1. A drug has a total body clearance of 45 mL/min and a volume of distribution of 35 L. It is completely absorbed. The therapeutic range is 10-20 µg/ml. Make a dosing recommendation for chronic use.

\[ C_{l_{tot}} = 45 \text{ ml/min}, \ V_d = 35 \text{ L} \]

Recommend a dosing regimen for achieving concentrations in the therapeutic range of 10-20 µg/ml.

Since the problem states the drug is completely absorbed, we will assume that an oral dosing regimen is needed.

We will also assume that the drug is fast-absorbing and IV bolus equations are sufficient to determine dose and dosing interval.

Start by finding \( \tau \):

\[
\tau = \frac{\ln \left( \frac{C_{p_{ss}}(\text{max})}{C_{p_{ss}}(\text{min})} \right)}{k_e}
\]

\( C_{p_{ss}}(\text{max}) = 20 \mu g/ml \)

\( C_{p_{ss}}(\text{min}) = 10 \mu g/ml \)

\( k_e \) may be calculated from \( Cl \) and \( Vd \)

\[
Cl = k_e \cdot Vd \rightarrow k_e = \frac{Cl}{Vd}
\]
\[ k_e = \frac{45 \, ml/min}{35L} \cdot \frac{1L}{1000ml} \cdot \frac{60 \, min}{1hr} = 0.077 \, hr^{-1} \]

The dosing interval is then

\[ \tau = \frac{\ln(20/10)}{0.077 \, hr^{-1}} = 9 \, hr \approx 8 \, hr \]

At steady-state, maximum plasma concentrations are:

\[ Cp_{ss}^{\text{max}} = \frac{D}{Vd \cdot (1 - e^{-k_e \cdot \tau})} \]

This equation may be used to determine the dose after solving for \( D \) and setting \( Cp_{ss}^{\text{max}} \) to 20 \( \mu \)g/ml.

\[ D = Cp_{ss}^{\text{max}} \cdot Vd \cdot (1 - e^{-k_e \cdot \tau}) \]

\[ = (20 \, \mu \text{g} / \text{ml}) \cdot (35L)(1 - e^{-0.077 \, hr^{-1} \cdot 8 \, hr}) \cdot \frac{1000ml}{L} \cdot \frac{1mg}{1000\mu g} = 322mg \]

This dosage would, of course, be rounded to a more convenient number depending on the tablets available.
2. A patient (m, 35y, 74 kg) with a subtherapeutic theophylline (5 µg/mL) is admitted to the ICU. Based on average pharmacokinetics parameters (Vd = 0.5 L/kg, t1/2 = 8 h), calculated an i.v. bolus loading dose and a maintenance dose (i.v. infusion) to increase the level to 15 µg/mL.

\[ V_d = 74 \times 0.5 = 37\text{L} \]
\[ LD = (15 - 5) \times 37 = 370\text{mg} \]
\[ CL = \frac{0.693}{8} \times 37 = 3.2\text{L/h} \]
\[ MD = 15 \times 3.2 = 48\text{mg/h or 1152 mg/d} \]
3. **Show the effect of changes in protein binding on the AUC of any drug given orally. Assume that the drug undergoes first pass metabolism.**

AUC depends on the amount of dose absorbed into systemic circulation and clearance.

\[
AUC = \frac{F \cdot D}{Cl}
\]

Assuming that first-pass effect and clearance are due to hepatic processes,

\[
F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu}
\]

\[
Cl_H = \frac{Q_H \cdot Cl_{int} \cdot fu}{Q_H + Cl_{int} \cdot fu}
\]

\[
AUC = \frac{Q_H}{(Q_H + Cl_{int} \cdot fu)} \cdot D \cdot \frac{(Q_H + Cl_{int} \cdot fu)}{Q_H \cdot Cl_{int} \cdot fu}
\]

\[
= \frac{D}{Cl_{int} \cdot fu}
\]

If fu increases, AUC decreases. As fu decreases, AUC increases. The magnitude of these changes will be dependent on the value of Cl_{int} (i.e. whether the drug is high- or low-extraction).
4. Calculate the extraction ratio of phenybutazone in a 70 kg patient, given the following information: liver blood flow, 1500 ml/min; half-life, 50 h; Vd, 0.1 l/kg; no non-hepatic elimination.

For hepatic clearance,
\[ Cl_H = E_H \cdot Q_H \]
Where \( E_H \) is the extraction ratio and \( Q_H \) is hepatic blood flow. In order to calculate \( E_H \) using this expression, we must know \( Cl_H \). Although \( Cl_H \) is not given, enough information is provided to calculate it.

For a 70 kg patient,
\[ Vd = \frac{0.1L}{kg} \cdot 70kg = 7.0L \]

The half-life may be used to find \( k_e \).
\[ k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{50hr} = 0.0139hr^{-1} \]

Clearance may now be calculated:
\[ Cl = k_e \cdot Vd \]
\[ = (0.0139 \text{ hr}^{-1}) \cdot (7.0L) \]
\[ = 0.0973L/hr \cdot \frac{1000ml}{L} \cdot \frac{1hr}{60\text{min}} = 1.62ml/min \]

Actually, total body clearance is calculated from this expression. Since the problem states "no non-hepatic elimination", we may assume \( Cl_H = 1.62 \text{ ml/min} \).

The extraction ratio is then
\[ E_H = \frac{Cl_H}{Q_H} \]
\[ = \frac{1.62ml/min}{1500ml/min} = 0.0011 \]
5. An 80 kg patient receives 500 mg theophylline i.v. by bolus injection every 6 hr. Assume that $V_d = 0.5 \text{ L/kg}$ and $t_{1/2} = 6.4 \text{ h}$. Predict steady state peak and trough concentration.

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

$$C_0 = \frac{500}{40} = 12.5 \mu\text{g} / \text{mL}$$

$$C_{\text{max}} = \frac{12.5}{1 - e^{-0.108\cdot6}} = \frac{12.5}{0.477} = 26.2 \mu\text{g} / \text{mL}$$

$$C_{\text{min}} = 26.2 \cdot e^{-0.108\cdot6} = 13.7 \mu\text{g} / \text{mL}$$
6. Propranolol, a high-extraction drug, is combined with phenobarbital. What is your expectation for a potential change in propranolol half-life (show evidence).

\[ CL = Q_H \]

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

no change