1. Estimate the half-life of gentamicin in two male patients with normal renal function (CL=0.12 L/min) if their weight is 55 kg vs. 90 kg. Assume a height of 6’.

- Since clearance is given, only $V_d$ remains to be found in order to calculate $t_{1/2}$ for the two patients. (remember $CL = k_e \cdot V_d$)
- From the note a series of equations was presented for aminoglycosides. The dosing weight (DW) was given as (this is the same as Equation 1.1, page 131 of Winter’s Basic Clinical Pharmacokinetics)

$$DW = IBW + 0.4(TBW - IBW)$$

then

$$V_d = (0.25L/kg) \cdot DW(+ESF) \ (Eq \ 1.2, \ page \ 131)$$

- To use these expressions, we must first calculate IBW for each patient:

$$IBW = 50 + 2.3(\text{height in inches} > 60 \text{ in}) [\text{kg}]$$

$$= 50 + 2.3 \cdot (12)$$

$$= 77.6 \text{ kg}$$

this is the IBW for both since both are 6’.

- Dosing weight may now be determined:

PATIENT 1

$$DW(55kg) = IBW + 0.4(TBW - IBW)$$

$$= 77.6 + 0.4(55 - 77.6)$$

$$= 68.6 \text{ kg}$$

PATIENT 2

$$DW(90kg) = 77.6 + 0.4(90 - 77.6)$$

$$= 82.6 \text{ kg}$$

- Volume of distribution for each patient is then:

$$V_d(55kg) = (0.25L/kg)(68.6kg) = 17.2L$$

$$V_d(90kg) = (0.25L/kg)(82.6kg) = 20.7L$$

- Half-lives may be calculated using the common expression relating $Cl$ and $V_d$ to $k_e$:

$$Cl = k_e \cdot V_d$$

Or $$k_e = Cl / V_d$$
And then applying \( t_{1/2} = \frac{\ln 2}{k_e} \)

For the 55 kg patient,

\[
k_e = \frac{C_l}{V_d} = \frac{0.12\text{L/min}}{17.2\text{L}} \cdot \frac{60\text{min}}{1\text{hr}} = 0.418\text{hr}^{-1}
\]

\[
t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.418\text{hr}^{-1}} = 1.7\text{hr}
\]

For the 90 kg patient,

\[
k_e = \frac{0.12\text{L/min}}{20.7\text{L}} \cdot \frac{60\text{min}}{1\text{hr}} = 0.3478\text{hr}^{-1}
\]

\[
t_{1/2} = \frac{0.693}{0.3478\text{hr}^{-1}} = 2.0\text{hr}
\]
2. Discuss the histogram shown below that represents the metabolic clearance of sulfametazine. Number of subjects (y-axis) is plotted vs. metabolic clearance (x-axis).

This histogram indicates 3 distinct populations (trimodal). Population 1 have metabolic clearances <0.25 (slow metabolizers), Population 2 have metabolic clearances between 0.5-1.0 (normal metabolizers) and Population 3 have metabolic clearances of >1.125 (fast metabolizers). This is suggests patients vary in the genetic for the metabolizing enzyme. If we indicate ‘A’ as the dominant allele (gene) and ‘a’ as the recessive allele, then the 3 populations would correspond to homozygote dominant (AA), heterozygote (Aa) and homozygote recessive (aa). (remember one allele is from mom and one allele is from dad)
3. Based on the Cockcroft-Gault-Equation, calculate the amount of creatinine that is produced every hour from muscle in a normal 20 year old and 90 year old male subject (body weight 70 kg) with a serum creatinine of 0.9 mg/dl.

- The Cockcroft-Gault equation allows us to predict the creatinine clearance (and therefore renal function/ GFR) for patients differing in age and weight. For male patients,

\[
Cl_{\text{creat}}(\text{male}) = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot C_{\text{creat}}} \]

where age is in years, weight is in kg, and \( C_{\text{creat}} \) is in mg/ dL. The \( Cl_{\text{creat}} \) is then in ml/ min. This is an empirical equation which works only if the age, weight, and \( C_{\text{creat}} \) (or Scr) are entered in the units specified.

- For the 20 y.o.

\[
Cl_{\text{creat}} = \frac{(140 - 20)(70)}{(72)(0.9)} = 129.6 \text{ml/min} 
\]

Although clearance is expressed in volume-per-time, the amount of creatinine eliminated-per-time may be found using the creatinine concentration given:

Creatinine cleared per hour =

\[
(129.6 \text{ml/min})(0.9 \text{mg/dL}) \cdot \frac{60 \text{min}}{1 \text{hr}} \cdot \frac{10 \text{dL}}{1 \text{L}} \cdot \frac{1 \text{L}}{1000 \text{ml}} 
\]

\[
= 69.98 \approx 70 \text{mg/hr} 
\]

(so in 1 day, almost 2 g of creatinine is lost which is balanced by eating and producing 2 g of creatine per day))

- For the 90 y.o.

\[
Cl_{\text{creat}} = \frac{(140 - 90)(70)}{(72)(0.9)} = 54.0 \text{ml/min} 
\]

Creatinine cleared per hour =

\[
(54.0 \text{ml/min})(0.9 \text{mg/dL}) \cdot \frac{60 \text{min}}{1 \text{hr}} \cdot \frac{10 \text{dL}}{1 \text{L}} \cdot \frac{1 \text{L}}{1000 \text{ml}} 
\]

\[
= 29.2 \text{mg/hr} 
\]
(remember, elderly have less muscle mass which means less creatinine production)
4. What rating is used to show products are interchangeable? Using the Orange Book, list 2 bioequivalent products for the following drugs
   a) Premarin®
   b) 50 mg ketoprofen
   c) 100 mg extended release theophylline

   o An ‘AB’ rating indicates bioequivalent/interchangeable products
   o Premarin = there are no interchangeable products
   o 50 ketoprofen: Key Labs, Geneva, Lederle, Teva, Wyeth all product equivalent products

• 100 mg extended release: Aventis, Inwood, Key make equivalents
5. The following data was obtained after oral administration of various calcium supplements. Calcium supplements also contained 200 IU of vitamin D. Determine the relative bioavailability of Os-Cal® and CitraCal® to calcium carbonate. Suppose the calcium carbonate was not given with vitamin D, would this change the method you calculated relative bioavailability? (FYI-vitamin D enhances the ability of bone to extract calcium from the blood)

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose (mg)</th>
<th>Tmax (h)</th>
<th>Cmax (mg dL⁻¹)</th>
<th>Total Calcium AUC (mg dL h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Carbonate</td>
<td>500</td>
<td>4.1</td>
<td>10.3</td>
<td>6.39</td>
</tr>
<tr>
<td>Os-Cal</td>
<td>500</td>
<td>4.2</td>
<td>10.3</td>
<td>6.69</td>
</tr>
<tr>
<td>CitraCal</td>
<td>500</td>
<td>4.8</td>
<td>10.3</td>
<td>5.91</td>
</tr>
</tbody>
</table>

Relative Bioavailability = \( \frac{\text{AUC}_{\text{PROD}_1}}{\text{AUC}_{\text{PROD}_2}} \)

\[
\text{Os-Cal} = F_{\text{RELATIVE}} = \frac{\text{AUC}_{\text{OSCAL}}}{\text{AUC}_{\text{CA CARBONATE}}} = \frac{6.69}{6.39} = 1.05
\]

\[
\text{CitraCal} = F_{\text{RELATIVE}} = \frac{\text{AUC}_{\text{CITRACAL}}}{\text{AUC}_{\text{CA CARBONATE}}} = \frac{5.91}{6.39} = 0.92
\]

- The addition of Vitamin D is an important consideration. If Vitamin D increases extraction of calcium, this would affect clearance (CL = E * Q). When calculating bioavailability, differences (or lack of differences) in clearance need to be considered (as well as dose). See below equation

\[
F = \frac{\text{CL}_{\text{PROD}_1} \cdot \text{AUC}_{\text{PROD}_1} \cdot \text{Dose}_{\text{PROD}_2}}{\text{CL}_{\text{PROD}_2} \cdot \text{AUC}_{\text{PROD}_2} \cdot \text{DOSE}_{\text{PROD}_1}}
\]

If the clearance and dose are the same, then the equation reduces to:

\[
F = \frac{\text{AUC}_{\text{PROD}_1}}{\text{AUC}_{\text{PROD}_2}}
\]