1: Predict the changes in Cl<sub>h</sub> given the following scenarios:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Direction of change</th>
<th>effect on Cl&lt;sub&gt;h&lt;/sub&gt; for a low Extraction drug</th>
<th>effect on Cl&lt;sub&gt;h&lt;/sub&gt; for a high Extraction drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>fraction of unbound drug</td>
<td>Increases</td>
<td>increases</td>
<td>no significant changes</td>
</tr>
<tr>
<td>intrinsic clearance</td>
<td>Decreases</td>
<td>decreases</td>
<td>no significant changes</td>
</tr>
<tr>
<td>hepatic blood flow</td>
<td>Increases</td>
<td>no significant changes</td>
<td>increases</td>
</tr>
</tbody>
</table>

Low Extraction Drug

\[ \frac{Q_{hep} \cdot f_u \cdot CL_{int}}{Q_{hep} + f_u \cdot CL_{int}} \]

\[ \Rightarrow CL_{hep} \approx f_u \cdot CL_{int} \]

High Extraction Drug

\[ \frac{Q_{hep} \cdot f_u \cdot CL_{int}}{Q_{hep} + f_u \cdot CL_{int}} \]

\[ \Rightarrow CL_{hep} \approx Q_{hep} \]

2: True or False Questions

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Total clearance is dependent on the half-life of the drug.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>F</td>
<td>Volume of distribution and clearance are two major pharmacokinetic parameters, and they are dependent on each other based on equation: [ CL = V_d \cdot k_e ]</td>
</tr>
<tr>
<td>T</td>
<td>F</td>
<td>Clearance defines the amount of drug eliminated from body per unit time.</td>
</tr>
<tr>
<td>T</td>
<td>F</td>
<td>According to the equation: [ AUC_\infty = \frac{Dose}{CL} = \frac{Dose}{V_d \cdot k_e} ], the change of volume of distribution does affect ( AUC_\infty ).</td>
</tr>
<tr>
<td>T</td>
<td>F</td>
<td>Intrinsic clearance is not dependent on blood flow, and it represents the activities of enzyme system when we talk about liver metabolism.</td>
</tr>
</tbody>
</table>
Liver blood flow affects high extraction drug much more than low extraction drug when drug major elimination pathway is hepatic elimination.

3: Gamma-hydroxybutyric Acid (GHB) is an abused drug and also an endogenous compound. Recently, a study in rats was carried out to understand pharmacokinetics of GHB. A couple of rats were given a dose at 100mg intravenously in this study. Blood samples were taken at several time points. A graduate student in this lab plotted concentration-time data. He found that drug concentration-time profile can be best described by a one-compartmental linear model. He also determined that total clearance is 150 mL/hr, and \( t_{1/2} \) is 0.5 hr.

A: Calculate Volume of Distribution of GHB, GHB concentration at time zero, and \( AUC_\infty \).

\[
\text{Dose} = 100 \text{ mg} \\
\text{CL} = 150 \text{ mL/hr} \\
\frac{t_{1/2}}{2} = 0.5 \text{ hr}
\]

\[
k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{0.5} = 1.386(\text{hr}^{-1})
\]

\[
V_d = \frac{\text{CL}}{k_e} = \frac{150 \text{ mL} \cdot \text{hr}^{-1}}{1.386 \text{hr}^{-1}} = 108.2(\text{ml})
\]

\[
C_0 = \frac{\text{Dose}}{V_d} = \frac{100 \text{ mg}}{108.2 \text{ml}} = 0.92(\text{mg} / \text{ml})
\]

\[
AUC_\infty = \frac{\text{Dose}}{\text{CL}} = \frac{100 \text{ mg}}{150 \text{ mL} \cdot \text{hr}^{-1}} = 0.67(\text{mg} / \text{ml} \cdot \text{hr})
\]

B: If liver metabolism is the major elimination pathway for GHB in rat, blood flow rate in rat is 1.5 L/hr, what is the extraction ratio for GHB in liver?

\[
\text{CL} = Q \cdot E \\
Q = 1.5(\text{L} / \text{hr}) = 1500(\text{ml} / \text{hr}) \\
\text{CL} = 150 \text{ mL/hr} \\
\text{CL} = Q \cdot E \\
\rightarrow 150 \text{ ml/hr} = 1500 \text{ ml/hr} \cdot E \\
\rightarrow E = 0.1
\]

C: According to the Question B, is GHB a high or low extraction drug? If the free fraction of GHB in plasma is 0.3, what is the intrinsic clearance?
Because E is 0.1 much less than 1, GHB is a low extraction drug, and

\[ CL_{hep} = \frac{Q_{hep} \cdot f_u \cdot CL_{int}}{Q_{hep} + f_u \cdot CL_{int}} \]

\[ \Rightarrow CL_{hep} \approx f_u \cdot CL_{int} \]

150 mL/hr \( \approx 0.3 \cdot CL_{int} \)

\[ CL_{int} = 500 (mL/hr) \]

OR

\[ CL_{hep} = \frac{Q_{hep} \cdot f_u \cdot CL_{int}}{Q_{hep} + f_u \cdot CL_{int}} \]

\[ CL_{int} = \frac{CL_{hep} \cdot Q_{hep}}{(Q_{hep} - CL_{hep}) \cdot f_u} \]

\[ CL_{int} = \frac{CL_{hep \cdot A} \cdot Q_{hep}}{(Q_{hep} - CL_{hep \cdot A}) \cdot f_u} = \frac{150 \cdot 1500}{(1500 - 150) \cdot 0.3} = 555.56 (mL/hr) \]

D: If liver blood flow in rat reduces to 1.0 L/hr after 2 hrs due to an anesthesia procedure, what is the intrinsic clearance and total clearance (still based on information from question B and C)? Compared to the values before anesthesia, do they change or not? Why?

Intrinsic clearances will not change since intrinsic clearance is controlled by enzyme activities, and blood flow rate will not affect intrinsic clearance. Since GHB is a low extraction one from question C, total clearance will not be altered too much after change of blood flow (\( CL_{hep} \approx f_u \cdot CL_{int} \)), the following calculation can also prove this.

\[ CL_{hep} = \frac{Q_{hep} \cdot f_u \cdot CL_{int}}{Q_{hep} + f_u \cdot CL_{int}} \]

\[ CL_{hep} = \frac{1000 \cdot 0.3 \cdot 555.56}{1000 + 0.3 \cdot 555.56} = 142.9 (mL/hr) \]

Before procedure,\n
\[ CL = 150 \text{ mL/hr} \]