Clinical PK and Hepatic Disease – Active Learning Problem Set Solution

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Active Learning Problem Set Solution - What happens to hepatic clearance, PK parameters, total and free concentrations of drug and pharmacologic effect for each of these problems. Provide a verbal description justifying the response and include numbers when applicable.

1. If f_{ub} increases by 50% for a low extraction ratio drug like diazepam due to a drug interaction.

Case 1 Example

a. **Q_H:** The decreased protein binding results in an increased free fraction of drug but no change in liver blood flow.

b. **Cl_{int}:** Decreased protein binding results in an increased free fraction of drug but no change in intrinsic ability of the hepatocytes to clear the drug.

c. **f_{ub}:** The fraction unbound will increase by 50% due to the drug interaction.

d. **Cl_H:** Hepatic clearance will increase by 50% because more unbound drug is free to leave the bloodstream and enter hepatocytes where it can be metabolized.

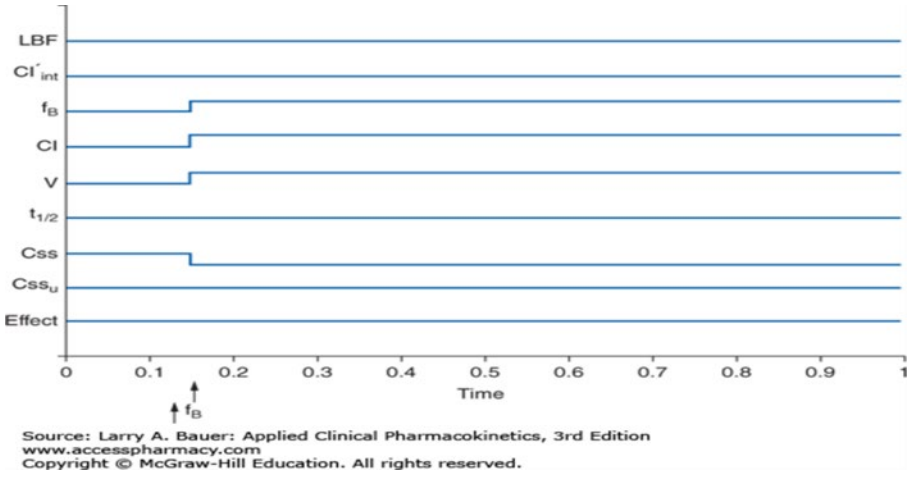
e. **V:** The volume of distribution increases because there is more drug free to leave the vascular system and enter various tissues. Increases because the fraction unbound increases.

f. **$t_{1/2}$:** This is dependent on the relative changes in clearance and volume of distribution. We don't know the relative changes in clearance and volume of distribution so half-life could either increase, decrease, or not change (if the increase in V = the increase in Cl) based on the extent of changes in these two variables.

g. **Css:** Steady state concentration decreases because the total clearance increased, so there is not as much diazepam in the blood.

h. **Css_u:** The unbound steady state concentration would remain unchanged because the decrease in total concentration is offset by the increase in free fraction of unbound drug. This presents a problem if therapeutic drug monitoring is being conducted using total drug levels.

i. **Effect:** The pharmacological effect will remain the same because the free steady state concentration of the drug did not change.



Clinical PK and Hepatic Disease – Active Learning Problem Set Solution

2. If CL_{int} decreases by 50% due to a drug interaction, when cimetidine is added to theophylline (a drug with a low extraction ratio)?

Case 2 Example

a. **Q_H:** The liver blood flow is not altered by a change in intrinsic clearance.

b. **Cl_{int}:** There is a decrease of 50% due to the drug interaction.

c. **f_{ub}:** Free fraction of drug is not altered because blood and tissue volume, plasma protein and tissue binding did not change.

d. **Cl_H:** Will decrease by 50% because f_{ub} was unchanged so it is directly proportional to the intrinsic clearance decrease.

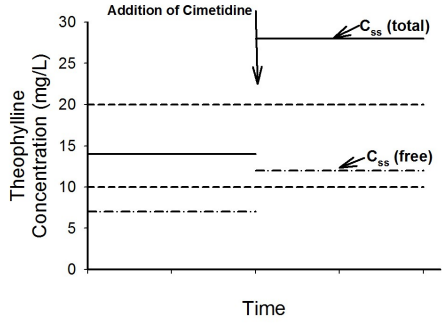
e. **V:** Stays the same because blood and tissue volume, plasma protein, and tissue binding did not change.

f. **$t_{1/2}$:** It will increase because of the decrease in clearance, drug will remain in system longer.

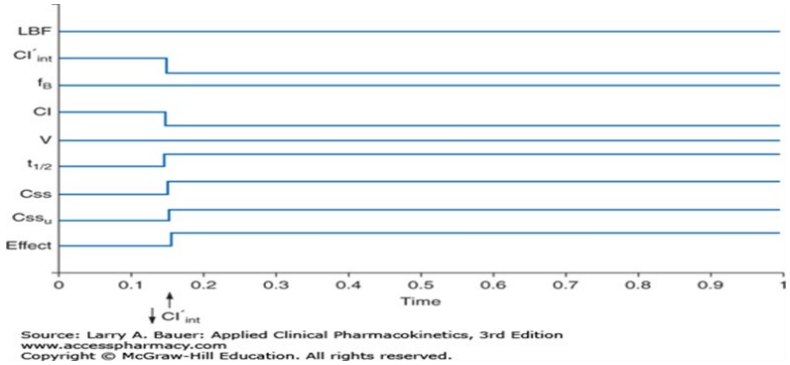
g. **Css:** Will increase due to decrease in clearance, this will result in drug remaining in higher concentration in the body.

h. **Css_u:** Increases because the overall total concentration increases and because the fraction unbound remains the same, there will be an increase in the amount of unbound drug remaining in the system. A decrease in dose will be required.

i. **Effect:** Pharmacologic response will increase because of the increase in unbound serum concentration so more drug to a cause the pharmacologic effect. An approximate 50% decrease in dose will be required.



You will have to lower the theophylline dose to keep concentrations within the therapeutic range.



Clinical PK and Hepatic Disease – Active Learning Problem Set Solution

3. If f_{ub} doubles for verapamil, a high extraction drug, due to a liver dysfunction resulting in hypoalbuminemia.

Case 3 Example

a. **Q_H:** Decreased plasma protein binding by doubling the unbound proteins for verapamil (a high extraction ratio drug) results in an increased free fraction of the drug in the blood, but no change in liver blood flow.

b. **Cl_{int}:** Stays the same because clearance is a function of liver blood flow so intrinsic clearance does not change. The liver dysfunction decreases production of albumin, but dot does not decrease hepatocyte activity.

c. **f_{ub}:** The unbound fraction doubles because of the decreased protein carrier, albumin.

d. **Cl_H:** For high extraction ratio drug, there is such an excess in the capacity of the liver to remove the drug, that a change in unbound drug fraction is not going to influence hepatic clearance.

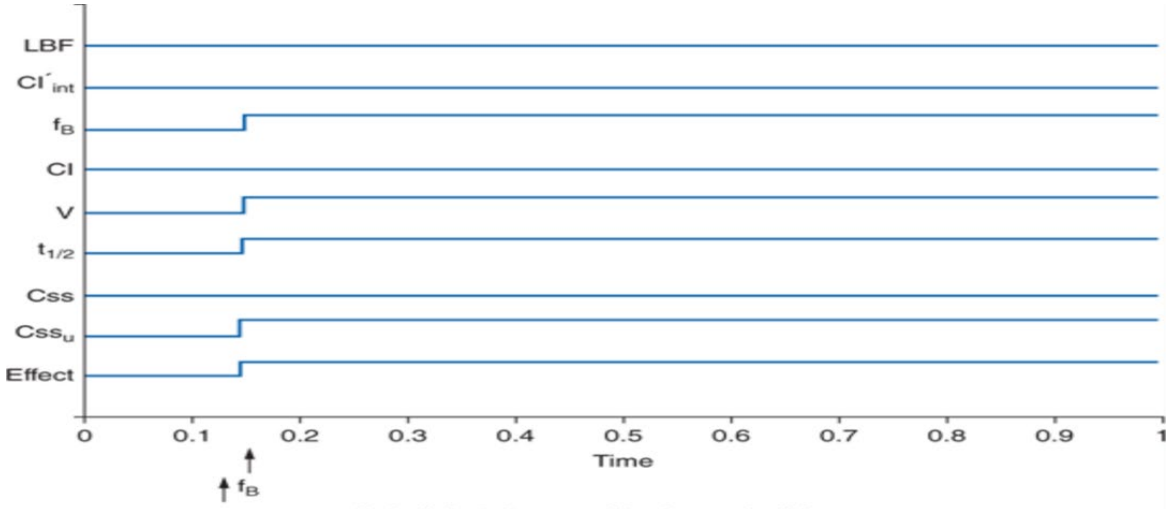
e. **V:** A higher free fraction of drug in the blood increases the volume of distribution because there is more free drug to move out of the vasculature.

f. **$t_{1/2}$:** The change in the volume of distribution (via a higher free fraction of drug in the blood) causes a longer half life for the drug because it takes longer for the drug to return to the blood after going out into the periphery.

g. **Css:** Total steady state will not change because the additional free drug goes into the tissues so total concentration in the blood remains the same.

h. **Css_u:** Unbound steady-state concentration increases because with more free fraction of drug in the blood, the proportion in the verapamil that is unbound will increase.

i. **Effect:** The overall pharmacological effect will increase with the increase of the unbound steady-state drug concentration. Since it is unbound drug which causes therapeutic/adverse effects, this higher free drug concentration could have clinical implications.



Clinical PK and Hepatic Disease – Active Learning Problem Set Solution

4. If the intrinsic clearance of lidocaine, a high extraction ratio drug, decreases by 40% due hepatitis.

Case 4 Example

a. **Q_H:** no change: increase in intrinsic clearance does not change blood flow.

b. **Cl_{int}:** changed because of hepatocyte damage.

c. **f_{ub}:** intrinsic clearance does not change protein binding.

d. **Cl_H:** A change in the intrinsic clearance is not going to influence hepatic clearance. Hepatic blood flow is the rate limiting step.

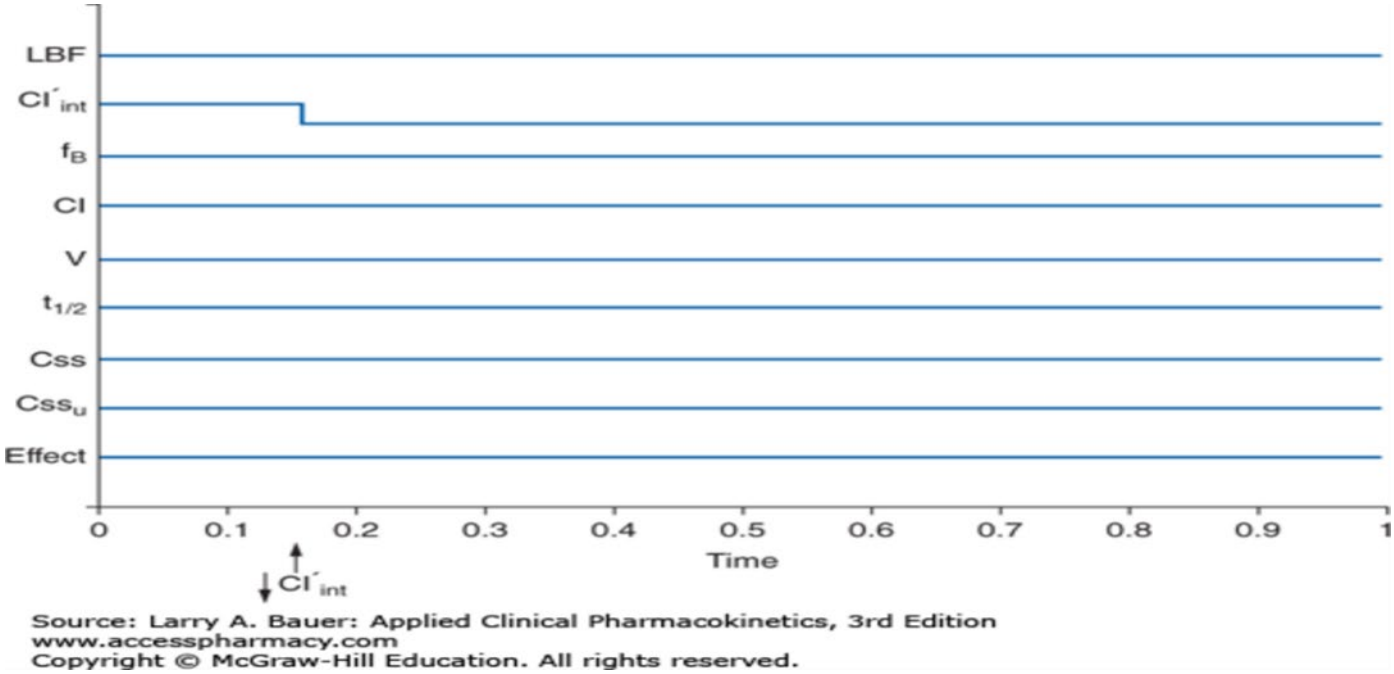
e. **V:** Volume of distribution and half-life will not be modified because intrinsic clearance has no effect on pharmacokinetic parameters.

f. **$t_{1/2}$:** Volume of distribution and half-life will not be modified because intrinsic clearance has no effect on pharmacokinetic parameters.

g. **Css:** Clearance did not change so the total concentration will not change.

h. **Css_u:** Same no change in concentration.

i. **Effect:** No change. However, **<u>if the drug were administered orally</u>**, the hepatic first-pass effect would be decreased, which would increase the bioavailability of the drug. Because this is effectively an increase in drug dosage, average total and unbound drug concentrations and pharmacologic effect would increase for this route of administration (Css = [F(D/τ)/Cl], where F is the bioavailability fraction, Css it the total steady-state drug concentration, D is dose, τ is the dosage interval, and Cl is clearance).



Clinical PK and Hepatic Disease – Active Learning Problem Set Solution

5. If hepatic blood flow decreases by 30% due to gastric tumor compressing the hepatic artery in a person on high extraction ratio drug such as morphine.

Case 5 Example

a. **Q_H:** Liver blood flow is decrease by 30% due to cirrhosis**.**

b. **Cl_{int}:** No change because the intrinsic clearance for high extraction ratio drugs, like morphine, will not change just because liver blood flow changes.

c. **f_{ub}:** Liver blood flow does not change unbound fraction of drug in the blood.

d. **Cl_H:** Will be decreased by 30% in proportion to the decrease in liver blood flow. (Simplified model.)

e. **V:** It will be unchanged because liver blood flow does not change volume of distribution.

f. **$t_{1/2}$:** It will increase because of clearance has decreased.

g. **Css:** Total steady state concentration increases, because of decrease in clearance allowing for higher concentration in the system.

h. **Css_u:** It will increase because of the increase in total steady-state concentration and constant fraction unbound will result in a larger amount of unbound drug in the blood.

i. **Effect:** The effect of the morphine will be increased because fraction unbound drug increases.