Problem 1 (Digoxin)

A.P., a 75-year-old, 65-kg man (non-obese), was admitted with complaints of increased shortness of breath and yellow sputum production. He has a medical history of congestive heart failure. During his hospital stay, he developed atrial fibrillation and was given digoxin to slow his ventricular rate. He received 3 doses 0.25-mg digoxin IV every 3 hours (starting at 9pm on day 1) and was given a maintenance dose of 0.25-mg tablets each morning (starting at 9am on day 2). His serum creatinine is stable at 1.3 mg/dL.

Calculate his expected digoxin plasma concentration at 9am on day 4. (Hint: A graph of the expected concentration time profile might be helpful to answer this problem)

\[
CL_{cr} = \frac{(140 - age)(weight \ in \ kg)}{72(Scr_{ss})} = \frac{(140 - 75)(65)}{72(1.3)} = 45.1 \frac{mL}{min}
\]

\[
VD[L] = 3.8(weight \ in \ kg) + 3.1(CL_{cr} \ in \ mL/min) = 3.8 \times 65 + 3.1 \times 45.1 \approx 387 \ L
\]

\[
CL_{CHF} \left[ \frac{mL}{min} \right] = 0.33(weight \ in \ kg) + 0.9(CL_{cr} \ in \ mL/min)
\]
\[
= 0.33 \times 65 + 0.9 \times 45.1 \approx 62 \frac{mL}{min}
\]

\[
62 \frac{mL}{min} = 3.72 \frac{L}{h} = 89.3 \frac{L}{day}
\]

\[
k_e = \frac{CL}{VD} = \frac{89.3 \frac{L}{day}}{387 \ L} = 0.231 \frac{1}{day}
\]

\[
t_{0.5} = \frac{\ln(2)}{k_e} = 3 \ days
\]

Note that his loading dose of 0.75-mg (3 doses of 0.25-mg) was given over a total of 6 hours and that

\[
time \ from \ start \ to \ end \ of \ loading \ (tin) = 6h \leq 12h = \frac{t_{0.5}}{6}
\]

Thus, we can group the entire loading dose together as though it was given as a single dose, all administered when the first dose was given.

\[
C_{Sum} = \frac{F \times D_1}{V} e^{-k_{e}t_1} + \frac{F \times D_2}{V} e^{-k_{e}t_2} + \frac{F \times D_3}{V} e^{-k_{e}t_3} =
\]
A digoxin level obtained at 9am on the morning of day 4 was 1.5 μg/L. Do you observe any discrepancy between expected and observed digoxin plasma concentration level? If yes, explain the discrepancy between expected and observed dose.

There are several reasons, among them:

- Clearance and/or volume of distribution estimates are not correct
- The oral bioavailability of the drug was reduced in this patient (0.7 is an average value across the population)

Problem 2 (Methotrexate)

V.A., a 53-year-old, 65-kg woman (non-obese, SCr = 1.2 mg/dL) is to receive a course of methotrexate (MTX) therapy for acute lymphoblastic leukemia. Her regimen will consist of 400-mg MTX loading dose to be administered over 15 minutes followed by an IV infusion of 50 mg/h for the next 36 hours. Calculate her anticipated MTX plasma levels (in μM) for the following scheduled sampling times: 24h, 48h, and 60h, after the beginning of the 50 mg/h infusion. You may assume that steady state has been achieved after 24h. A sketch of the expected plasma-concentration-time profile may be helpful to answer this problem.

\[
\frac{750\mu g}{387L} e^{-0.231 \frac{1}{day} \cdot 2.5 days} + \frac{0.7 \cdot 250\mu g}{387L} e^{-0.231 \frac{1}{day} \cdot 2 days} + \frac{0.7 \cdot 250\mu g}{387L} e^{-0.231 \frac{1}{day} \cdot 1 day} = \\
\frac{\mu g}{387L} (750 \cdot e^{-0.5775} + 0.7 \cdot 250 \cdot e^{-0.462} + 0.7 \cdot 250 \cdot e^{-0.231}) = \\
\frac{\mu g}{387L} (421 + 110 + 139) = 1.73 \frac{\mu g}{L}
\]

\[
750 \mu g \quad e^{-0.231 \frac{1}{day} \cdot 2.5 \text{ days}} + 0.7 \cdot 250 \mu g \quad e^{-0.231 \frac{1}{day} \cdot 2 \text{ days}} + 0.7 \cdot 250 \mu g \quad e^{-0.231 \frac{1}{day} \cdot 1 \text{ day}} = \\
\frac{\mu g}{387L} \left( 750 \cdot e^{-0.5775} + 0.7 \cdot 250 \cdot e^{-0.462} + 0.7 \cdot 250 \cdot e^{-0.231} \right) = \\
\frac{\mu g}{387L} (421 + 110 + 139) = 1.73 \frac{\mu g}{L}
\]

\[
CL_{Cr} = (0.85) \frac{(140 - \text{age})(\text{weight in kg})}{72(SCR_{SS})} = (0.85) \frac{(140 - 53)(65)}{72(1.2)} = 55.6 \frac{mL}{min}
\]

\[
55.6 \frac{mL}{min} = 3.34 \frac{L}{h}
\]

\[
CL_{MTX} = (1.6)CL_{Cr} = (1.6)(3.34 \frac{L}{h}) = 5.34 \frac{L}{h}
\]

\[
C_{24} = C_{ss,avg} = \frac{\text{Dose}}{T \cdot CL} = \frac{50mg}{(1h) \left( 5.34 \frac{L}{h} \right)} = 9.36 \frac{mg}{L}
\]

\[
9.36 \frac{mg}{L} = 20.6\mu M
\]

\[
C_{48} = C_{36} \left( e^{-k_e(>0.5\mu M) \cdot 12h} \right)
\]

\[
t_{0.5(>0.5\mu M)} = 3h
\]
Let $t^*$ be the time (after stop of the infusion) that is required to for MTX concentration to fall to 0.5 $\mu$M.

$$
C_{48} = 20.6\mu M \left( e^{-0.231 \frac{1}{h} \cdot 12h} \right) = 1.29\mu M
$$

Thus, use 150-mg theophylline tablets.

**Problem 3 (Theophylline)**

S.R., a 66-kg (non-obese), 40-year-old woman, has been receiving an IV aminophylline infusion at a rate of 35 mg/h. Her steady state theophylline concentration is 15 mg/L and her therapeutic response is considered optimal at this concentration. Calculate an appropriate oral dosing regimen (for theophylline tablets and $\tau = 6h$) and ESTIMATE the peak and trough concentrations that would be produced by the regimen. Assume that theophylline tablets are available in doses of 100-mg, 150-mg, and 200-mg. (Hint: Textbook (Fifth Edition): p.423 – p.426)

$$
Dose_{IV}(aminophylline) = (6h) \left( \frac{35mg}{h} \right) = 210mg
$$

$$
Dose_{IV}(theophylline) = (0.8)210mg = 168mg
$$

Thus, use 150-mg theophylline tablets.

$$
\frac{C_{ss,avg,IV}}{Dose_{IV}} = \frac{C_{ss,avg,oral}}{Dose_{oral}}
$$

$$
C_{ss,avg,oral} = \left( \frac{15mg}{168mg} \right) \cdot 150mg = 13.4 \frac{mg}{L}
$$

**Method 1**

Based on the maximum difference between peak and trough concentrations at steady state
Method 2

Based on calculated CL and VD based on infusion data

\[ \frac{\Delta C}{VD} = \frac{150 \text{mg}}{0.5 \ \frac{L}{kg} \times 66 \text{kg}} = 4.5 \ \frac{mg}{L} \]

\[ C_{\text{max,ss}} = C_{\text{ss,avg}} + \frac{\Delta C}{2} = 13.4 \ \frac{mg}{L} + \frac{4.5 \ \frac{mg}{L}}{2} = 15.7 \ \frac{mg}{L} \]

\[ C_{\text{min,ss}} = C_{\text{ss,avg}} - \frac{\Delta C}{2} = 13.4 \ \frac{mg}{L} - \frac{4.5 \ \frac{mg}{L}}{2} = 11.2 \ \frac{mg}{L} \]

Problem 4 (Cyclosporine)

R.I., a 39-year-old, 102-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 steady state concentrations of 40 and 15 ng/mL. Cyclosporine is available in oral doses of 25-mg and 100-mg. Calculate the anticipated total cyclosporine plasma concentrations (in ng/mL) based on dosing regimen that you suggest. You may assume a rapid absorption process and, thus, use the equations for IV bolus administration.

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

\[ C_{\text{min,ss,free}} = \frac{C_{\text{min,ss}}}{f_u} = \frac{15 \ \frac{ng}{mL}}{0.1} = 150 \ \frac{ng}{mL} \]
Thus,

\[ CL = \left(0.5 \frac{L}{h(kg)}\right)102kg = 51 \frac{L}{h} \]

\[ VD = \left(4.5 \frac{L}{kg}\right)102kg = 459L \]

\[ k_e = \frac{CL}{VD} = \frac{51 \frac{L}{h}}{459L} = 0.111 \frac{1}{h} \]

\[
\tau = \frac{\ln\left(\frac{C_{\text{max,ss,total}}}{C_{\text{min,ss,total}}}\right)}{k_e} = \frac{\ln\left(\frac{400 \text{ ng mL}^{-1}}{150 \text{ ng mL}^{-1}}\right)}{0.111 \frac{1}{h}} = 8.84h \approx 8h
\]

\[ C_{\text{max,ss,total}} = \frac{F(Dose)}{VD} \frac{1}{(1 - e^{-k_e \tau})} \]

Thus,

\[ Dose = \left(\frac{C_{\text{max,ss,total}}}{VD}\right)\left(1 - e^{-k_e \tau}\right) = \frac{\left(400 \frac{\mu g}{L}\right)(459L)\left(1 - e^{-0.111 \frac{1}{h}8h}\right)}{0.3} \approx 360mg \]

Thus, give three 100-mg and two 25-mg tablet TID.

\[ C_{\text{max,ss,total}} = \frac{0.3(350mg)}{459L} \frac{1}{\left(1 - e^{-0.111 \frac{1}{h}8h}\right)} \approx 389 \frac{ng}{mL} \]

\[ C_{\text{min,ss,total}} = C_{\text{max,ss,total}}(e^{-k_e \tau}) = 389 \frac{ng}{mL} \left(e^{-0.111 \frac{1}{h}8h}\right) \approx 160 \frac{ng}{mL} \]

**Problem 5 (Lidocaine)**

P.M., a 45-year-old, 65-kg man, was admitted to the coronary care unit with a diagnosis of heart failure, probable myocardial infarction. Calculate a bolus dose that achieves lidocaine plasma level of 3mg/L which should achieve an immediate response. (Note: Lidocaine is available as lidocaine hydrochloride).

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

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

Calculate a maintenance infusion rate of that will achieve a steady-state lidocaine concentration of 3 mg/L. (Note: Lidocaine is available as lidocaine hydrochloride).
\[ MD = \frac{(CL)(C_{ss,avg})}{S} = \left(0.36 \frac{L}{h(kg)} \cdot 65kg\right) \left(3 \frac{mg}{L}\right) \frac{0.87}{0.87} = 80.7 \frac{mg}{h} \]