The Aminoglycosides

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Introduction

- Aminoglycoside antibiotics are bactericidal, and the drugs exhibit concentration dependent bacterial killing.

- The aminoglycosides are eliminated almost completely (≥90%) unchanged in the urine primarily by glomerular filtration.

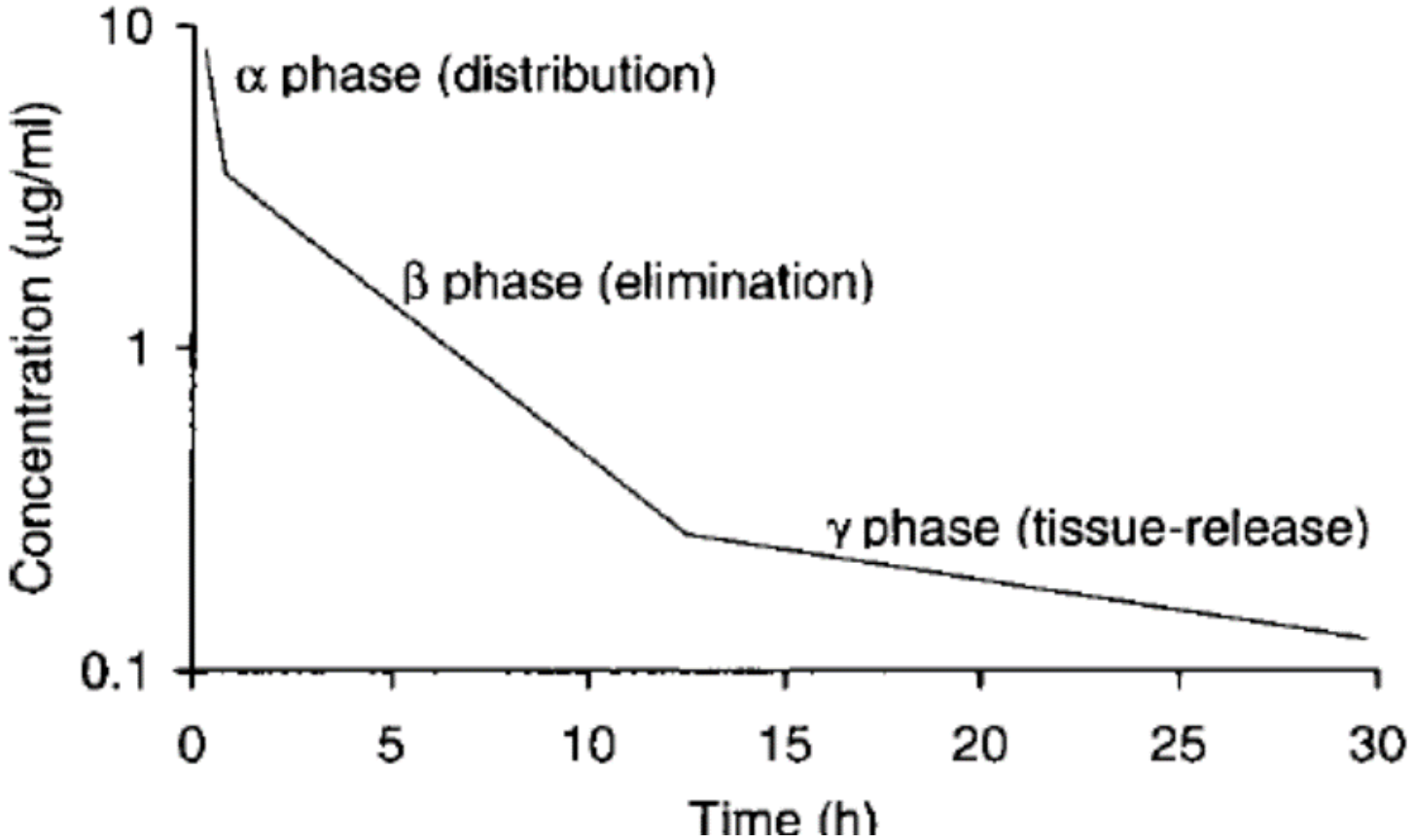
- Concentration-efficacy relationships: The pharmacodynamic properties of aminoglycosides are:

  - ***Concentration-dependent killing***
  - ***Significant post-antibiotic effect***

Introduction

- Antibiotics with concentration-dependent killing characteristically kill bacteria at a faster rate when drug concentrations are higher.
- Also, aminoglycosides have a concentration-dependent post antibiotic effect.
- The post antibiotic effect is the phenomenon of continued bacterial killing even though serum concentrations have fallen below the minimum inhibitory concentration (MIC).
- Because the post antibiotic effect is concentration-dependent for the aminoglycosides, higher drug concentrations lead to a longer post antibiotic effect.

Administration



- When given by IV infusion over 30 minutes, aminoglycosides follow a 3-compartment pharmacokinetic model; alpha (distribution), ß (elimination), and gamma (tissue release).

Administration

- When infused over one hour, the distribution phase is usually not observed. The gamma phase begins approximately sixteen hours post infusion.

- Aminoglycoside antibiotics are given as short-term (1/2–1 hour) infusions.

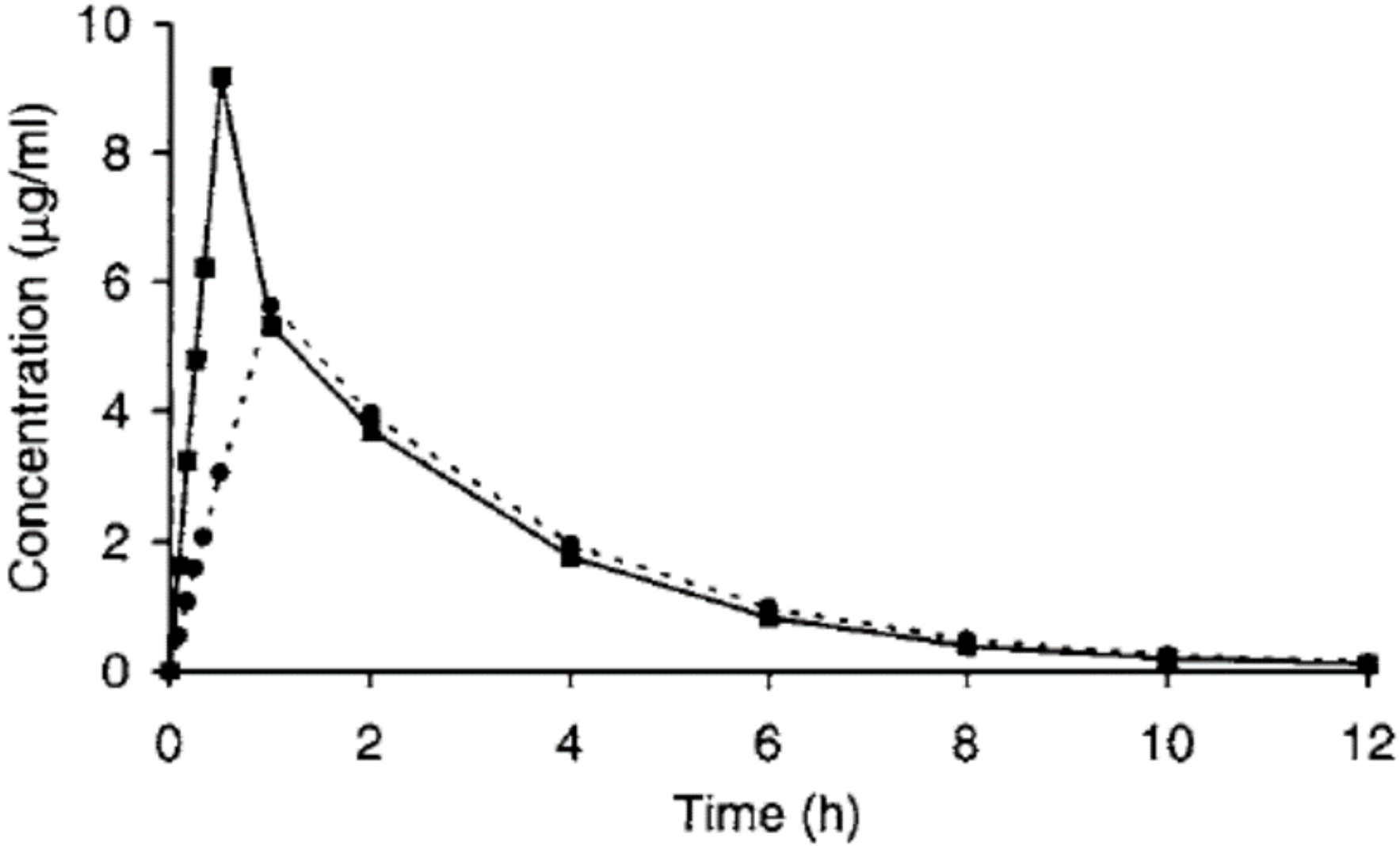
- If a 1-hour infusion is used, maximum end of infusion “peak” concentrations are measured when the infusion is completed.

Administration

- If a 1/2-hour infusion is used, 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-hour waiting period is allowed for distribution to finish if a 1/2-hour infusion is used before peak concentrations are measured.

- That mean the peak always measured after 1 hr.


Concentration (µg/ml)
10
8
6
4
2
0
0
2
4
6
8
10
12
Time (h)

Therapeutic and toxic concentrations

- The MIC for susceptible bacteria is higher for amikacin than it is for the other aminoglycosides.

- Because the pharmacokinetics is similar for all these drugs, higher doses of amikacin are needed to treat infections.

Method of administration

- Aminoglycoside antibiotics are given by two methods:

1. The **conventional method** of dosing is to administer multiple daily doses (usually every 8 hours).

- Steady-state when using conventional dosing:

A. Steady-state peak concentration selection

5–10 µg/mL for gentamicin, tobramycin, or netilmicin

15–30 µg/mL for amikacin

Therapeutic and toxic concentrations

B. Steady-state trough concentration selection

< 2 µg/mL for gentamicin, tobramycin or netilmicin.

< 5 µg/mL for amikacin

In using conventional dosing, exceeding the below peak steady-state concentrations leads to an increased risk of ototoxicity:

- 12–14 µg/mL for gentamicin, tobramycin, or netilmicin
- 35–40 µg/mL for amikacin when

Therapeutic and toxic concentrations

- Trough steady-state concentrations (predose or minimum concentrations usually obtained within 30 minutes of the next dose) above the following levels predispose patients to an increased risk of nephrotoxicity
    - 2–3 μg/mL for tobramycin, gentamicin, or netilmicin
    - 10 μg/mL for amikacin.

Therapeutic and toxic concentrations

2. Extended-interval method

- Usually the total daily dose is given once per day. It takes the advantage of
  - ***concentration-dependent bacterial killing***
  - ***the post antibiotic effect***

- Steady-state when using extended interval dosing for gentamicin, tobramycin, or netilmicin:

A. Peak concentration selection

20–30 µg/mL

B. Steady-state trough concentration selection

< 1 µg/mL

Therapeutic and toxic concentrations

Question/ why **increased toxicity** is not seen in patients with **extremely high peak concentrations** obtained during extended-interval dosing of aminoglycosides?

- The hypothesized reason is that

1. both nephrotoxicity and ototoxicity are due to accumulation of aminoglycoside in the relevant tissue. Because the dosage interval is prolonged in extended-interval administration, aminoglycoside concentrations are low for a long period of time and may allow for diffusion of drug out of tissue and into the blood which avoids drug accumulation in the ear and kidney.
2. Also, some of the uptake mechanisms into the ear and kidney may be saturable, so that high peak serum concentrations of aminoglycosides may not result in high renal or ear tissue concentrations.

Methods to initiate aminoglycoside therapy

- ***The pharmacokinetic dosing method***
- ***The Hull and Sarubbi nomogram***
- ***The Hartford nomogram***
- ***Literature-based recommended dosing***

The pharmacokinetic dosing method

- Most flexible method. It allows for individualized target serum concentrations to be chosen for a patient, so it can be used for both conventional and extended-interval dosing.

- To calculate initial dose by pharmacokinetic dosing method

1. Calculating the estimated pharmacokinetic parameter

   A. Elimination rate constant estimate

$$Ke\ (in\ h^{-1}) = 0.00293(CrCl\ in\ mL/min) + 0.014$$

The pharmacokinetic dosing method

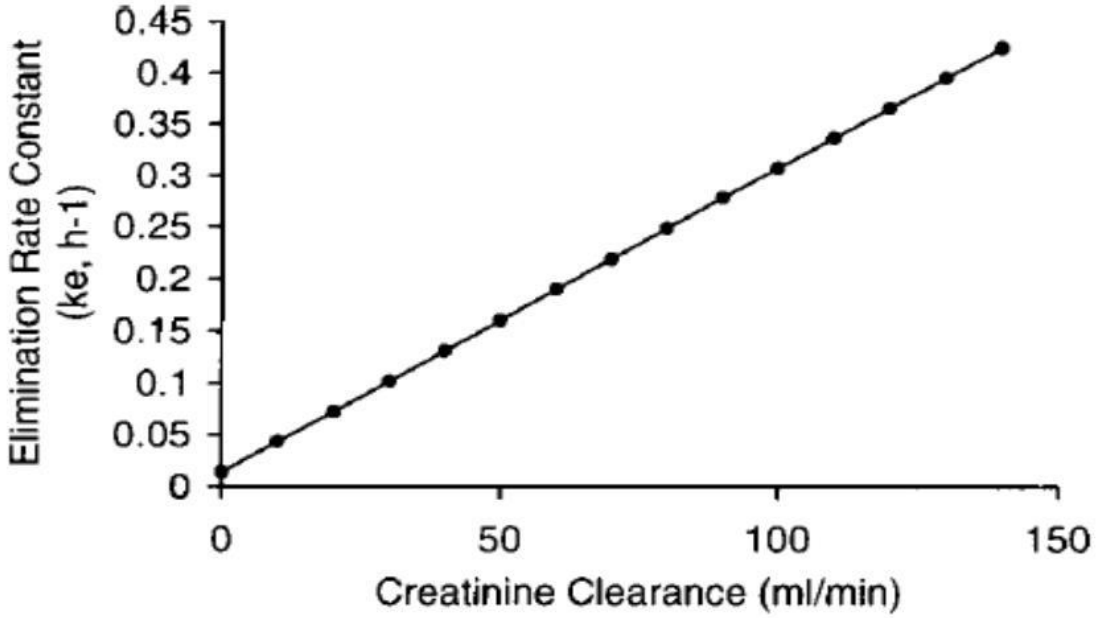


FIGURE 4-2 Relationship between renal and aminoglycoside elimination. The elimination rate constant (k_e) for aminoglycoside antibiotics increases in proportion with creatinine clearance (CrCl). The equation for this relationship is k_e (in h^{-1}) = 0.00293(CrCl in mL/min) + 0.014. This equation is used to estimate the aminoglycoside elimination rate constant in patients for initial dosing purposes.

The pharmacokinetic dosing method

B. Volume of distribution estimate

- The average volume of distribution for patients without disease states and conditions that change this parameter is:

Vd= 0.26 L/kg

- For ***cystic fibrosis*** patient ***Vd= 0.35 L/ kg***

- If a patient weighs less than their ideal body weight, or **within** 30% of the ideal body weight actual body weight is used to estimate volume of distribution.

The pharmacokinetic dosing method

- In patients who are **more than** 30% of their IBW, (Vd) estimates should include both ideal and actual total body weighs using the following equation:

$$V = 0.26\,[IBW + 0.4\,(TBW - IBW)]$$

- In patients who are overhydrated or have ascites, their dry body weight can be used to provide an improved volume of distribution estimate (V in L) using the following formula:

$$V = (0.26 \cdot DBW) + (TBW - DBW)$$

IBW: ideal body weight, TBW: total body weight, DBW: dry body weight

Selection of pharmacokinetic model and equations

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR K_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min}) / k_e$ $D = Css_{max}\, V(1 - e^{-k_e\tau})$ $LD = Css_{max}\, V$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$ $LD = k_0 / (1 - e^{-k_e\tau})$

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, t' is the infusion time.

Selection of pharmacokinetic model and equations

Note:

- Loading doses should be considered for patients with creatinine clearance values below 60 mL/min.

- One approach is to use different equations depending upon the renal function of the patient so use (Intermittent intravenous infusion for creatinine clearances >30 mL/min, while Intravenous bolus for creatinine clearances ≤30 mL/min).

- Alternatively, intermittent intravenous infusion equations can be used for all patients regardless of renal function.

Selection of pharmacokinetic model and equations

B. Steady-state concentration selection

Conventional dosing

- Severe infections, such as gram-negative pneumonia or septicemia, or infections with organisms that have a high minimum inhibitory concentration (MIC) such as Pseudomonas aeruginosa generally require

Peak steady-state serum concentrations

8–10 µg/mL for gentamicin, tobramycin, or netilmicin

25–30 µg/mL for amikacin

Selection of pharmacokinetic model and equations

- Moderate infections at sites that are easier to penetrate or with organisms that display lower MIC values, such as intra-abdominal infections are usually treated with

Peak steady-state serum concentrations

5–7 μg/mL for gentamicin, tobramycin, or netilmicin

15–25 μg/mL for amikacin

Selection of pharmacokinetic model and equations

- Aminoglycosides in combination with penicillins or other antibiotics for the treatment of gram positive infections such as infective endocarditis

Peak steady-state serum concentrations

3–5 μg/mL for gentamicin, tobramycin, or netilmicin

12–15 μg/mL for amikacin

Selection of pharmacokinetic model and equations

- For conventional dosing,

Steady-state trough concentrations should be maintained

<2 μg/mL for tobramycin, gentamicin, and netilmicin

<5–7 μg/mL for amikacin

Extended-interval dosing

steady-state trough concentrations should be

<1 μg/mL for gentamicin, tobramycin, and netilmicin

Hartford Nomogram Method (for Extended-Interval Dosing)

- It’s is designed for use when extended interval dosing is desired.
- This nomogram also incorporates a method to adjust aminoglycoside doses based on serum concentration feedback.
- The most widely used extended-interval for patients with renal dysfunction which uses a **7-mg/kg dose**
- The dosage interval is set according to the patient’s creatinine clearance.

Hartford Nomogram Method (for Extended-Interval Dosing)

Calculations:

1. Administer 7 mg/kg gentamicin with initial dosage interval:

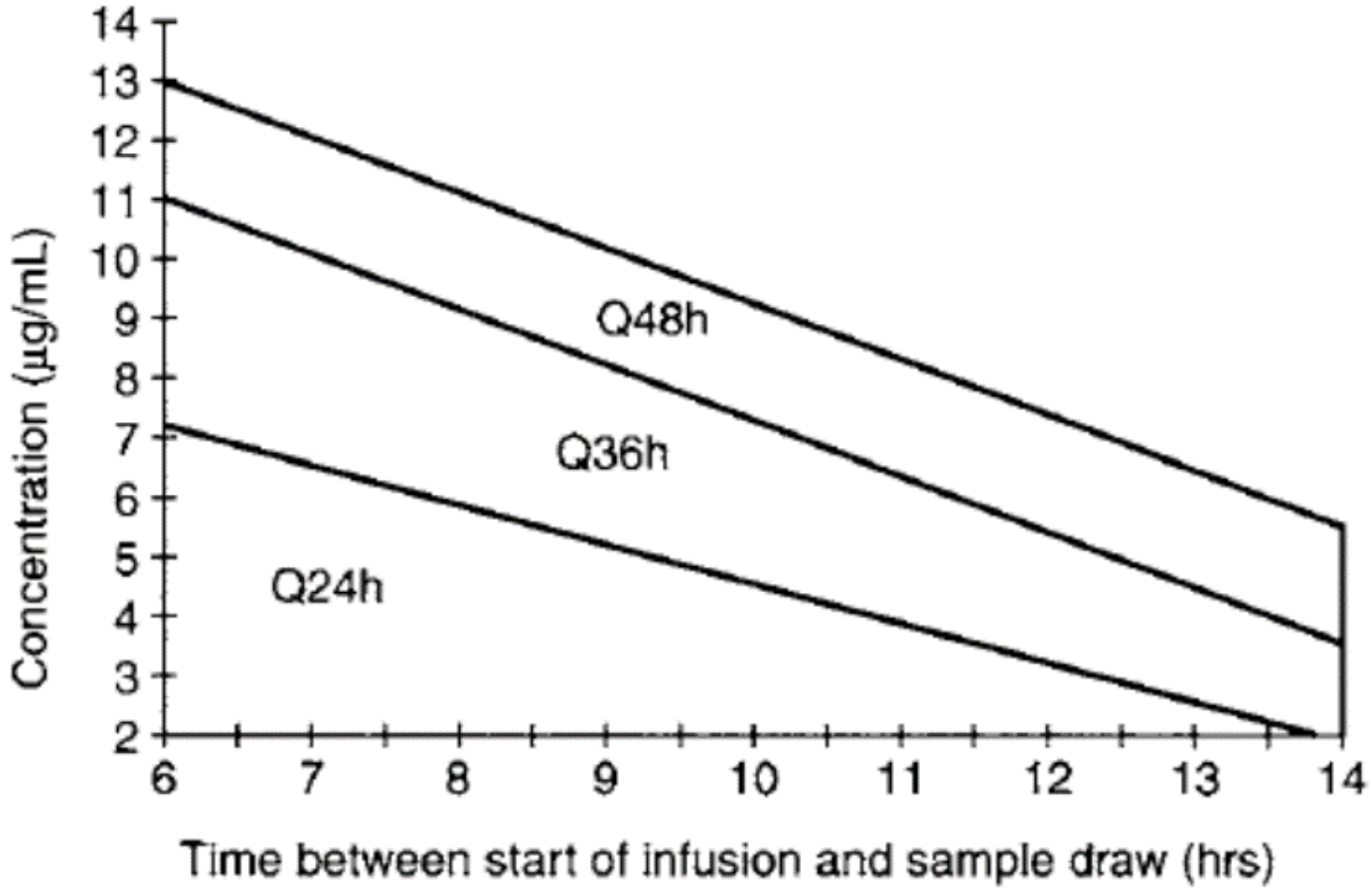
ESTIMATED CrCl	INITIAL DOSAGE INTERVAL
≥60 mL/min	q24 h
40–59 mL/min	q36 h
20–39 mL/min	q48 h
<20 mL/min	monitor serial concentrations and administer next dose when <1 µg/mL

Hartford Nomogram Method (for Extended-Interval Dosing)

2. Obtain timed serum concentration, 6–14 hours after dose (ideally first dose).

3. Alter dosage interval to that indicated by the nomogram zone (above q48 h zone, monitor serial concentrations, and administer next dose when <1 µg/mL).

Hartford Nomogram Method (for Extended-Interval Dosing)



Hartford Nomogram Method (for Extended-Interval Dosing)

- JM is a 50 year old, 70kg (height = 5 ft 10 in) male with gram negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient.

1. *Estimate creatinine clearance*

$$CrClest = [(140 - age)BW] / (72 \cdot SCr)$$

$$= [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrClest = 97\ mL/min$$

Dosage interval would be 24 hours using the nomogram.

Hartford Nomogram Method (for Extended-Interval Dosing)

2. *Dose = 7mg/kg*
   = 7mg/kg X 70kg
   = 490

The prescribed maintenance dose would be: 500 mg every 24 hours.

3. *Determine dosage interval using serum concentration monitoring.*

- A gentamicin serum concentration measured 10 hours after the dose equals **3 µg/mL**.
- Based on the nomogram, a dosage interval of 24 hours is the correct value and does not need to be altered.

Literature-based recommended dosing

Conventional dosing

- Recommended doses for conventional dosing in patients with normal renal function are

3–5 mg/kg/d for gentamicin and tobramycin

4–6 mg/kg/d for netilmicin

15 mg/kg/d for amikacin

- These amounts are divided into three equal daily doses for gentamicin, tobramycin, or netilmicin, or two or three equal daily doses for amikacin.

Literature-based recommended dosing

- **Extended-interval doses** for patients with normal renal function are

4–7 mg/kg/d for gentamicin

4–7 mg/kg/d for tobramycin

4–7 mg/kg/d for netilmicin

11–20 mg/kg/d for amikacin

Use of Aminoglycoside Serum Concentrations to Alter Dosages

1. ***Linear pharmacokinetics***
2. ***Pharmacokinetic concepts***
3. ***Sawchuk-Zaske method***

Linear Pharmacokinetics Method

$$D_{new} / Css_{new} = D_{old} / Css_{old}$$

Or

$$D_{new} = (Css_{new} / Css_{old}) D_{old}$$

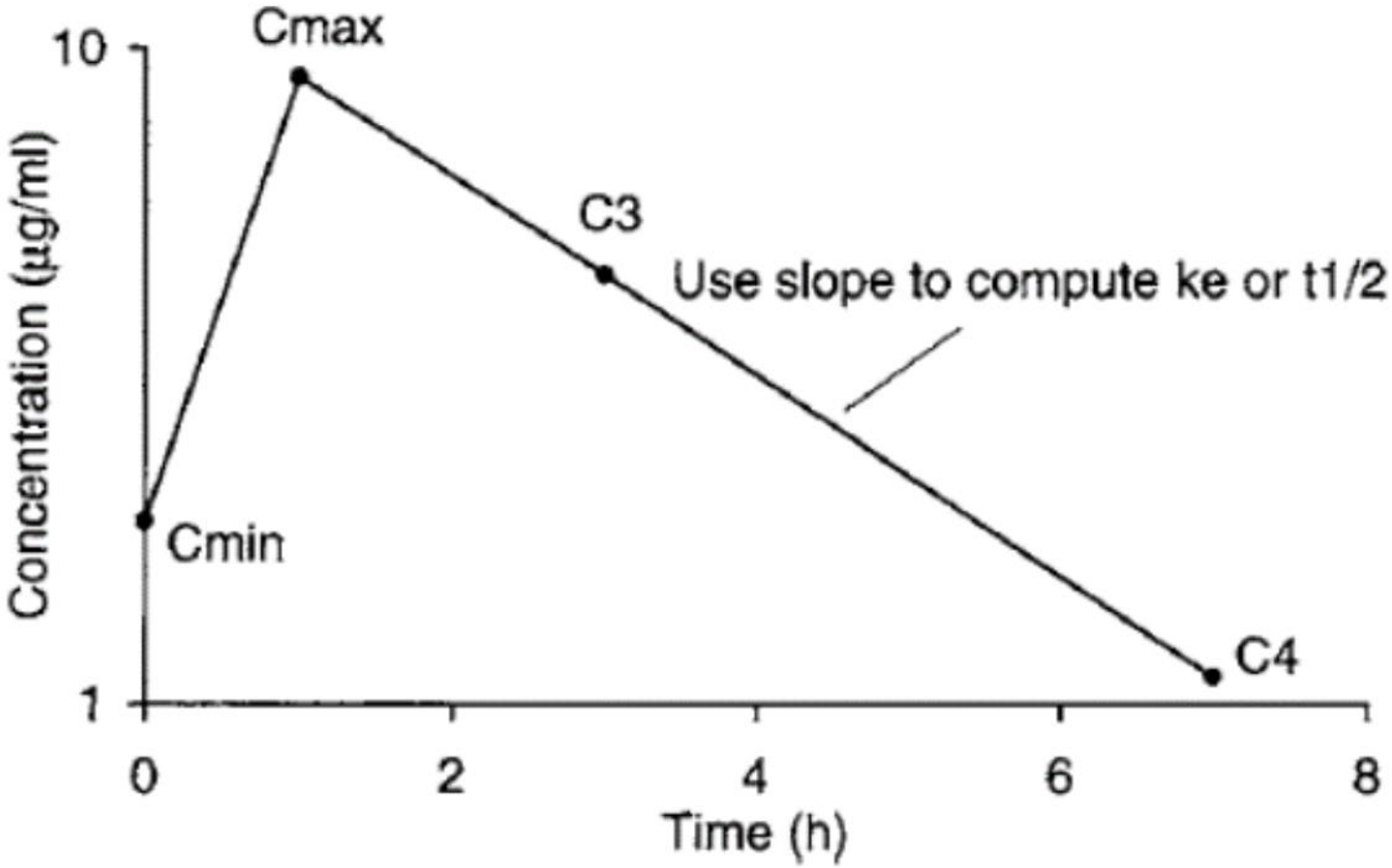
D is the dose, Css is the steady-state peak or trough concentration

Sawchuk-Zaske Method

The **Standard** Sawchuk-Zaske method

Conducts a small pharmacokinetic experiment using 3–4 aminoglycoside serum concentrations obtained during a dosage interval and does not require steady-state conditions.

The Standard Sawchuk-Zaske method



The Standard Sawchuk-Zaske method

Calculations:

1. ***Calculate actual Ke***

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

- Where C_1 and C_2 are postdose serum concentrations and Δt is the time that expired between the times that C1 and C2 were obtained

2. ***Calculate actual half-life*** can be computed using Ke

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

The Standard Sawchuk-Zaske method

3. Calculate actual Vd

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e\,[C_{max} - (C_{min} e^{-k_e t'})]}$$

D: aminoglycoside dose, t′:infusion time, ke: elimination rate constant, C_{max}: peak concentration, C_{min}: trough concentration

The Standard Sawchuk-Zaske method

4. Use the actual Vd and Ke to calculate new dosage regimen after determination of C_{max} and C_{min} according to the question

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR K_0), AND LOADING DOSE (LD) EQUATIONS
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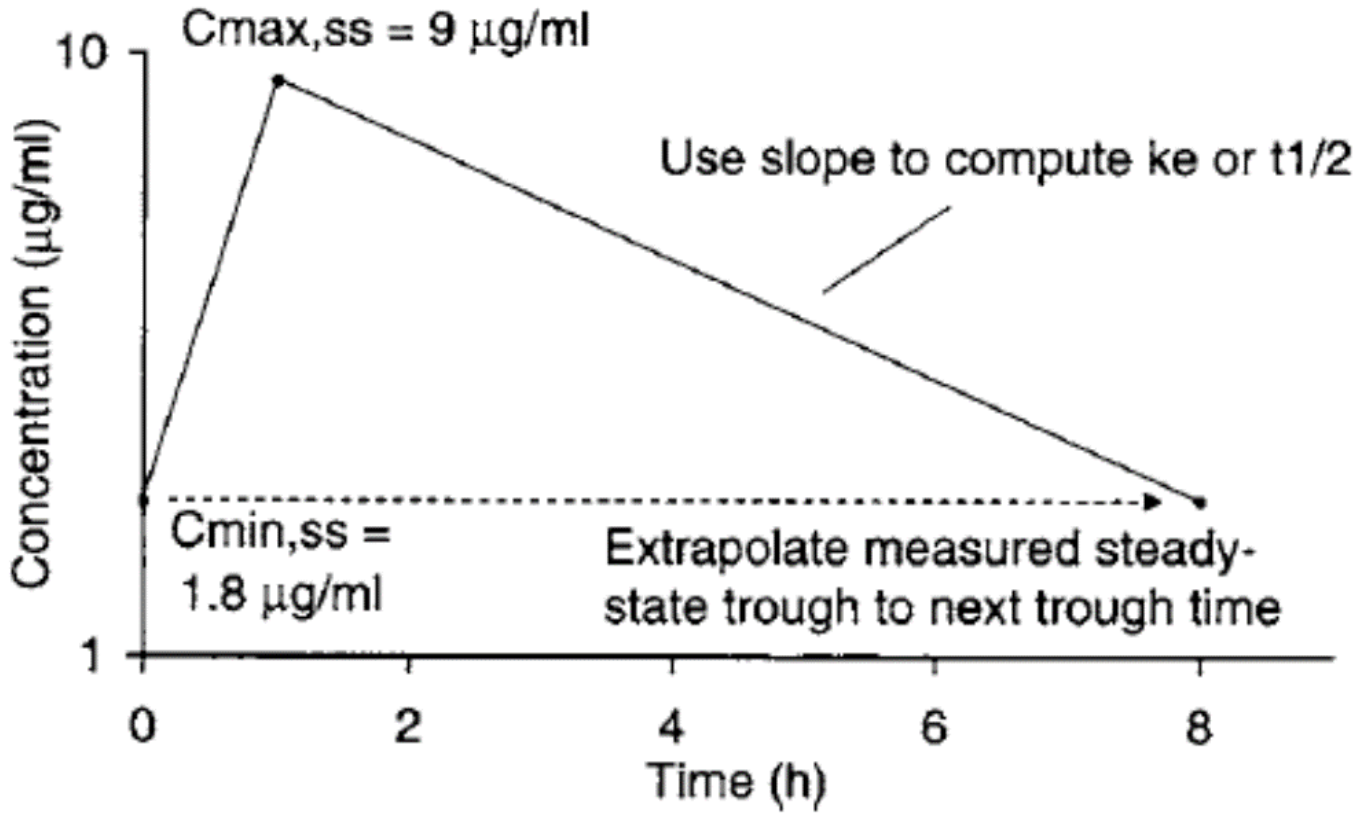
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$ $LD = k_0 / (1 - e^{-k_e\tau})$

The Modified Sawchuk-Zaske methods

I. **PEAK/TROUGH VERSION** at steady state

- If a steady-state peak and trough aminoglycoside concentration pair is available for a patient, the Sawchuk-Zaske method can be used to compute patient pharmacokinetic parameters and aminoglycoside doses.

The Modified Sawchuk-Zaske methods



The Modified Sawchuk-Zaske methods

Calculations

1. Use C_{max} and C_{min} to calculate actual Ke and Vd

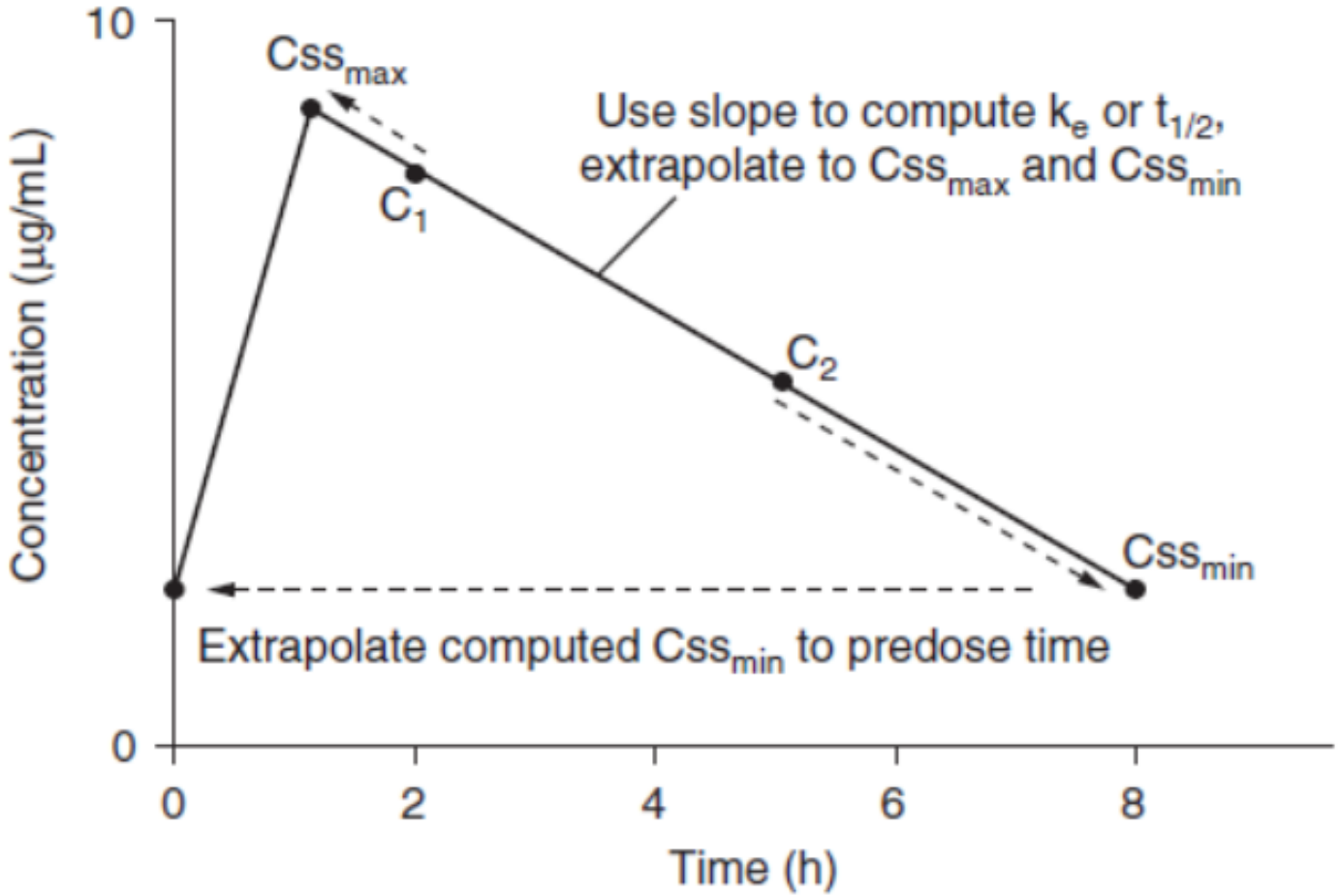
$$Ke = (\ln C_1 - \ln C_2) / \Delta t$$

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e\,[C_{max} - (C_{min}\, e^{-k_e t'})]}$$

2. Use the actual Vd and Ke to calculate new dosage regimen after determination of C_{max} and C_{min} according to the question

The Modified Sawchuk-Zaske methods

II. STEADY-STATE SAWCHUK-ZASKE METHOD: two postdose concentrations version



The Modified Sawchuk-Zaske methods

Calculations

1. Use C_1 to calculate C_{max}:

$$Css_{max} = C_1 / (e^{-ket})$$

2. Use C_2 to calculate C_{min} :

$$Css_{min} = C_2 \, e^{-ket}$$

3. Use any of 2 concentrations like C_1, C_2, C_{max}, C_{min} to calculate actual Ke

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

The Modified Sawchuk-Zaske methods

4. Use Cmax, Cmin to calculate actual Vd

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e\,[Css_{max} - (Css_{min}\, e^{-k_e t'})]}$$

5. Use the actual Vd and Ke to calculate new dosage regimen after determination of Cmax and Cmin according to the question


Any Questions?