal function	3–4 hours	V = 0.7 IBW*	Total daily doses are based on TBW*, V estimates based on IBW*. Because of shorter half-life, some patients may require every 8-hour dosage interval to maintain therapeutic trough concentrations

*IBW = ideal body weight,
TBW = total body weight

The vancomycin clearance



Cl (in mL/min/kg) = 0.695 (CrCl in mL/min/kg) + 0.05

The vancomycin clearance

- Dose for vancomycin in patients with normal renal function is 30 mg/kg/d given as 2 g or 4 g divided daily doses.

- In normal weight adults, the dose is usually 2 g/d given as 1000 mg every 12 hours.

The dosing method

1. ***The pharmacokinetic dosing method***
2. ***The Moellering nomogram***
3. ***The Matzke nomogram***
4. ***Literature-based recommended dosing***

Pharmacokinetic Dosing Method

1. Clearance estimate

$$Cl\ (in\ mL/min/kg) = 0.695\ (CrCl\ in\ mL/min/kg) + 0.05$$

Cl is vancomycin clearance in mL/min/kg

CrCl is creatinine clearance in mL/min/kg

- The weight factor that is used for all individuals, including obese patients is the total body weight (TBW)

- Then the result should be multiply by (Weight × 60/1000) to convert CL from mL/min/kg to **L/hr**.

Pharmacokinetic Dosing Method

2. Volume of distribution estimate

- The average volume of distribution of vancomycin is **0.7 L/kg**

- The weight factor that is used to calculate vancomycin volume of distribution for **obese** patients is ideal body weight (**IBW**).

Pharmacokinetic Dosing Method

- Thus, for an 80-kg patient, the estimated vancomycin volume of distribution would be:

$$V = 0.7\ L/kg \times 80\ kg$$

$$= 56\ L$$

- For a 150-kg obese patient with an ideal body weight of 60 kg, the estimated vancomycin volume of distribution is:

$$V = 0.7\ L/kg \times 60\ kg$$

$$= 42\ L$$

Pharmacokinetic Dosing Method

3. **Elimination rate constant estimates**

$$Ke = Cl/V$$

4. **Half-life estimates**

$$t_{1/2} = 0.693/ke$$

Pharmacokinetic Dosing Method

5. Steady-state concentration selection

A. steady-state peak concentrations

- Steady-state peak vancomycin concentrations are chosen to provide adequate antibiotic penetration to the site of infection and to avoid adverse drug reactions. A commonly used range for this value is **30-50 µg/mL**.

- In severe, life threatening infections of the central nervous system, peak vancomycin serum concentrations as high as **60 µg/mL** may be necessary to facilitate drug penetration.

Pharmacokinetic Dosing Method

B. Minimum (predose) or trough steady-state concentrations (10–20 µg/ml)

- Because of reports of therapeutic failures, current treatment guidelines recommend vancomycin steady state trough concentrations equal to **10-15 µg/mL** for lower intensity dosing.

- Use **15 -20 µg/mL** for complicated infections due to **MRSA**, such as bacteremia, endocarditis, meningitis, osteomyelitis, severe skin infections, and hospital acquired pneumonia.

Pharmacokinetic Dosing Method

- Steady state vancomycin trough levels less than 10 µg/mL are discouraged due to the possibility of lower levels contributing to treatment failure or to the development of resistance.

- Whenever vancomycin doses are used that exceed steady state trough concentrations of **20 µg/mL**, serum creatinine concentrations and signs or symptoms of hearing or vestibular disturbance should be monitored daily to detect early signs of toxicity.

Pharmacokinetic Dosing Method

6. Selection of appropriate pharmacokinetic model and equations

TABLE 5-2C Equations Used to Compute Individualized Dosage Regimens for Vancomycin

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ $D = Css_{max}\, V(1 - e^{-k_e\tau})$ $LD = Css_{max}\, V$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, k_0 is the continuous infusion rate.

The Moellering nomogram

- Is designed to achieve average steady-state concentrations equal to **20 µg/mL**.
- Some clinicians find this approach confusing since target steady-state peak and trough concentrations are not stated by the nomogram.
- Since the computed dose provided by the nomogram is expressed in mg/kg/24 h, it can be difficult to determine the best dosage interval.
- A modification of the vancomycin clearance/creatinine clearance equation can be made that provides a direct calculation of the vancomycin maintenance dose.

The Moellering nomogram

- Because the equation computes vancomycin clearance, it can be converted to the maintenance dose required to provide an average steady-state concentration of 15-20 mg/L by multiplying the equation by the concentration

$$(MD = Css \cdot Cl)$$

$$Cl \text{ (in mL/min/kg)} = 0.695(\text{CrCl in mL/min/kg}) + 0.05$$

$$D \text{ (mg/h/kg)} = [(20 \text{ mg/L} \cdot 60 \text{ min/h}) / 1000 \text{ mL/L}][0.695(\text{CrCl in mL/min/kg}) + 0.05]$$

$$\boldsymbol{D \text{ (mg/h/kg)} = 0.834 (\text{CrCl in mL/min/kg}) + 0.06}$$

The Moellering nomogram

- Note : In patients with good renal function [Crcl> 60] the dosing interval can be regarded
    - ***12 hours for non-obese***
    - ***8 hours for obese***

Loading dose = [15 mg/kg] * 1.33

Use of Vancomycin Serum Concentrations to alter Dosages

Use of Vancomycin Serum Concentrations to alter Dosages

1. **Linear Pharmacokinetics Method**

$$D_{New} = (Css_{New}/Css_{Old})D_{Old}$$

Use of Vancomycin Serum Concentrations to alter Dosages

2. Trough-only Method

$$\tau_{New} = (Css_{Old}/Css_{New})\tau_{Old}$$

Use of Vancomycin Serum Concentrations to alter Dosages

3. One-Compartment Model Parameter Method

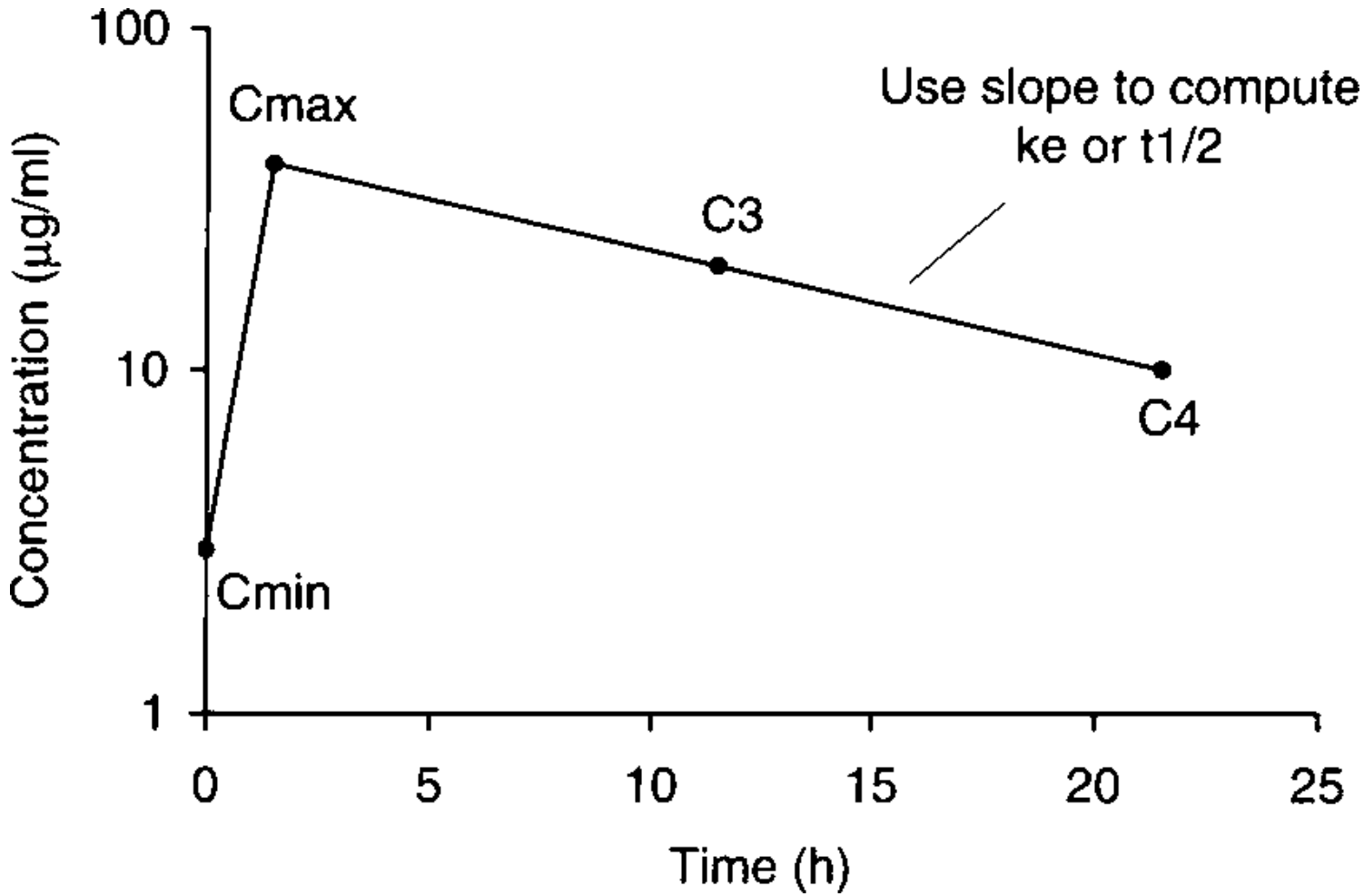
A. Standard one-compartment model parameter method

- The standard version of the one-compartment model parameter method does not require steady-state concentrations.

- A trough vancomycin concentration is obtained before a dose, a peak vancomycin concentration is obtained after the dose is infused (1/2–1 hour after a 1-hour infusion), and 1–2 additional post dose serum vancomycin concentrations are obtained.

- You will get 4 concentration that not reached steady state.

Use of Vancomycin Serum Concentrations to alter Dosages



Use of Vancomycin Serum Concentrations to alter Dosages

To answer

1. Calculate actual Ke by using any post dose concentrations.

$$Ke = (\ln C_1 - \ln C_2)/\Delta t$$

2. Calculate actual Vd

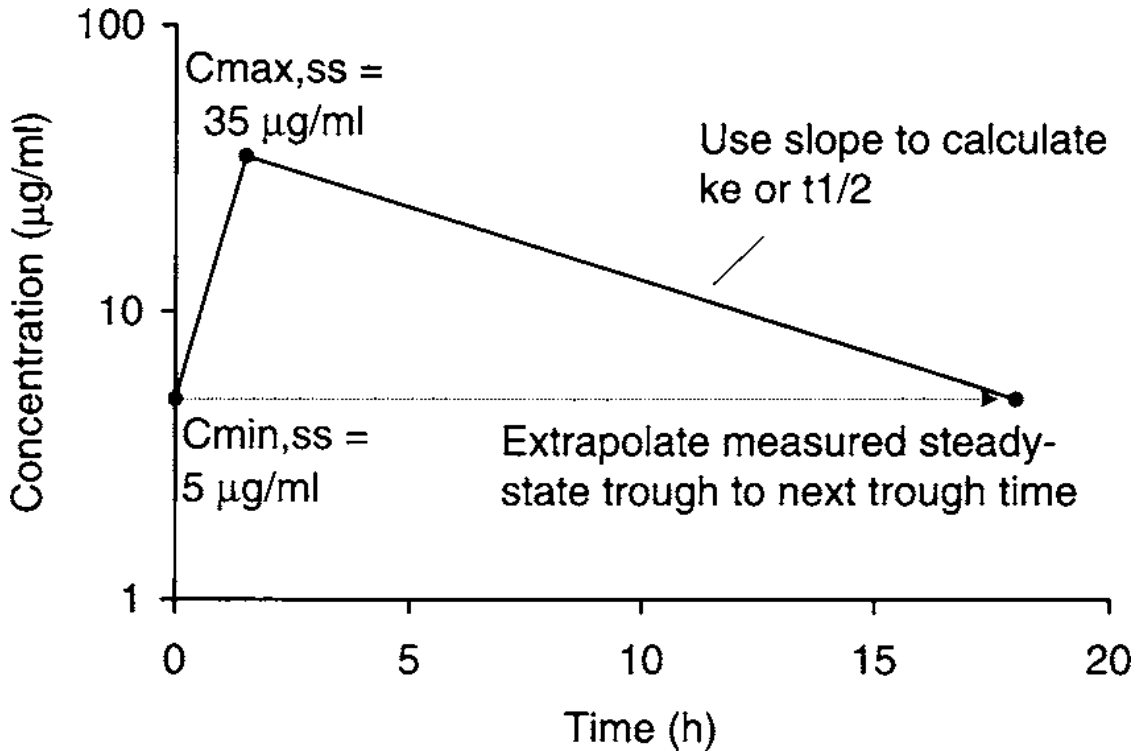
$$V = D / (C_{max} - C_{min})$$

3. Using actual Ke and Vd to calculate new dose by using I.V bolus equations.

Use of Vancomycin Serum Concentrations to alter Dosages

B. Steady-state one-compartment model parameter method

- You will get 2 concentrations (C_{max} and C_{min}) that reached steady state.



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Thank you for listening!