Case Study I

1. A patient (m, 37y, 74 kg) with a subtherapeutic theophylline (5 \( \mu g/mL \)) is admitted to the ICU. Based on average pharmacokinetics parameters \( (V_d = 0.5 \text{ L/kg}, t_{1/2} = 8 \text{ h}) \), calculated an i.v. loading dose and a maintenance dose (i.v. infusion) to increase the level to 15 \( \mu g/mL \).

\[
V_d = 37 \text{L}
\]

\[
LD = (15 - 5) \cdot 37 = 370 \text{mg}
\]

\[
CL = \frac{0.693}{8} \cdot 37 = 3.2 \text{L/h}
\]

\[
MD = 15 \cdot 3.2 = 48 \text{mg/h or 1152 mg/d}
\]

2. What change in drug activity would you expect for a low-extraction drug if plasma protein binding is decreased 50%?

\[
CL = f_u \cdot CL_{int}
\]

\[
C_{ss} = \frac{R_0}{CL} = \frac{R_0}{f_u \cdot CL_{int}} \quad \text{(total concentration)}
\]

\[
f_u \cdot C_{ss} = \frac{R_0}{f_u \cdot CL_{int}} = \frac{R_0}{CL_{int}} \quad \text{(unbound concentration)}
\]

↑responsible for drug activity
no change if protein binding is decreased.

3. One hour after an intravenous dose of gentamicin the plasma level was 7.3 \( \mu g/mL \). Six hours after the dose the plasma level was 2.9 \( \mu g/mL \). Predict the plasma level at 10 hours after the dose.

\[
\ln \frac{7.3}{6 - 1} = 0.1846h^{-1}
\]

\[
C_{min} = 2.9 \cdot e^{-0.1846} = 1.39 \mu g / mL
\]
4. An 80 kg patient receives 500 mg theophylline i.v. by bolus injection every 6 hr. Assume that Vd = 0.5 L/kg and t1/2 = 6.4 h. Predict steady state peak and trough concentration.

\[ V_d = 40L, \quad k = \frac{0.693}{6.4} = 0.108h^{-1} \]

\[ C_0 = \frac{500}{40} = 12.5\mu g/mL \]

\[ C_{\text{max}} = \frac{12.5}{1-e^{-0.108 \cdot 6}} = \frac{12.5}{0.477} = 26.2\mu g/mL \]

\[ C_{\text{min}} = 26.2 \cdot e^{-0.108 \cdot 6} = 13.7\mu g/mL \]

5. Propranolol, a high-extraction drug, is combined with phenobarbital. What is your expectation for a potential change in propranolol half-life (show evidence).

\[ CL = Q \]

\[ t_{1/2} = \frac{0.693 \cdot V_d}{Q} \rightarrow \text{independent of } Cl_{int} \]

May be induced by phenobarb

no change

6. Lidocaine has a total body clearance of 9.2 mL/kg/minute. What zero-order infusion rate would be needed to induce a steady-state concentration of 10 µg/mL?

\[ R_0 = C \cdot CL \]

\[ = 10 \cdot 9.2 = 92 \frac{\mu g}{Kg \cdot min} \quad \text{or} \quad 5.5 \frac{mg}{h \cdot kg} \]
7. A 40 year-old female patient (60 kg, SeCr 0.8 mg/dL) is treated with 100 mg gentamicin TID infused over 30 minutes.

a) Assuming normal pharmacokinetics (Vd = 0.25 L/kg, CL=CLcr), predict the measured peak concentration and one hour after the infusion was started and the measured trough concentration one half-hour before the next infusion at steady state.

\[
CL_{cr} = \frac{(140 - 40) \cdot 60}{85 \cdot 0.8} = 88.2 \text{mL/min} = 5.3 \text{L/h}
\]

\[
k = \frac{CL}{V_d} = \frac{5.3}{15} = 0.35 \text{h}^{-1}
\]

\[
C_{\text{max}}^* = C_{\text{max}} \cdot e^{-0.35 \cdot 0.5} = 6.4 \cdot e^{-0.35 \cdot 0.5} = 5.4 \mu g / \text{mL} \quad \text{(to calculate } C_{\text{max}} \text{, see b)}
\]

\[
C_{\text{min}}^* = C_{\text{max}} \cdot e^{-0.35 \cdot 7.5} = 0.55 \mu g / \text{mL}
\]

b) In the same patient, calculate the peak and trough concentration.

\[
C_{\text{max}} = \frac{100}{5.3 \cdot 0.5} \cdot \frac{(1 - e^{-0.35 \cdot 0.5})}{(1 - e^{-0.35 \cdot 8})} = 37.7 \cdot \frac{0.161}{0.939} = 6.4 \mu g / \text{mL}
\]

\[
C_{\text{min}} = 6.4 \cdot e^{-0.35 \cdot 7.5} = 0.46 \mu g / \text{mL}
\]

c) Calculate the true volume of distribution in this patient.

\[
V_d = \frac{100}{0.35 \cdot 0.5} \cdot \frac{(1 - e^{-0.35 \cdot 0.5})}{(6.4 - 0.39 \cdot e^{-0.35 \cdot 0.5})} = 571 \cdot \frac{0.161}{6.073} = 15.1 \text{L}
\]

or 0.25 L/kg

d) Design a dosing regiment to produce a peak of 6 µg/mL and a trough of 1 µg/mL.

\[
\tau = \frac{\ln \frac{6}{k} + 0.5}{5.6} = 6 \text{h} \rightarrow 6h
\]

\[
D = 6 \cdot 0.35 \cdot 15.1 \cdot 0.5 \cdot \frac{(1 - e^{-0.35 \cdot 6})}{(1 - e^{-0.35 \cdot 0.5})} = 86 \text{mg}
\]

\[\rightarrow 80 \text{ or } 100 \text{ mg Q6H}\]