PHA 5128

Exam 1

Spring 2013

1. Antibiotics (5 points)
2. Body Weight/Pediatrics (5 points)
3. Renal Disease (10 points)
4. Aminoglycosides (5 points)
5. Amikacin (10 points)
6. Gentamicin (10 points)
7. Aminoglycosides (5 points)
8. Bioavailability (10 points)
9. Basic Principles (10 points)
10. Basic Principles (5 points)
11. Basic Principles (10 points)
12. Basic Principles (5 points)
13. Antibiotics (5 points)
14. Aminoglycosides (5 points)
**Problem 1 (5 points)**

An antibiotic pharmacokinetic behavior is best described by a 2-compartment model. The drug is administered as an intravenous bolus and its pharmacokinetic profile is best characterized by the following equation,

\[ C(t) = 20 \times e^{-0.135t} + 18 \times e^{-0.067t} \]

where the concentration is in mg/L and time is in hour. Estimate the area under the curve and determine whether the AUC/MIC ratio is greater than 400 if the MIC against the infection is 2 mg/L.

Use the following equation to compute the AUC

\[ AUC = \frac{A}{\alpha} + \frac{B}{\beta} \]

A. AUC = 432 mg*h/L; AUC/MIC ratio is greater than 400
B. AUC = 834 mg*h/L; AUC/MIC ratio is greater than 400
C. AUC = 417 mg*h/L; AUC/MIC ratio is greater than 400
D. AUC = 208 mg*h/L; AUC/MIC ratio is less than 400
E. AUC = 417 mg*h/L; AUC/MIC ratio is greater than 400

\[
AUC = \frac{A}{\alpha} + \frac{B}{\beta} = \frac{20}{0.135} + \frac{18}{0.067} = 417 \text{ mg} \times \text{h/L}
\]

\[
\frac{AUC}{MIC} = \frac{417}{2} = 208
\]
Problem 2 (5 points)

Which of the following statements about body weight are TRUE?

(1) Obese patients may experience an overdose of a weakly or moderately lipophilic drug compared to a patient with ideal body weight if the total body weight based dosing approach is used, since they are poorly distributed in obese patients.

(2) The total body water (in % of body weight) in neonates is usually smaller than that in adults.

(3) Lipophilic drugs tend to have a larger volume of distribution when given to patients with an increased body weight compared to patients with an ideal body weight.

(4) The plasma protein binding of drugs in neonates is usually less than in adults.

A. 1&2&3
B. 2&4
C. 3&4
D. **1&3&4**
E. All the statements are correct
**Problem 3 (10 points)**

After measuring her serum creatinine concentration, you calculate the creatinine clearance of a 20 year old female patient (60 kg, 165 cm) to be 6 L/h. What is her serum creatinine concentration?

A. 14.12 mg/dL  
B. 0.85 mg/dL  
C. 14.12 µg/dL  
D. 0.85 µg/dL  
E. The information provided is not enough to answer the question

**Calculation:**

IBW = 45 + 0.9(165 - 150) = 45 + 0.9(15) = 45 + 13.5 = 58.5 kg

TBW

\[
\frac{TBW}{IBW} = \frac{60}{58.5} \times 100\% = 102.6\% < 120\%
\]

Since TBW is less than 120% of IBW, we should use TBW as dosing weight to calculate creatinine clearance.

CLcr = 6 L/h = 100 mL/min

\[
Cp_{cr} = \frac{(140 - \text{age}) \times BW}{CL_{cr} \times 85} = \frac{(140 - 20) \times 60}{100 \times 85} = 0.85 \text{ mg/dL}
\]
Problem 4 (5 points)

J.C. is a 57 kg female patient with methicillin-resistant *S. aureus* infection. Which of the following would be a recommended dosing regimen if the tobramycin plasma concentration was 8mg/L at 8 hours after the start of the infusion? Please assume average population PK parameters for J.C. and use the nomogram that is given below.

![ODA Nomogram for Gentamicin and Tobramycin at 7 mg/kg](image)

A. 400mg Q24h  
B. 500mg Q24h  
C. **400mg Q36h**  
D. 500mg Q36h  
E. 400mg Q48h
Problem 5 (10 points)

A 9-year-old boy is hospitalized with possible bacterial infection. 500 mg amikacin (IV infusion for 45 min, Q12h) was given for several days. The dosing time is 8 am and 8 pm. His plasma samples at steady state were analyzed and the results are listed as follows:

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 am</td>
<td>30 µg/mL</td>
</tr>
<tr>
<td>6:30 pm</td>
<td>4 µg/mL</td>
</tr>
</tbody>
</table>

Calculate the volume of distribution (round appropriately).

A. 12 L
B. 16 L
C. 20 L
D. 24 L
E. 30 L

\[
k_e = \frac{\ln C_{\text{max}}^*}{\Delta t} = \frac{\ln \frac{30}{4}}{9.5} = 0.212 h^{-1}
\]

\[t_1=0.25h, \ t_2=1.5h\]

\[C_{\text{max}} = \frac{C_{\text{max}}^*}{e^{-k_{t_1}}} = \frac{30}{e^{-0.212\times0.25}} = 31.6 \mu g/ml\]

\[C_{\text{min}} = C_{\text{min}}^* \times e^{-k_{t_2}} = 4.0 \times e^{-0.212\times1.5} = 2.9 \mu g/ml\]

\[V_d = \frac{Dose \times (1-e^{-k_{T}})}{k_e \times T \times (C_{\text{max}} - C_{\text{min}} \times e^{-k_{T}})} = \frac{500 \times (1-e^{-0.212\times0.75})}{0.212\times0.75 \times (31.6 - 2.9 \times e^{-0.212\times0.75})} = 15.9 L\]
Problem 6 (10 points)

A 40 year old female patient, who suffers from post-surgical wound infection, has been treated with gentamicin for several days. She is 5’2” tall and 55 kg weight. Her serum creatinine is 1.5 mg/dL. The gentamycin is given by IV infusion over 30 min with dose of 7mg/kg once daily.

Calculate the measured peak concentration one hour after the infusion was started? (Round appropriately)

A. Cmax=15 mg/L  
B. Cmax=20 mg/L,  
C. Cmax=25 mg/L  
D. Cmax=30 mg/L  
E. Cmax=35 mg/L

IBW=45+2.3(height in inches-60)=45+2.3(62-60)=45+4.6=49.6 kg

\[
\frac{TBW}{IBW} = \frac{55}{49.6} \times 100\% = 110.9\% < 120\%
\]

Since TBW is smaller than 120% of IBW, TBW will be used to calculate creatinine clearance

\[
CL \approx CL_{cr} = \frac{(140 - age) \times BW}{Cp_{cr} \times 85} = \frac{(140 - 40) \times 55}{1.5 \times 85} = 43.1 ml/min = 2.6 L/h
\]

\[
Vd = 0.25 L/kg \times 55kg = 13.75L
\]

\[
k_e = \frac{CL}{Vd} = \frac{2.6}{13.75} = 0.189 h^{-1}
\]

\[
\tau = 24h \text{ and } T=0.5h
\]

\[
C_{max} = \frac{Dose}{Vd \times k_e \times T \times \left(\frac{1 - e^{-k_e \cdot \tau}}{1 - e^{-k_e \cdot T}}\right) \times \left(\frac{1 - e^{-0.189 \times 24}}{1 - e^{-0.189 \times 0.5}}\right)} = 27.0 mg/L
\]

\[
t_1 = 0.5h,
\]

\[
C_{max}^* = C_{max} \times e^{-k_e \cdot t_1} = 27.0 \times e^{-0.189 \times 0.5} \approx 25 mg/L
\]
Problem 7 (5 points)

Which of the following statements about aminoglycosides are TRUE?

1. The volume of distribution of aminoglycosides is usually 0.25 L.
2. Aminoglycosides are mostly cleared by the kidney.
3. Therapeutic drug monitoring is not recommended for aminoglycosides.
4. Three times daily dosing is highly recommended for aminoglycosides.
5. A patient’s creatinine clearance can be used to estimate his total systemic clearance.

A. 1&2&5  
B. 1&3&4  
C. 2&5  
D. 1&5  
E. All the statements are correct
Problem 8 (10 points)

Based on the table of pharmacokinetic parameters obtained after a 50 mg dose of drug A, please calculate the bioavailability of drug A for the three age groups.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>CL (L/h)</th>
<th>T_{1/2} (h)</th>
<th>Oral AUC (mg·h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>42.5</td>
<td>21</td>
<td>0.35</td>
</tr>
<tr>
<td>40-59</td>
<td>35.7</td>
<td>29</td>
<td>0.47</td>
</tr>
<tr>
<td>60-79</td>
<td>26.0</td>
<td>36</td>
<td>0.79</td>
</tr>
</tbody>
</table>

A. \( F_{20-39} = 0.35, F_{40-59} = 0.47, F_{60-79} = 0.79 \)
B. \( F_{20-39} = 0.30, F_{40-59} = 0.34, F_{60-79} = 0.41 \)
C. \( F_{20-39} = 0.25, F_{40-59} = 0.29, F_{60-79} = 0.53 \)
D. \( F_{20-39} = 1, F_{40-59} = 0.84, F_{60-79} = 0.61 \)
E. \( F_{20-39} = 0.44, F_{40-59} = 0.59, F_{60-79} = 1 \)

\[
AUC = \frac{Dose \times F}{CL}
\]

\[
F_{20-39} = \frac{AUC \times CL_{20-39}}{Dose} = \frac{0.35 \times 42.5}{50} = 0.30
\]

\[
F_{40-59} = \frac{AUC \times CL_{40-59}}{Dose} = \frac{0.47 \times 35.7}{50} = 0.34
\]

\[
F_{60-79} = \frac{AUC \times CL_{60-79}}{Dose} = \frac{0.79 \times 26.0}{50} = 0.41
\]
Problem 9 (10 points)

How will an increase in plasma protein binding affect the clearance (CL), bioavailability (F), and AUC, of a low-extraction drug? (Please note that ↔ means no change) (10 points)

A. ↑ CL, ↓ F, AUC ↓,
B. ↓ CL, ↑ F, AUC ↑
C. ↑ CL, ↔ F, AUC ↓
D. ↓ CL, ↔ F, AUC ↑
E. ↔ CL, ↔ F, AUC ↔

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

\[Q \gg CL_{int} \times f_u\]

\[
CL = f_u \times CL_{int} \downarrow
\]

\[
F = 1 - E = 1 - \frac{CL_{int} \times f_u}{CL_{int} \times f_u + Q} = \frac{Q}{CL_{int} \times f_u + Q} \approx 1 \leftrightarrow
\]

\[
AUC = \frac{Dose \times F}{CL} = \frac{Dose \times Q}{Q + CL_{int} \times f_u} \times \frac{Q + CL_{int} \times f_u}{Q \times CL_{int} \times f_u} = \frac{Dose}{CL_{int} \times f_u} \uparrow
\]
Problem 10 (5 points)

10. Which statement is incorrect?

A. Creatinine clearance is a measurement for kidney function.
B. Bioavailability of high extraction drugs is dependent on plasma protein binding.
C. Clearance and volume of distribution determine the half-life of a drug.
D. A multi-compartment-body model has only one volume of distribution.
E. Changes in clearance affect average steady-state plasma levels.
**Problem 11 (10 points)**

Drug B is administered via multiple short-term infusions. Determine an appropriate dosing regimen for a multiple two-hour infusion (dosing rate \( R_0 \) and dosing interval) of drug B to achieve desired steady state plasma concentrations of 12.5 mg/L for the peak (drawn 2 h after the end of a 2 h infusion) and approximately 3.5 mg/L for the trough. Assume that drug B’s plasma-concentration-time profile follows a one-compartment body model. (CL = 15 L/h, VD = 100 L). Round appropriately and use a clinically used dosing interval.

A. \( R_0 = 815\text{mg/h Q24h} \)
B. \( R_0 = 1630\text{mg/h Q12h} \)
C. \( R_0 = 1630\text{mg/h Q24h} \)
D. \( R_0 = 815\text{mg/h Q12h} \)
E. \( R_0 = 815\text{mg/h Q8h} \)

\[
\frac{CL}{VD} = 0.15 \text{ L/h}
\]

\[
\tau = \frac{\ln(C_{\text{peak,desired}}) - \ln(C_{\text{trough,desired}})}{k} + T + t^* = \frac{1.27}{0.15}h + 2h + 2h = 12.47 \text{ h (round down to 12 h)}
\]

\[
Dose = \frac{C_{\text{peak,desired}} \cdot CL \cdot T \cdot (1 - e^{-k_\epsilon \tau})}{(1 - e^{-k_\epsilon T})(e^{-k_\epsilon t^*})} = 1630 \text{ mg in 2 h or 815 mg in 1 h}
\]
Problem 12 (5 points)

Select the incorrect statement

A. In a one-compartment body model, the volume of distribution decreases with an increase in plasma protein binding
B. In a two compartment body model, the volume of distribution at steady state (VD_{SS}) is always larger than the volume of distribution of the central body compartment (V_c)
C. The plasma concentration at steady state is a function of dosing rate (R_0) and clearance (CL)
D. In a two compartment body model, VD_{area} is not independent of the clearance (CL)
E. For a high extraction drug, the free plasma concentration at steady increases with a decrease in tissue protein binding
Problem 13 (5 points)

Which of the following statements is/are true regarding ceftazidime? (see graph below). The graph below shows the efficacy parameters of ceftazidime against K. pneumonia infection in neutropenic mice. The target level for efficacy is 7.2 log$_{10}$ CFU/Thigh at 24 hours.

![Graph showing efficacy parameters of ceftazidime against K. pneumonia infection in neutropenic mice.]

i. The effect profile for this drug is a concentration-dependent one.

ii. The time above MIC is the parameter of choice to evaluate efficacy of ceftazidime against K. pneumonia.

iii. The parameter value that achieves the minimum effect is approximately 35 hr above MIC, which corresponds to the target value of 7.2 log$_{10}$ CFU/Thigh.

iv. The 24-hour AUC/MIC ratio greater than 1000 is required to achieve the effect of lowering the log$_{10}$ CFU/Thigh below 7.2.

v. Increasing the time above MIC, peak drug concentration and AUC/MIC ratio resulted in a decrease in CFU, suggesting that this drug has bactericidal effect.

A. I, IV, V
B. II, III, V
C. II, III
D. II, III, IV, V
E. I, III, IV
Problem 14 (5 points)

A 45-year-old female patient (50 kg, 5’4”, C_{p,crea} = 1.1 mg/dL,) is treated with 100 mg gentamicin i.v. short-term infusions (T = 30 min) Q8h. Assuming linear pharmacokinetics (Vd=0.25L/kg, CL=Cl_{Cr}), predict the “true” peak concentration at the end of the infusion and the “true” trough concentration before the next infusion at steady state.

A. C_{max} : 8.79 mg/L  C_{min} : 1.41 mg/L
B. C_{max} : 6.79 mg/L  C_{min} : 0.85 mg/L
C. C_{max} : 8.79 mg/L  C_{min} : 1.85 mg/L
D. C_{max} : 10.79 mg/L  C_{min} : 0.85 mg/L
E. C_{max} : 10.79 mg/L  C_{min} : 1.41 mg/L

\[
\text{IBW}_{female} = 45.5 \text{ kg} + 2.3 \text{ kg} \times (64 - 60) = 54.7 \text{ kg}
\]

TBW= 50 (kg) is smaller than IBW*120%, use TBW to calculate the Cl_{Cr}

\[
CL_{Cr} = \frac{(140 - 45) \times 50}{1.1 \times 85} = 50.8 \ \text{mL/min} = 3.05 \ \text{L/h}
\]

\[
k = \frac{CL}{V_D} = \frac{3.05 L}{0.25 L/kg \times 50 kg} = 0.244 \ \text{L/h}
\]

\[
C_{max,SS} = \frac{Dose}{V_D \times k \times T} \left(1 - e^{-k \times T}\right) = \frac{100 \text{mg}}{12.5L \times 0.244 \frac{L}{h} \times 0.5h} \left(1 - e^{-0.244 \frac{1}{h} \times 0.5h}\right) = \frac{65.57 \text{mg}}{L} \times 0.115 = 8.79 \frac{mg}{L}
\]

\[
C_{min,SS} = C_{max,SS} \times e^{-k \times (T-T)} = 8.79 \frac{mg}{L} \times e^{-0.244 \frac{1}{h} \times 7.5h} = 1.41 \frac{mg}{L}
\]