Problem 1 (Carbamazepine)

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

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

2. 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?

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

\[
Dose = \frac{C_{pss} \cdot CL \cdot \tau}{F \cdot S} = \frac{7.5 \text{ mg/L} \times 0.064 \text{ L/h/kg} \times 83.3 \text{ kg} \times 24 \text{ h/day}}{1 \times 0.8} = 1199.52 \sim 1200 \text{ mg/day}
\]

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

\[
MD = \frac{C_{pss} \cdot CL \cdot \tau}{F \cdot S} = \frac{7 \text{ mg/L} \times 0.1 \text{ L/kg} \times 83.3 \text{ kg} \times 24 \text{ hour/day}}{1 \times 0.8} = 1749.3 \text{ mg/day}
\]

\[
\frac{12.5 \text{ mg/L}}{7 \text{ mg/L}} = \frac{1749.3 \text{ mg/day}}{x} \Rightarrow x = 979.6 \sim 1000 \text{ mg/day}
\]
Problem 2 (Phenytoin)

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:

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

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

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

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

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

\[ = \left( 0.696 \times \ln \left( \frac{26}{15} \right) + (26 - 15) \right) \times \frac{35.75}{308 \times 0.92} = 1.44 \text{ day} \times 24 \]

\[ = 34.5 \text{ hr} \]
Problem 3 (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)

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

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

\[
CL_{CHF} \left[ \frac{\text{mL}}{\text{min}} \right] = 0.33(\text{weight in kg}) + 0.9(CL_{cr} \text{ in mL/min})
\]

\[
= 0.33 \times 65 + 0.9 \times 45.1 \approx 62 \frac{\text{mL}}{\text{min}}
\]

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

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

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

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

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

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.

\[
C_{sum} = \frac{F \ast D_1}{V} e^{-k_e t_1} + \frac{F \ast D_2}{V} e^{-k_e t_2} + \frac{F \ast D_3}{V} e^{-k_e t_3} =
\]

\[
\frac{750 \mu g}{387 \text{ L}} e^{-0.231 \frac{1}{\text{day}}} e^{0.7 \ast 250 \mu g} e^{-0.231 \frac{1}{\text{day}}} e^{0.7 \ast 250 \mu g} e^{-0.231 \frac{1}{\text{day}}} =
\]

\[
\frac{\mu g}{387 \text{ L}} \left( 750 \ast e^{-0.5775} + 0.7 \ast 250 \ast e^{-0.462} + 0.7 \ast 250 \ast e^{-0.231} \right) =
\]
\[
\frac{\mu g}{387L} (421 + 110 + 139) = 1.73 \frac{\mu g}{L}
\]

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 4 (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.

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

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

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

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

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

\[
C_{48} = C_{36}(e^{-k_e(>0.5\mu M)\times12h})
\]

\[
t_{0.5}(>0.5\mu M) = 3h
\]

\[
k_e(>0.5\mu M) = \frac{ln(2)}{3h} = 0.231 \frac{1}{h}
\]

\[
C_{48} = 20.6 \mu M(e^{-0.231 \frac{1}{h} \times 12h}) = 1.29 \mu M
\]

Let \( t^* \) be the time (after stop of the infusion) that is required to for MTX concentration to fall to 0.5 μM.

\[
t^* = \frac{ln\left(\frac{20.6 \mu M}{0.5 \mu M}\right)}{0.231 \frac{1}{h}} = 16.1h
\]

\[
60h - 36h - 16.1h = 7.9h
\]

\[
k_e(<0.5\mu M) = \frac{ln(2)}{10h} = 0.0693 \frac{1}{h}
\]

\[
C_{60} = 0.5 \mu M(e^{-0.0693 \times 7.9h}) = 0.29 \mu M
\]