1. (10 pt.) One hour after the end of an intravenous 30 min. infusion of 160 mg gentamicin, the plasma level was 6.3 µg/mL. Six hours later the plasma level was 2.9 µg/mL. Predict the plasma level at 12 hours after the dose was started.

\[
\ln\left(\frac{6.3}{2.9}\right) = 0.129 \text{ h}^{-1}
\]

\[
C = 2.9 \cdot e^{-0.129 \cdot 4.5} = 1.6 \text{ µg/mL}
\]

2. (15 pt.) A 40 year-old female patient (65 kg, SeCr 0.9 mg/dL) is treated with 80 mg gentamicin TID infused over 30 minutes. Assuming normal pharmacokinetics (Vd = 0.25 L/kg, CL=CLcr), predict the steady-state peak concentration that can be expected one hour after the infusion was started and the expected measured trough concentration one half-hour before the next infusion at steady state.

\[
CL = \frac{(140 - 40) \cdot 65}{85 \cdot 0.9} = 85 \text{ mL/min} = 5.1 \text{ L/h}
\]

\[
V_d = 0.25 \cdot 65 = 16.3 \text{ L}
\]

\[
k = \frac{5.1}{16.3} = 0.31 \text{ h}^{-1}
\]

\[
C_{max} = \frac{80}{5.1 \cdot 0.5} \cdot \frac{\left(1 - e^{-0.310.5}\right)}{\left(1 - e^{-0.318}\right)} = 4.93 \text{ µg/mL}
\]

\[
C^*_{max} = C_{max} \cdot e^{-0.310.5} = 4.2 \text{ µg/mL}
\]

\[
C_{min}^* = C_{max} \cdot e^{-0.317} = 0.56 \text{ µg/mL}
\]
3. (15 pt.) K.L., a 75 kg male smoker with chronic obstructive pulmonary disease, is to be started on an oral regimen of aminophylline (85% of which is theophylline). The pharmacokinetic parameters for this patient are Vd (0.5 L/kg), CL (80 mL/h/kg) and F (1.0).

a. Design an oral dosage regimen of aminophylline (100- and 200 mg tablets are marketed) for this patient to attain and maintain a plasma concentration within the therapeutic range (10-20 gg/ml). The absorption of theophylline is complete and rapid.

\[ \text{CL} = 80 \times 75 = 6 \text{ L/h} \]
\[ \text{Vd} = 0.5 \times 75 = 37.5 \text{ L} \]
\[ k = \frac{6}{37.5} = 0.16h^{-1} \]
\[ \tau = \frac{\ln \left( \frac{20}{10} \right)}{0.16} = 4.3 \rightarrow 4h \]
\[ D = 15 \times 6.4 = 360 \text{ mg theophylline} = 424 \text{ mg aminophylline} \]
\[ \rightarrow 400 \text{ mg Q 4h} \]

b. Discuss the result and make an alternative treatment recommendation.

Too frequent → poor compliance

→ give sustained release product
4. (10 pt.) PT is a patient stabilized on chronic phenytoin therapy. She has just been diagnosed with rheumatoid arthritis and her physician would like to start her on high dose aspirin therapy. However, the physician is concerned about a possible drug interaction with aspirin. You find in your pocket reference that high dose aspirin is known to displace phenytoin from its plasma protein binding sites. Also, you find that phenytoin is a low-extraction drug. Describe (as you would to the physician) the clinical relevance of this interaction and your therapeutic recommendations.

CL ~ fu · CL_int

\[ C_{p_{ss}} = \frac{F \cdot D}{CL \cdot \tau} = \frac{F \cdot D}{fu \cdot CL_{int} \cdot \tau} \]

\[ C_{p_{ss(free)}} = fu \cdot C_{p_{ss}} = \frac{F \cdot D}{CL_{int} \cdot \tau} \text{ clinically relevant, not changed} \]

→ no dose adjustment needed

5. (15 pt.) Lidocaine has the following average pharmacokinetic parameters: CL 9.2 ml/min/kg, Vd 1.1 l/kg, Fren (% renally eliminated) 2%, Foral (% orally absorbed) 35%, fb (% bound to plasma proteins) 70%. If the drug were given orally, estimate the expected bioavailability if hepatic first-pass effect is the only mechanism for incomplete bioavailability. Interpret the result.

\[ F_H = 1 - E = \frac{Q}{Q + fu \cdot CL_{int}} \]

\[ E_H = \frac{CL_H}{Q} = \frac{631}{1500} = 0.42 \]

CL_H = 0.98 · 9.2 · 70 = 631 mL/min

Expected F = 1 - 0.42 = 0.58

The difference between the observed F of 35% and the expected F of 58% is due to additional, non-hepatic first-pass effect, e.g. gut wall metabolism.
6. (15 pt.) Ceftriaxone has the following average pharmacokinetic parameters: CL 0.24 ml/min/kg, Vd 0.161/kg, f_u 93%, F_{ren} 49%. For a 70 kg, 50 yo male patient with a serum creatinine of 0.8 mg/dl, calculate the necessary intravenous daily dose to produce an average unbound serum concentration of 15 mg/l. How would you have to modify the dose, if the patient develops renal problems and his serum creatinine rises to 2.4 mg/dl?

CL = 0.24 \cdot 70 = 16.8 \text{ mL/min} = 1 \text{ L/h}

V_d = 0.16 \cdot 70 = 11.2 \text{L}

CL_R = 0.49 \cdot 16.8 = 8.2 \text{ mL/min} = 0.49 \text{ L/h}

\[
D = \frac{C_u \cdot CL \cdot \tau}{f_u \cdot F} = \frac{15 \cdot 1.24}{0.07 \cdot 1} = 5.1 g
\]

new CL_R = 0.33 \cdot 0.49 = 0.16 \text{ L/h}

new CL = 0.51 + 0.16 = 0.67 \text{ L/h}

new dose

\[
D = \frac{15 \cdot 0.67 \cdot 24}{0.07 \cdot 1} = 3.4 g
\]
7. (10 pts) Theophylline is administered as a constant rate infusion over 2 days. A plasma concentration profile is obtained which is shown in the two figures below.

a. In the graph below, add the expected curve for a patient with twice the clearance and twice the volume of distribution.

b. In the graph below, add the expected curve in a smoker with half the volume of distribution but equal clearance.
8. (10 pt.) Show how an increase in tissue binding will affect the clearance, bioavailability and half-life of a low-extraction drug.

a. \( \text{CL} = \text{fu} \cdot \text{CL}_{\text{int}} \) no change

b. \( F = 1 - E = \frac{Q}{Q + \text{fu} \cdot \text{CL}_{\text{int}}} \) no change

c. \( V_d = V_b + \frac{\text{fu}}{\text{fu}_T \cdot V_T} \) increase in tissue binding

\[ \rightarrow \downarrow \text{fu}_T \rightarrow \uparrow V_d \]

\( t_{1/2} = \frac{0.693 \cdot V_d}{\text{CL}} \) \( \rightarrow \) increase in \( t_{1/2} \).