Questions

1. Digoxin (5 points)
2. Phenytoin (5 points)
3. Cyclosporin (10 points)
4. Digoxin (10 points)
5. Phenytoin (5 points)
6. Digoxin (5 points)
7. Theophylline (5 points)
8. Cyclosporin (10 points)
9. Carbamazepine (5 points)
10. Lidocaine (5 points)
11. Vancomycin (10 points)
12. Anticonvulsants (5 points)
13. Basic principles (5 points)
14. Methotrexate (10 points)
15. Phenytoin (5 points)

Total: 100 points
Question 1 (5 points)

Which of the following statement(s) is/are CORRECT regarding digoxin.

1. Digoxin is a substrate of P-glycoprotein.
2. Digoxin follows a one compartment body model for its pharmacokinetic profile.
3. Digoxin levels are increased in patients with hyperthyroid function.
4. Digoxin distributes rapidly into the myocardial tissue.
5. Digoxin is only renally eliminated.

A. 1, 4
B. 2, 3
C. 2, 3, 4
D. 2, 4, 5
E. None of the above

Key: E
Question 2 (5 points)

Which of following statement is FALSE about phenytoin?

A. The clinical usefulness of the phenytoin half-life is limited because the time required to achieve steady state can be much longer than the usual 3 to 5 times the apparent half-life.

B. The bioavailability of phenytoin is difficult to evaluate because of the drug’s capacity–limited metabolism.

C. When the oral loading dose of phenytoin is divided into three separate doses, the possibility of nausea and vomiting decreases. And the time to peak concentration decreases too.

D. The metabolism of phenytoin is capacity–limited which means that its clearance increases with increasing plasma concentrations.

E. The rate of change in phenytoin concentration in the body can be approximated by first-order kinetics at low concentrations and zero-order kinetics at high concentrations.

Key: D
Question 3 (10 points)

K.F., a 42 year old, 64 kg woman, 5'6” tall, who received a liver transplant, is to be started on oral treatment with cyclosporine. Recommend a dosing regimen that would achieve free and unbound steady state concentrations of 40 and 15 ng/mL. Cyclosporine is available in oral doses of 25 mg and 100 mg. You should assume a rapid absorption process and a 90% protein binding for cyclosporine.

A. three 100-mg tablet TID (thrice-daily)
B. three 100-mg and one 25-mg tablet QID (once-daily)
C. two 100-mg and one 25-mg tablet TID (thrice-daily)
D. two 100-mg tablet TID (thrice-daily)
E. two 100-mg tablet BID (twice-daily)

Key: C

\[ C_{\text{max,ss,total}} = \frac{C_{\text{max,ss,free}}}{\text{fu}} = \frac{40 \, \text{ng/mL}}{0.1} = 400 \, \text{ng/mL} \]

\[ C_{\text{min,ss,total}} = \frac{C_{\text{min,ss,free}}}{\text{fu}} = \frac{15 \, \text{ng/mL}}{0.1} = 150 \, \text{ng/mL} \]

\[ \text{CL} = (0.5 \frac{L}{h \times \text{kg}}) \times 64 \, \text{kg} = 32 \, \text{L/h} \]

\[ \text{VD} = (4.5 \, \text{L/kg}) \times 64 \, \text{kg} = 288 \, \text{L} \]

\[ k_e = \frac{\text{CL}}{\text{VD}} = \frac{32 \, \text{L/h}}{288 \, \text{L}} = 0.111 \, \text{h}^{-1} \]

\[ \tau = \frac{\ln \frac{C_{\text{max,ss,\text{total}}}}{C_{\text{min,ss,\text{total}}}}}{k_e} = \frac{\ln 400 - \ln 150}{0.111 \times 8} = 8.84 \, \text{h} \sim 8 \, \text{h} \]

\[ C_{\text{max,ss,\text{total}}} = \frac{F \times \text{Dose}}{\text{VD}} \times \frac{1}{1 - \exp(-ke \times \tau)} \]

\[ \Rightarrow \text{Dose} = \frac{C_{\text{max,ss,\text{total}}} \times \text{VD} \times (1 - \exp(-ke \times \tau))}{F} \]

\[ = \frac{400 \, \text{µg}}{L} \times 288 \, \text{L} \times (1 - \exp(-0.111 \times 8)) \]

\[ = 225,992 \, \text{µg} = 226 \, \text{mg} \]

Thus, give two 100-mg and one 25-mg tablet TID.
Question 4 (10 points)

M.J., a 75-year-old, 81 kg male, 5'9" in height, with serum creatinine of 1.2 mg/dL, has been taking 0.25mg of digoxin tablets (S=1, F=0.7) orally for his chronic heart failure, and at 9:00 am on the day of admission, a digoxin plasma concentration of 0.75μg/L was measured. He continued on his outpatient maintenance doses which were administered at 9:00 am of Days 1 and 2 of his routine maintenance regimen. On Day 3, just before his morning dose, a second digoxin sample was obtained. What would be the predicted concentration for the second sample taken on the morning of the third day?

A. 0.78 μg/L
B. 0.88 μg/L
C. 0.99 μg/L
D. 1.09 μg/L
E. 1.17 μg/L

Key: C

IBW = 50 kg + 2.3*(Height – 5") = 50 + 2.3*9 = 70.7 kg
1.2 * IBW = 70.7 * 1.2 = 84.84 kg
TBW < 120% IBW

CL\text{Creat. (male)} = (140-75)*81/(72*1.2) = 60.94 mL/min

CL\text{Digoxin} = 0.33*IBW + 0.9*CL\text{Creat. (with-CHF)} = 0.33*70.7 + 0.9*60.94 = 78.18 mL/min

\[
= 78.18 \times 1440/1000 = 112.6 \text{ L/day}
\]

Vd\text{Digoxin} = 3.8 * IBW + 3.1 * CL\text{Creat.} = 3.8 * 70.7 + 3.1 * 60.94 = 457.57 L

ke = CL/Vd = 112.6/457.57 = 0.246 day\(^{-1}\)

C_{\text{min (day 3)}} = C_{\text{measured}} \times e^{ke*t1} + F*D/Vd \times e^{ke*t1} + F*D/Vd \times e^{ke*t2}

\[
= 0.75 \times e^{-0.246*2} + 0.7*250/457.57 \times (e^{-0.246*2} \times e^{-0.246*1})
\]

\[
= 0.99 \mu g/L
\]
Question 5 (5 points)

A male patient of 85 kg in weight was administered sodium phenytoin capsules by oral route. This patient exhibited phenytoin $K_M$ of 3.5 mg/L and phenytoin $V_{max}$ of 7.2 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. LD: 1200 mg sodium phenytoin; MD: 500 mg phenytoin
B. LD: 1200 mg sodium phenytoin; MD: 500 mg sodium phenytoin
C. LD: 1200 mg phenytoin; MD: 540 mg phenytoin
D. LD: 1200 mg phenytoin; MD: 500 mg sodium phenytoin
E. LD: 1200 mg phenytoin; MD: 540 mg sodium phenytoin

Key: A

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

$$V_d = 0.65 \frac{L}{kg} \times 85kg = 55.25L$$

$$LD = \frac{C_0 \times VD}{S \times F} = \frac{20 \frac{mg}{L} \times 55.25L}{0.92 \times 1} = 1201.1mg \ (sodium \ phenytoin)$$

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

$$MD = \frac{V_{max} \cdot C_{ss} \cdot \tau}{(K_m + C_{ss}) \cdot S \cdot F} = \frac{7.2 \frac{mg}{kg \cdot day} \times 85kg \times 15 \frac{mg}{L}}{(3.5 \frac{mg}{L} + 15 \frac{mg}{L}) \times 0.92 \times 1}$$

$$= 539.2mg \ (sodium \ phenytoin) = 496.2mg(phenytoin)$$
**Question 6 (5 points)**

R.J. is a 50-year-old, 70-kg man (non-obese) and has a serum creatinine of 1.2 mg/dL. R.J. is on long-term medication with verapamil. Calculate an oral maintenance dose at that will achieve an average steady state digoxin plasma concentration of 750ng/L. You may assume a rapid absorption process.

A. 100 mg  
B. 150 mg  
C. 100 μg  
D. 150 μg  
E. 200 mg

Key: C or D

\[
CL_{cr} = \frac{(140 - \text{age})(\text{weight in kg})}{72(SCR_{ss})} = \frac{(140 - 50)(70)}{72(1.2)} = 72.9 \text{ mL/min}
\]

\[
CL\left[\frac{\text{mL}}{\text{min}}\right] = (f_{\text{verapamil}})\left(0.8(\text{weight in kg}) + \left(CL_{cr}\frac{\text{mL}}{\text{min}}\right)\right)
\]

\[
= 0.75(0.8 \times 70 + 72.9) \approx 97 \frac{\text{mL}}{\text{min}}
\]

\[
97 \frac{\text{mL}}{\text{min}} = 5.8 \frac{L}{h} = 139.2 \frac{L}{\text{day}}
\]

\[
MD = \frac{CL \times C_{ss,avg} \times \tau}{F} = \frac{139.2 \frac{L}{\text{day}} \times 0.75 \frac{\mu g}{L} \times 1 \text{ day}}{0.7} \approx 150 \mu g
\]

\[
MD = \frac{CL \times C_{ss,avg} \times \tau}{F} = \frac{139.2 \frac{L}{\text{day}} \times 0.75 \frac{\mu g}{L} \times 1 \text{ day}}{1} \approx 100 \mu g
\]
**Question 7 (5 points)**

J.D. is a 2-year-old, 9 kg male child in the hospital who is placed on a theophylline drip at 1 mg/kg/hr after first receiving a 5 mg/kg bolus at 1 pm. The infusion is discontinued at 10pm. Plasma concentration samples were obtained at 2pm and 8pm and were 12 mg/L and 18 mg/L, respectively. Estimate his theophylline half-life based on the Chiou-equation?

A. 10 h  
B. 12 h  
C. 14 h  
D. 16 h  
E. Chiou-Equation is not applicable for this situation

**Key:** A

\[ VD = \left( 0.5 \frac{L}{kg} \right) (9 kg) = 4.5L \]

\[ R_0 = 9 \frac{mg}{h} \]

\[ CL = \frac{2R_0}{C_1 + C_2} + \frac{2Vd(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)} = \frac{2 \left( 9 \frac{mg}{h} \right)}{(12 + 18) \frac{mg}{L}} + \frac{2(4.5L)(12 - 18) \frac{mg}{L}}{(12 + 18) \frac{mg}{L} (6h)} = \]

\[ 0.6 \frac{L}{h} - 0.3 \frac{L}{h} = 0.3 \frac{L}{h} \]

\[ k_e = \frac{CL}{VD} = \frac{0.3 \frac{L}{h}}{4.5L} = 0.0666 \frac{1}{h} \]

\[ t_{0.5} = 10.4h \]
Question 8 (10 points)

I.K. is a 25 year old 50 kg female. She, after receiving a kidney transplant, is on cyclosporine 250 mg BID. Her trough level is measured and comes back as 80 ng/mL. Design a new dosing regimen based on this information with a target total drug $C_{\text{max}}$ of 400 ng/mL and a total drug $C_{\text{min}}$ of 150 ng/mL. You should assume a rapid absorption process and a 90% protein binding for cyclosporine.

A. 125 mg TID  
B. 250 mg TID  
C. 200 mg BID  
D. 200 mg TID  
E. 250 mg QD

Key : D

\[ V_d = 4.5 \text{ L/kg} \times 50 \text{ kg} = 225 \text{ L} \]

\[ C_{\text{max}} = F \times D / V_d + C_{\text{min}} = 0.3 \times 250 \text{ mg} \times 10^6 / 225 \text{ L} \times 10^3 + 80 \text{ ng/mL} = 413 \text{ ng/mL} \]

\[ k_c = \ln (413/80) / 12h = 1.642 / 12h = 0.137 \text{ h}^{-1} \]

\[ \tau = \ln (400/150) / 0.137 \text{ h}^{-1} = 7.16 \text{ h} \approx 8 \text{ h} \]

\[ \text{Dose} = C_{\text{max}} \times (1-\exp(-k_c\tau)) \times V_d / (F \times S) = 400 \text{ ng/mL} \times (1-\exp(-0.137*8)) \times 225 \text{ L} \times 10^3 / 0.3 = 199,740,000 \text{ ng} = 199.7 \text{ mg} \approx 200 \text{ mg} \]

$\Rightarrow$ 200 mg q8h
Question 9 (5 points)

What is the general reason that the ultimate desired maintenance dose of Carbamazepine is much higher than the starting dose?

A. Carbamazepine is a high hepatic extraction drug  
B. Metabolic enzyme autoinduction  
C. Pharmacodynamic drug tolerance  
D. Disease progression  
E. Renal function increased

Key : B
Question 10 (5 points)

P.M., a 45-year-old, 70-kg man, 5’2”, was admitted to the coronary care unit with a diagnosis of heart failure, probably myocardial infarction. Calculate a bolus dose that achieves lidocaine plasma level of 2.8 mg/L which should achieve an immediate response and calculate a maintenance infusion rate that will achieve a steady-state lidocaine concentration of 2.5 mg/L. (Note: Lidocaine is available as lidocaine hydrochloride). Round appropriately.

A. LD = 70 mg, MD = 55 mg/h  
B. LD = 80 mg/h, MD = 55 mg  
C. LD = 90 mg, MD = 65 mg/h  
D. LD = 90 mg/h, MD = 65 mg  
E. LD = 100 mg, MD = 65 mg/h

Key: A

\[
IBW_{male} = 50kg + 2.3kg(2) = 54.6kg
\]

\[
IBW * 1.2 = 65.5kg
\]

Thus, the patient is obese. Use TBW for Vc and IBW for CL.

\[
V_c = \left(0.3 \frac{L}{kg}\right)70kg = 21L
\]

\[
LD = \frac{(V_c)(c_{max,desired})}{S} = \frac{(21L)(2.8 \frac{mg}{L})}{0.87} = 67.6mg
\]

\[
MD = \frac{(CL)(c_{ss,avg})}{S} = \frac{(0.36 \frac{L}{h(kg)}54.6kg)(2.5 \frac{mg}{L})}{0.87} = 56.5 \frac{mg}{h}
\]
**Question 11 (10 points)**

A male patient, 75 years of age, 6'2" in height and 220 lbs in weight acquired *S. pneumonia*. His serum creatinine is 1.7 mg/dL. The MIC of vancomycin against his infection was estimated in the laboratory to be 1 µg/mL. Compute a dosing regimen so that the peak is 45 µg/mL and the trough is 20 µg/mL. Is the therapeutic goal attained (i.e. the 24-hour AUC divided by MIC is greater than 400)?

A. 550 mg q12h; 24h AUC/MIC is 980. Yes, therapeutic goal is achieved.
B. 1170 mg q12h; 24h AUC/MIC is 390. No, therapeutic goal is not achieved.
C. 1000 mg q8h; 24h AUC/MIC is 600. Yes, therapeutic goal is achieved.
D. 360 mg q8h; 24h AUC/MIC is 380. No, therapeutic goal is not achieved.
E. 1170 mg q12h; 24h AUC/MIC is 780. Yes, therapeutic goal is achieved.

Key: E

Solution:

220 lbs = 100 kg

6'2" = 74 inches

\[
IBW = 50 + 2.3(\text{height in inches} - 60) = 82.2
\]

\[
ABW = IBW + 0.4(TBW - IBW) = 89.3 \text{ kg}
\]

We will use the adjusted body weight given that he is over the 120% of the ideal body weight.

\[
CL_{cr}(male) = \frac{89.3 \times (140 - 75)}{72 \times (1.7)} = 47.4 \frac{mL}{min}
\]

\[
= 47.4 \frac{mL}{min} \times \frac{1L}{1000mL} \times \frac{60min}{hr} = 2.84 \frac{L}{h}
\]

\[
V_d = 0.17(age \text{ in yrs}) + 0.22(TBW \text{ in kg}) + 15 = 0.17(75) + 0.22(100) + 15 = 50 L
\]

\[
k = \frac{CL}{V_d} = \frac{2.84}{50} = 0.0568 \text{ h}^{-1}
\]

To compute the dosing interval,
\[ \tau = \frac{\ln \left( \frac{45}{20} \right)}{0.0568} = 14 \text{ hr} \sim 12 \text{ hr} \]

Dose = \( V_d \times C_{\text{max}} \times (1 - \exp(-k\tau)) = 50 \times 45 \times (1 - \exp(-0.0568 \times 12)) = 1112 \text{ mg} \)

Use 1170 mg since this is the closest choice.

\[
24h \ AUC = 2 \times \frac{Dose}{CL} = 2 \times \frac{1112 \text{ mg}}{2.84 \frac{L}{h}} = 783 \text{ mg.h/L}
\]

\[
\frac{24h \ AUC}{MIC} = 783
\]

E is the closest choice.
Question 12 (5 points)

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

1. The loading dose of phenytoin is usually administered all at once to alleviate its side effects.
2. The bioavailability of phenobarbital is difficult to determine due to its drug capacity-limited metabolism.
3. Phenobarbital target concentration is between 100 to 150 mg/L.
4. Carbamazepine taken over long period of time could result in autoinduction of its own metabolism.
5. Carbamazepine is both an inhibitor and an inducer of CYP3A4.

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

Key: B
Question 13 (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 (Cpss) of drug A? (5 points)

A. Cpss does not change
B. Cpss increases
C. Cpss decreases
D. Change in Cpss is not predictable since the protein tissue binding of drug A is unknown
E. Change in Cpss is not predictable since the volume of distribution is unknown

Key: B

ClInt of drug will decrease when its metabolic enzyme is inhibited. So the Cpss will increase.
Question 14 (10 points)

N.R. is a 54 kg female patient (48 years old) on methotrexate (MTX) therapy. Her serum creatinine is 1.5 mg/dL. She is treated with a loading dose (20 mg) followed by an infusion of 25 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 steady-state concentration, and the predicted concentrations at 24, 48 and 60 hours after the start of the infusion.

A. $C_{ss} = 6.7 \mu M, C_{24} = 6.7 \mu M, C_{48} = 0.42 \mu M, C_{60} = 0.26 \mu M$
B. $C_{ss} = 6.7 \mu M, C_{24} = 6.7 \mu M, C_{48} = 0.42 \mu M, C_{60} = 0.22 \mu M$
C. $C_{ss} = 13.0 \mu M, C_{24} = 13.0 \mu M, C_{48} = 0.5 \mu M, C_{60} = 0.13 \mu M$
D. $C_{ss} = 14.9 \mu M, C_{24} = 14.9 \mu M, C_{48} = 0.93 \mu M, C_{60} = 0.26 \mu M$
E. $C_{ss} = 10.8 \mu M, C_{24} = 10.8 \mu M, C_{48} = 0.67 \mu M, C_{60} = 0.2 \mu M$

Key: D

\[
CL_{cr\,female} = \frac{0.85 \times (140 - 48) \times 54}{72 \times 1.5} = 39.1 \frac{\text{mL}}{\text{min}} = 2.3 \frac{L}{h}
\]

\[
CL(\text{MTX}) = CL_{cr} \times 1.6 = 3.68 \frac{L}{h}
\]

\[
C_{ss} = \frac{R_0}{CL/mg} = \frac{25}{3.68} = 6.79 \frac{mg}{L}
\]

\[
\text{MTX (\mu M)} = \frac{\text{MTX (mg/L)}}{0.454} = \frac{6.79 \frac{mg}{L}}{0.454} = 14.9 \mu M
\]

24 h: 14.9 \mu M

48 h: $C_p = 14.9 \times e^{-0.231 \times 12} = 0.93 \mu M$

\[
t_1 = \frac{\ln \left( \frac{14.9}{0.5} \right)}{0.231} = 14.69 \text{ h}
\]

0.5 \mu M is reached after 36 + 14.69 = 50.69 h

60 h: $C_p = 0.5 \times e^{-0.069 \times 9.31} = 0.26 \mu M$
Question 15 (5 points)

A female patient of 60 kg in weight and 78 years in age was administered sodium phenytoin capsules by oral route. Phenytoin (not the salt form) has a volume of distribution of 0.7 L/kg. She is undergoing hemodialysis treatment thrice weekly and has a serum albumin of 3.3 g/dL and takes 300 mg/day of phenytoin. Her reported steady state plasma concentration is 7.5 mg/L. What would her phenytoin level if she had a normal serum albumin concentration and normal renal function? Should you adjust her daily phenytoin dose to achieve 10 to 20 mg/L in patient with normal protein binding?

A. Phenytoin concentration in normal protein binding is 23.15 mg/L; decrease her dose
B. Phenytoin concentration in normal protein binding is 13.15 mg/L; no change to her dose
C. Phenytoin concentration in normal protein binding is 3.5 mg/L; increase her dose
D. Phenytoin concentration in normal protein binding is 15.5 mg/L; decrease her dose
E. Phenytoin concentration in normal protein binding is 35.8 mg/L; increase her dose

Key: B is closest but accepts all answers (A, B, C, D, E)

Previous incorrect solution

\[
\text{Phenytoin Concentration (normal)} = \frac{\text{Phenytoin concentration (dialysis)}}{0.9 \times 0.48 \left( \frac{\text{Patient's serum albumin}}{4.4 \text{ g/dL}} \right)}
\]

\[
= \frac{7.5}{0.9 \times 0.48 \times \left( \frac{3.3}{4.4} \right)} = 23.15 \text{ mg/L}
\]

Correct solution

\[
\text{Phenytoin Concentration (normal)} = \frac{\text{Phenytoin concentration (dialysis)}}{0.9 \times \left( \frac{\text{Patient's serum albumin}}{4.4 \text{ g/dL}} \right) + 0.1}
\]
\[ = \frac{7.5}{\left[ 0.9 \times \left( \frac{3.3}{4.4} \right) + 0.1 \right]} = 9.7 \text{ mg/L} \]