1. Estimate the half-life of gentamicin in two male patients with normal renal function (CL=0.12 L/min) if their weight is 63 kg and 88 kg, respectively. Assume a height of 6’ for both patients. (2 points)

We can easily determine $t_{1/2}$ from the equation $CL = ke \cdot Vd$. Since clearance is given, only $Vd$ remains to be found in order to calculate $t_{1/2}$ for the two patients.

In the notes, a series of equations was presented for aminoglycosides. We can determine the $Vd$ of a patient by using the equation: $Vd = 0.25(\text{TBW})$ for patients within 20% of their ideal body weight (and no excess third space fluid), therefore, we must first calculate IBW for each patient:

$$\text{IBW} = 50 + 2.3(\text{height in inches} > 60 \text{ in})$$
$$= 50 + 2.3 \cdot (12)$$
$$= 77.6 \text{ kg}$$

for both patients, since they are of equal height. We see that both patients are within 20% of their IBW, and now we can determine the volume of distribution for each patient:

For patient 1: $Vd(63\text{kg}) = (0.25 \text{ L/kg}) \cdot 63 \text{ kg} = 15.8 \text{ L}$
For patient 2: $Vd(88\text{kg}) = (0.25 \text{ L/kg}) \cdot 88 \text{ kg} = 22 \text{ L}$

Since $CL = ke \cdot Vd$, and

$$t_{1/2} = \frac{0.693}{ke}$$

For the 63 kg patient, $ke = \frac{0.12 \text{ L/min}}{15.8 \text{ L}} \cdot \frac{60 \text{ min}}{1 \text{ hour}} = 0.46 \text{ hr}^{-1}$ and $t_{1/2} = \frac{0.693}{0.46 \text{ hr}^{-1}} = 1.51 \text{ hr}$

For the 88 kg patient, $ke = \frac{0.12 \text{ L/min}}{22 \text{ L}} \cdot \frac{60 \text{ min}}{1 \text{ hour}} = 0.327 \text{ hr}^{-1}$ and $t_{1/2} = \frac{0.693}{0.327 \text{ hr}^{-1}} = 2.12 \text{ hr}$
2. Drug A has the following average pharmacokinetic parameters: \( CL \) 0.08 ml/min/kg, \( Vd \) 0.16 l/kg, \( fb \) 93%, \( Fren \) 49%. For a 70 kg, 50 year old male patient with a serum creatinine of 0.7 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 2.8 mg/dl? (2 points)

\[
CL = 0.08 \times 70 = 5.6 \text{ mL/min} = 0.336 \text{ L/hr}
\]

\[
Vd = 0.16 \times 70 = 11.2 \text{ L}
\]

Since the total \( CL \) is the sum of the \( CL_{R} \) and \( CL_{NR} \), we know that:

\[
CL_{R} = 0.49 \times 0.336 \text{ L/hr} = 0.165 \text{ L/hr} \quad \text{and} \quad CL_{NR} = 0.171 \text{ L/hr}
\]

The dose can now be calculated:

\[
D = \frac{Cu \times CL \times \tau}{fu \times F} = \frac{15 \times 0.336 \times 24}{0.07 \times 1} = 1728 \text{ mg} = 1.73 \text{ g}
\]

The change in renal clearance would result in new parameters:

\[
CL_{R} = 0.25 \times 0.165 = 0.041 \text{ L/h} \quad \text{(since renal clearance was reduced to 1/4, as evidenced by the serum creatinine levels rising from 0.7 mg/dL to 2.8 mg/dL)}
\]

\[
CL = 0.171 + 0.041 = 0.212 \text{ L/h}
\]

The new dose can now be calculated:

\[
D = \frac{15 \times 0.212 \times 24}{0.07 \times 1} = 1090 \text{ mg} = 1.09 \text{ g}
\]

3. A drug has a total body clearance of 40 ml/min and a volume of distribution of 35 L. It is quickly and completely absorbed. The therapeutic range is 10-25 mg/ml. Make an oral dosing recommendation for chronic use. (2 points)

We start by finding \( \tau \), using the equation:

\[
\tau = \frac{\ln(Cp_{ss, \text{max}} / Cp_{ss, \text{min}})}{k_e}
\]

To obtain \( ke \), we use \( Cl \) and \( Vd \), as follows:

\[
Cl = k_e \times Vd \rightarrow k_e = \frac{Cl}{Vd} \quad \text{so} \quad k_e = \frac{40 \text{ ml/min}}{35 \text{ L}} \times \frac{1 \text{ L}}{1000 \text{ ml}} \times \frac{60 \text{ min}}{1 \text{ hr}} = 0.069 \text{ hr}^{-1}
\]
The dosing interval is then:

\[
\tau = \frac{\ln(25/10)}{0.069\text{hr}^{-1}} = 13.3\text{hr} \approx 12\text{hr}
\]

At steady-state, maximum plasma concentrations are:

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

This equation may be used to determine the dose after solving for D and setting Cpss(max) to 25 mg/ml.

\[
D = C_{p_{ss}}(\text{max}) \cdot Vd \cdot (1 - e^{-k_{e}\tau})
\]

\[
= (25mg / ml) \cdot (35L)(1 - e^{-(0.069hr^{-1} \times 12hr)}) \cdot \frac{1000ml}{L} = 492g
\]

Recommended dose based on the therapeutic range is: 500 g b.i.d.

4. a) You are working as a pharmacokineticist in a pharmaceutical company, and have been assigned the task of assessing what kind of studies will have to be performed to approve a new syrup form of a drug that your company currently has on the market as an oral solution. Your team asks if it will be necessary to perform a clinical study. What is your answer? Please elaborate. (1 point)

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, BA and/or BE can be demonstrated using nonclinical studies. Generally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption.

b) Under what circumstances can product quality BA and BE can be documented using in vitro approaches? (1 point)

For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) is appropriate based on the biopharmaceutics classification system. This approach may also be suitable under some circumstances in assessing BE during the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved NDAs and ANDAs.

5. a) Your patient, a pharmacy student, is suffering from generalized anxiety disorder. He was prescribed Xanax 0.5 mg tablets t.i.d. by his doctor. Look up in the Orange Book how many AB-rated products are available right now, and what are the brand name and generic product prices. What would be the monthly savings for your patient if he were to take the generic product(s)? (1point)
For Xanax 0.5mg generic manufacturers include: Alphapharm, Ivax Pharms, Mylan, Purepac Pharm, Sandoz, Teva and Watson Labs.

The following prices were obtained from drugstore.com:

Xanax 0.5 mg tablets are $103.94 for 90 tablets
Three generic manufacturers currently make alprazolam 0.5 mg tablets
Alprazolam 0.5 mg tablets are $10.97 for 90 tablets, a savings of $92.97

b) The same patient returns the following month complaining that he cannot remember to take his drug three times a day. He has seen very enticing commercials on TV for an extended release version of Xanax, which can be taken once daily. Is generic Xanax XR available? If not, when is the earliest that a Xanax XR AB-rated product could be available? (1 point)

The Xanax XR exclusivity expiration date was January 17, 2006. An AB-rated product was approved January 26, 2006.