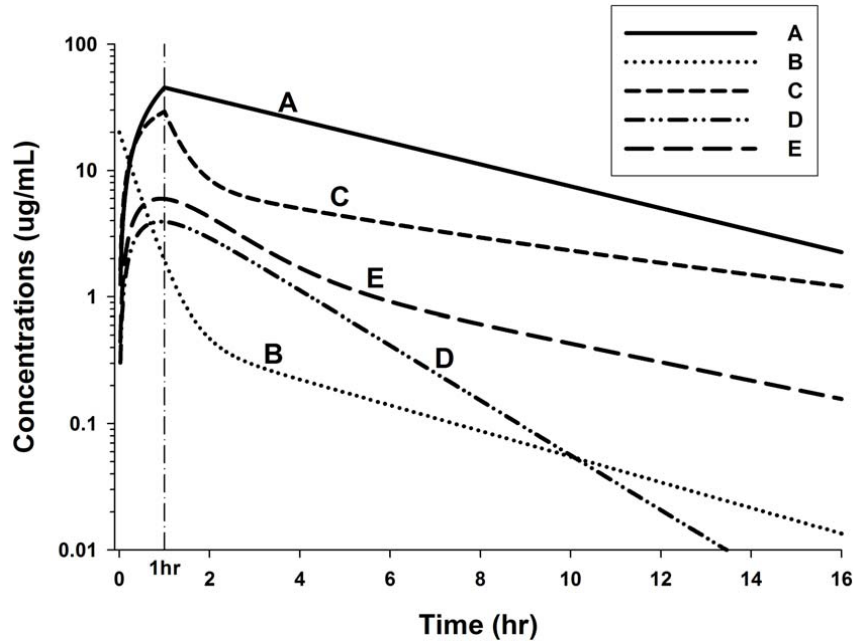


#1) Vancomycin concentration-time profiles can be described via a three-compartment model. Which profile will represent a 1-hour infusion of vancomycin in the following graph? Please provide an explanation for your answer choice.



A)

B)

C) The only 1-hour infusion profiles are choices A & C. Profile A shows a straight line on a semi-log scale after the time-point 1 hour that indicates a one-compartment model. Therefore, the remaining choice is C.

D)

E)

#2) Please select the correct statement(s) concerning oral drug administration

- 1 The elimination rate constant (k_e) can always be determined from concentrations at late time points (after C_{max}).
- 2 The absorption rate constant can be determined from the concentration-time profile (if no flip flop).
- 3 The oral bioavailability (F) of a low extraction drug can be changed by CYP-P450 enzyme induction.
- 4 Using extended release tablets will reduce the fluctuation compared to immediate release tablets (same dose, same dosing interval).
- 5 Clearance (CL) and volume of distribution (V_d) for two drugs, showing the same AUC (same dose), are identical.

- A) 1, 2, 3
- B) 2, 3, 4, 5
- C) 2, 3, 4
- D) 1, 3, 5
- E) None of the above**

1 The elimination rate constant (k_e) can always be determined from concentrations at late time points (after C_{max}).

False: In case of flip flop kinetics, the final slope characterizes k_a .

2 The absorption rate constant can be determined from the concentration-time profile (if no flip flop).

True: "Method of Residuals" (Feathering)

3 The oral bioavailability (F) of a low extraction drug can be changed by CYP-P450 enzyme induction.

$$F = 1 - E_H = \frac{Q_H}{Q_H + f_u \cdot Cl_{int}}$$

False: since $Q_H \gg f_u \cdot Cl_{int}$

$$\Rightarrow F = 1$$

\Rightarrow enzyme induction does not matter

4 Using extended release tablets will reduce the fluctuation compared to immediate release tablets (same dose, same dosing interval).

True: C_{max} and C_{min} are coming closer together \rightarrow Fluctuation gets smaller

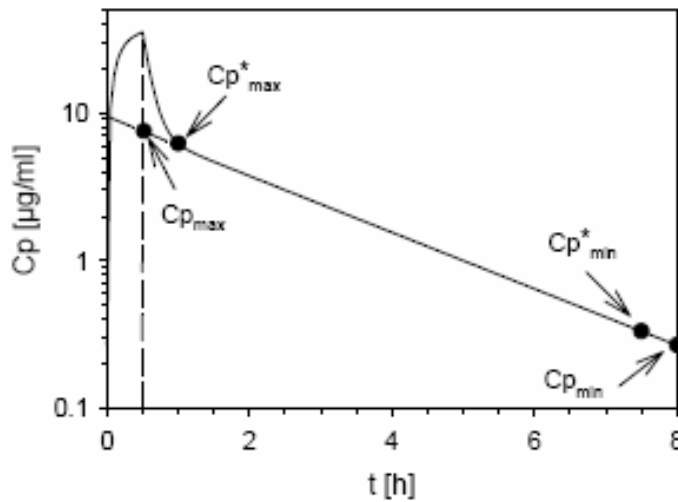
5 Clearance (CL) and volume of distribution (V_d) can be calculated from Dose and AUC only.

False: $AUC_{\infty} = \frac{Dose \cdot F}{Cl_{tot}}$

$$\frac{Cl}{F} = k_e \cdot \frac{V_d}{F} \rightarrow \text{They can change with bioavailability}$$

#3) W.G. is a 5' 4", 72 kg, 30 year old female who suffered a severe burn that has since been infected by S. aureus. To treat her infection she is given an aminoglycoside by a half hour infusion every 8 hours. She is given an infusion starting at 8:00 am. At 9:00 am a plasma sample is taken and yields a Cp^*_{max} of 10.2 $\mu\text{g/ml}$. Another sample is taken at 3:30 pm to give a Cp^*_{min} of 1.4 $\mu\text{g/ml}$. Please explain why the samples are not taken at 8:30 am and 4 pm and calculate the true C_{max} and C_{min} values. (Aminoglycosides exhibit two-compartment body-model kinetics.)

PHA 5127 Fall 2007
Case Study #1



Gentamicin, along with the other aminoglycosides, undergoes a distribution phase after administration. This means that it takes time for the drug to distribute to the tissues. If the peak concentration were taken immediately after the infusion the elimination rate constant calculated would be too high and the half-life would be shorter than it actually is. This can lead to an erroneous interpretation and underestimate the risk or potential toxicity.

The blood draw 30min before the next dose is more a practical issue than of clinical concern. Since it is oftentimes hard to give the next dose and drawn blood samples at the same time, blood samples are simply taken earlier (usually 30min) and trough values calculated.

First we need to calculate k_e :

$$k_e = \frac{\ln \frac{C_{\max}^*}{C_{\min}^*}}{t_{\min}^* - t_{\max}^*} = \frac{\ln \frac{10.2 \frac{\mu\text{g}}{\text{mL}}}{1.4 \frac{\mu\text{g}}{\text{mL}}}}{(15:30 - 9:00)\text{h}} = 0.31\text{h}^{-1}$$

In order to determine the true C_{\max} and C_{\min} values, we use the slope of the linear regression line (k_e) to calculate concentrations at 8:30 am and 2:00pm, respectively.

$$C_{\max}^* = C_{\max} * \exp^{-k_e * t} \leftrightarrow C_{\max} = \frac{C_{\max}^*}{\exp^{-k_e * t}} = \frac{10.2 \frac{\mu\text{g}}{\text{mL}}}{\exp^{-0.31\text{h}^{-1} * 0.5\text{h}}} = 11.91 \frac{\mu\text{g}}{\text{mL}}$$

$$C_{\min} = C_{\min}^* * \exp^{-k_e * t} = 1.4 \frac{\mu\text{g}}{\text{mL}} * \exp^{-0.31\text{h}^{-1} * 0.5\text{h}} = 1.12 \frac{\mu\text{g}}{\text{mL}}$$

#4) *Please select the correct statement(s) concerning one/two-compartment body models.*

- 1 For a two-compartment-body model drug, the parameter alpha is always larger than the parameter beta.
- 2 The volume of distribution during the beta phase is larger than that of the volume of distribution at steady state.
- 3 We often use one compartment model pharmacokinetics, although a number of drugs show a distinct distribution phase, especially if the higher concentrations during the alpha phase are not related to toxicity.
- 4 Assume that a low extraction drug, showing a one compartment model behavior is metabolized via enzymes that are subject to enzyme induction by other drugs. The volume of distribution might be decreased by such enzyme-inducers.

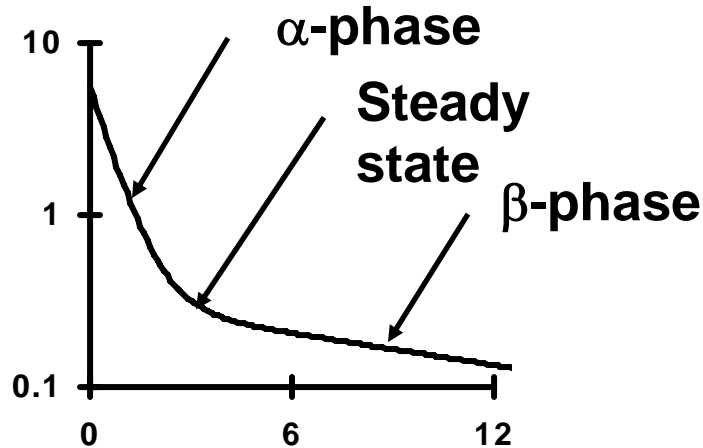
A) 1, 2

B) 2, 4

C) 1, 3, 4

D) 1, 2, 3

None of the above



In a two-compartment model the steeper phase is called the α -phase. Thus, the parameter characterizing the slope of the α -phase (feathering) is bigger than the one characterizing the β -phase.

→ #1 is correct

$$Vd_c < Vd_{ss} < Vd_{area}$$

→ #2 is correct

For many drugs, this alpha-phase is very short (in minutes) and the concentration time profile can be handled like a one compartment body model drug. However, do not make the mistake of taking blood samples for TDM during the alpha phase!

→ #3 is correct

Clearance and volume of distribution are independent of each other (in a one-compartment body model!) – k_e as a fudge factor.

→ #4 is NOT correct