1. A patient is admitted with an acute theophylline overdose. This patient is a 55 year old male who smokes. A serum level is measured at 44 μg/mL. Assuming a 5 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 (20μg/mL)?

\[ t_{1/2} = 5 \text{ hours} \]
\[ ke = \frac{0.693}{5 \text{ hours}} = 0.1386 \text{ hours}^{-1} \]
\[ C = C_0 e^{-ke t} \]
\[ \frac{C}{C_0} = e^{-ke t} \]
\[ \ln\left(\frac{C}{C_0}\right) = -ke t \]
\[ t = \frac{\ln\left(\frac{20}{44}\right)}{-0.1386 \text{ hours}^{-1}} = 5.69 \text{ hours} \]

2. Please answer the following questions with true or false:
   a) for high extraction drugs:
      1) In case of a increasing fraction unbound, the extraction ratio of the drug stays the same,
      
      **Answer:**
      TRUE, for high extraction drugs, \( E \approx 1 \), independent on fraction unbound

   2) In case of increased hepatic blood flow, the clearance stays the same
      
      **Answer:**
      FALSE : for high extraction drugs , \( CL_{\text{hep}} = Q_H \), when \( Q \) increase, \( CL_{\text{hep}} \) increases

   b) for low extraction drugs:
      1) In case of increasing fraction unbound, the extraction ratio of the drug stays the same,
      
      **Answer:**
      FALSE: for low extraction drugs, \( E \approx \frac{Cl_{\text{int}} \cdot fu}{Q} \), when \( fu \) increase, \( E \) increases
2) In case increasing hepatic blood flow, the clearance of the drug stays the same.

**Answer:**
TRUE: for low extraction drugs, $\text{Cl}_{\text{hep}} \approx \text{Cl}_{\text{int}} \cdot \text{fu}$, independent of liver blood flow.

3. K.M. is a 50 year old male weighing 70 kg with a subtherapeutic theophylline level (5µg/mL). Base on population pharmacokinetic parameters ($V_d=0.5L/kg$, $t_{1/2}=8 hours$) calculate an IV bolus loading dose and a daily maintenance dose to increase the level to 12 µg/mL.

$V_d=0.5L/kg \cdot 70kg=35L$

$LD=(12mg/L-5mg/L) \cdot 35L=245mg \sim 250mg$

$K_e=0.693/8hours=0.0866hours^{-1}$

$C_l=k_e \cdot V_d=3.03L/hr$

$M_D=12mg/L \cdot 3.03L/hr=36.4mg/hr \cdot 24hr/day=36.4mg/hr \cdot 24hr/day=873.6 \sim 874mg/day$

If this drug were to be given as aminophylline dehydrate ($S=0.8$) what would be the maintenance dose?

$Dose = 874mg/day/0.8 = 1093mg/day$

4. A drug is given via continuous IV infusion for 24 hours. It is infused at a rate of 50 mg/hr. The clearance for this drug is 7.5 L/hr and the volume of distribution is 0.25L/kg (the patient weighs 70kg). The concentration-time profile is presented below.
A. What would the concentration-time profile look like if the volume of distribution were doubled?

We know that it takes approximately 5 half-lives to reach steady state. How long to steady state?

\[ t_{1/2} = \frac{0.693}{0.429\text{ hr}^{-1}} = 1.62 \times 5 \approx 8 \text{ hours} \]

If Vd is doubled, ke is half, and the time to reach steady state is twice as long, \( \approx 16 \text{ hours} \). If Vd is doubled, the concentration as steady state is not changed because

\[ C_{ss} = \frac{D}{\text{CL} \times \tau} = \frac{50\text{mg/hr}}{7.5\text{L/hr}} = 6.67\text{ mg/L} \]

Using this information, we can now draw a rough concentration-time profile.

B. What would the concentration-time profile look like if the clearance were doubled?
If the clearance is doubled using the same reason as above we see that steady state is reached in about 4 hours. Also our new stead state concentration is 3.33 mg/L. \( \text{Css} = \frac{50 \text{mg/hr}}{15 \text{L/hr}} = 3.33 \text{mg/L} \). We can now draw a rough concentration-time profile.