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

\[ \text{Cl}_{\text{tot}} = 45 \text{ ml/min}, \text{ Vd} = 35 \text{ L} \]

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.

Since the drug is fast-absorbing, IV bolus equations are sufficient to determine dose and dosing interval.

Start by finding τ:

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

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

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

\[ k_e \text{ may be calculated from Cl and Vd} \]

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

The dosing interval is then

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

At steady-state, maximum plasma concentrations are:

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

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

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

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

This dosage would, of course, be rounded to a more convenient number depending on the tablets available.
2. A patient (male, 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, t_{1/2} = 8 h)), calculated an i.v. bolus loading dose and a maintenance dose (i.v. infusion) to increase the level to 15 μg/mL.

\[ V_d = 74 \cdot 0.5 = 37 \text{L} \]
\[ LD = (15 - 5) \cdot 37 = 370 \text{mg} \]
\[ CL = \frac{0.693}{8} \cdot 37 = 3.2 \text{L/h} \]
\[ MD = 15 \cdot 3.2 = 48 \text{mg/h or } 1152 \text{mg/d} \]
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 \( k_e \).
\[ k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{50hr} = 0.0139/hr^{-1} \]

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

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

The extraction ratio is then
\[ E_H = \frac{Cl_H}{Q_H} \]
\[ = \frac{1.62ml/min}{1500ml/min} = 0.0011 \]
5. A patient is admitted with an acute theophylline overdose. A serum level is measured at 45 µg/ml. Assuming an 8 hour half-life and no further drug absorption, how long does it take for the serum level to drop to the upper limit of the therapeutic range (20 µg/ml)?

\[ k = \frac{0.693}{8} = 0.087 h^{-1} \]

\[ 20 = 45 \cdot e^{-0.087t} \]

\[ \frac{20}{45} = e^{-0.087t} \]

\[ \ln(0.44) = -0.087 \cdot t \]

\[ -0.811 = -0.087 \cdot t \]

\[ t = 9.3 \text{ h} \]