1. A patient with pulmonary disease is receiving IV bolus injections of theophylline. The dose is 200 mg every 6 hr with satisfactory response. Recently, steady state theophylline plasma concentrations were determined to be 15 mg/L 1 hour after the last dose administration and 8.2 mg/L 6 hr after the last dose administration (trough).

   a. Determine the elimination rate constant.
   \[ C_{t1} = C_{t2} \cdot e^{-Ke(t1-t2)} \]
   \[ 8.2 = 15 \cdot e^{-Ke(6-1)} \]
   \[ Ke = \frac{\ln(8.2/15)}{-5} = 0.12/\text{hr} \]

   b. Volume of distribution.
   At steady state,
   \[ C_{pss}(t) = \frac{C_{p0} \cdot e^{-kt}}{(1-e^{-kt})} = \frac{D \cdot e^{-kt}}{V_d \cdot (1-e^{-kt})} \]
   where \( t \) is the time after last i.v. bolus injection. So, plug in the given plasma concentration one hour after administration.
   \[ V_d = \frac{D \cdot e^{-kt}}{C_{pss}(t) \cdot (1-e^{-kt})} = \frac{(200\text{mg}) \cdot e^{-0.12\text{hr}^{-1} \cdot 1\text{hr}}}{(15\text{mg/L}) \cdot [1 - e^{-0.12\text{hr}^{-1} \cdot 6\text{hr}}]} \]
   \[ V_d = 23 \text{ L} \]

   c. Determine the clearance.
   \[ Cl = ke \cdot V_d = (0.12\text{hr}^{-1})(23\text{L}) = 2.76 \text{ L/hr} \]

   d. Estimate also the average steady state theophylline concentration (\( C_{pss} \)) with this regimen.
   \[ \bar{C}_{pss} = \frac{D}{Cl \cdot r} = \frac{200\text{mg}}{(0.12\text{hr}^{-1} \cdot 23\text{L}) \cdot (6\text{hr})} = 12.07 \text{mg/L} \]
2. The population pharmacokinetics of a drug for a 70kg person are: V=260 liters, Cl=5L/hr. If a patient (69kg) take 40 mg of this drug daily after breakfast.
   a. The accumulation factor at steady state.
      \[ K_e = \frac{C_l}{V_d} = \frac{5}{260} = 0.019/\text{hr} \]
      \[ R_{ss} = \frac{1}{1 - \exp(-K_e \cdot \tau)} = \frac{1}{1 - \exp(-0.019 \cdot 24)} = 2.73 \]
   b. How long it takes to achieve 50% of the steady state.
      Need one half life to achieve 50% of the steady state.
      \[ T_{1/2} = \frac{0.693}{0.019} = 36.5 \text{ hr} \]
   c. The maximum and minimum amount in the body at steady state.
      \[ C_{\text{max}} = \frac{D}{V_d} \cdot R_{ss} = \frac{40}{260} \cdot 2.73 = 0.42 \text{ mg/L} \]
      \[ A_{\text{max}} = C_{\text{max}} \cdot V_d = 0.42 \cdot 260 = 109.2 \text{ mg} \]
      \[ C_{\text{min}} = C_{\text{max}} \cdot \exp(-K_e \cdot 24) = 0.42 \cdot \exp(-0.019 \cdot 24) = 0.27 \text{ mg/L} \]
      \[ A_{\text{min}} = C_{\text{min}} \cdot V_d = 0.27 \cdot 260 = 70.2 \text{ mg} \]

3. True and False

1. The smaller elimination constant, the bigger fluctuation.
   False. \( F = C_{\text{max}}/C_{\text{min}} = \exp(K_e \cdot \tau) \)

2. The higher dose, the higher steady state average concentration.
   True. \( C_{\text{ave}} = \frac{Dose}{C_l \cdot \tau} \)

3. The longer dosing interval, the longer to achieve steady state.
   False. Time to achieve steady state is about 5 half-lives.

4. The longer half life, the smaller degree of accumulation.
   False. The longer half-life, smaller \( K_e \). \( R_{ss} = \frac{1}{1 - \exp(-K_e \cdot \tau)} \).

5. The higher clearance, the smaller AUC during one dosing interval at steady state.
   True. \( AUC = \frac{Dose}{C_l} \). The AUC during one dosing interval at steady state.
   Is identical to \( AUC_{\text{inf}} \) of the first dose.