1. Gentamicin (5 points)
2. Digoxin (10 points)
3. Methotrexate (10 points)
4. Phenytoin (10 points)
5. Valproic Acid (5 points)
6. Carbamazepine (10 points)
7. Anticonvulsants (5 points)
8. Theophylline (10 points)
9. Lidocaine (5 points)
10. Phenytoin (10 points)
11. Methotrexate (5 points)
12. Bioavailability/Bioequivalence (5 points)
13. Pediatrics/Geriatrics (5 points)
14. Basic Principle/Drug Interaction (5 points)

Total: 100 points
Problem 1 (5 points)

W.G. is a 30-year-old female who suffered a severe burn that has since been infected by \textit{S. aureus}. To treat her infection she is given 150mg of gentamicin by a half hour infusion every 12 hours. She was started on her first infusion at 8:00 am and at 9:00 am a plasma sample was taken that yielded a clinical maximum concentration (C*$_{\text{max}}$) of 10.4 μg/ml. In order to determine clinical minimum concentration (C*$_{\text{min}}$), another plasma sample is taken at 7:30pm (0.9 μg/ml). Please calculate her respective volume of distribution. Use ONLY short-term infusion equations in this problem.

A) 11.6 L

\textbf{B) 12.9 L}

C) 13.7 L

D) 14.9 L

E) 15.6 L

\[
\kappa_e = \frac{\ln \left( \frac{C^*_{\text{max}}}{C^*_{\text{min}}} \right)}{t^*_{\text{min}} - t^*_{\text{max}}} = \frac{\ln (\frac{10.4}{0.9})}{(11.5 - 1)hr} = 0.233 \text{hr}^{-1}
\]

\[
C^*_{\text{max}} = \frac{C^*_{\text{max}}}{e^{-\kappa_e \times (t^*_{\text{max}} - t^*_{\text{max}})}} = \frac{10.4}{e^{-0.233 \times 0.5}} = 11.685 \approx 11.7 \text{ μg/ml}
\]

\[
C^*_{\text{min}} = C^*_{\text{min}} \times e^{-\kappa_e \times (t^*_{\text{min}} - t^*_{\text{min}})} = 0.9 \times e^{-0.233 \times 0.5} = 0.80 \text{ μg/ml}
\]

\[
V_d = \frac{Dose \times 1 - e^{-\kappa_e \times T}}{\kappa_e \times T} \left( \frac{C^*_{\text{max}} - C^*_{\text{min}} \times e^{-\kappa_e \times T}}{(1 - e^{-0.233 \times 0.5})} \right)
\]

\[
= \frac{150}{0.233 \times 0.5} \times \frac{11.7 - 0.8 \times e^{-0.233 \times 0.5}}{0.110 \times 10.99} \approx 12.9 L
\]
Problem 2 (10 points)

T.P., a 75-year-old, 72 kg male (5’9”, SrCr: 1.2mg/dL), has been taking 0.25mg of digoxin tablets (S=1, F=0.7) orally for his CHF, and at 9.00am on the day of admission, a digoxin plasma concentration of 0.75µg/L was measured. He was continued on his outpatient maintenance dose. On the third day, just before his morning dose (two doses of digoxin have been administered each day at 9.00am), a second digoxin sample was obtained. What will be the predicted concentration for the second sample taking on the morning of the third day?

A) 0.75 µg/L  
B) 0.83 µg/L  
C) 0.95 µg/L  
D) 1.03 µg/L  
E) 1.15 µg/L  

Answer: 

\( IBW = 50 \, kg + 2.3 \, kg \times (Height - 5') = 50 + 2.3 \times 9 = 70.7 \, kg \)

\[ 1.2 \times IBW = 70.7 \times 1.2 = 84.84 \, kg \]

\( TBW = 72 \, kg < 1.2 \, IBW \) So use TBW in Cockcroft-Gault Equation

\[
Cl_{\text{creat(male)}} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times C_{\text{pcreat}}} = \frac{(140 - 75) \times 72}{72 \times 1.2} = 54.17 \, ml/min
\]

\[
Cl_{\text{Digoxin}} = 0.33 \times IBW + 0.9 \times Cl_{\text{creat(with-CHF)}} = 0.33 \times 70.7 + 0.9 \times 54.17 = 72.1 \, ml/min
\]

\[
Vd_{\text{Digoxin}} = 3.8 \, L/kg \times IBW + 3.1 \times Cl_{\text{crea}} = 3.8 \times 70.7 + 3.1 \times 54.17 = 436.6 \, L
\]

\[
k_e = \frac{Cl}{Vd} = \frac{103.8}{436.6} = 0.238 \, day^{-1}
\]

\[
C_{\text{min(day3)}} = C_{\text{measured}} \times e^{-k_e \times t_1} + \frac{F \times D}{Vd} \times e^{-k_e \times t_1} + \frac{F \times D}{Vd} \times e^{-k_e \times t_2}
\]

\[
= 0.75 \times e^{-0.238 \times 2} + \frac{0.7 \times 250}{436.6} \times (e^{-0.238 \times 2} + e^{-0.238 \times 1}) = 0.47 + 0.40 \times 1.41 = 1.03 \, \mu g/L
\]
Problem 3 (10 points)

E.R. is a 55 kg (non-obese) female patient (61 years old) on methotrexate therapy. Her serum creatinine is 1.4 mg/dL. She is treated with a loading dose (36 mg) followed by an infusion of 35 mg/h over 36 hours. She will then receive a 10 mg/m² dose of leucovorin q6h (four doses) followed by eight oral doses (q6h) of 20 mg. Calculate the expected MTX concentrations at 24, 48 and 60 hours after the start of the infusion.

A) Cₜₜ = 10 μM L; C₂₄ = 22 μM, C₄₈ = 0.6 μM, C₆₀ = 0.3 μM

B) Cₜₜ = 22 μM; C₂₄ = 22 μM, C₄₈ = 1.4 μM, C₆₀ = 0.08 μM

C) Cₜₜ = 10 μM; C₂₄ = 10 μM, C₄₈ = 0.6 μM, C₆₀ = 0.2 μM

D) Cₜₜ = 22 μM; C₂₄ = 22 μM, C₄₈ = 1.4μM, C₆₀ = 0.3 μM

E) Cₜₜ = 10 μM; C₂₄ = 10 μM, C₄₈ = 0.6 μM, C₆₀ = 0.04 μM

Answer:

\[
Cl_{crea}(female) = \frac{(140 - age) \times weight}{85 \times C_{pcrea}} = \frac{(140 - 61) \times 55}{85 \times 1.4} = 36.51 \text{ ml/min}
\]
\[
\approx 2.19 \text{ L/hr}
\]
\[
CL = 1.6 \times CL_{crea} = 1.6 \times 2.19 \frac{L}{hr} = 3.50 \text{ L/hr}
\]
\[
C_{ss} = \frac{R_0}{CL} = \frac{35}{3.50} = 10 \text{ mg/L}
\]
\[
C_{ss}(μM) = \frac{10}{0.454} = 22.03\text{μM}
\]

24 h: 22.03 μM

48 h: \(C_p(48hr) = C_p(36hr) \times e^{-k_e \times t} = 22.03 \times e^{-0.231 \times 12} = 1.38μM \approx 1.4μM\)

60 h: \(t = \frac{\ln\left(\frac{22.03}{0.5}\right)}{0.231} = 16.4hr \rightarrow 0.5\text{μM at }36+16.4=52.4hr\)

So

\(C_p(60hr) = C_p(52.4hr) \times e^{-k_e \times t} = 0.5 \times e^{-0.0693 \times 7.6} = 0.295\text{μM} \approx 0.3 \text{μM}\)
Problem 4 (10 points)

A male patient of 113 kg in weight was administered sodium phenytoin capsules by oral route. Phenytoin (not the salt form) has a volume of distribution of 0.65 L/kg. This patient exhibited phenytoin $K_M$ of 4.7 mg/L and a $V_{\text{max}}$ of 8.2 mg/kg/day. Compute the following:

(i) The loading dose required to achieve an initial phenytoin concentration of 20 mg/L
(ii) The daily maintenance dose to obtain the target average steady-state concentration of 15 mg/L.

A. Loading dose of 2400 mg; Maintenance dose of 300 mg/day
B. Loading dose of 1400 mg; Maintenance dose of 500 mg/day
C. Loading dose of 600 mg followed by three 500 mg doses at two-hour interval apart; maintenance dose of 770 mg/day
D. Loading dose of 700 mg followed by three 500 mg doses at two-hour interval apart; maintenance dose of 500 mg/day
E. Loading dose of 400 mg followed by three 400 mg doses at two-hour interval apart; maintenance dose of 770 mg/day

Answer: E

(i) To compute the loading dose required to achieve an initial concentration of 20 mg/L

$$V_d = 0.65 L/kg \times 113 kg = 73.45 L$$

$$LD = \frac{C_p \cdot V_d}{S \cdot F} = \frac{20 mg/L \times 73.45 L}{0.92 \times 1} = 1596.74 mg \approx 1600 mg$$

In order to relieve the side effects associated with phenytoin, the loading dose should be given in short intervals, such that the first dose is 400 mg followed by three 400 mg doses at two-hour interval apart.

(ii) The daily maintenance dose needed to obtain the target average steady-state concentration of 15 mg/L is

$$MD = \frac{V_{\text{max}} \cdot Cp_{ss} \cdot \tau}{(K_m + C) \cdot S \cdot F} = \frac{8.2 mg/kg/day \times 113 kg \times 15 mg/L \times 1 day}{(4.7 mg/L + 15) \times 0.92 \times 1} = 766.88 \approx 770 mg/day$$
Problem 5 (5 points)

M.P., a 37 year-old female patient of 67 kg in weight, receives 300 mg valproic acid (2 x 150 mg) p.o. Q8h to control her seizure. Compute her steady-state valproic acid concentration. What dose adjustment would you recommend for this patient?

A. 250 mg/L, decrease the dose to 200 mg Q8h
B. **70 mg/L, stay with the current dosing regimen**
C. 15 mg/L, increase the dose to 500 mg Q12h
D. 65 mg/L, increase the current dosing to 400 mg Q8h
E. 90 mg/L, stay with the current dosing regimen

Answer: B

\[
CL = 0.008 \frac{L}{h/\text{kg}} \times 67 \text{ kg} = 0.536 L/h
\]

\[
C_{P_{ss,ave}} = \frac{1 \times 1 \times 300 \text{ mg/hr}}{0.536 L/h} = 69.96 \text{ mg/L}
\]

We want to achieve valproic acid concentration such that \( C_{\text{max}} < 100 \text{ mg/L} \) and \( C_{\text{min}} > 50 \text{ mg/L} \)
Problem 6 (10 points)

A 49 year old male patient, 83.3 kg in weight, is to receive immediate release carbamazepine regimen.

(i) Compute the daily dose required to achieve a steady state plasma concentration of 7.5 mg/L, assuming monotherapy.

(ii) If the patient receives phenobarbital medication of 2.0 mg/kg Q12h for the past 3 months and the doctor decides to include a concomitant therapy of carbamazepine in order to better control his seizure, compute the daily maintenance dose required to attain a target steady state concentration of 7 mg/L carbamazepine, using an immediate release formulation. Later on, over the course of treatment, blood samples were evaluated for carbamazepine and were reported to be 12.5 mg/L. How should his daily dose be adjusted to get to the desired concentration?

A. 1200 mg/day for monotherapy; adjust his daily dose to 1000 mg for polytherapy
B. 1400 mg/day for monotherapy; adjust his daily dose to 1200 mg for polytherapy
C. 700 mg/day for monotherapy; adjust his daily dose to 900 mg for polytherapy
D. 200 mg/day for monotherapy; adjust his daily dose to 500 mg for polytherapy
E. 600 mg/day for monotherapy; adjust his daily dose to 500 mg for polytherapy

Answer: A

(i) Carbamazepine has a clearance of 0.064 L/h/kg for monotherapy. For immediate release carbamazepine, the oral bioavailability is 0.8

\[
Dose = \frac{C_p^{ss} \cdot CL \cdot \tau}{F \cdot S} = \frac{7.5 \text{ mg/L} \times 0.064 \text{ L/h/kg} \times 83.3 \text{ kg} \times 24 \text{ h/day}}{1 \times 0.8} = 1199.52 \text{ mg/day}
\]

(ii) Carbamazepine has a clearance of 0.1 L/h/kg for polytherapy.

\[
MD = \frac{C_p^{ss} \cdot CL \cdot \tau}{F \cdot S} = \frac{7 \text{ mg/L} \times 0.1 \text{ L/h/kg} \times 83.3 \text{ kg} \times 24 \text{ h/day}}{1 \times 0.8} = 1749.3 \text{ mg/day}
\]

\[
\frac{12.5 \text{ mg/L}}{7 \text{ mg/L}} = \frac{1749.3 \text{ mg/day}}{x} \Rightarrow x = 979.6 \text{ mg/day}
\]
**Problem 7 (5 points)**

Which of the following statement(s) is/are FALSE regarding anticonvulsants?

i. Phenobarbital target concentration is between 100 to 150 mg/L.

ii. The loading dose of phenytoin is usually administered all at once to alleviate its side effects.

iii. Carbamazepine is both an inhibitor and an inducer of CYP3A4.

iv. The bioavailability of phenobarbital is difficult to determine due to its drug capacity-limited metabolism.

v. Carbamazepine taken over long period of time could result in autoinduction of its own metabolism.

A. V

B. I, II

C. III, IV

D. II, IV

E. I, II, IV

Answer: E
Problem 8 (10 points)

T.J. is a 2-year-old, 11 kg male child in the hospital who is placed on a theophylline drip at 1 mg/kg/h after first receiving a 5 mg/kg bolus at 1 pm. The infusion is discontinued at 9pm. Plasma concentration samples were obtained at 3pm and 8pm and were 13 mg/L and 18 mg/L, respectively. Estimate his theophylline half-life based on the Chiou-equation.

\[ VD = \left( 0.5 \frac{L}{kg} \right) (11kg) = 5.5L \]

\[ R_0 = 11 \frac{mg}{h} \]

\[ CL = \frac{2R_0}{C_1 + C_2} + \frac{2Vd(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)} = \frac{2\left(11 \frac{mg}{h}\right)}{(13 + 18) \frac{mg}{L}} + \frac{2(5.5L)(13 - 18) \frac{mg}{L}}{(13 + 18) \frac{mg}{L} (5h)} = \]

\[ 0.71 \frac{L}{h} - 0.35 \frac{L}{h} = 0.36 \frac{L}{h} \]

\[ k_e = \frac{CL}{VD} = \frac{0.36 \frac{L}{h}}{5.5L} = 0.0655 \frac{1}{h} \]

\[ t_{0.5} \approx 10.6h \]

A 16.6 h
B 14.6 h
C 12.6 h
D 10.6 h
E Chiou-Equation is not applicable in this situation
**Problem 9 (5 points)**

P.M., a 45-year-old, 65-kg man (TBW = IBW), was admitted to the coronary care unit with a diagnosis of heart failure, probable myocardial infarction. (Note: Lidocaine is available as lidocaine hydrochloride).

(i) Calculate a loading dose (LD) that achieves lidocaine plasma level of 3mg/L which should achieve an immediate response.

(ii) Calculate a maintenance infusion rate ($R_0$) of that will achieve a steady-state lidocaine concentration of 3 mg/L.

A. Since 3 mg/L is not appropriate target concentration for lidocaine, a loading dose of 200 mg and a maintenance infusion rate of 300 mg/h should be administered

B. $LD = 67.2$ mg and $R_0 = 80.7$ mg/h

C. LD = 50.3 mg and $R_0 = 71.4$ mg/h

D. LD = 74.1 mcg and $R_0 = 80.7$ mcg/h

E. LD = 67.2 mg and $R_0 = 71.4$ mg/h

\[
V_c = \left(0.3 \frac{L}{kg}\right)65kg = 19.5L
\]

\[
LD = \frac{(V_c)(C_{\text{max.desired}})}{S} = \frac{(19.5L)(3 \frac{mg}{L})}{0.87} = 67.2mg
\]

\[
R_0 = \frac{(CL)(C_{ss,avg})}{S} = \frac{(0.36 \frac{L}{h(kg)}65kg)(3 \frac{mg}{L})}{0.87} = 80.7 \frac{mg}{h}
\]
Problem 10 (10 points)

M.T., a 49-year-old, 55kg female, had been taking 250mg/day of sodium phenytoin; however, her dose had been increased to 300mg/day because her seizures were poorly controlled and because her phenytoin plasma concentration was only 3mg/L. Now she complains about minor CNS side effects and her measured plasma phenytoin concentration is 26mg/L. This level was decided to be too high for this patient, so the maintenance dose was discontinued. How long would it take for the phenytoin concentration to drop to 15 mg/L after discontinuation of dose?

The following equation may be helpful to solve this problem:

\[
T = \left( K_M \times \ln\left(\frac{C_0}{C}\right) + \left(C_0 - C\right) \right) \times \frac{V_d}{V_{\text{max}}} \]

A. 29.3 h  
B. **34.5 h**  
C. 35.9 h  
D. 38.1 h  
E. 40.2 h

**Answer:**

\[
V_d = 0.65 \frac{L}{kg} \times 55 \, kg = 35.75 \, L
\]

\[
V_{\text{max}} = \frac{(D_1) \times (D_2) \times (C_2 - C_1)}{C_2 \times (D_1) - C_1 \times (D_2)} = \frac{(250) \times (300) \times (26 - 3)}{26 \times 250 - 3 \times 300} = 308 \, \frac{mg}{day} \, \text{(sodium phenytoin)}
\]

\[
K_M = \frac{C_1 \times (V_{\text{max}} - D_1)}{D_1} = \frac{3 \times (308 - 250)}{250} = 0.696 \, mg/L
\]

\[
T = \left( K_M \times \ln\left(\frac{C_0}{C}\right) + \left(C_0 - C\right) \right) \times \frac{V_d}{V_{\text{max}} \times S} = \left( 0.696 \times \ln\left(\frac{26}{15}\right) + (26 - 15) \right) \times \frac{35.75}{308 \times 0.92} = 1.44 \, day \times 24 \, = \, 34.5 \, hr
\]
Problem 11 (5 points)

The methotrexate (MTX) plasma concentration of a patient, who had received MTX as an constant IV infusion, was measured to be 0.29 µM 24 hours after the stop of the constant rate infusion. Assuming that steady state had been reached, calculate the patient’s MTX plasma concentration at steady state.

A. 20.8 mg/L
B. 9.45 µM
C. 9.45 mg/L
D. 20.8 g/L
E. 14.5 µM

\[
\frac{\ln \left( \frac{0.29 \mu M}{0.5 \mu M} \right)}{0.0693 \frac{1}{h}} = \frac{-7.86 h}{t'}
\]

Thus, the MTX plasma concentration reached 0.5 µM 16.14 h after the infusion had been stopped.

\[
C_{ss} = \frac{C_t}{e^{-kt}} = \frac{0.5 \mu M}{e^{-0.231 \frac{1}{h} \cdot 16.14 h}} = 20.8 \mu M = 9.45 \frac{mg}{L}
\]
Problem 12 (5 points)

Which statement(s) is (are) correct?

1. Bioavailability is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action
2. Bioequivalence is the presence of a significant difference in rate and extent to which the active ingredient from a pharmaceutical alternative becomes available
3. Bioequivalent drug products are therapeutically equivalent
4. Bioequivalence studies are required for all strengths of a pharmaceutical alternative
5. Bioavailability of high extraction drugs is dependent on plasma protein binding

A. 1, 2, 3
B. 1, 3, 5
C. 2, 3, 4
D. 1, 4, 5
E. all of the statements are correct
Problem 13 (5 points)

Which combinations of the following pharmacokinetic changes usually apply to both the elderly and neonates?

1. Low renal clearance
2. Longer half-lives
3. Low metabolic clearance
4. Relatively less body water (as % body weight)
5. Decreased protein binding

A) 1, 2 & 5
B) 1, 2, 3 & 4
C) 1, 2, 3 & 5
D) 1, 4, &5
E) all of the above
Problem 14 (5 points)

Drug A, which is known to be a low-extraction drug, is given as an IV infusion. How would simultaneous administration of drug B that is known to significantly inhibit the main metabolic enzymes of drug A affect the total plasma concentration at steady state ($C_{p_{ss}}$) of drug A?

A. $C_{p_{ss}}$ increases
B. $C_{p_{ss}}$ decreases
C. $C_{p_{ss}}$ does not change
D. Change in $C_{p_{ss}}$ is not predictable since the volume of distribution is unknown
E. Change in $C_{p_{ss}}$ is not predictable since the protein tissue binding of drug A is unknown

$Cl_{int}$ of drug will decrease when its metabolic enzyme is inhibited. So the $C_{p_{ss}}$ will increase.