Exam 1 Key, 2011
1 Gentamicin (5)
2 Gentamicin (10)
3 Renal Disease (5)
4 Basic Principles (10)
5 Basic Principles (5)
6 Basic Principles (5)
7 Basic Principles/Bioavailability/Renal Disease (10)
8 Vancomycin (10)
9 Geriatrics (10)
10 Antibiotics (5)
11 Carbamazepine
12 Phenobarbital/Carbamazepine (10)
13 Basic Principles (5)
14 Vancomycin (5)

Total Points: 100
**Problem 1 (5 points)**

A 35-year-old male patient (70kg, C\text{p, creat} = 1.2mg/dL, 165cm) is treated with 100mg gentamicin i.v. short-term infusions (T = 30min) Q8h. Assuming linear pharmacokinetics (CL=CL\text{Cr}, Vd=0.25L/kg), predict the measured peak concentration 1 hour after the infusion was started and the measured trough concentration 30min before the next infusion at steady state. (Calculate $k_e$ via $k_e=CL/Vd$)

A) $C_{\text{max}}^* = 5.9mg/L$, $C_{\text{min}}^* = 1.5mg/L$
B) $C_{\text{max}}^* = 6.7mg/L$, $C_{\text{min}}^* = 1.5mg/L$
C) $C_{\text{max}}^* = 5.0mg/L$, $C_{\text{min}}^* = 0.8mg/L$
D) $C_{\text{max}}^* = 4.5mg/L$, $C_{\text{min}}^* = 0.6mg/L$
E) $C_{\text{max}}^* = 4.2mg/L$, $C_{\text{min}}^* = 0.6mg/L$

For male: IBW= 50+0.9*(165-150) = 63.5(kg)
TBW=70kg is smaller than IBW*120%, use TBW to calculate the Clcr

$$CL_{Cr} = \frac{(140-\text{age})\cdot BW}{Cp_{Cr}\cdot 72}$$

$$= \frac{(140-35)\cdot 70}{1.2/72} = 85.07 \text{ (ml/min)} = 5.10 \text{ (L/h)}$$

$K_e=CL/Vd=5.10/ (0.25\cdot 70) =0.291(h^{-1})$

$$C_{\text{max}} = \frac{\text{dose}}{CL\cdot T\cdot (1-e^{-k_e\cdot T})}$$

$$= \frac{100}{5.10\cdot 0.5\cdot (1-e^{-0.291\cdot 1})}$$

$$=5.88\text{ (mg/ml)}$$

$$C_{\text{max}}^* = C_{\text{max}}\cdot e^{(-k_e\cdot t_1)} = 5.88\cdot e^{(-0.291\cdot 0.5)} = 5.01\text{ (mg/L)}$$

$$C_{\text{min}}^* = C_{\text{max}}\cdot e^{(-k_e\cdot t_2)} = 5.88\cdot e^{(-0.291\cdot (8-0.5-0.5))} = 0.77\text{ (mg/L)}$$
Problem 2 (10 points)

A 50-year-old female patient is treated with 100mg gentamicin i.v. short-term infusions (T = 30min) Q8h. The steady-state clinical pharmacokinetic data is shown below:

1 h after the infusion was started, the gentamicin concentration is 8.5 mg/L
30 min before the next infusion, the gentamicin concentration is 1.6 mg/L

Predict the true Cmax and Cmin based on the given information.

A) Cmax 7.8mg/L, Cmin 1.0mg/L
B) Cmax 9.7mg/L, Cmin 1.4mg/L
C) Cmax 11.2mg/L, Cmin 1.0mg/L
D) Cmax 8.8mg/L, Cmin 1.4mg/L
E) Not enough information to calculate the answer

\[
K = \frac{\ln\left(\frac{c_1}{c_2}\right)}{t_2-t_1} = \frac{\ln(8.5)}{8-1-0.5} = 0.257(/h)
\]

\[
C_{\text{max}} = \frac{C_{\text{max}}'}{e^{-k*t_1}} = \frac{8.5}{e^{-0.257*(1-0.5)}} = 9.67 \text{ (mg/L)}
\]

\[
C_{\text{min}} = C_{\text{max}} \cdot e^{-k*t_2} = 9.67 \cdot e^{-0.257*(8-0.5)} = 1.41 \text{ (mg/L)}
\]
Problem 3 (5 points)

Which combination of the following factors makes the serum creatinine level a good choice to estimate renal function?

1) Creatinine is endogenous
2) Creatinine is only eliminated by the kidney
3) Creatinine is not bound to protein in plasma
4) Creatinine urinary excretion rate is not affected by diseases
5) Creatinine is usually constantly formed by muscle

A) 1, 2, & 4
B) 1, 2, 3, & 5
C) 1, 3, 4, & 5
D) 2, 3, 4 & 5
E) all of the above
Problem 4 (10 points)

Calculate the clinical peak and trough concentrations at steady state after administration of 1250 mg drug A via multiple short-term infusions (infusion time = 75 min, dosing interval = 8 h). The clinical peak is defined as the plasma concentration 30 min after the end of an infusion. The clinical trough is defined as the plasma concentration 30 min before the start on an infusion. Drug A is known to follow a one-compartment body model and shows linear pharmacokinetics. The clearance and volume of distribution of drug A are 20 L/h and 50 L, respectively. Round appropriately.

\[ k_e = \frac{CL}{VD} = 0.4 \frac{L}{h} \]

\[ C_{peak,true} = \frac{Dose \times \left(1 - e^{-k_e \cdot T}\right)}{CL \times \bar{T} \times \left(1 - e^{-k_e \cdot \tau}\right)} = \frac{1250mg \times \left(1 - e^{-0.4h^{-1} \cdot 1.25h}\right)}{20L \times 1.25h \times \left(1 - e^{-0.4h^{-1} \cdot 0.8h}\right)} = 20.51 \frac{mg}{L} \]

\[ C_{peak,clinical} = C_{peak,true} \times e^{-k_e \cdot t^*} = 20.51 \frac{mg}{L} \times e^{-0.4h^{-1} \cdot 0.5h} = 16.79 \frac{mg}{L} \]

\[ C_{trough,true} = C_{peak,true} \times e^{-k_e \cdot (\tau - T)} = 20.51 \frac{mg}{L} \times e^{-0.4h^{-1} \cdot 6.75h} = 1.38 \frac{mg}{L} \]

\[ C_{trough,clinical} = 20.51 \frac{mg}{L} \times e^{-0.4h^{-1} \cdot 6.25h} = 1.68 \frac{mg}{L} \]

A 16.8 and 0.17 mg/mL
B 1.68 and 0.17 mg/L
C 16.8 and 1.7 mg/L
D 16.8 and 0.17 mg/L
E 16.8 and 1.7 mg
Problem 5 (5 points)

Drug B is administered via multiple short-term infusions. Determine an appropriate dose for 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). (Hint: Calculate the required dosing interval first). Round appropriately and use a clinically used dosing interval.

\[
\dot{k}_e = \frac{CL}{VD} = 0.15 \frac{L}{h}
\]

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

\[
Dose = \frac{C_{peak,desired} \cdot CL \cdot T \cdot (1 - e^{-k_e \cdot \tau})}{(1 - e^{-k_e \cdot \tau})(e^{-k_e \cdot \tau})} = \frac{12.5 mg}{L} \cdot \frac{15 L}{h} \cdot 2h \cdot (1 - e^{-0.15h^{-1} \cdot 12h})}{(1 - e^{-0.15h^{-1} \cdot 2h})(e^{-0.15h^{-1} \cdot 2h})} = 1630 mg \text{ in 2 h or 815mg in 1h}
\]

A  815 mg in 2h

B  1630 mg in 2h

C  1630 mg in 1h

D  1000 mg in 1h

E  1000mg in 2h
Problem 6 (5 points)

Select the correct statement

A  In a one-compartment body model, the volume of distribution decreases with a decrease 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  In a one-compartment body model, the plasma concentration at steady state is a function of dosing interval (R_0) and the volume of distribution (V_D).

D  In a two compartment body model, VD_{area} is independent of the clearance (CL)

E  For a high extraction drug, the free plasma concentration at steady state increases with an increase in plasma protein binding
Problem 7 (10 points)

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

1. Poorly water soluble drugs that show a high first-pass effect usually have a low systemic bioavailability after IV bolus administration

2. For antibiotics, the total concentration at the infection site is highly correlated to their pharmacodynamic effect

3. For bioequivalence assessment, statistical tests and decision criteria (i.e. 90% confidence intervals) are applied to $C_{\text{max}}$ and AUC

4. An Abbreviated New Drug Application (ANDA) is filed by a company to receive market approval for a generic alternative to a reference listed drug that is already on the market

5. Creatinine is used to estimate hepatic function in humans

A 1, 2, 3, 4, 5
B 1, 3, 5
C 2, 4
D 3, 4, 5
E None of the combinations
Problem 8 (10 points)

A 37-year-old, 78 kg, 5’9”, male patient with serum creatinine level of 1.1 mg/dL receives vancomycin to fight against his infection. In order to target a steady-state peak and trough concentration of 15 and 50 mg/L, estimate the dose and dosing frequency for the patient. Do not use the nomogram table for this computation; rather compute the dosing interval and dose based on the information given.

A) Not enough information is provided to answer the question
B) 1400 mg q8h
C) 950 mg q4h
D) 1000 mg q12h
E) 3000 mg q24h

Solution:

\[ V_d \text{(in L)} = 0.178(37) + 0.22(78) + 15 \]
\[ V_d = 38.5 L \]
\[ IBW = 50 + 2.3(69 - 60) = 70.7 \]

Since 78 kg is less than 120% of IBW, we will use TBW

\[ CL_{Cr} \text{ for male(mL/min)} = \frac{(140 - Age)(78)}{72(1.1)} = 101.4 \text{mL/min} \]

\[ K_e = \frac{CL}{V_d} = \frac{6.08 \text{L/hr}}{38.5 \text{L}} = 0.16 \text{hr}^{-1} \]

\[ \tau = \frac{\ln \left( \frac{50}{15} \right)}{0.16 \text{hr}^{-1}} = 7.5 \text{hr} \approx 8 \]

\[ Dose = V_d \times C_{max \ast} \times (1 - e^{-\frac{\tau}{\tau}}) = 38.5 \times 50 \times (1 - e^{-\frac{0.16}{8} \text{hr}^{-1}}) = 1390 \text{mg} \approx 1400 \text{mg} \]

Answer: B
Problem 9 (10 points)

Which of the following statement(s) best describe(s) drug behavior in the elderly population?

i. Gastric emptying time is shortened

ii. \( C_{p_{tot \text{ (free)}}} = \frac{R_0}{CL_{int}} \) for low extraction drugs, therefore unbound plasma concentration remains unchanged but total plasma concentration will change.

iii. \( C_{p_{tot \text{ (free)}}} = \frac{f_u \cdot R_0}{Q} \) for high extraction drugs, therefore total plasma concentration will remain unchanged but unbound drug will change.

iv. Oral bioavailability of low extraction drugs are often changed in the geriatric population.

v. Oral bioavailability of high extraction drugs are often different from the young population

A) None of the above
B) i, ii, iv
C) ii, iv
D) iv, v
E) ii, iii, v

Answer: E
Problem 10 (5 points)

Which of the following statement(s) is/are FALSE of temafloxacin against S. pneumonia in neutropenic mice based on the graph below?

i. Graphs show that the time above MIC provides the best description of its effect.

ii. The drug is bactericidal if the 24-hr AUC/MIC-ratio is higher than 500.

iii. The drug is bactericidal if you keep the concentration above MIC at all times.

iv. The drug is bactericidal if the peak/MIC-ratio is more than 100.

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

A) i, iii, iv
B) i, iii
C) ii, iv, v
D) iii, iv, v
E) i, ii, iv

Answer: B
**Problem 11 (5 points)**

A 35-year old, 48 kg female is to be given carbamazepine as an anticonvulsant agent. Calculate a daily dose to achieve average steady state plasma concentration of 5 mg/L. Bioavailability of carbamazepine is 0.8 and salt factor is 1.

F=0.8 S=1.0 Cl= 0.1 L/h/kg
Dose=Cl*Cpss*T/ (S* F ) = 0.1 L/h/kg * 48kg * 5 mg/L * 24 hr/day / ( 1*0.8) = 720 mg/day

A). 460 mg/day
B). 200 mg/day
C). 720 mg/day
D). 550 mg/day
E). 800 mg/day

Answer: C
Problem 12 (10 points)

T.S. is a 67 kg 65 year old male receiving 1.5 mg/kg Phenobarbital every 12 hours for the past 2 months. However this patient’s seizures are not controlled and it was decided to start this patient on a concomitant therapy of carbamazepine. Calculate the daily maintenance dose to produce a target steady state concentration of 6 mg/L using the immediate release formulation. Later the results come back from the lab and the level of carbamazepine was 4mg/L. What dose should be given to get the desired serum concentration?

A) 1200mg/day, 1800mg/day
B) 400mg BID, 1800mg/day
C) 1200mg/day, 2400mg/day
D) 600mg/day, 2400mg/day
E) 1200mg/day, 500 BID

\[ MD = \frac{C_{pss} \times Cl \times T}{S \times F} = \frac{6 \text{ mg/L} \times 0.1 \text{ L/hr/kg} \times 67 \text{ kg} \times 24 \text{ hr}}{0.8} = 1206 \text{ mg} \sim 1200 \text{ mg} \]

\[ \frac{4 \text{ mg/L}}{6 \text{ mg/L}} = \frac{1000 \text{ mg}}{X \text{ mg}} \to X = 1800 \text{ mg} \]

Answer: A
Problem 13 (5 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)

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

Answer:D
Problem 14 (5 points)

Vancomycin concentration-time profile can be described via a two compartment model. Which profile will represent a 1-hr infusion of vancomycin in the following graph?

Answer: C
Aminoglycosides

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
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<td>Vd [L/kg]</td>
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<tr>
<td>CL [L/h/kg]</td>
<td>CL&lt;sub&gt;Cr&lt;/sub&gt;</td>
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<tr>
<td>t₁/₂ [h]</td>
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<tr>
<td>% renal</td>
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<tr>
<td>F</td>
<td>-</td>
</tr>
<tr>
<td>S</td>
<td>-</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; [mg/L]</td>
<td>&gt;8-10·MIC</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; [mg/L]</td>
<td>&lt;2 (G, T) &lt;10 (A)</td>
</tr>
</tbody>
</table>

Dosing Weight

If TBW > 1.2·IBW: IBW + 0.4·(TBW-IBW)

Third Space Fluids: Add to Vd (1L/kg)

Dettli Equation:
k = 0.00293·CL<sub>Cr</sub>[ml/min] + 0.014 [h⁻¹]

Vancomycin

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Vd [L]</td>
<td>0.17·age+0.22·TBW+15</td>
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<tr>
<td>CL</td>
<td>CL&lt;sub&gt;Cr&lt;/sub&gt;</td>
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<td>t₁/₂ [h]</td>
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<tr>
<td>% renal</td>
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<tr>
<td>f&lt;sub&gt;u&lt;/sub&gt;</td>
<td>0.5</td>
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<tr>
<td>F</td>
<td>-</td>
</tr>
<tr>
<td>S</td>
<td>-</td>
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<td>C&lt;sub&gt;max&lt;/sub&gt; [mg/L]</td>
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<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; [mg/L]</td>
<td>~15-20</td>
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<tr>
<td>AUC/MIC</td>
<td>&gt;400 mg·h/L</td>
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### Phenobarbital

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<th>Value</th>
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<tbody>
<tr>
<td>$V_d$ [L/kg]</td>
<td>0.7</td>
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<tr>
<td>$CL$ [L/h/kg]</td>
<td>0.004 (ad.)</td>
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<tr>
<td></td>
<td>0.008 (ch.)</td>
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<tr>
<td>$t_{1/2}$ [h]</td>
<td>120 (ad.)</td>
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<tr>
<td></td>
<td>60 (ch.)</td>
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<tr>
<td>% renal</td>
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<tr>
<td>$F$</td>
<td>1</td>
<td></td>
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<tr>
<td>$S$</td>
<td>0.9 (sodium)</td>
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<td>$C_{max}$ [mg/L]</td>
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### Carbamazepine

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<td>1.4 (variable)</td>
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<td>$CL$ [L/h/kg]</td>
<td>0.064 (mono)</td>
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<tr>
<td></td>
<td>0.1 (poly)</td>
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<td>$t_{1/2}$ [h]</td>
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<tr>
<td></td>
<td>15 (mono)</td>
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<tr>
<td></td>
<td>10 (poly)</td>
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<tr>
<td>% renal</td>
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<tr>
<td>$F$</td>
<td>0.8 IR (0.7 XR)</td>
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<td>$C_{min}$ [mg/L]</td>
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**Autoinduction**

$fu$ 0.25
Valproic Acid

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<td>(variable)</td>
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<tr>
<td>CL [L/h/kg]</td>
<td>0.008 (adults)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.013 (children)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t_{1/2} [h]</td>
<td>11 (adults)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (children)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% renal</td>
<td>2</td>
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</tr>
<tr>
<td>F</td>
<td>1</td>
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<td>S</td>
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<tr>
<td>C_{max} [mg/L]</td>
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<td>C_{min} [mg/L]</td>
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Once-a-day Aminoglycosides

ODA Nomogram for Gentamicin and Tobramycin at 7 mg/kg
Vancomycin

Figure 1. Detroit Receiving Hospital and University Health Center vancomycin dosing nomogram. (Updated 5/99)

[Table with CLcr values and corresponding dosing intervals]