

## Questions

1. Basic PK (5 points)
2. Basic PK (5 points)
3. Aminoglycosides – Amikacin (10 points)
4. Aminoglycosides – Gentamicin (10 points)
5. Antibiotics (5 points)
6. Vancomycin (5 points)
7. Aminoglycosides – Gentamicin (10 points)
8. Basic PK (10 points)
9. Pediatrics/Geriatrics (5 points)
10. Vancomycin (5 points)
11. Aminoglycosides – Gentamicin (10 points)
12. Basic PK (5 points)
13. Basic PK (5 points)
14. Basic PK (5 points)
15. Aminoglycosides – Gentamicin (5 points)

Total Points: 100

### Question 1 (5 points)

A decrease in plasma protein binding will affect the pharmacokinetic profile of a low-extraction drug, keeping all other parameters unchanged:

- A.  $\uparrow CL$        $\downarrow V_d$        $\downarrow AUC$
- B.  $\downarrow CL$        $\uparrow V_d$        $\uparrow AUC$
- C.  $\downarrow CL$        $\leftrightarrow V_d$        $\leftrightarrow AUC$
- D.  $\uparrow CL$        $\leftrightarrow V_d$        $\downarrow AUC$
- E.  $\uparrow CL$        $\uparrow V_d$        $\downarrow AUC$

Answer: E

$$CL = Q \times E = \frac{Q \times CL_{int} \times f_u}{Q + CL_{int} \times f_u}$$

$$Q \gg CL_{int} \times f_u$$

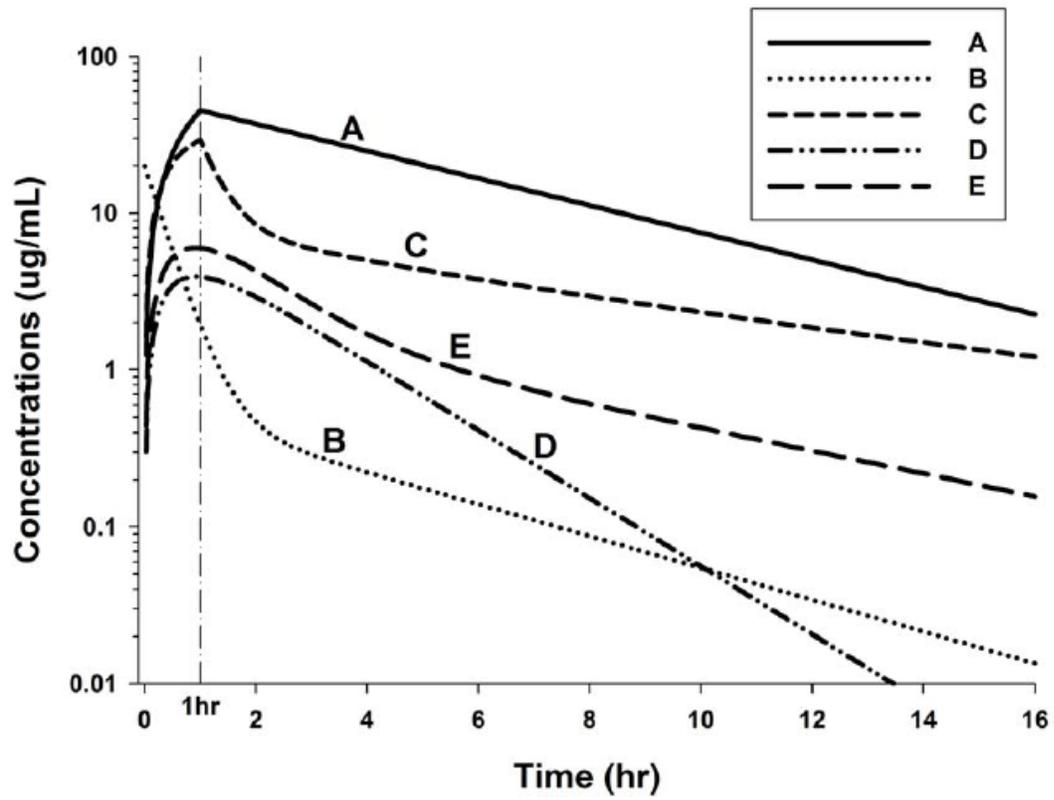
$$CL = f_u \times CL_{int} \uparrow$$

$$V = V_p + V_T \frac{f_u}{f_{uT}} \uparrow$$

$$AUC = \frac{Dose \times F}{CL} = Dose \times \frac{Q}{Q + CL_{int} \times f_u} \times \frac{Q + CL_{int} \times f_u}{Q \times CL_{int} \times f_u} = \frac{Dose}{CL_{int} \times f_u} \downarrow$$

**Question 2 (5 points)**

Drug X concentration-time profile can be described by a two-compartment body model. Which profile will represent a 1-hr infusion of Drug X in the following graph?



- A.
- B.
- C.
- D.
- E.

Answer: C

### Question 3 (10 points)

Design a dosing regimen of amikacin to achieve a steady-state true peak concentration of 25 mg/L and concentration of 5 mg/L at 12 h after the start of dosing, assuming a twice-daily regimen via IV infusion of 0.5 hour for a specific patient: male, 45 years of age, 5'6" in height, 198 lbs. Use amikacin  $V_d = 0.25L/kg$  and estimate  $k_e$  from the slope.

- A. 400 mg q12h
- B. 200 mg q12h
- C. 700 mg q24h
- D. 100 mg q8h
- E. 400 mg q8h

Answer: A

$$IBW_{male} = 50 + 2.3(66 - 60) = 63.8 \text{ kg}$$

Weight of 198 is equivalent to 90 kg.

$$TBW = \frac{198}{2.2} = 90 \text{ kg} > 120\% IBW = 76.8 \text{ kg}$$

Volume of distribution of amikacin can be estimated from the adjusted body weight, since the patient is obese.

$$V_d = 0.25[IBW + 0.38(TBW - IBW)] = 0.25[63.8 + 0.38(90 - 63.8)] = 18.4 \text{ L}$$

$$k_e = -\frac{\ln(25) - \ln(5)}{0 - 11.5} = 0.14 \text{ h}^{-1}$$

$$V_d = \frac{Dose}{k_e T} \cdot \frac{(1 - e^{-k_e T})}{Cp_{max} - (Cp_{min})e^{-k_e T}} \rightarrow \frac{Dose}{0.14 * 0.5} \cdot \frac{1 - \exp(-0.14 * 0.5)}{25 - 5 \exp(-0.14 * 0.5)} = 18.4 \text{ L}$$

$$Dose = 387 \sim 400 \text{ mg}$$

#### Question 4 (10 points)

Design a dosing regimen (dose and dosing interval) for gentamicin to achieve steady state peak and trough concentrations of 20 mg/L and 6 mg/L, respectively, assuming a short-term infusion of 2 hour infusion duration. The approximation for gentamicin volume of distribution is 0.25 L/kg. The patient characteristics are: male, 25 years of age, 5'11", 195 lbs, serum creatinine is 1.5 mg/dL. Use Cockcroft-Gault equation to estimate the clearance of gentamicin. Round the dose to the nearest 100 mg. Use the Dettli's aminoglycoside  $k_e$  equation to estimate the dosing regimen.  $k_e = 0.00293CL_{cr} + 0.014$ , where  $CL_{cr}$  is in mL/min.

- A. 200 mg q12h
- B. 1200 mg q24h
- C. 400 mg q8h
- D. 100 mg q4h
- E. 500 mg q6h

Answer: E

$$IBW_{male} = 50 + 2.3(71 - 60) = 75.3 \text{ kg}$$

$$TBW = \frac{195}{2.2} = 88.6 \text{ kg} < 120\% IBW = 90.4 \text{ kg}$$

We can use the TBW to compute creatinine clearance

$$CL_{cr} = \frac{(140 - 25)88.6}{72 * 1.5} = 94.3 \text{ mL/min}$$

Converting the units for creatinine clearance,

$$CL_{gentamicin} = 94.3 \frac{\text{mL}}{\text{min}} * \frac{60 \text{ min/h}}{1000 \frac{\text{mL}}{\text{L}}} = 5.66 \frac{\text{L}}{\text{h}}$$

$$k_e = 0.00293 * 94.3 + 0.014 = 0.29 \text{ h}^{-1}$$

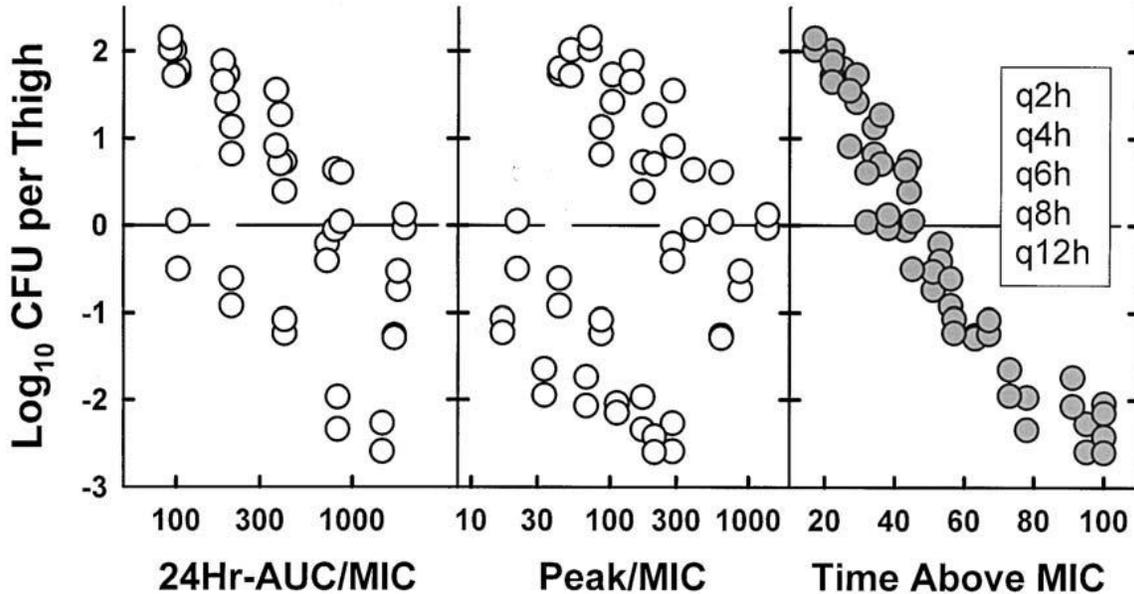
$$\tau = \frac{\ln\left(\frac{C_{max}}{C_{min}}\right)}{k_e} + T = \frac{\ln\left(\frac{20}{6}\right)}{0.29} + 2 \approx 6 \text{ h}$$

$$V_d = 0.25L/kg * 88.6 kg = 22.15 L$$

$$Dose = C_{\max(\text{desired})} k_e V_d T \frac{1 - \exp(-k_e \tau)}{1 - \exp(-k_e T)} = 20 \times 0.29 \times 22.15 \times 2 \times \frac{1 - \exp(-0.29 \times 6)}{1 - \exp(-0.29 \times 2)}$$
$$= 481 mg \sim 500 mg$$

**Question 5 (5 points)**

Which of the following statement(s) is/are **FALSE** of ceftazidime against *P. aeruginosa* in the thighs of neutropenic mice after 24 hours of therapy with multiple doses of ceftazidime using 2-, 4-, 6-, 8-, and 12-hourly dosing regimens. Each point represents data for one mouse. The y-axis represents the log-change in CFU after 24 h from the initial inoculum.



Data from Vogelmann B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetics parameters with therapeutic efficacy in an animal model. *J Infect Dis* 1988;158:831–47.

- Graphs show that Peak/MIC is most correlated with efficacy characterized by log<sub>10</sub> CFU per thigh. (F)
- Ceftazidime is bactericidal if the Time above MIC ratio is greater than 60% of the dosing interval. (T)
- The drug is bactericidal if you keep the concentration above MIC at all times. (T)
- The drug is bacteriostatic if the Time above MIC is at 20% of the dosing interval. (F)
- The pharmacodynamic index for ceftazidime is a time-dependent one. (T)

- ii, iii, v
- ii, iv, v
- i, iii, iv
- iii, iv, v
- i, iv

Answer: E

**Question 6 (5 points)**

With aminoglycosides, the  $C_{max}$  and  $C_{min}$  are calculated using IV infusion equations. However, with vancomycin it is acceptable to use IV bolus equations to calculate  $C_{max}$  and  $C_{min}$  instead of IV infusion equations. Why is it justified to use these equations with vancomycin compared to aminoglycosides?

- A. Vancomycin has a lower clearance which results in a smaller fluctuation.
- B. Vancomycin has a smaller volume of distribution which results in a larger fluctuation.
- C. Vancomycin has a longer half-life which results in a smaller fluctuation
- D. Vancomycin has a higher clearance which results in a larger half-life.
- E. Vancomycin has a smaller half-life which results in a smaller fluctuation.

Answer: C

### Question 7 (10 points)

M.D., a 29 years old female patient (5'2", 75kg, Serum creatinine =1.1mg/dL), needs to be treated with gentamicin. Assuming linear pharmacokinetics ( $V_d=0.25L/kg$ ,  $CL=CL_{cr}$ ) and an infusion time of 30 minutes. Calculate the TOTAL daily dose and dosing interval that will produce a steady state peak concentration of 10 mg/L and trough concentration of 1 mg/L. (Use  $k_e = CL/V_d$ ; use the same body weight for the approximation of  $V_d$  and  $CL_{cr}$ ).

- A. 180 mg, 6hr
- B. 140 mg, 8hr
- C. 440 mg, 8 hr
- D. 550 mg, 12 hr
- E. 600 mg, 12 hr

Answer: C

$$TBW = 75 \text{ kg}$$

$$5'2'' = 62''$$

$$IBW = 45.5 + 2.3 * (62-60) = 50.1 \text{ kg}$$

$$120\% \text{ IBW} = 60.12 \text{ kg}$$

$$TBW > 120\% \text{ IBW}$$

Therefore, ABW will be used for calculating creatinine clearance.

$$ABW = IBW + 0.4 * (TBW-IBW) = 50.1 + 0.4 * (75-50.1) = 60.06 \text{ kg}$$

$$CL_{Cr} = \frac{(140 - 29) * 60.06}{85 * 1.1} = 71.30 \frac{\text{ml}}{\text{min}} = 4.27 \text{ L/h}$$

$$V_d = 0.25 * ABW \text{ [L]}$$

$$V_d = .25 * 60.06 \text{ [L]}$$

$$= 15.02 \text{ L}$$

$$k_e = \frac{CL}{V_d} = \frac{4.27}{15.02} = 0.28 \text{ h}^{-1}$$

$$t_{1/2} = \frac{\ln(2)}{0.28} = 2.47 \text{ h}$$

$$\tau = \frac{\ln \frac{10}{1}}{0.28} + 0.5 = 8.7 \text{ h} \approx 8 \text{ h for a convenient dosing regimen}$$

$$\text{Dose}_{\text{daily}} = 3 * C_{\text{max}} * CL * T * \frac{(1 - e^{-k_e \tau})}{(1 - e^{-k_e T})} = 3 * 10 * 4.27 * 0.5 * \frac{(1 - e^{-0.28 * 8})}{(1 - e^{-0.28 * 0.5})} = 438.07 \text{ mg}$$

$\approx 440 \text{ mg}$

### Question 8 (10 points)

B.J., is a 30 years old male. He is currently taking 200 mg/day of drug X that has 40% renal elimination. Assuming that the renal clearance of the drug =  $CL_{cr}$ , how would you modify the dose, if the patient develops renal problems and his serum creatinine rises from 1 to 2.0 mg/dl?

- A. 160 mg/day
- B. 195 mg/day
- C. 260 mg/day
- D. 100 mg/day
- E. 280 mg/day

Answer: A

$$C_{ss} = \frac{D_{old}}{CL_{old}} = \frac{D_{new}}{CL_{new}}$$

$$\therefore D_{new} = D_{old} * \frac{CL_{new}}{CL_{old}}$$

$$\frac{CL_{new}}{CL_{old}} = \frac{CL_{NR} + CL_{cr\ new}}{CL_{NR} + CL_{cr\ old}} = \frac{CL_{NR}}{CL_{NR} + CL_{cr\ old}} + \frac{CL_{cr\ new}}{CL_{NR} + CL_{cr\ old}}$$

$$= f_{NR} + \frac{CL_{cr\ old}}{CL_{cr\ old}} * \frac{CL_{cr\ new}}{CL_{NR} + CL_{cr\ old}}$$

$$= f_{NR} + f_R * \frac{CL_{cr\ new}}{CL_{cr\ old}}$$

$$\therefore D_{new} = D_{old} * \left( f_{NR} + f_R * \frac{CL_{cr\ new}}{CL_{cr\ old}} \right)$$

$$= 200 * \left( 0.6 + 0.4 * \frac{1.0}{2.0} \right)$$

$$= 160 \text{ mg /day}$$

**Question 9 (5 points)**

Which of the following statement(s) is/are TRUE?

- 1 The total body water (in % of body weight) in neonates is usually smaller than in adults
- 2 The glomerular filtration rate (GFR) in neonates is usually larger than in adults
- 3 The effect of body weight on volume of distribution does not depend on the lipophilicity of the drug
- 4 Aminoglycosides cannot pass membranes very well because of their low protein binding

- A. 1
- B. 2
- C. 3
- D. 4
- E. None of the above

**Answer: E**

**Question 10 (5 points)**

What is the pharmacokinetic parameter that should be monitored for vancomycin therapy to achieve the desired efficacy?

- A. Clearance
- B. AUC
- C. Peak concentration
- D.  $V_d$
- E. Trough concentration

**Answer: E**

**Question 11 (10 points)**

JS is a 70-year-old, 80 kg, 5'6" man with gram-negative sepsis. His serum creatinine is 1.5mg/dL and has been stable since hospital admission. Compute a gentamicin dosing regimen to provide a steady-state peak concentration of 9 µg/mL and a steady-state trough concentration of 1.5 µg/mL after short-term infusion (30min). Use the Dettli Equation to calculate  $k_e$ , ( $k_e=0.00293 \times CL_{cr} [mL/min] + 0.014 [h^{-1}]$ ); use the same body weight for the approximation of  $V_d$  and  $CL_{cr}$ .

- A. 200mg every 12 hours
- B. 140mg every 12 hours
- C. 180mg every 12 hours
- D. 180mg every 24 hours
- E. 140mg every 24 hours

**Answer: B**

$$IBW \text{ (male)} = 50 + 2.3 \times 6'' = 63.8 \text{ kg}$$

120% IBW = 76.56 kg < 80 kg = TBW, this is obese patient. So ABW is used.

$$ABW = IBW + 0.4 \times (TBW - IBW) = 63.8 + 0.4 \times (80 - 63.8) = 70.28 \text{ kg}$$

$$CL_{cr \text{ (male)}} = \frac{(140 - age) \times ABW}{72 \times Cp_{cr}} = \frac{(140 - 70) \times 70.28}{72 \times 1.5} = 45.55 \text{ mL/min} = 2.73 \text{ L/h}$$

$$K_e = 0.00293 \times 45.55 + 0.014 = 0.147 \text{ h}^{-1}$$

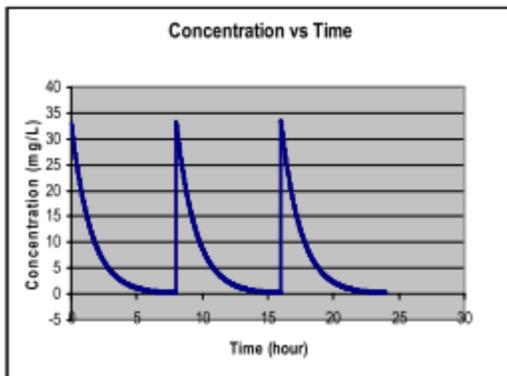
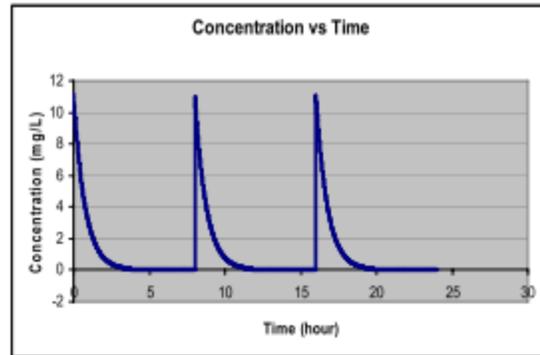
$$V_d = 0.25 \times ABW = 0.25 \times 70.28 = 17.57 \text{ L}$$

$$\tau = \frac{\ln\left(\frac{C_{max,desired}}{C_{min,desired}}\right)}{k_e} + T = \frac{\ln\left(\frac{9}{1.5}\right)}{0.147} + 0.5 = 12.69 \text{ h} \approx 12 \text{ h}$$

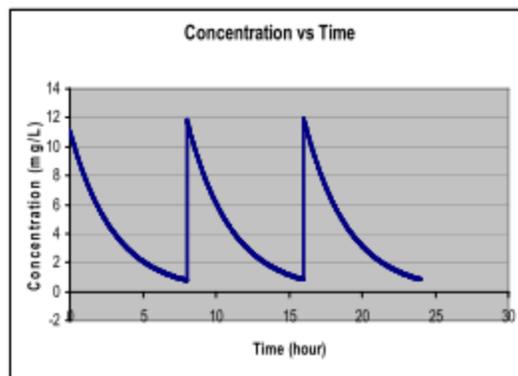
$$D = C_{max,desired} \times k_e \times V_d \times T \times \frac{1 - e^{-k_e \times \tau}}{1 - e^{-k_e \times T}} = 9 \times 0.147 \times 17.57 \times 0.5 \times \frac{1 - e^{-0.147 \times 12}}{1 - e^{-0.147 \times 0.5}} = 135.9 \text{ mg}$$

**Question 12 (5 points)**

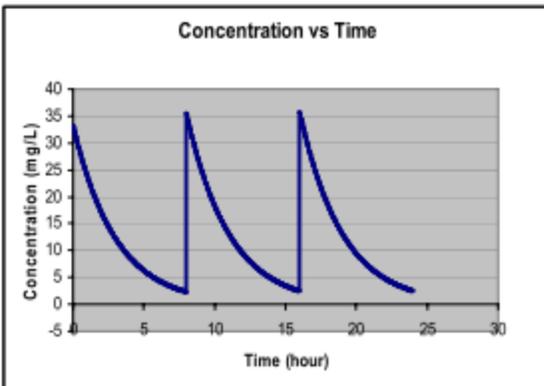
Drug X is given as i.v bolus of 200 mg (TID) dose. The concentration-time profile for the first three doses is shown. This patient has a clearance of 24L/hr (top graph). Another patient came in and was started on the same dosing regimen. However, this patient had a clearance 6 L/hr. What would his concentration-time profile look like for this patient? ( $V_d=18L$  for both patients)



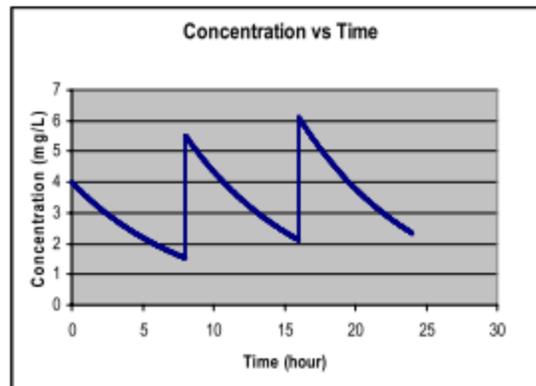
**A**



**B**



**C**



**D**

**Answer: B**

### Question 13 (5 points)

Select all TRUE statements.

- 1) Clearance can be thought of as a volume of plasma from which the drug is removed in a specific time period.
- 2) Given  $C_p = C_{p0} \cdot e^{-k_e \cdot t}$ , and two data points  $(t_1, C_{p1})$  and  $(t_2, C_{p2})$ , the elimination rate constant can be calculated as the slope  $[= (\ln C_{p2} - \ln C_{p1}) / (t_2 - t_1)]$  multiplied by -1.
- 3) If elimination from the central/body compartment is first order we can assume that a one compartment pharmacokinetic model is applicable
- 4) Appropriate unit for AUC is mg·hr·L.
- 5) If the infusion rate constant ( $k_0$ ) is doubled the steady state plasma concentration ( $C_{pss}$ ) will be doubled, assuming the other parameters are unchanged.

- A. 1, 2, 3
- B. 2, 3, 4
- C. 2, 3, 5
- D. 1, 3, 4
- E. 1, 2, 5

Answer: E

**Question 14 (5 points)**

Which of the following changes goes along with an increased clearance and no change in volume of distribution, assuming that the same dose of drug was administered in both situations? (5 points)

- A. shorter time to steady state, lower steady state concentration
- B. shorter time to steady state, higher steady state concentration
- C. shorter half-life, higher steady state concentration
- D. increased initial concentration after an i.v. bolus, longer time to steady state
- E. longer time to steady state, shorter half life

Answer: A

**Question 15 (5 points)**

H. K., a 70 kg female patient was given 60 mg gentamicin over 30 minutes (i.v. infusion) from 8:30 to 9:00 am. The following two serum levels were measured: 6.5 µg/mL at 9:30 am and 1.0 µg/ml at 4:00 pm. Calculate her peak concentration at 9:00 am.

- A. 7.0 µg/mL
- B. 7.2 µg/mL
- C. 7.5 µg/mL
- D. 8.2 µg/mL
- E. 8.6 µg/mL

Answer: C

$$k_e = \ln (6.5/1.0) / 6.5 \text{ h} = 1.8718 / 6.5 \text{ h} = 0.288 \text{ h}^{-1}$$

$$\text{the peak conc. at 9.00 AM is: } C_{\max} = 6.5 \text{ µg/mL} / (\exp(-0.288 \text{ h}^{-1} * 0.5 \text{ h})) = 7.51 \text{ µg/mL}$$