PHARMACOKINETICS SMALL GROUP I:

Question 1
Absorption of the anti-fungal agent, itraconazole, is dependent on a low gastric pH. Calculate the relative concentrations of a weak acid (with a pKa of 5.4) in the plasma (pH 7.4) and in the stomach (pH 1.4). If the total steady state concentration of itraconazole in the stomach were 1 µg/ml, what concentration would be expected in the plasma? If a 55-year old male were taking large doses of antacids for heartburn, how would a change in the pH of the stomach alter absorption of this drug?

Question 2
2A. Define the term bioavailability and list at least four reasons why the bioavailability of a drug is often less than 100%?

Question 3
Digoxin is a digitalis glycoside that exerts positive inotropic effects on the heart. It is indicated in the treatment of atrial fibrillation or flutter and may be used as adjunctive therapy for congestive heart failure. The bioavailability (F) of digoxin varies depending on formulation.

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>100</td>
</tr>
<tr>
<td>Tablet</td>
<td>70</td>
</tr>
<tr>
<td>Elixir</td>
<td>80</td>
</tr>
<tr>
<td>Capsules</td>
<td>90-100</td>
</tr>
<tr>
<td>IM</td>
<td>90-100</td>
</tr>
</tbody>
</table>

Patient E.F. has been admitted for a closed head injury and has a nasogastric tube for the administration of medication and nutrition. Prior to admission, E.F. was on a therapeutic dose of digoxin 0.2 mg capsule once a day. With the nasogastric tube, E.F. will receive digoxin tablets crushed and administered via the tube. Determine the dose (mg) of digoxin tablets that should be prescribed.

Question 4
a. How will the plasma protein binding of drugs be altered by the following conditions, and what are the expected effects of this on Volume of Distribution (Vd) and Clearance of Elimination (CL)?
- Burns
- Chronic Liver Disease
- Renal Failure
- Co-administration of Sulfadiazine (highly protein-bound antibiotic)

b. Daptomycin is an antibacterial drug that exhibits high plasma protein binding (protein binding 90–93%, 60% to albumin). How would daptomycin loading dose and maintenance dosing rate be adjusted in patients with thermal burn injury?

**Question 5**

Aminoglycosides (e.g. gentamicin, tobramycin, amikacin) are antibiotics used in the treatment of aerobic gram-negative bacterial infections. Aminoglycosides are water-soluble medications that primarily distribute into extracellular fluid. In ‘normal’ individuals, the extracellular fluid compartment approximates 25% of total body weight, whereas in the adipose tissue of obese individuals the extracellular fluid is only about 10% of total body weight.

In a normal healthy individual the volume of distribution of gentamycin is 0.25 L/kg and the loading dose is 2 mg/kg. What effect would you anticipate each of the following conditions to have on the loading dose of gentamycin and other aminoglycosides in such patients?

- a) Dehydration
- b) Cystic Fibrosis
- c) Congestive Heart Failure (CHF)
- d) Gross obesity
- e) Neonates

**Question 6**

Define first- and zero-order kinetics of elimination.

**Question 7**

Vancomycin is a glycopeptide antibiotic primarily used for the treatment of infections due to gram-positive aerobic bacteria. Vancomycin therapy is generally reserved for the treatment of resistant organisms or in patients with allergies to conventional therapy. Vancomycin is eliminated primarily by the kidneys, with 80-90% of an intravenously administered dose being recovered in the urine in patients with normal or moderately impaired renal function. The half-life of vancomycin is markedly prolonged in patients with renal failure. Vancomycin undergoes
significant first pass metabolism and does not achieve systemic levels after oral administration, thus requiring intravenous administration for systemic infections.

7A. WC is a 82 year old male admitted from an outside hospital for management of enterococcal endocarditis. As he has a history of penicillin allergy (develops shortness of breath and wheezing), it has been decided that he will receive 6 weeks of vancomycin and gentamicin therapy. The serum concentration - time profile after a 1 gram dose of vancomycin for this patient is depicted in the following graph. Calculate the half-life of the drug using the graph.
7B. After one week of therapy, CW.’s renal function starts to deteriorate and then stabilizes, but he is continued on the same dose of vancomycin. After several days serum levels are checked and are found to be elevated. The vancomycin therapy is then held with orders to restart therapy once the level is <15 mg/L. Using the following serum concentration - time data, estimate the drug's half-life and the time when the patient should receive another dose of vancomycin (in relation to when the last serum concentration was obtained).

<table>
<thead>
<tr>
<th>Serum Concentration (mg/L)</th>
<th>Day and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1: 55.2</td>
<td>Monday 8pm</td>
</tr>
<tr>
<td>Level 2: 27.3</td>
<td>Tuesday 8am</td>
</tr>
</tbody>
</table>
Question 8
A drug has a volume of distribution of 50 L and undergoes zero order elimination at a rate of 2 mg/hr at a plasma concentration greater than 2 mg/L. If a patient is brought to the emergency room with a plasma concentration of 4 mg/L of the drug, how long will it take (in hours) for the plasma concentration to decrease by 50%?

Question 9
For a drug exhibiting one-compartment distribution and first-order kinetics of elimination, calculate the following:

8A. The fraction of an i.v. dose remaining in the body at 3 hr, when the half-life is 6 hr.

8B. The half-life of a drug, when 18% of the dose remains in the body 4 hr after an i.v. bolus dose.

Question 10
Valproic acid is an anti-epileptic drug that is also used in the treatment of bipolar disorder. If the values of clearance and volume of distribution for valproic acid for an individual patient are 0.5 L/hr and 9 L, respectively.

10A. Calculate the half-life of valproic acid.

10B. What is the total amount of valproic acid in the body at distribution equilibrium when the plasma concentration is 60 mg/L?

10C. What is the expected plasma concentration of valproic acid 12 hr after i.v. administration of a 700 mg dose?

Question 11.
A 10 mg dose of diazepam is injected i.v. into a patient with status epilepticus. The half-life of the drug is 48 hrs and the volume of distribution is 80 L in this patient. Based upon these data calculate each of the following?
11A. The elimination rate constant.

11B. The plasma diazepam concentration 12 hr after giving the dose.

11C. The fraction of the dose remaining in the body 48 hr after the dose is given.

11D. The clearance of diazepam.

11E. The amount of drug in the body (in mg) 1 week after giving the dose.
**Formulae/Equations for Pharmacokinetics Lectures and Small Groups**

\[
\text{CL/F} = \frac{\text{DOSE p.o.}}{\text{AUC}}
\]

\[
\text{CL} = \frac{\text{DOSE i.v.}}{\text{AUC}}
\]

**Zero-order elimination**

\[
\frac{dC}{dt} = -k
\]

\[
C = C_0 e^{-kt}
\]

**First-order elimination**

\[
\frac{dC}{dt} = -kC
\]

\[
C = C_0 e^{-kt}
\]

\[
t_{\frac{1}{2}} = \frac{0.69 V_d}{\text{CL}}
\]

\[
k = \frac{0.69}{t_{\frac{1}{2}}}
\]

\[
t_{0.9C_{ss}} = 3.3 t_{\frac{1}{2}}
\]

**Cockcroft & Gault Eq:**

\[
\text{CrCL (ml/min)} = \frac{(140- \text{age}) \times \text{wt (kg)}}{72 \times \text{[serum Cr]} (\text{mg/dL})} \times 0.85
\]

**Dosage adjustment in Renal Failure:**

\[
\text{Adjusted LD} = \frac{V_d \times [C_{\text{desired}} - C_{\text{initial}}]}{S \times F}
\]

\[
\text{CL}_{\text{total}} = \text{CL}_{\text{renal}} + \text{CL}_{\text{hepatic}} + \text{CL}_{\text{other}}
\]

\[
\text{CL} = k \times V_d
\]

\[
\text{Infusion Rate} = \frac{1}{C_{ss}}
\]

**The Rowland’s Equation**

\[
\text{CL}_H = Q \left( \frac{f \times \text{CL}_{\text{int}}}{Q + (f \times \text{CL}_{\text{int}})} \right)
\]

**Abbreviations:** AUC = area under the curve; C\text{t} = plasma concentration at time = t\text{; Css = steady-state concentration; CL= clearance of elimination; CL}_H = hepatic clearance; CL\text{int} = intrinsic clearance; CrCL = creatinine clearance; F = bioavailability; f = free fraction (unbound); k = elimination rate constant; LD = loading dose; MD = maintenance dose; Q = liver blood flow; S = salt factor; T = dosing interval; t\text{\(_{1/2}\)} = half-life of elimination; TC = target concentration; V\text{d} = volume of distribution.