Therapeutic Drug Monitoring TDM

Chapter 3: Drug Dosing in Special Populations

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- **Renal or hepatic disease** will decrease the elimination or metabolism of the majority drugs and change the clearance of the agent.

- **Dialysis procedures**, conducted using artificial kidneys in patients with renal failure, remove some medications from the body while the pharmacokinetics of other drugs are not changed.

- **Heart failure** results in low cardiac output which decreases blood flow to eliminating organs, and the clearance rate of drugs with moderate-to-high extraction ratios are particularly sensitive to alterations in organ Blood flow.

- **Obesity** adds excessive adipose tissue to the body which may change the way drugs distribute in the body and alter the volume of distribution for the medication.

- **Drug interactions** can
  - inhibit or induce drug metabolism
  - alter drug protein binding
  - change blood flow to organs that eliminate or metabolize the drug.

Renal Disease

The equation that describes these various routes of renal elimination is:

$$Cl_R = \left[(f_B \cdot GFR) + \frac{RBF \cdot (f_B Cl'_{sec})}{RBF + (f_B Cl'_{sec})} \right] (1 - FR)$$

where f_B is the free fraction of drug in the blood, GFR is glomerular filtration rate, RBF is renal blood flow, Cl'_{sec} is the intrinsic clearance for tubular secretion of unbound drug, and FR is the fraction reabsorbed.

Methods of estimating renal function

- GFR
- Creatinine clearance

1-Measurement of glomerular filtration rate:

- Glomerular filtration rate (GFR) can be estimated using the modified Modification of Diet in Renal Disease (MDRD) equation:

GFR (in mL/min / 1.73 m^2) = $186 \cdot SCr^{-1.154} \cdot Age^{-0.203} \cdot$ (0.742, if female) (1.21, if African-American).

- **For example**, the estimated GFR for a 53-year-old African-American male with a SCr = 2.7 mg/dL would be computed as follows:
- $GFR = 186 \cdot (2.7\ mg/dL)^{-1.154} \cdot (53\ y)^{-0.203} \cdot 1.21 = 32\ mL/min / 1.73\ m^2$

- What if patient is a white male?

2. Measurement and Estimation of Creatinine Clearance, method 1

CrCl (in mL/min) = ($U_{Cr} \cdot V_{urine}$) / (SCr · T)

Where

U_{Cr} is the urine creatinine concentration in mg/dL

V_{urine} is the volume of urine collected in mL

SCr is the serum creatinine collected at the midpoint of the urine collection in mg/dL

T is the time in minutes of the urine collection.

- Because creatinine renal secretion exhibits diurnal variation, most nephrologists use a 24-hour urine collection period for the determination of creatinine clearance.
- **For example**, a 24-hour urine was collected for a patient with the following results: U_{Cr} = 55 mg/dL, V_{urine} = 1000 mL, SCr = 1.0 mg/dL, calculate creatinine clearance?

- T = 24 h × 60 min/h = 1440 min

- CrCl (in mL/min) = $(U_{Cr} \cdot V_{urine}) / (SCr \cdot T)$

  = (55 mg/dL · 1000 mL) / (1.0 mg/dL · 1440 min)

  = 38 mL/min

2. Measurement and Estimation of Creatinine Clearance, method 2

Cockcroft and Gault: The Cockcroft-Gault method should only be used in patients:

1. ≥18 years old
2. Actual weight within 30% of their ideal body weight.
3. Stable serum creatinine concentrations

For male …**CrCl = [(140 – age) BW]/ (72 · SCr)**

For females…**CrCl= [0.85(140 – age) BW] / (72 · SCr)**

Where **CrCl** is estimated creatinine clearance in mL/min, age is in years, **BW** is body weight in kg, and **SCr** is serum creatinine in mg/dL.

2. Measurement and Estimation of Creatinine Clearance, method 2

- The **0.85** correction factor for females is present because women have smaller muscle mass than men and, therefore, produce less creatinine per day.

IBW (in kg) = 50 + 2.3(Ht – 60) for male or

IBW (in kg) = 45 + 2.3(Ht – 60), for female

Where **Ht** is height in inches

IBW is ideal body weight in kilograms

- **For example**, a 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be:

$$\mathbf{CrCl = [(140 - age)\ BW]/\ (72 \cdot SCr)}$$

IBW males= 50 + 2.3 (Ht − 60) = 50 + 2.3(71 − 60) = 75 kg,

So the patient is within 30% of his ideal body weight and the Cockcroft-Gault method can be used;

CrCl= [(140 -age) BW]/ (72 · SCr)

= [(140 − 55 y) 80 kg] / (72 · 1.9 mg/dL)

= 50 mL/min.

2. Measurement and Estimation of Creatinine Clearance, method 3

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Jelliffe and Jelliffe method: Used if serum creatinine values are not stable

1. Estimate creatinine production. The formula for this is different for males and females due to gender-dependent differences in muscle mass:

Ess male = IBW [29.3 – (0.203 · age)]

Ess female = IBW [25.1 – (0.175 · age)]

Where **Ess** is the excretion of creatinine

IBW is ideal body weight in kilograms

age is in years.

Jelliffe and Jelliffe method:

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2. Correct creatinine production for renal function

$$\textbf{Ess corrected} = \textbf{Ess}\,[1.035 - (0.0337 \cdot \textbf{Scr}_{\textbf{ave}})]$$

3. Adjust the estimated creatinine clearance value according to whether the renal function is getting better or worse

$$E = Ess_{corrected} - \frac{[4IBW(Scr_2 - Scr_1)]}{\Delta t}$$

Jelliffe and Jelliffe method:

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4. Calculate CrCl

$$\textbf{CrCl (in mL/min / 1.73m2)} = \textbf{E/ (14.4} \cdot \textbf{Scr}_{\textbf{ave}}\textbf{)}$$

Scr_{ave} is the average of the two serum creatinine determinations in mg/dL, Scr1 is the first serum creatinine and Scr2 is the second serum creatinine both in mg/dL

Δt is the time that expired between the measurement of Scr1 and Scr2 in minutes.

2. Measurement and Estimation of Creatinine Clearance, method 4

Salazar and Corcoran: If patients are

1. **not** within 30% of their ideal body weight (obese)
2. ≥18 years old
3. Stable serum creatinine concentrations

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

Where **age** is in years, **Wt.** is weight in kg, **Ht** is height in m, and **SCr** is serum creatinine in mg/dL

Methods to estimate creatinine clearance for children and young adults:

1. Age 0–1 year:

$$\mathbf{CrCl_{est}\ (in\ mL/min\ /\ 1.73\ m2) = (0.45 \cdot Ht)\ /\ SCr}$$

2. Age 1–20 years,

$$\mathbf{CrCl_{est}\ (in\ mL/min\ /\ 1.73\ m2) = (0.55 \cdot Ht)/SCr}$$

Where **Ht** is in cm and **SCr** is in mg/dL.

- Note that for these formulas, estimated creatinine clearance is normalized to 1.73 m2 which is the body surface area of an adult male with a height and weight of approximately 5 ft 10 in and 70 kg, respectively

Methods for estimating creatinine clearance

CrCl (in mL/min) =
$(U_{Cr} \cdot V_{urine}) / (SCr \cdot T)$

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Jelliffe and Jelliffe

Unstable SrCr

Cockcroft and Gault:

≥18 years old

weight within 30% of IBW

Stable SrCr

Salazar and Corcoran:

not within 30% of IBW

≥18 years old

Stable SrCr

Q/ What is the best way to correct the dose of a drug eliminated mainly by kidney if renal impairment occurred

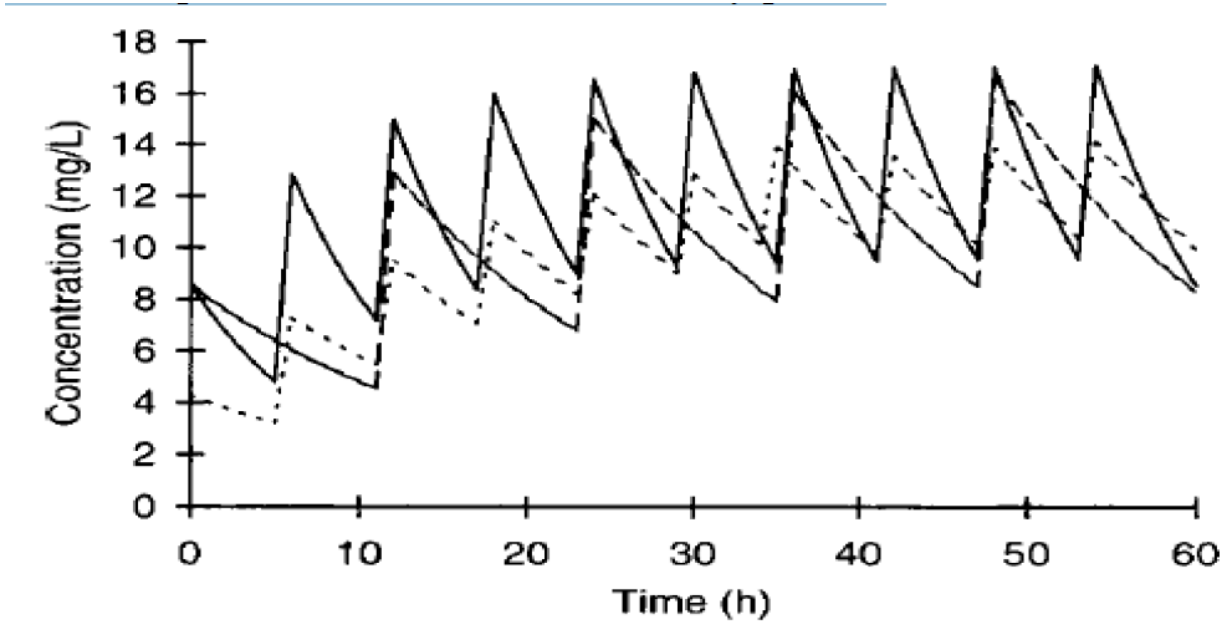
A-decrease the dose without any change in time interval

or

B- increase the time interval without any change in a dose?

Answer:

B- Increase the time interval without any change in a dose since this way produce concentration time profile similar to that of healthy patient



- FIGURE 3-2 Serum concentration versus time profile for a patient with normal kidney function receiving a renally eliminated drug at the dose of 300 mg every 6 hours (solid line). In a patient with renal dysfunction, it is possible to give the same dose and prolong the dosage interval (300 mg every 12 hours, dashed line), or a reduced dose at the same dosage interval (150 mg every 6 hours, dotted line). Giving the same dose at a longer dosage interval in the patient with renal disease usually results in a concentration/time profile similar to that seen in a normal patient receiving the normal dose. However, giving a smaller dose and keeping the dosage interval the same usually produces a concentration/time profile with a lower peak steady-state concentration and a higher trough steady-state concentration. Note that since the total daily dose is the same for both renal disease dosage regimens (600 mg/d), the average steady-state concentration is identical for both dosage schemes.

The relationship between drug clearance and creatinine clearance

- The relationship between drug clearance and creatinine clearance is usually approximated by a straight line with a slope that is a function of the renal clearance for the drug and an intercept that is related to the non-renal clearance of the drug.
- **For digoxin**, an equation that describes the relationship between digoxin clearance (Cl) and creatinine clearance (CrCl in mL/min) is:

$$\textbf{Cl (in mL/min)} = 1.303 \cdot \textbf{CrCl} + \textbf{ClNR}$$

ClNR is non-renal clearance and equals **20 mL/min** in patients with moderate-severe heart failure and **40mL/min** in patients with no or mild heart failure

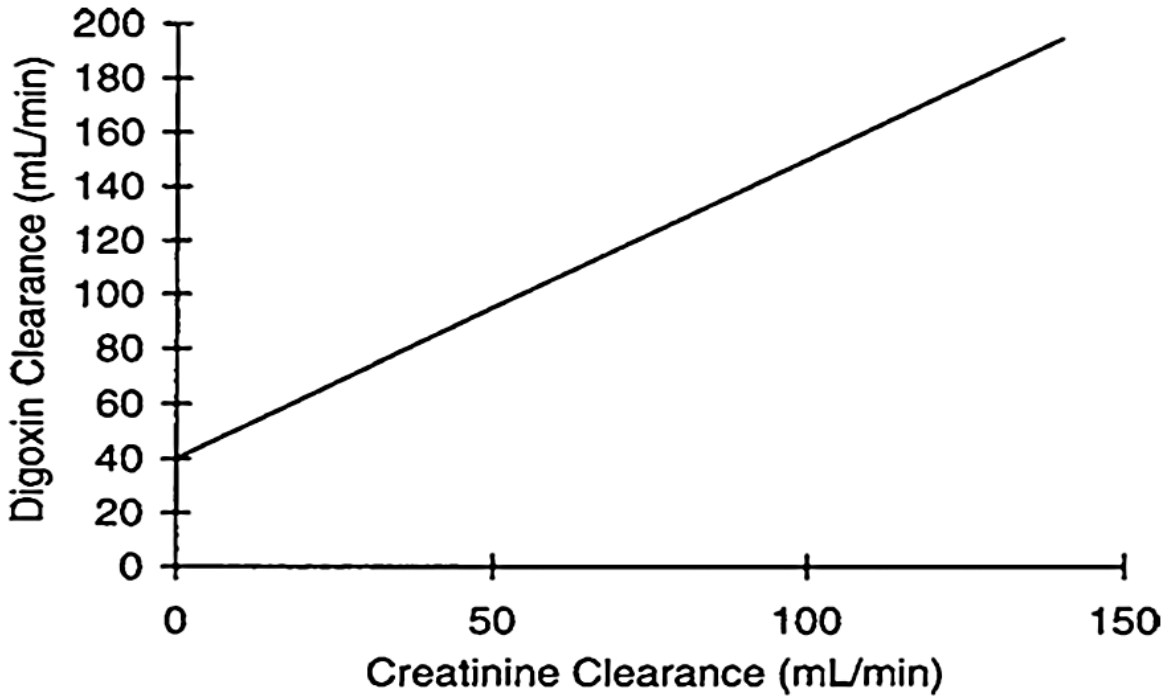


FIGURE 3-3 Relationship between creatinine clearance and digoxin clearance used to estimate initial digoxin clearance when no drug concentrations are available. The y-axis intercept (40 mL/min) is nonrenal clearance for digoxin in patients with no or mild heart failure. If the patient has moderate to severe heart failure, nonrenal clearance is set to a value of 20 mL/min.

- **Elimination rate constant** (ke) can also be estimated using creatinine clearance, but it is a *dependent pharmacokinetic parameter* whose result is reliant on the relative values of clearance and volume of distribution **(ke = Cl/V)**

- Because of this, changes in elimination rate constant may not always be due to changes in the renal elimination of the drug.

- For the aminoglycoside antibiotics, an equation that represents the relationship between aminoglycoside antibiotic elimination rate constant (ke) and creatinine clearance (CrCl in mL/min) is:

$$\textbf{Ke (in } h^{-1}\textbf{)} = 0.00293 \cdot \textbf{CrCl} + 0.014$$

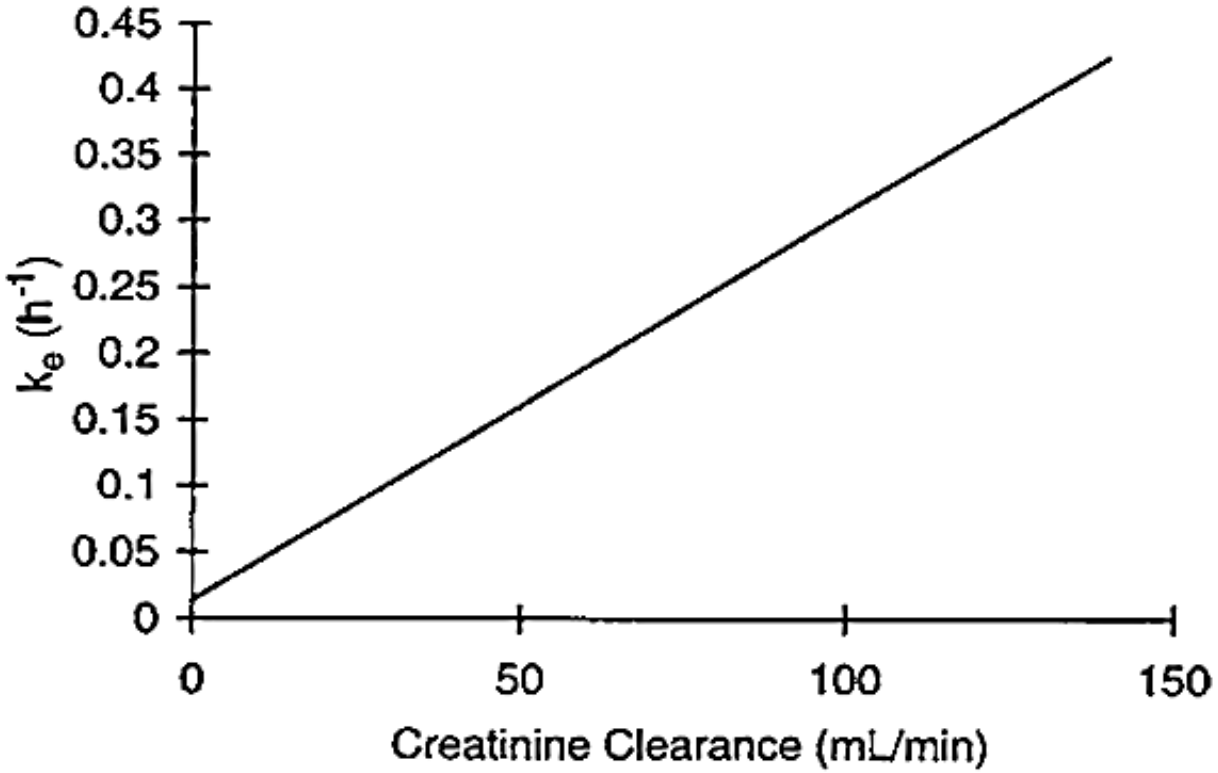


FIGURE 3-4 Relationship between creatinine clearance and aminoglycoside elimination rate constant *(k_e)* used to estimate initial aminoglycoside elimination when no drug concentrations are available. The y-axis intercept (0.014 h^{-1}) is nonrenal elimination for aminoglycosides.

- **Volume of distribution in decreased renal function**
- Volume of distribution can also change in patients with decreased renal function.

1. The volume of distribution of drugs **can increase** in patients with poor kidney function if p**lasma protein binding displacement of drug** occur by endogenous or exogenous substances that would normally be eliminated by the kidney but accumulate in the blood of patients with poor kidney function.
2. The volume of distribution of a drug can **decrease** if compounds normally excreted by the kidney accumulate to the extent that displacement of drug from **tissue binding sites** occurs

$$V = V_B + \frac{f_B}{f_T} V_T$$

Digoxin volume of distribution decreases in patients with decreased renal function according to the following equation:

$$\mathbf{V\ (in\ L) = 226 + [(298 \cdot CrCl)/\ (29.1 + CrCl)]}$$

Where CrCl is in mL/min.

The decline in volume of distribution presumably occurs because of displacement of tissue-bound digoxin.

Hepatic Disease

Liver blood flow averages **1–1.5 L/min** in adults with about one-third coming from the hepatic artery and about two-thirds coming from the portal vein.

Orally administered medications must pass through the liver before entering the systemic circulation, so if the drug is metabolized by the liver, a portion of the dose may be inactivated by the hepatic first-pass effect before having a chance to exert a pharmacologic effect .

In addition to hepatic metabolism, drugs can be eliminated unchanged by liver in the bile. The equation that describes hepatic drug metabolism is

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

- Where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance.
- There are two major types of liver disease: hepatitis and cirrhosis.
- Patients with acute hepatitis usually experience mild, transient decreases in drug metabolism that require no or minor changes in drug dosing.
- If the patient develops chronic hepatitis, it is likely that irreversible hepatocyte damage will be more widespread, and drug dosage changes

- In patients with hepatic cirrhosis, there is a permanent loss of functional hepatocytes so drug dosage schedules usually need to be modified.

- When hepatocytes are damaged they are no longer able to metabolize drugs efficiently, and intrinsic clearance decreases which reduces the hepatic clearance of the drug. If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and **bioavailability will increase**.

- A simultaneous decrease in hepatic clearance and liver first-pass effect results in extremely **large increases in steady-state concentrations** for orally administered drugs.

- Liver blood flow also decreases in patients with cirrhosis because hepatocytes are replaced by nonfunctional connective tissue which increases intraorgan pressure causing portal vein hypertension and shunting of blood flow around the liver.
- The decrease in liver blood flow results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further.
- The liver produces **albumin and, probably, α1-acid glycoprotein**, the two major proteins that bind acidic and basic drugs, respectively, in the blood.
- In patients with cirrhosis, the production of these proteins decline. When this is the case, the free fraction of drugs in the blood **increases** because of a lack of binding proteins.

- Additionally, high concentrations of endogenous substances in the blood that are normally eliminated by the liver, such as bilirubin, can displace drugs from plasma protein binding sites.
- o The increased free fraction in the blood will alter hepatic and renal drug clearance as well as the volume of distribution for drugs that are highly protein bound
- **(V = VB + (fB/fT) VT)**

- Since clearance typically decreases and volume of distribution usually increases or does not appreciably change for a drug in patients with liver disease, the elimination rate constant (ke) almost always decrease in patients with decreased liver function
- **(Ke = Cl/V)**

Determination of Child-Pugh Scores

- Unfortunately, there is no single laboratory test that can be used to assess liver function in the same way that measured or estimated creatinine clearance is used to measure renal function.

- The most common way to estimate the ability of the liver to metabolize drug is to determine the Child-Pugh score for a patient.

- The Child-Pugh score consists of five laboratory tests or clinical symptoms. The five areas are serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy.

TABLE 3-2 Child-Pugh Scores for Patients with Liver Disease[27]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

- Each of these areas is given a score of 1 (normal)–3 (severely abnormal; Table 3-2), and the scores for the five areas are summed

- The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15.

- A Child-Pugh score equal to **8–9** is grounds for a moderate **decrease (~ 25%) in initial daily drug dose** for agents that are primarily (≥60%) hepatically metabolized

- Score of **10** or greater indicates that a significant **decrease in initial daily dose (~ 50%) is** required for drugs that are mostly liver metabolized.

- As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects.

- **For example**, the usual dose of a medication that is 95% liver metabolized is 500 mg every 6 hours, and the total daily dose is 2000 mg/d.
- For a hepatic cirrhosis patient with a Child-Pugh score of 12, an appropriate initial dose would be 50% of the usual dose or 1000 mg/d. The drug could be prescribed to the patient as 250 mg every 6 hours or 500 mg every 12 hours.
- The patient would be closely monitored for pharmacologic and toxic effects due to the medication, and the dose would be modified as needed.

Implications of Hepatic Disease on Serum Drug Concentration Monitoring and Drug Effects

- The pharmacokinetic alterations that occur with hepatic disease result in complex changes for total and unbound steady-state concentrations and drug response.
- The changes that occur depend on whether the drug has a low or high hepatic extraction ratio.
- As previously discussed, hepatic drug metabolism is described by the following equation:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

1. For drugs with a low hepatic extraction ratio (≤30%)

- The numeric value of liver blood flow is much greater than the product of unbound fraction of drug in the blood and the intrinsic clearance of the compound (LBF>>fB · Cl’int), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [LBF ≈ LBF + (fB · Cl’int)]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug for a drug with a low hepatic extraction ratio

2-For drugs with a high hepatic extraction ratio (≥70%)

Similarly, for drugs with a high hepatic extraction ratio (≥70%), the numeric value of liver blood flow is much less than the product of unbound fraction of drug in the blood and the intrinsic clearance of the agent ($LBF \ll f_B \cdot Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to the product of free fraction of drug in the blood and intrinsic clearance [$f_B \cdot Cl'_{int} \approx LBF + (f_B \cdot Cl'_{int})$]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to liver blood flow for a drug with a high hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{f_B \cdot Cl'_{int}} = LBF$$

3-For drugs with intermediate hepatic extraction ratios

For drugs with intermediate hepatic extraction ratios, the entire liver clearance equation must be used and all three factors, liver blood flow, free fraction of drug in the blood, and intrinsic clearance are important parameters that must be taken into account. An extremely important point for clinicians to understand is that the factors which are important determinants of hepatic clearance are different depending on the liver extraction ratio for the drug.

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

Drug Interactions

- Pharmacokinetic drug interactions occur between drugs when one agent changes the clearance or volume of distribution of another medication. There are several drug interaction mechanisms that result in altered drug clearance. A drug can inhibit or induce the enzymes responsible for the metabolism of other drugs, or it can inhibit or induce membrane transporters of other drugs.

- Enzyme inhibition decreases intrinsic clearance, and enzyme induction increases intrinsic clearance.

- If two drugs are eliminated by the same enzyme, they may compete for the metabolic pathway and decrease the clearance of one or both compounds.

- Two drugs eliminated by the same active renal tubular secretion mechanism can compete for the pathway and decrease the renal clearance of one or both agents.

- Induction or inhibition of membrane transporters by one drug can also increase or decrease the volume of distribution of another drug.

- Another type of drug interaction displaces a drug from plasma protein–binding sites because the two compounds share the same binding site, and the two compete for the same area on plasma proteins.

- By virtue of its pharmacologic effect, a drug may increase or decrease blood flow to an organ that eliminates or metabolizes another medication and thereby decrease the clearance of the medication. Changes in plasma protein binding also cause alterations in volume of distribution.

Drug interactions
Answering the question of drug interaction

Equation used to answer the questions

1. The hepatic clearance

drugs with **low hepatic extraction** ratios **(Cl_H = fB.Cl').**

drugs with **high hepatic extraction** ratios **(Cl_H= LBF).**

2. Volume of distribution= $(V = V_B + [f_B/f_T]V_T)$

3. Half-life: $(t_{1/2} = [0.693 \cdot V]/Cl)$

4. Steady-state concentration: Affected by bioavailability (F) and clearance (CL)

$$Css = [F(D/\tau)] / Cl$$

5. The unbound steady-state concentration of drug in the blood equals the product of the total steady-state concentration and the unbound fraction of drug in the blood

$$Css_u = f_B Css$$

6. The effect of the drug:-increases when the unbound steady-state concentration increases and decreases when Css_u declines.

7. Bioavailability (F): When hepatocytes are damaged they are no longer able to metabolize drugs efficiently, and intrinsic clearance decreases which reduces the hepatic clearance of the drug.

If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and bioavailability will increase.

So bioavailability used only for oral drugs and inversely proportional to LBF ,FB ,CLint

ملاحظة: يجب مراجعة امثلة الكتاب

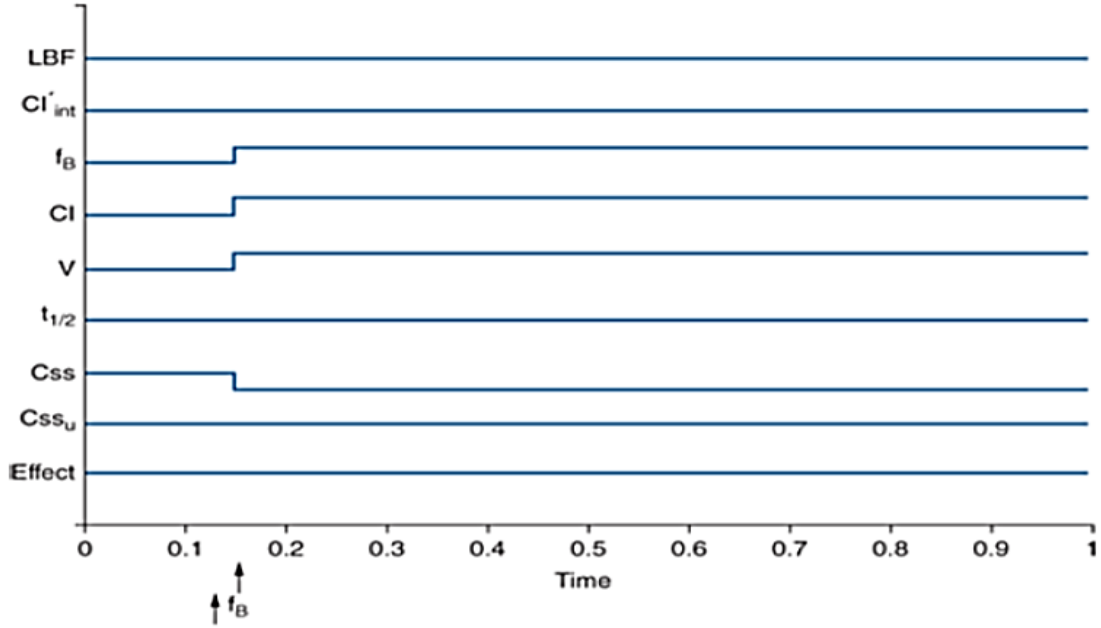
To answer questions:

1. You have to know if the drug is low or high extraction ratio to know what the factors that effect on CL are

2. You have to know what is the parameter that changed according to the question and what are the effect of this change in the factors from 1 to 7 according to their equations

Plasma Protein–Binding Displacement Drug Interactions

- **A-For a drug with a low hepatic extraction ratio**, plasma protein–binding displacement drug interactions cause major pharmacokinetic alterations, but these interactions are not clinically significant because the pharmacologic effect of the drug does not change (see Figure 3-7).



Source: Larry A. Bauer: Applied Clinical Pharmacokinetics, 3rd Edition

- Because the clearance of the drug is dependent on the fraction of unbound drug in the blood and intrinsic clearance for a low hepatic extraction ratio agent, addition of a plasma protein–binding displacing compound will increase clearance (↑Cl = ↑fBCl'int) and volume of distribution (↑V = VB +[↑fB/fT]VT).

- Because halflife depends on clearance and volume of distribution, it is likely that because both increase, half-life will not substantially change (t1/2 = [0.693 • ↑V]/↑Cl).

- However, it is possible that if either clearance or volume of distribution changes disproportionately, halflife will change.

- The total SteadyState concentration will decline because of the increase in clearance (↓Css = k0/↑Cl, where k0 is the infusion rate of drug).

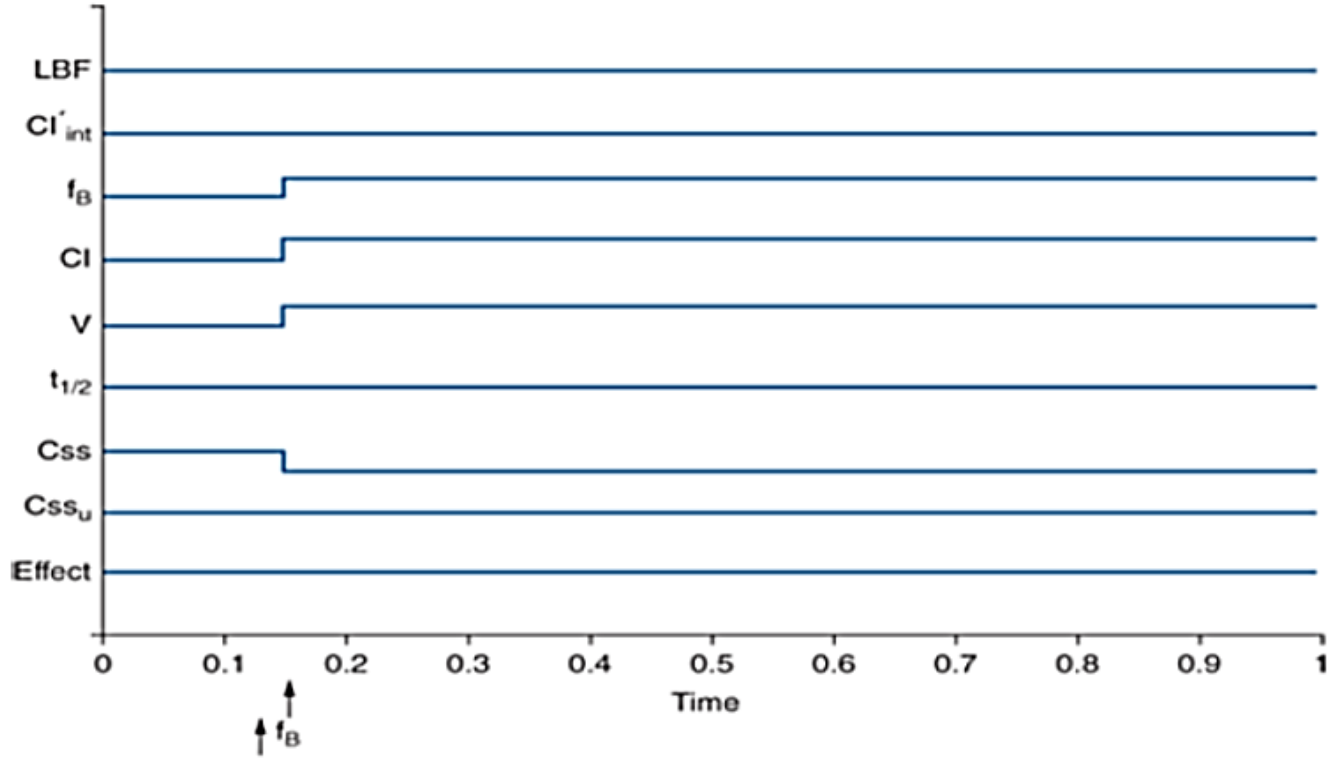
- However, the unbound SteadyState concentration will remain unaltered because the free fraction of drug in the blood is higher than it was before the drug interaction occurred ($Css_u = \uparrow fB \downarrow Css$).

- The pharmacologic effect of the drug does not change because the free concentration of drug in the blood is unchanged.

- An example of this drug interaction is the addition of diflunisal to patients stabilized on warfarin therapy.

- Diflunisal displaces warfarin from plasma protein–binding sites but does not augment the anticoagulant effect of warfarin.

- If drug concentrations are available for the medication, it can be difficult to convince clinicians that a drug dosage increase is not needed even though total concentrations decline as a result of this interaction. When available, unbound drug concentrations can be used to document that no change in drug dosing is needed.



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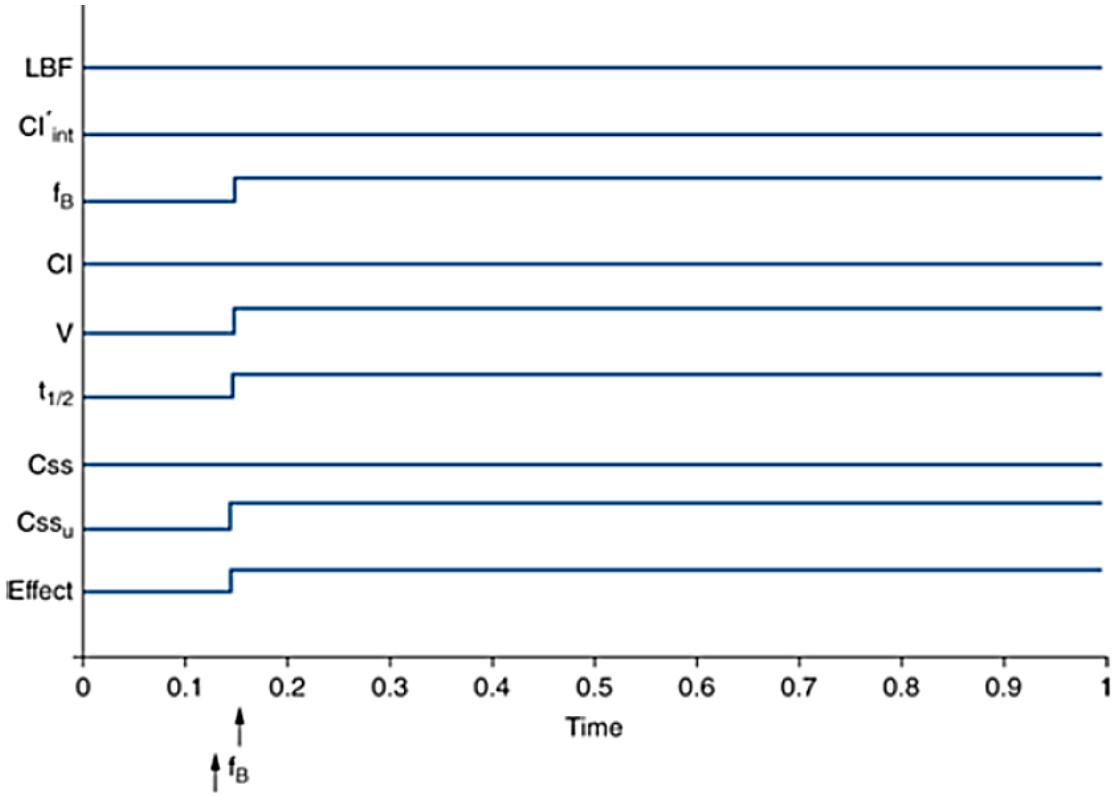
- **B- For drugs with high hepatic extraction** ratios given intravenously, plasma protein–binding displacement drug interactions cause both major **pharmacokinetic and pharmacodynamics** changes (see Figure 3-9).



- Because the clearance of the drug is dependent solely on liver blood flow for an agent of this type, total clearance does not change. However, both volume of distribution [↑V = VB + (↑fB/fT) VT] and half-life [↑t1/2 = (0.693 •↑V)/Cl] will increase because of plasma protein–binding displacement of the drug.

- Because total clearance did not change, the total SteadyState concentration remains unaltered. However, the free concentration (↑Cssu = ↑fB Css) and pharmacologic effect of the drug will both increase (↑effect ∝ ↑Cssu).

- Currently, there are no clinically significant drug interactions of this type. However, clinicians should be on the outlook for this profile for highly protein bound drugs with high hepatic extraction ratios given intravenously because the interaction is very subtle.

- Most noteworthy is the fact that although total concentrations remain unchanged, the pharmacologic effect of the drug is augmented. If available, unbound drug concentration could be used to document the drug interaction.

- If a drug with a high hepatic extraction ratio is given orally, a plasma protein–binding displacement drug interaction will cause a simultaneous increase in the unbound fraction of drug in the blood (↑fB) and the hepatic presystemic metabolism of the drug.

- Hepatic presystemic metabolism increases because the higher unbound fraction of drug in the blood allows more drug molecules to enter the liver where they are ultimately metabolized. The increase in hepatic presystemic metabolism leads to an increased first pass effect and decreased drug bioavailability (↓F).

- Total SteadyState drug concentrations will be lower because of decreased drug bioavailability [↓Css = (↓F [D/t])/Cl].

- However, the unbound SteadyState drug concentration and pharmacologic effect remain unchanged due to this type of drug interaction because the increase in unbound fraction is offset by the decrease in the total SteadyState concentration (~Cssu = ↑fB↓Css).

- Route of administration plays an important role in how important plasma protein–binding displacement drug interactions are for agents with high hepatic extraction ratios.

- **Inhibition Drug Interactions**
- Inhibition of hepatic drug metabolism is probably the most common drug interaction encountered in patients. For drugs with low hepatic extraction ratios, this type of drug interaction produces clinically significant changes in drug pharmacokinetics and effect (see Figure 3-6 in the book)

- The addition of a hepatic enzyme inhibitor will decrease intrinsic clearance and total clearance for the drug (↓Cl = fB↓Cl'int). Because volume of distribution remains unaltered, the half-life of the drug will increase (↑t1/2 = [0.693 • V]/↓Cl).

- As a result of the total clearance decrease, total SteadyState drug concentrations will increase (↑Css = k0/↓Cl). The rise in unbound SteadyState drug concentration will mirror that seen with total drug concentration, and the effect of the drug will increase in proportion to unbound concentration.

- An example of this drug interaction is the addition of ciprofloxacin to a patient stabilized on theophylline therapy.

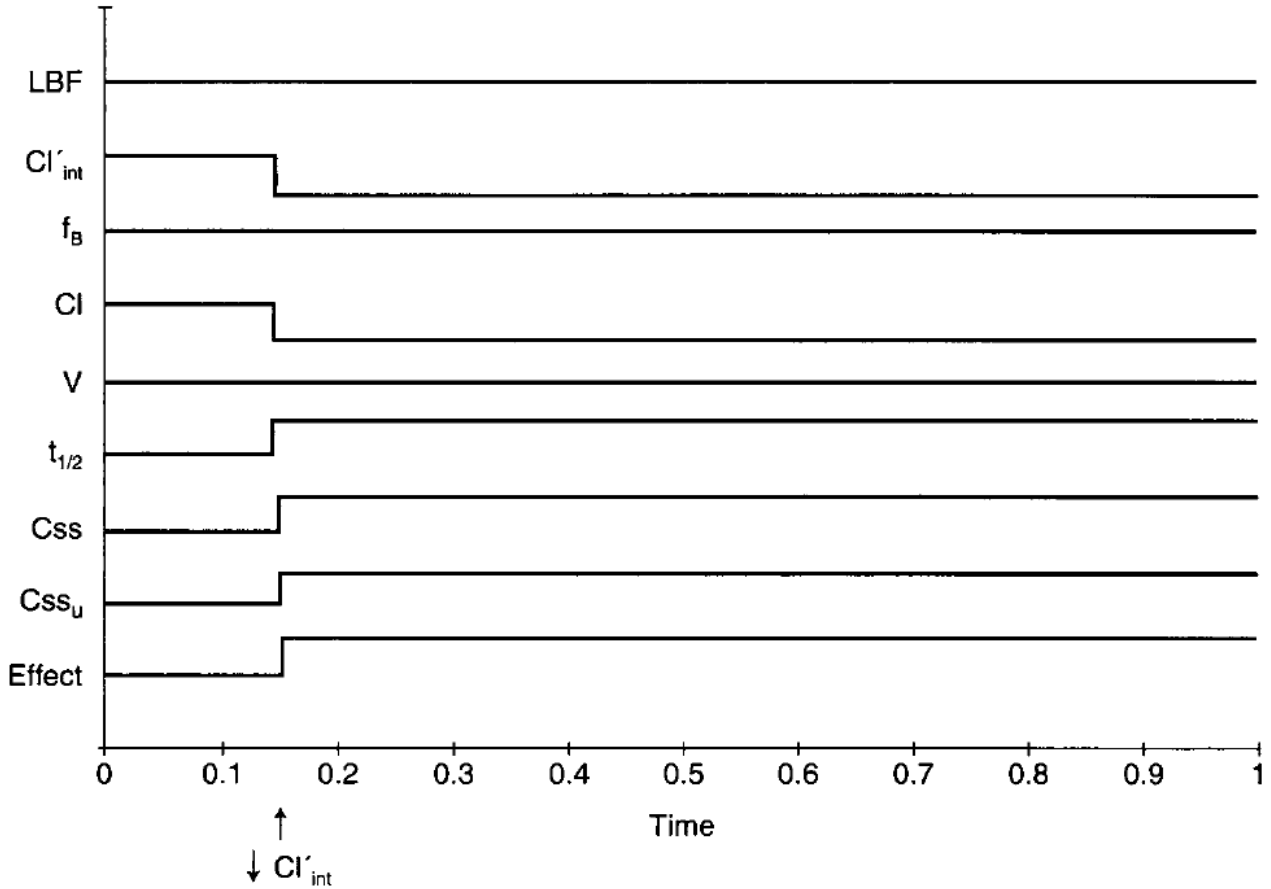


FIGURE 3-6 Changes in physiologic parameters (*LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance decreases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

- For drugs with *high hepatic extraction* ratios, this category of drug interaction produces variable effects depending on the route of administration for the drug. If the drug is given intravenously and an enzyme inhibitor is added, the decrease in intrinsic clearance is usually not substantial enough to cause major pharmacokinetic and pharmacodynamics effects because clearance is a function of liver blood flow (see Figure 3-8 in the book)

- However, if the drug is given orally and an enzyme inhibitor is added to therapy, presystemic metabolism of the medication may be greatly depressed and the firstpass effect can decrease dramatically leading to improved drug bioavailability.

- This effective increase in administered oral dose will increase the total and unbound steady state drug concentrations, and lead to an increase in the pharmacologic effect of the drug.

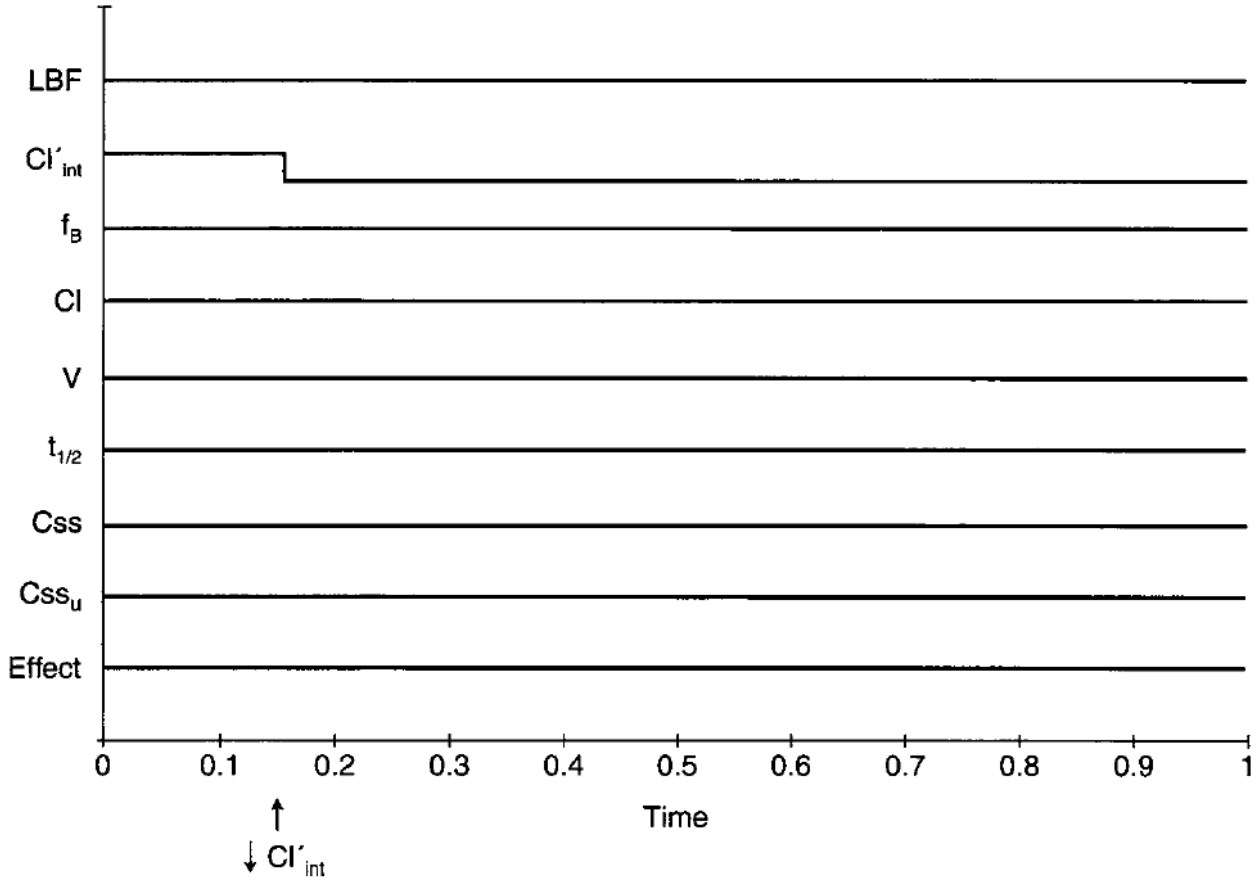


FIGURE 3-8 Changes in physiologic parameters (*LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance decreases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

- **Induction Drug Interactions**
- Drugs with low hepatic extraction ratios exhibit clinically significant drug interactions that alter drug pharmacokinetics and pharmacologic response when hepatic enzyme inducers are coadministered (Figure 3-17 in the book)

- Enzyme inducers increase intrinsic clearance of the drug and thereby increase the total clearance of the medication (↑Cl = fB↑Cl'int).

- The increase in total clearance will cause a shorter half-life as volume of distribution remains unchanged (↓t1/2 = [0.693 • V]/↑Cl).

- Increased total clearance will also cause decreased total SteadyState concentration (↓Css= k0/↑Cl), unbound SteadyState concentration (↓Cssu = fB↓Css), and pharmacologic effect (↓effect ∝ ↓Cssu).

- Carbamazepine is a potent enzyme inducer that, when added to a patient's therapy, can cause this type of drug interaction with many other medications such as warfarin. (FIGURE 3-17 in the book)

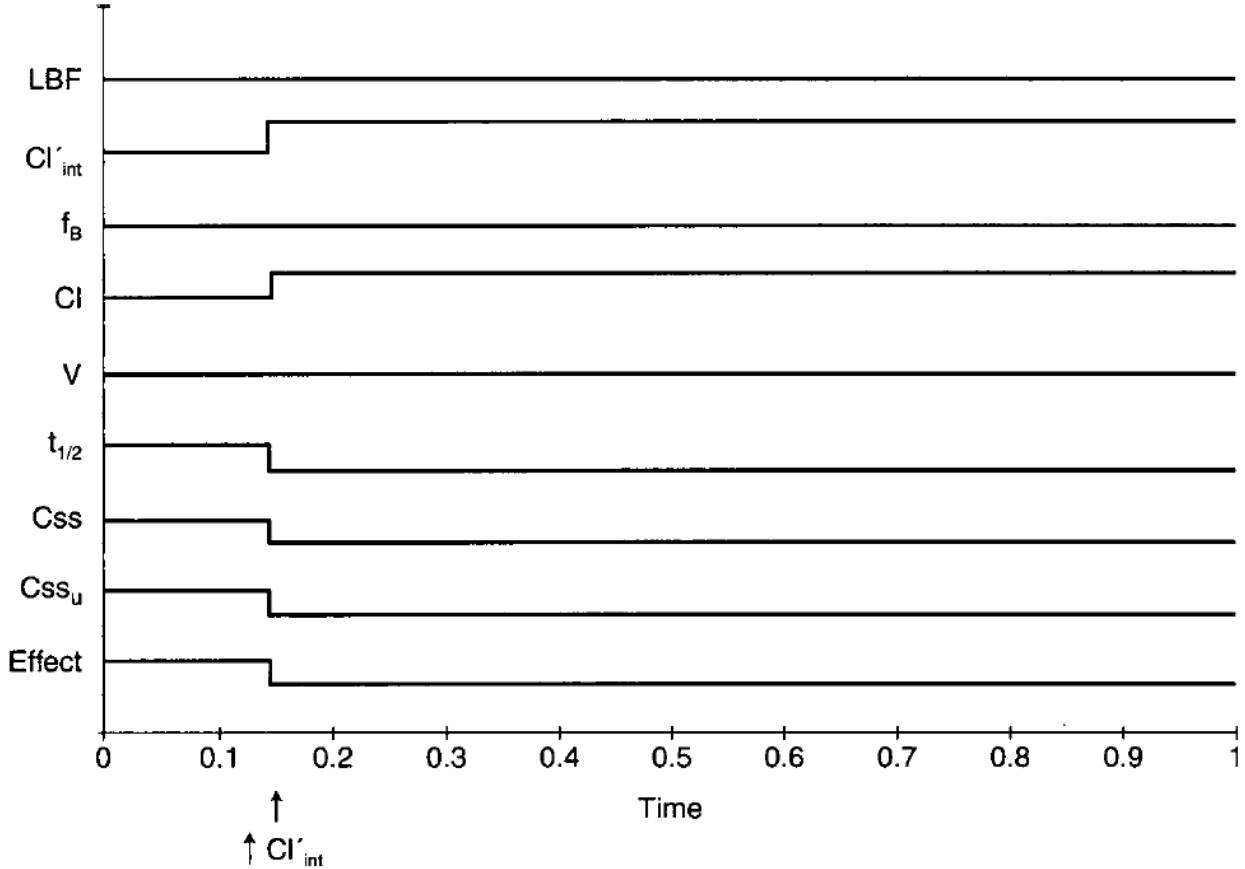


FIGURE 3-17 Changes in physiologic parameters (*LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance increases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

- **For drugs with high hepatic extraction ratios**, this type of drug interaction results in variable effects depending on the route of administration for the drug. If the drug is given intravenously and an enzyme inducer is added, the increase in intrinsic clearance is usually not large enough to cause major pharmacokinetic and pharmacologic effect alterations because total clearance is a function of liver blood flow (Figure 3-18)

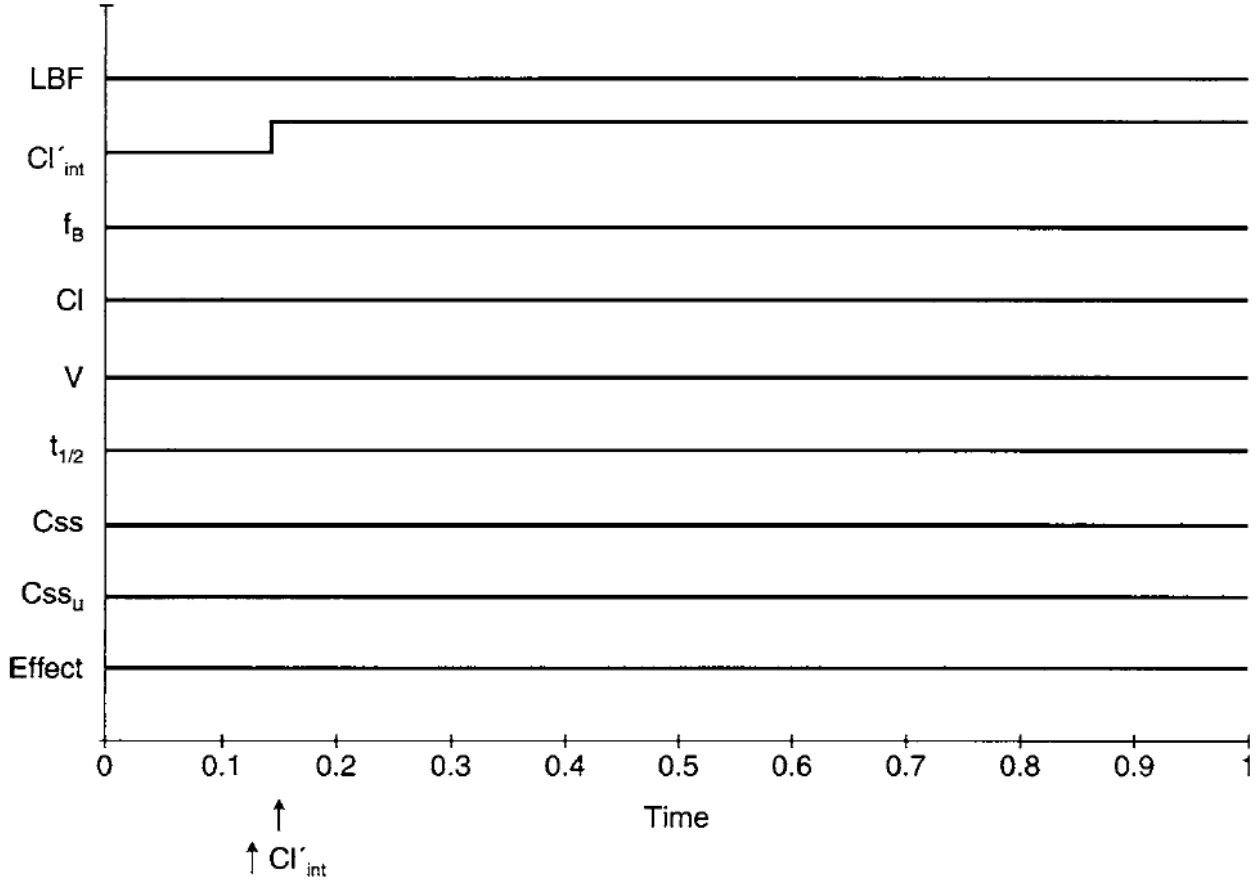


FIGURE 3-18 Changes in physiologic parameters (*LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance increases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

- However, if the drug is given orally and an enzyme inducer is added to the treatment regimen, presystemic metabolism of the medication may be increased and the firstpass effect augmented leading to decreased drug bioavailability. This effective decrease in administered oral dose will decrease the total and unbound steadystate drug concentrations and lead to a decrease in the pharmacologic effect of the agent.

- **Heart Failure**
- Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow.
- Changes in drug pharmacokinetics due to decreased renal blood flow are not widely reported.
- However, declines in hepatic clearance, especially for compounds with moderate to high hepatic extraction ratios, are reported for many drugs.
- Additionally, decreased drug bioavailability has been reported in patients with heart failure. The proposed mechanisms for decreased bioavailability are collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult and decreased blood flow to the gastrointestinal tract.
- The volume of distribution for some drugs decreases in patients with heart failure. Because clearance and volume of distribution may or may not simultaneously change, the alteration in halflife, if any, is difficult to predict in patients with heart failure.

- **Obesity**

- The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution. The general physiologic equation for volume of distribution can be broken down into separate parameters for individual tissue types:

$$V = V_B + \frac{f_B}{f_T} V_T = V_B + \frac{f_B}{f_{heart}} V_{heart} + \frac{f_B}{f_{muscle}} V_{muscle} + \frac{f_B}{f_{fat}} V_{fat} + \ldots + \frac{f_B}{f_n} V_n$$

- Because of this, the sheer amount of adipose tissue will be a primary determinant of how much obesity will affect the volume of distribution of the drug. Also, the magnitude of effect that adipose tissue has on the volume of distribution for a drug is dependent on the binding of drug in the tissue itself.

- If the drug has a large affinity for adipose tissue and is highly bound there, the free fraction in adipose tissue will be small (↓ ffat) and a large amount of drug will accumulate in that tissue. Medications that have high lipid solubility tend to partition into adipose tissue, and the volume of distribution in obese patients for these drugs can be dramatically larger than that in normal weight patients.

- **<u>Please note:</u>**
- This lecture includes multiple figures that summarize each section. On test, you might be required to reproduce the figure or show effect of a disease condition or drug interaction using figure, however, if you understand the concept, you should be able to draw the figure easily

- For equations, you do not need to memorize the equations, but you should be able to show how the equation changes in special population

- The subject of dialysis and hemodialysis is not required for this course and this applies for upcoming chapters as well