Due February 7th 2014

Please provide all answers with their appropriate units. 0.5 points will be deducted for each missing or inappropriate unit.

1) The pharmacokinetic profile of vancomycin after an intravenous bolus administration is best characterized by the two compartment model equation: \( \text{Conc} = A \exp(-\alpha t) + B \exp(-\beta t) \), where the concentration is in mg/L and time is in hour. \( A = 53 \) mg/L and \( B = 26 \) mg/L and the \( t_{1/2} \) for the \( \alpha \) and \( \beta \) phases are 5 hours and 9 hours respectively. Compute the area under the curve of vancomycin. MIC of vancomycin against the infection was estimated to be 1.5 ug/mL. Determine whether the AUC/MIC ratio is greater than 400. \( (\text{Hint: } AUC = \frac{A}{\alpha} + \frac{B}{\beta}) \)

\( \text{(2.5 points)} \)

We will compute the parameter values for \( \alpha \) and \( \beta \) using the equation \( k_e = \frac{\ln(2)}{t_{1/2}} \)

\[
\alpha = \frac{0.693}{5} = 0.138 \text{ } h^{-1}
\]

\[
\beta = \frac{0.693}{9} = 0.077 \text{ } h^{-1}
\]

\[
AUC = \frac{53}{0.138} + \frac{26}{0.077} = 721.72 \text{ } \frac{mg.h}{L}
\]

\[
\frac{AUC}{MIC} = \frac{721.72}{1.5} = 481.14
\]

The AUC/MIC ratio is greater than 400.
2) S.J., a 43 year old female, weighing 126 lbs, was started on 1000mg vancomycin administered as a 30 minute IV infusion q12h for the treatment of staphylococcal infection. Her vancomycin plasma concentrations measured 1.5 hours after the start of infusion and 15 minutes before the second dose were 39.4 mg/L and 12.3 mg/L respectively. Compute the elimination rate constant. What are the estimated steady state peak and trough vancomycin plasma concentrations for S.J.? (2.5 points)

Use the following equation to calculate the volume of distribution (Vd) for vancomycin.

\[ Vd = 0.17 \times \text{age} + 0.22 \times \text{TBW} + 15 \]

TBW = 126 lbs = 126 * 0.454 kg = 57.2 kg

Elimination rate constant:

\[ k_e = -\frac{\ln(39.4) - \ln(12.3)}{1.5 - 11.75} = 0.113 \text{ h}^{-1} \]

Volume of distribution:

\[ Vd = 0.17 \times \text{age} + 0.22 \times \text{TBW} + 15 = 0.17 \times 43 + 0.22 \times 52.7 + 15 = 34.9 \text{ L} \]

Steady-state peak concentration:

\[ C_{ss, max} = \frac{\text{Dose} \times (1 - e^{-k_eT})}{Vd \times k_e \times T \times (1 - e^{-k_e\tau})} = \frac{1000 \times (1 - e^{-0.113 \times 0.5})}{34.9 \times 0.113 \times 0.5 \times (1 - e^{-0.113 \times 12})} = 37.5 \text{ mg L}^{-1} \]

Steady-state trough concentration:

\[ C_{ss, min} = C_{ss, max} \times e^{-k_e(\tau - T)} = 37.5 \times e^{-0.113 \times (12 - 0.5)} = 10.2 \text{ mg L}^{-1} \]
3) Which of the following is true in case of the elderly population? (1 point)
   1) Extent of oral absorption is usually unaltered.
   2) Increased total body water and less fat tissue.
   3) $CP_{ss}^{free} = \frac{R_0}{Cl_{int}}$ for low extraction drugs, therefore unbound plasma concentration remains unchanged but total plasma concentration will change with changes in protein binding.
   4) No change in liver blood flow and liver mass.
   5) $CP_{ss}^{free} = \frac{f_u \cdot R_0}{Q}$ for high extraction drugs, therefore total plasma concentration remains unchanged but unbound plasma concentration will change with changes in protein binding.
   6) There is age related increase in the volume of distribution of many hydrophilic drugs.

A) 1, 4, 5
B) 1, 2, 6
C) 3, 5, 1
D) 3, 2, 5
E) None of these

Answer: C

1) True
2) False
Decreased total body water and more fat tissue.
3) True
4) False
Decrease in liver blood flow and liver mass.
5) True
6) False
There is age related decrease in the volume of distribution of many hydrophilic drugs.
4) B.R., a 65 year old male, is 5’5” tall, weighs 61 kg and has a serum creatinine of 0.9 mg/dL. He was started with 1000 mg vancomycin by one hour IV infusion administration q12h for the treatment of MRSA infection. During the course of his therapy his serum creatinine level increased by 25%. Use the nomogram to adjust his dosing regimen based on his increased serum creatinine level. Calculate the steady state peak and trough concentrations of vancomycin based on the adjusted dosing regimen for an IV bolus administration. Is the therapeutic goal attained with the new dosing regimen (i.e. is the steady-state trough concentration less than 20mg/L and between 15 and 20mg/L)? If the therapeutic goal is not attained then compute a dosing regimen for B.R. for IV bolus administration to achieve a desired steady-state peak concentration of 45 mg/L and trough concentration of 15 mg/L. (3 points)

Vancomycin is primarily eliminated by the kidneys.
Vancomycin CL \( \approx CL_{Cr} \)
TBW = 61 kg
5’5” = 65”
IBW = 50 + 2.3 * (65 – 60) = 61.5 kg
120%IBW = 73.8 kg
TBW < 120%IBW
Therefore total body weight will be used for calculation of clearance.

\[
CL_{Cr\ (male)} = \frac{(140-65)*61}{72+0.9} = 70.6 \text{ mL/min} = 4.2 \text{ L/h}
\]

New \( CL_{Cr\ (male)} = \frac{(140 - 65) * 61}{72 * 1.25 * 0.9} = 56.5 \text{ mL/min} = 3.4 \text{ L/h} \]
Based on the nomogram, B.R.’s dosing regimen needs to be adjusted. His new vancomycin dosing regimen based on the nomogram is **500 q12h**

\[ V_d = 0.17 \times \text{age} + 0.22 \times \text{TBW} + 15 = 0.17 \times 65 + 0.22 \times 61 + 15 = 39.5 \text{ L} \]

\[
ke = \frac{\text{New CL}}{V_d} = \frac{3.4}{39.5} = 0.086 \text{ h}^{-1}
\]

**Steady-state peak concentration for 500 q12h dosing:**

\[
CSS_{\text{max}} = \frac{\text{Dose}}{V_d(1 - e^{-ke\tau})} = \frac{500}{39.5(1 - e^{-0.086 \times 12})} = 19.7 \text{ mg/L}
\]

**Steady-state trough concentration 500 q12h dosing:**

\[
CSS_{\text{min}} = CSS_{\text{max}} \times e^{-ke\tau} = 19.7 \times e^{-0.086 \times 12} = 7.02 \text{ mg/L}
\]

Based on this dosing regimen, the steady-state trough concentration falls below 15mg/L. Therefore the therapeutic goal is not attained.

Dosing interval computation for attaining a steady-state peak and trough concentrations of 45mg/L and 15mg/L respectively:

\[
\tau = \frac{\ln \frac{45}{15}}{0.086} = 12.77 \text{ h} \approx 12 \text{ h} \text{ for a convenient dosing regimen}
\]

\[
\text{Dose} = V_d \times CSS_{\text{max}} \times (1 - e^{-ke\tau})
\]

\[
= 39.5 \times 45 \times (1 - e^{-0.086 \times 12})
\]

\[
= 1144.2 \text{ mg} \approx 1200 \text{ mg for convenience of dose administration}
\]

B.R.’s vancomycin dosing regimen should be adjusted to **1200 q12h**
5) Which of the following statements is/are incorrect about vancomycin pharmacokinetics and pharmacodynamics? (1 point)

1) AUC/MIC is a predictive pharmacokinetic parameter for vancomycin.
2) Peak plasma concentrations are monitored for vancomycin efficacy and dose adjustments.
3) Vancomycin exhibits concentration-dependent killing
4) Vancomycin has good oral absorption
5) Vancomycin is 80-90% eliminated by kidneys and has good tissue penetration except in bile, eye and noninflamed meninges.
6) Conventional dosing strategies fail when MIC ≥ 2

A) 1, 2, 4
B) 3, 4, 6
C) 1, 2, 3
D) 2, 3, 4
E) 1, 3, 5

Answer: D

1) True
2) False
   Trough concentrations are monitored for vancomycin efficacy and dose adjustments.
3) False
   Vancomycin exhibits time-dependent killing.
4) False
   Vancomycin has poor oral absorption.
5) True