Vertilmicin is an investigational aminoglycoside being evaluated for its antimicrobial effect. The route of administration for this drug is via intravenous bolus. Approximately 99.9% of this drug is eliminated by the kidney. Tubular secretion and reabsorption do not play a role in its elimination. Vertilmicin has no significant plasma protein binding. Assuming ideal body weight for this individual (male, 47 years of age, 190 lbs with serum creatinine of 2.1 mg/dL), compute the following pharmacokinetic parameters:

1) Clearance

\[
\text{Body weight (kg)} = 190 \times 0.454 = 86.3 \text{ kg}
\]

\[
CL_{\text{Vertilmicin, male}} \sim CL_{\text{Cr, male}} = \frac{(140 - 47) \times 86.3}{72 \times 2.1} = 53.1 \text{ mL/min}
\]

2) Half-life, assuming that volume of distribution was related to body weight at 0.35 l/kg

\[
k_e = \frac{CL}{V_d} = \frac{53.1 \times 60/1000}{0.35 \times \frac{190}{2.2}} = \frac{3.2}{30} = 0.11 \text{ h}^{-1}
\]

\[
t_{1/2} = \frac{\ln(2)}{k_e} = \frac{0.693}{0.11} = 6.3 \text{ h}
\]

3) Area under the concentration-time curve, assuming a single dose of 100 mg

\[
AUC = \frac{Dose}{CL} = \frac{100 \text{ mg}}{3.2 \text{ L/h}} = 31.3 \text{ mg.h/L}
\]

4) The concentration of vertilmicin at 5 h post dose if the doctor were to give a dose of 200 mg

\[
C(t) = \frac{Dose}{V_d} \exp(-k_e \times t)
\]

\[
C(t) = \frac{200}{30} \exp(-0.11 \times 5) = 3.85 \text{ mg/L}
\]
A patient was administered via IV infusion for duration of 2 hours of a 200 mg β-lactam antibiotic every 8 hours. At **STEADY STATE**, two plasma samples were collected and measured. The first sample was taken right before drug administration (predose) and the second sample was taken 1 hour after stopping infusion. The measured drug concentrations were 2.1 and 9.8 mg/L, respectively. Assuming that the drug follows a one-compartment body model, compute the elimination rate constant ($k_e$), half-life ($t_{1/2}$), volume of distribution ($V_d$), clearance (CL), and average steady-state concentration ($C_{ss}$).

$$k_e = -\frac{\ln(C_1) - \ln(C_2)}{t_1 - t_2} = -\frac{\ln(2.1) - \ln(9.8)}{8 - 3} = 0.308 \text{ h}^{-1}$$

$$t_{1/2} = \frac{\ln(2)}{k_e} = \frac{0.693}{0.308} = 2.25 \text{ h}$$

You are told that the plasma samples were taken at steady state, so you need to factor in steady-state, 

$$C(t = 1) = C_{p_{\text{max}}} \exp(-0.308 \times 1) = 9.8 \text{ mg/L}$$

$$C_{p_{\text{max}}} = 13.3 \text{ mg/L}$$

$$V_d = \frac{Dose}{k_e T} \cdot \frac{1 - e^{-k_e T}}{C_{p_{\text{max}}} - (C_{p_{\text{min}}})e^{-k_e T}} = \frac{200}{0.308 \times 2} \cdot \frac{1 - \exp(-0.308 \times 2)}{13.3 - 2.1 \exp(-0.308 \times 2)} = 12.2 L$$

$$CL = k_e \cdot V_d = 0.308 \times 12.2 = 3.8 \text{ L/h}$$

$$C_{ss} = \frac{Dose}{CL \times \tau} = \frac{200 \text{ mg}}{3.8 \frac{L}{h} \times 8h} = 6.6 \text{ mg/L}$$
For the table below, fill out what to expect of high and low extraction drugs if the protein binding were to double on the following pharmacokinetic parameters. Also make recommendation for dose adjustments. Assume constant infusion and that steady state is achieved.

<table>
<thead>
<tr>
<th></th>
<th>High extraction drugs</th>
<th>Low extraction drugs</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CL</strong></td>
<td>( CL = Q )</td>
<td>( CL = fu \cdot CL_{int} )</td>
<td>Provide equation</td>
</tr>
<tr>
<td>( \bar{C} )</td>
<td>( \bar{C} = \frac{R_0}{Q} )</td>
<td>( \bar{C} = \frac{R_0}{fu \cdot CL_{int}} )</td>
<td>Provide equation</td>
</tr>
<tr>
<td>( \bar{C_u} )</td>
<td>( \bar{C_u} = fu \cdot \bar{C} )</td>
<td>( \bar{C_u} = \frac{R_0}{CL_{int}} )</td>
<td>Provide equation</td>
</tr>
<tr>
<td>( f_b )</td>
<td>↑</td>
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<td>Show trend using ↑, ↓, or ↔</td>
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<tr>
<td>( f_u )</td>
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<tr>
<td>( \bar{C_u} )</td>
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<td>↔</td>
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</tbody>
</table>

**Dosing recommendation**
- Dose increase
- No change in dose
- Increase, decrease or no change in dose
Drug X is administered as 250 mg IV bolus dose. Two hours after administration, the concentration in the plasma was 5 mg/L and 10 hours after administration the plasma concentration was 1 mg/L. The drug is a lipophilic compound and is cleared by the liver. This patient has a liver blood flow of 90 L/h. The fraction of drug bound to tissue is 0.6.

A. Compute $C_0$

First, we compute the slope.

$$k_e = -\frac{\ln(C_1) - \ln(C_2)}{t_1 - t_2} = -\frac{\ln(5) - \ln(1)}{2 - 10} = 0.201 \text{ h}^{-1}$$

$$C(t) = C_0 \exp(-k_e t)$$

$$C_0 = \frac{5}{\exp(-0.201 \times 2)} = 7.5 \text{ mg/L}$$

B. Compute $V_d$

$$V_d = \frac{\text{Dose}}{C_0} = \frac{250 \text{ mg}}{7.5 \text{ mg/L}} = 33 \text{ L}$$

C. Comment whether this drug is a high extraction or low extraction drug. Assuming that hepatic clearance is 80% of total body clearance, compute the extraction ratio for this drug.

We can compute the clearance and evaluate whether the magnitude of clearance is close to the liver blood flow.

$$CL = k_e \cdot V_d = 0.201 \text{ h}^{-1} \times 33 \text{ L} = 6.6 \frac{L}{h} \ll \text{liver blood flow}$$

The drug is a low extraction drug.

For hepatic clearance, $CL_H = E_H \cdot Q_H$, where $E_H$ is the extraction ratio and $Q_H$ refers to the liver blood flow.

The extraction ratio is computed as follows:

$$E_H = \frac{CL_H}{Q_H} = \frac{0.8 \times 6.6 \text{ L/h}}{90 \text{ L/h}} = 0.0587$$
D. If Drug Y induces the enzymes responsible for Drug X metabolism, would you expect to see a change in clearance?

Yes, the clearance of Drug X will be affected (increase), given that the clearance of a low extraction drug is dependent on the fraction of free drug and the intrinsic clearance.

\[ CL \uparrow = f_u \cdot CL_{int} \uparrow \]
True or False

A. Assuming no loading dose and a constant dosing interval, it takes less time to reach steady state for a drug with higher degree of accumulation. (F)

B. Induction of hepatic biotransformation enzymes will affect the clearance of low extraction drugs. (T)

C. Assuming that the volume of distribution stays constant, when clearance decreases, it will take a longer time to steady state and result in an increased half-life. (T)

D. Bioequivalence is assessed as the absence of a statistically significant difference in the rate and extent which the active pharmaceutical ingredient becomes available. (F)

E. Bioequivalent products are therapeutically interchangeable. (T)

F. A multicompartmental body model only has one volume of distribution. (F)