# CLINICAL PHARMACOKINETICS: DOSE ADJUSTMENT IN HEPATIC DISEASE

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# INTRODUCTION

The liver performs various functions to maintain the proper workflow of the body

Its primary function is metabolism and detoxification. It causes various drug substances' metabolism into an active metabolite, the inactive metabolite, toxic metabolite, etc.

Any damage to the liver results in a decrease in metabolism, which may cause the failure of drug therapy or an increase in drug toxicity

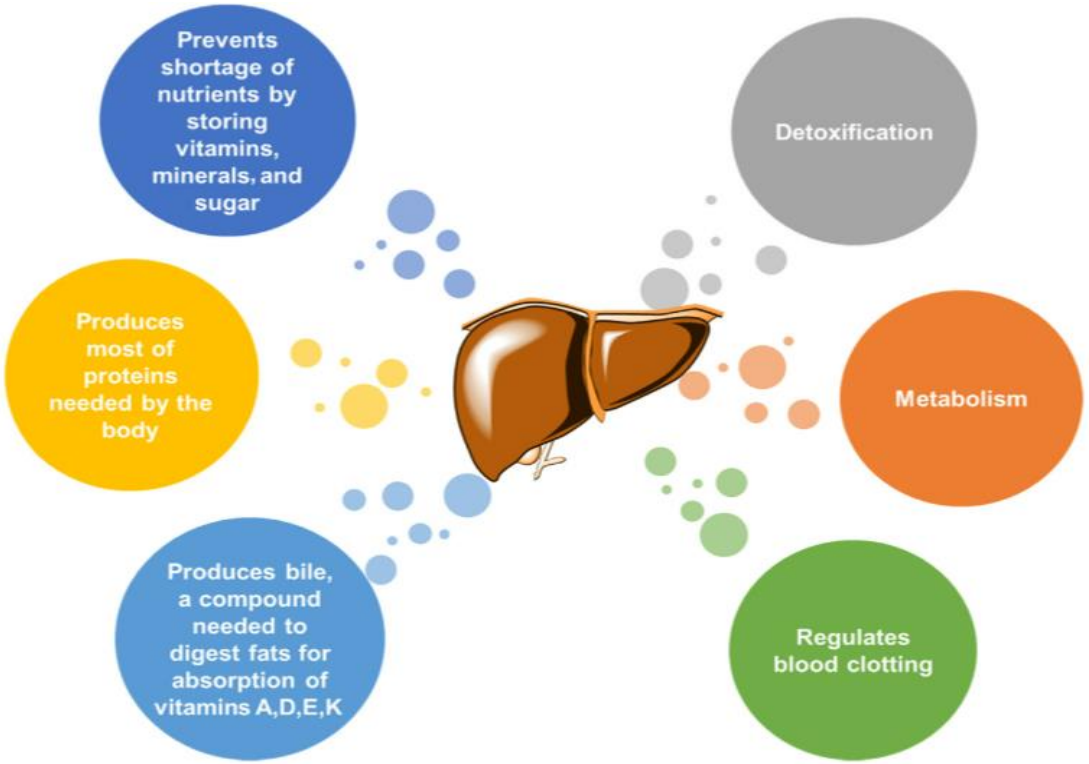



FIGURE 3.3 Functions of the liver.

# INTRODUCTION

Drugs are primarily eliminated from the body by metabolism and excretion. Of these two biologic processes, the liver plays a pivotal role in the metabolism of parent drugs and formation of metabolites prior to their excretion by the kidneys.

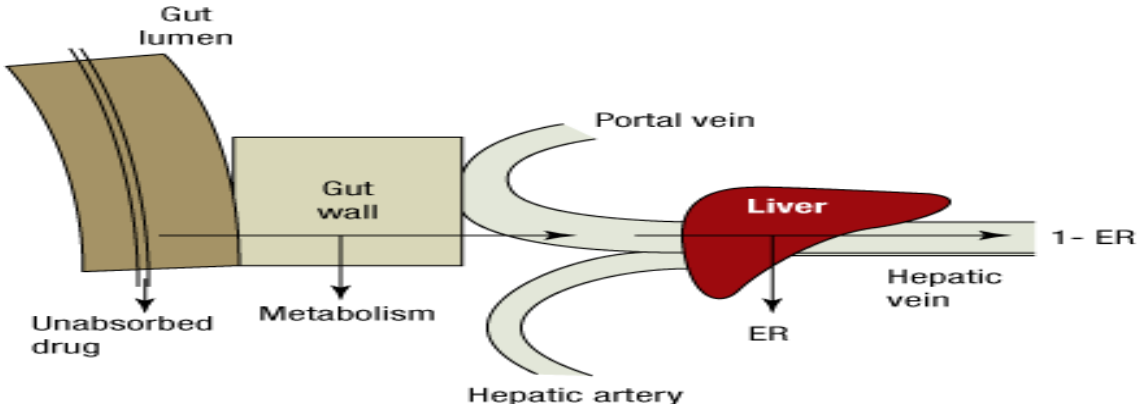
**The overall capacity of the liver to carry out its metabolic role is primarily dependent on <u>three factors</u>:**

1. The **liver blood flow**, which delivers drugs to the hepatocyte via the portal vein for orally administered drugs and via the systemic circulation for all administered drugs.

2. The **activity of the metabolizing enzymes** within the smooth endoplasmic reticulum and the cytosol of the hepatocyte

3. The **fraction** of drug in the blood that is **free** or not bound to plasma proteins and capable of interacting with hepatic enzymes

# LIVER BLOOD FLOW




- Perfusion of the liver is provided by blood supply from the hepatic artery, which carries oxygenated blood from the aorta, and the portal vein, which carries nutrient-rich blood from the gastrointestinal tract.
- The usual effective hepatic blood flow is 1.5 L/min, but it may vary from 1 to 2 L/min depending on diet, food intake, physical activity, or drug intake.
- The portal vein provides approximately 75% of the liver's total blood supply
- The liver is the first site of elimination for orally administered drugs before they reach the systemic circulation

# INTRINSIC CLEARANCE

Intrinsic clearance ($Cl_{int}$) is used to describe the total ability of the liver to metabolize a drug **in the absence of flow limitations**, and **binding to cells or proteins in the blood reflecting** the inherent activities of the mixed-function oxidases and all other enzymes

Thus, intrinsic clearance is a **distinct characteristic of a particular drug**, and as such, it reflects the inherent ability of the liver to metabolize the drug

Intrinsic clearance may be shown to be analogous to the ratio $V_{max}/K_M$ for a drug that follows Michaelis–Menten kinetics

# HEPATIC CLEARANCE

The hepatic clearance ($Cl_H$), or elimination of a drug, is related to the three physiologic determinants by the following mathematical relationship:

$$Cl_H = \frac{Q_H \times fu_B \times Cl_{int}}{Q_H + fu_B \times Cl_{int}}$$ Equation 1

where $Q_H$ is hepatic blood flow, $fu_B$ is unbound drug fraction in the blood, and Clint is intrinsic clearance.

Based on this mathematical relationship, when enzyme activity ($Cl_{int}$) and $fu_B$ are very low relative to hepatic blood flow, they will become the primary determinants and rate-limiting process for hepatic clearance, as $Cl_H$ approximates $fu_B \times Cl_{int}$.

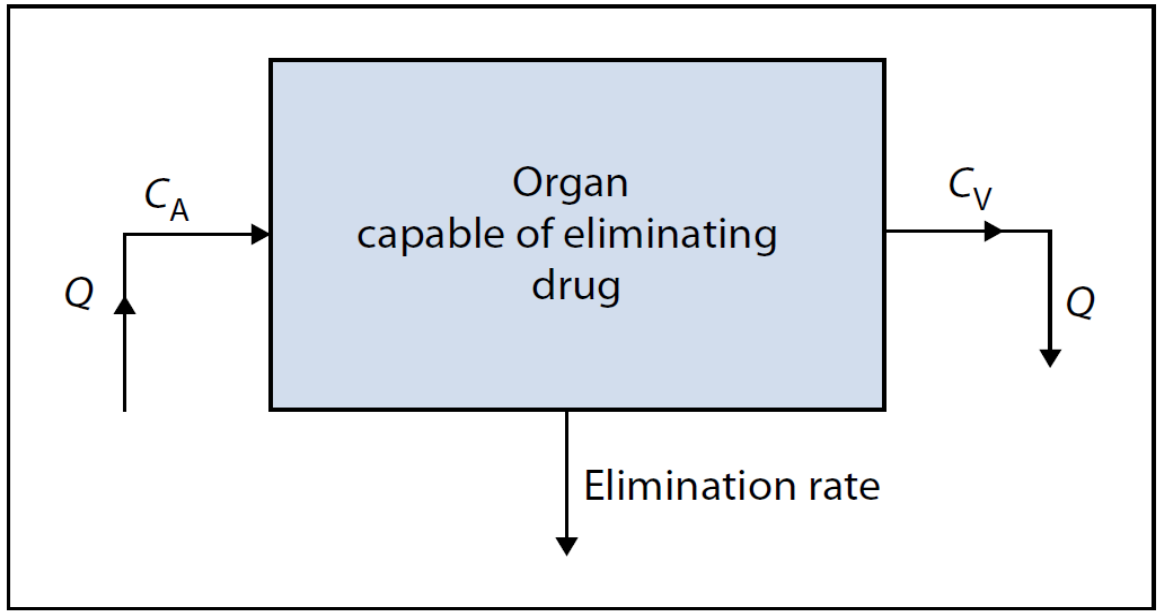
On the other hand, when **enzyme activity and $fu_B$ are very high** in relation to blood flow, **$Cl_H$ would approximate $Q_H$** and blood flow carrying drug to the liver is the rate-limiting process for hepatic elimination.

# HEPATIC CLEARANCE

The hepatic clearance for any drug can also be conceptualized as the product of blood flow across the liver and the hepatic extraction ratio ($ER_H$) for that drug

$$\mathbf{Cl_H} = Q_H * \mathbf{ER_H}$$

The liver extraction ratio (ER) provides a direct measurement of drug removal from the liver after oral administration of a drug.




$$ER = \frac{C_a - C_v}{C_a}$$

Where $C_a$ is the drug concentration in the blood entering the liver and $C_v$ is the drug concentration leaving the liver.

The ER may vary from 0 to 1.0.

What does an ER of 0.35 mean?

# HIGH EXTRACTION RATIO DRUGS

- The liver effectively removes high extraction ratio drugs (usually defined as $ER_H > 0.7$) from the blood as soon as they are presented via the blood supply
- As such, the elimination of these drugs is more sensitive to changes in, and rate ***limited by, hepatic blood flow***
- Thus, an increase in blood flow to the liver will increase the rate of drug removal by the organ. **Propranolol**, a b-adrenergic blocking agent, decreases hepatic blood flow by decreasing cardiac output. In such a case, the drug decreases its own clearance through the liver when given orally.
- Many drugs that demonstrate first-pass effects are drugs that have high extraction ratios with respect to the liver. Examples of drugs with this flow-dependent elimination characteristic are metoprolol, nitroglycerin, and verapamil

**Intermediate extraction ratio (ER: 0.3-0.7)**

- Hepatic clearance of these drugs is dependent on both hepatic blood flow, intrinsic metabolising capacity of the liver and the free drug fraction

# LOW EXTRACTION RATIO DRUGS

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 (**Q >> fub . $Cl_{int}$**), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow

When this substitution is made into the hepatic clearance equation (equation 1 in the previous slides), 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:

$$\mathbf{Cl_H = fu_B \times Cl_{int}}$$

# LOW EXTRACTION RATIO DRUGS

- Based on the degree of plasma protein binding, drugs with a low extraction ratio are sometimes further subgrouped as binding sensitive (e.g., phenytoin) and binding insensitive (e.g.,theophylline)
- Thus, the hepatic clearance of a **highly protein-bound, low-extraction-**ratio drug would depend on **both intrinsic clearance and the degree of plasma protein binding**, whereas the **intrinsic clearance** of unbound drug is the primary factor affecting hepatic clearance for a **low-extraction-ratio drug with a low degree of plasma protein binding.**

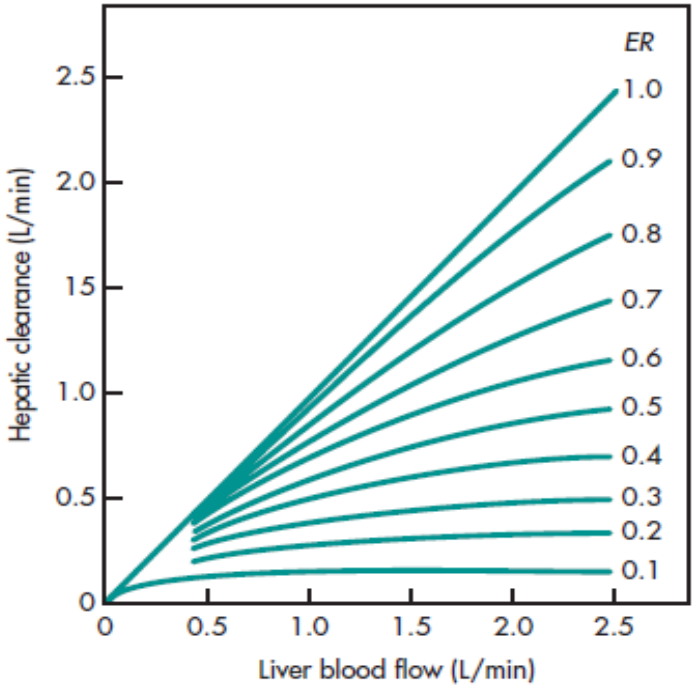
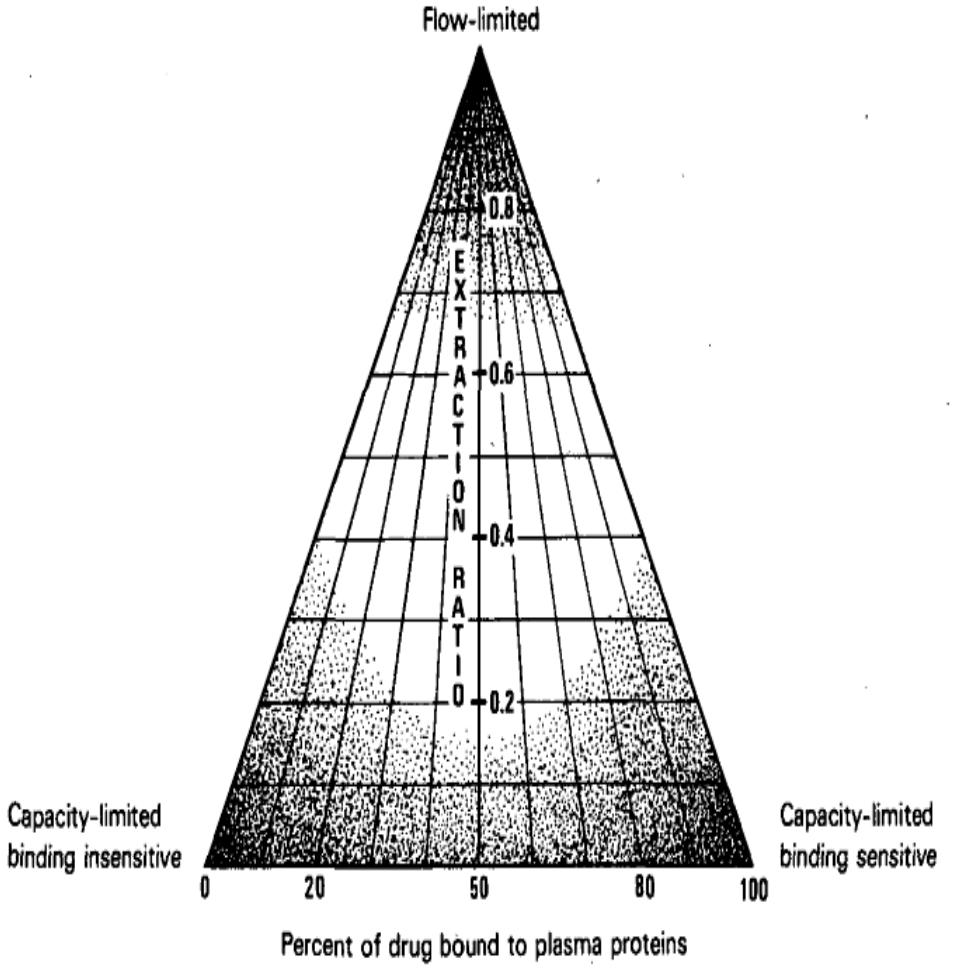



**FIGURE 12-18** The relationship between liver blood flow and total hepatic clearance for drugs with varying extraction rates (ER).

# LOW EXTRACTION RATIO DRUGS

- For a drug that has a low extraction ratio and is less than 75% to 80% bound, small changes in protein binding will **not produce significant changes in hepatic clearance**
- These drugs are considered capacity-limited, binding-insensitive drugs
- Drugs that are **highly bound to plasma protein but with low extraction** ratios are considered capacity limited and binding sensitive, because a small displacement in the protein binding of these drugs will cause a very large increase in the free drug concentration.
- A large increase in free drug concentration will cause an increase in the rate of drug metabolism, **resulting in an overall increase in hepatic clearance.**

- This diagram illustrates the way in which two pharmacokinetic parameters (hepatic extraction ratio and percent plasma protein binding) are used to assign a drug into one of three classes of hepatic clearance (flow limited; capacity limited, binding sensitive; and capacity limited, binding insensitive).
- Any drug metabolized by the liver can be plotted on the triangular graph. **However, the classification is important only for those eliminated primarily by hepatic processes.**
- The closer a drug falls to a corner of the triangle (shaded areas), the more likely it is to have the characteristic changes in disposition in liver disease as described previously for the three drug classes (Capacity limited binding insensitive, Capacity limited binding sensitive, flow limited)



# PHARMACOKINETIC CLASSIFICATION OF DRUGS ELIMINATED PRIMARILY BY HEPATIC METABOLISM

| Drug Class | Extraction Ratio (Approx.) | Percent Bound |
|---|---|---|
| | **Flow Limited** | |
| Lidocaine | 0.83 | 45–80[a] |
| Propranolol | 0.6–0.8 | 93 |
| Pethidine (meperidine) | 0.60–0.95 | 60 |
| Pentazocine | 0.8 | — |
| Propoxyphene | 0.95 | — |
| Nortriptyline | 0.5 | 95 |
| Morphine | 0.5–0.75 | 35 |

# PHARMACOKINETIC CLASSIFICATION OF DRUGS ELIMINATED PRIMARILY BY HEPATIC METABOLISM

| Drug Class | Extraction Ratio (Approx.) | Percent Bound |
|---|---|---|
| **Capacity Limited, Binding Sensitive** | | |
| Phenytoin | 0.03 | 90 |
| Diazepam | 0.03 | 98 |
| Tolbutamide | 0.02 | 98 |
| Warfarin | 0.003 | 99 |
| Chlorpromazine | 0.22 | 91–99 |
| Clindamycin | 0.23 | 94 |
| Quinidine | 0.27 | 82 |

| Drug Class | Extraction Ratio (Approx.) | Percent Bound |
|---|---|---|
| **Capacity Limited, Binding Insensitive** | | |
| Theophylline | 0.09 | 59 |
| Hexobarbital | 0.16 | — |
| Amobarbital | 0.03 | 61 |
| Antipyrine | 0.07 | 10 |
| Chloramphenicol | 0.28 | 60–80 |
| Thiopental | 0.28 | 72 |
| Acetaminophen | 0.43 | 5[a] |

# CHANGES IN PK WITH HEPATIC DISEASES

- Hepatic disease may include common hepatic diseases, such as alcoholic liver disease (**cirrhosis)** and chronic infections with **hepatitis** viruses B and C, and less common diseases, such as acute hepatitis D or E, primary biliary cirrhosis, primary sclerosing cholangitis, and *a*1-antitrypsin deficiency. In addition, **drug-induced hepatotoxicity.**
- Hepatic disease may lead to drug **accumulation**, failure to form an active or inactive metabolite, **increased bioavailability** after oral administration, and other effects including possible alteration in drug–protein binding.
- Liver disease may also alter **kidney function**, which can lead to accumulation of a drug and its metabolites even when the liver is not primarily responsible for elimination

# PATHOPHYSIOLOGICAL CHANGES IN CIRRHOSIS

Hepatic disease, and in particular cirrhosis, results in numerous pathophysiologic changes in the liver that may influence drug pharmacokinetics

Histologically, cirrhosisis a diffuse process characterized by **fibrosis** and a conversion of **normal liver architecture into structurally abnormal nodules**. These modifications are associated with or are responsible for

A) a reduction in liver blood flow

B)  presence of intra- and extrahepatic portal-systemic **shunting**

C) reduction in the number and in the activity of the hepatocytes

The importance of the above-mentioned alterations in liver function may vary following the **etiology of the cirrhosis**, and there is marked interindividual variation in the rate of progression of the disease

# PATHOPHYSIOLOGICAL CHANGES IN CIRRHOSIS

- Moreover, such progression will inevitably lead to the development of clinical manifestations such **as esophageal varices, edema, ascites, severe impaired parenchymal function, and hepatic encephalopathy**, which may contribute to alterations in the pharmacokinetic and pharmacodynamic behavior of many drugs.
- Added to these features will be the effect of an **impaired production of albumin,** which results in reduced plasma binding of several drugs and thus an increased availability of the circulating drug pool for tissue uptake and pharmacodynamic effects.
- Impaired secretion of **bile acids**, bilirubin, and other organic anions is also observed in cirrhosis, mainly when its aetiology is linked to lesions of the extrahepatic biliary track

# EFFECT OF HEPATIC DISEASES ON DRUG ABSORPTION

The liver has no functional role in affecting the absorption of drug from the gastrointestinal tract per se, its unique anatomical positioning within the circulating system makes it a **primary site of loss for orally administered drug** prior to its entry into the systemic circulation.

Drugs with an intermediate to high extraction ratio will undergo an important presystemic elimination or first pass effect. The fraction of an absorbed oral dose that escapes first pass hepatic clearance has been described by the following equation:

$$F = 1 - ER$$

assuming that the fraction of drug removed by nonhepatic process prior to reaching the circulation is negligible.

# EFFECT OF HEPATIC DISEASES ON DRUG ABSORPTION

- The oral bioavailability of a number of drugs with **low or intermediate bioavailability** has been shown to significantly increase in patients with liver **cirrhosis**. The increase in the bioavailability in combination with the reduced systematic clearance of flow-limited drugs in patients with cirrhosis may lead to substantial increases in AUC necessitating a significant reduction in the administered dose.
- How about low extraction drugs??

| Drug | Normal | Cirrhosis | Fold increase |
|---|---|---|---|
| Carvedilol | 0.19 | 0.83 | 4.4 |
| Chlormethiazole | 0.10 | 1.16 | 11.6 |
| Labetalol | 0.33 | 0.63 | 1.9 |
| Meperidine | 0.48 | 0.87 | 1.8 |
| Metoprolol | 0.50 | 0.84 | 1.7 |
| Midazolam | 0.38 | 0.76 | 2.0 |
| Morphine | 0.47 | 1.01 | 2.1 |
| Nifedipine | 0.51 | 0.91 | 1.8 |
| Nisoldipine | 0.04 | 0.15 | 3.8 |
| Pentazocine | 0.18 | 0.68 | 3.8 |
| Propranolol | 0.36 | 0.60 | 1.7 |
| Verapamil | 0.10 | 0.16 | 1.6 |

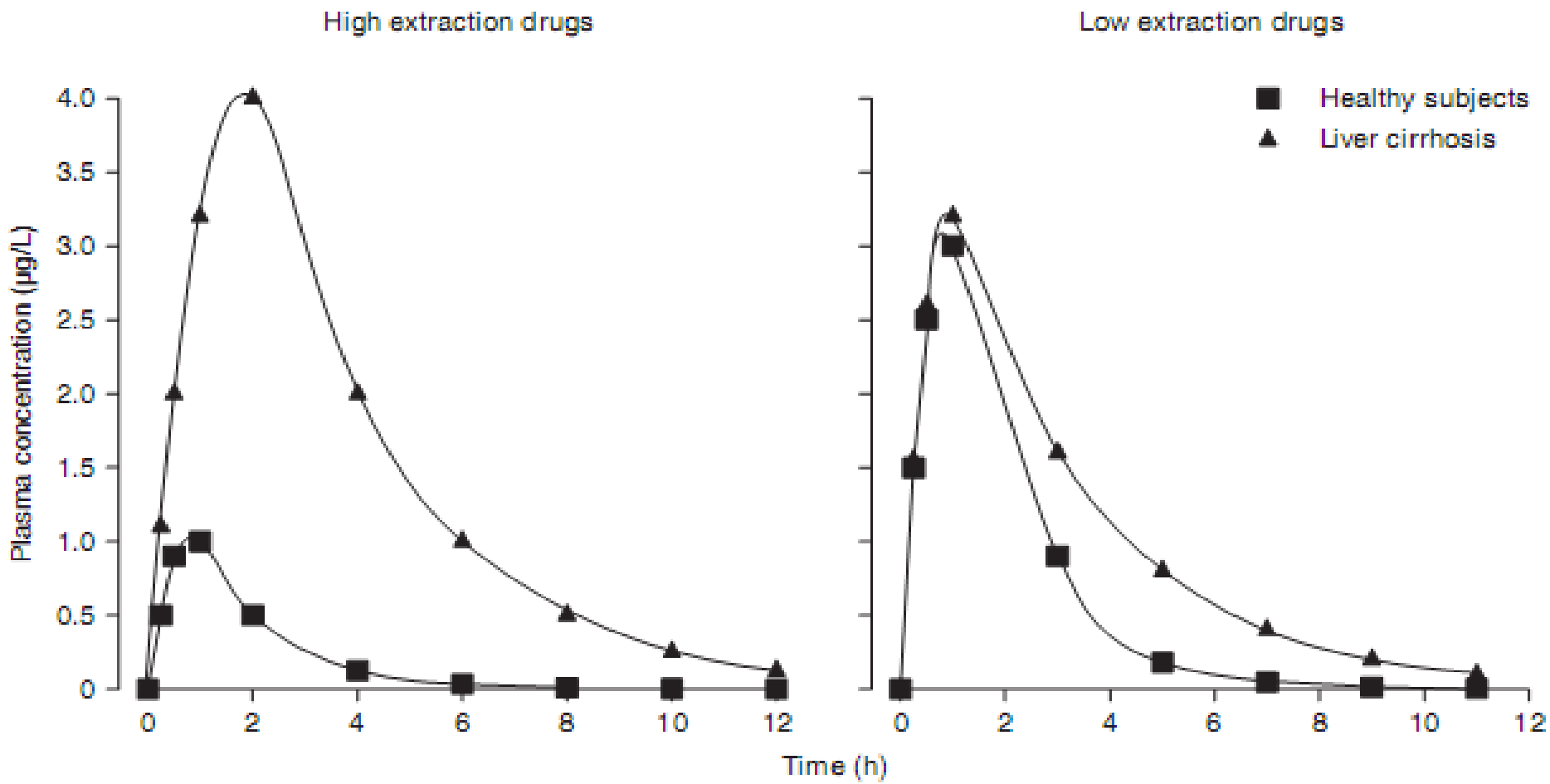
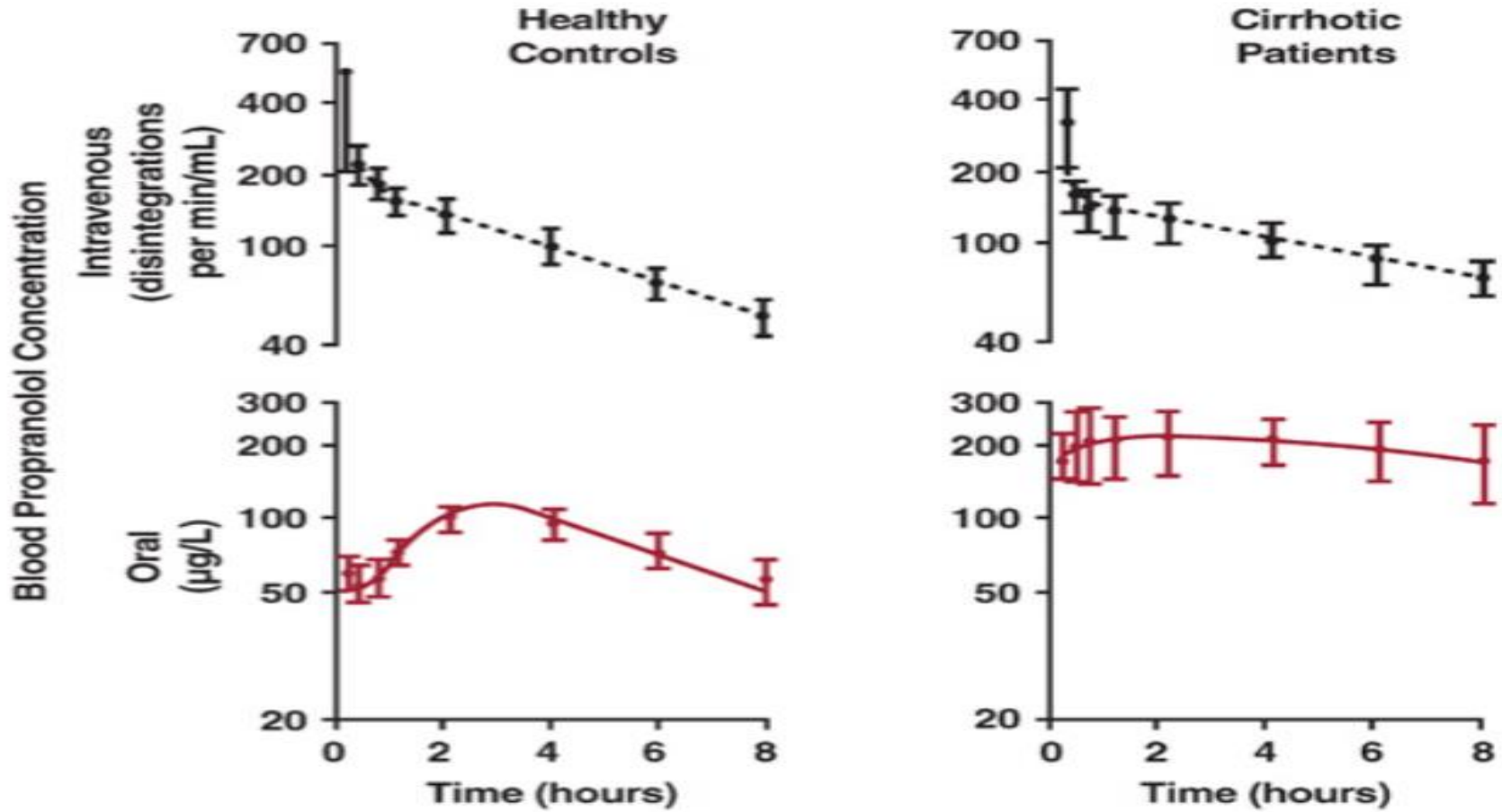



**Fig. 2.** Effect of liver cirrhosis on the kinetics of drugs with high or low hepatic extraction. For drugs with a high hepatic extraction, the maximal plasma concentration and bioavailability of the drug increases and elimination is slowed. For drugs with a low hepatic extraction, only elimination is slowed. Accordingly, for drugs with a high hepatic extraction that are administered orally, both initial and maintenance doses have to be reduced, whereas for drugs with a low hepatic extraction, only the maintenance dose has to be adapted.


Healthy Controls
Cirrhotic Patients
Blood Propranolol Concentration
Intravenous (disintegrations per min/mL)
Oral (µg/L)
700
400
200
100
40
300
200
100
50
20
0
2
4
6
8
Time (hours)

# CHANGES IN DRUG DISTRIBUTION

- Since only the unbound drug is capable of entering and leaving the tissue compartments, the **distribution** of a drug within the body depends on its reversible binding to blood cells, plasma proteins, and tissue macromolecules. Many **drugs that are highly bound** to albumin or α1-acid glycoprotein have a significantly **higher unbound fraction** in patients with chronic liver disease
- Mechanisms for decreased binding of certain drugs to plasma proteins include- changes in albumin binding affinity, accumulation of endogenous compounds, such as bilirubin, reduced albumin and α1-acid glycoprotein synthesis
- As a result of the **lower** plasma binding, **the distribution volume of certain drugs may be larger in these patients.**

# CHANGES IN DRUG DISTRIBUTION

Moreover, **water-soluble drugs** will have a significant increase in their volumes of distribution in patients with ascites possibly necessitating larger loading doses.

For example, the apparent volume of distribution of the β-lactam antibacterial **cefodizime** was shown to be three times larger in patients with cirrhosis compared to healthy individuals.

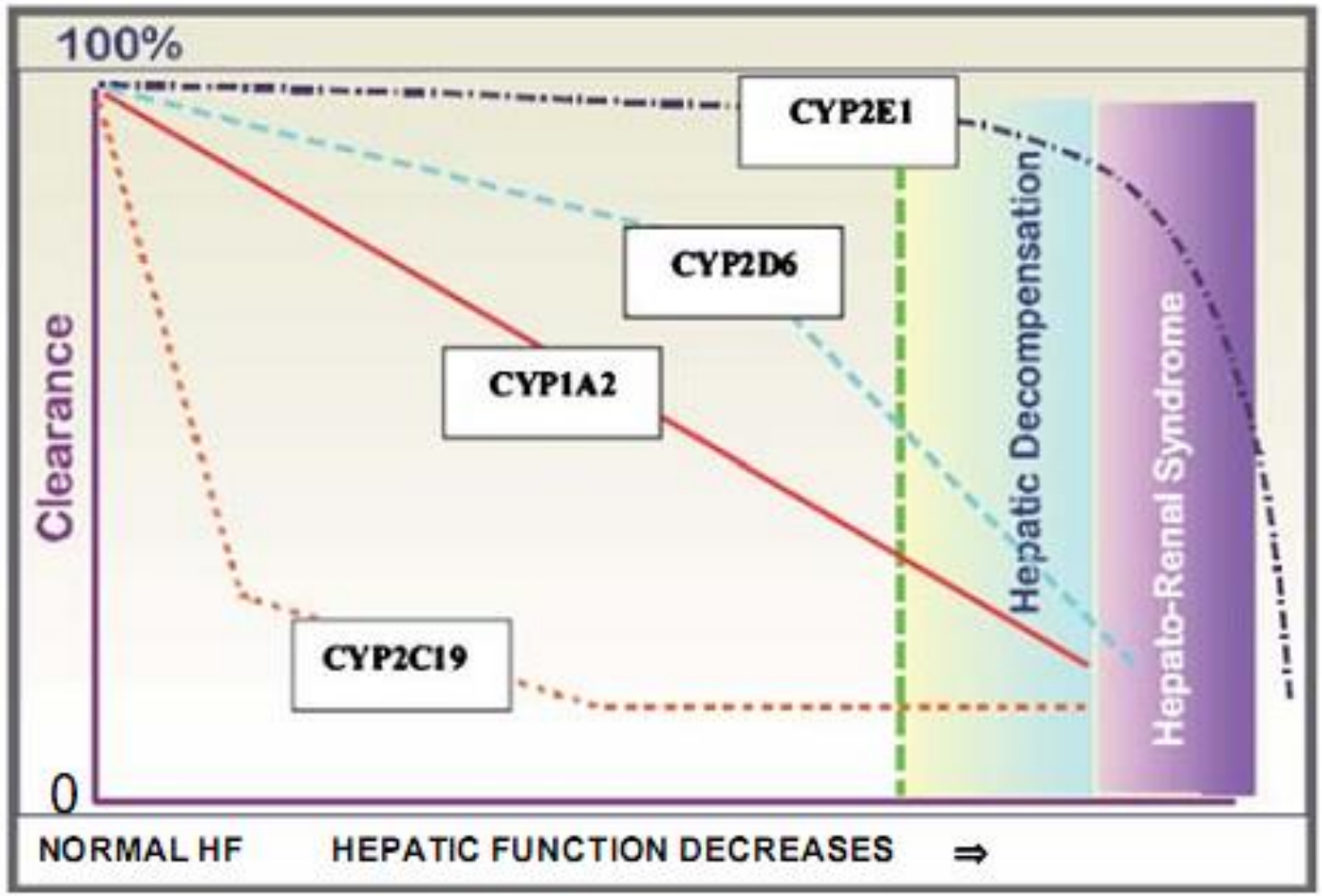
Chronic liver disease, such as cirrhosis, is more likely to be associated with altered drug binding than are acute conditions such as viral hepatitis

# CHANGES IN METABOLIC CAPACITY

- **Cirrhosis** causes irreversible hepatic damage and cell death
- Although it is anticipated that extensive hepatic damage is associated with reduced drug metabolism with resultant decreased $Cl_{int}$ and impaired hepatic drug elimination, the **extent of impairment is variable among patients**, as well as **among different metabolic reactions**
- In general, **phase I oxidative** metabolism mediated by the cytochrome P450 (CYP) enzyme system is more sensitive to the effect of cirrhosis than phase II conjugation reactions such as glucuronidation.
- Despite the general belief of "sparing" of phase II conjugation reactions in patients with cirrhosis, it is important to note that more recent studies have shown conjugation reactions can be reduced in patients with liver dysfunction, especially those with severe liver cirrhosis

# CHANGES IN METABOLIC CAPACITY

- Unfortunately, most liver function tests indicate **only that the liver has been damaged;** they do not assess the function of the cytochrome P-450 enzymes or intrinsic clearance by the liver.
- It is clear that based on in vitro studies at the protein level the extent of hepatic dysfunction-induced impairment in drug metabolism is dependent on both **severity and type of disease**, as well as the specific **isoenzyme affected**, the exact mechanism for this differential effect remains to be elucidated


100%
CYP2E1
CYP2D6
CYP1A2
CYP2C19
Clearance
0
Hepatic Decompensation
Hepato-Renal Syndrome
NORMAL HF
HEPATIC FUNCTION DECREASES ⇒

# EFFECTS OF HEPATIC DISEASE ON DRUG EXCRETION

- Advanced liver disease is often complicated by impaired renal function – hepatorenal syndrome, such as unexplained progressive renal failure occurring in patients with chronic liver disease without other causes of renal failure
- The elimination of drugs that are partly excreted in unchanged form by the kidneys will be impaired in patients with the **hepato-renal syndrome**
- Conventional creatinine-based GFR measurements often inadequate due to **reduced muscle mass**, impaired **metabolism of creatine to creatinine** and increases fractional tubular **secretion of creatinine**
- Creatinine clearance significantly overestimates the glomerular filtration rate in these patients
- In these patients, **dosage reduction would need to be considered even for drugs that are primarily excreted unchanged by the kidney**

# CHANGES IN PHARMACODYNAMIC RESPONSE

- Patients with cirrhosis may display an altered therapeutic response unrelated to changes in the pharmacokinetic behaviour of the drug
- Theoretically, altered pharmacodynamics could result from changes in drug receptor binding, in the affinity of a drug. Examples of pharmacodynamic changes include:

1) Decreased therapeutic effect to β-blockers and diuretics

2) Increased sensitivity to opioid analgesics, anxiolytics, and sedatives; and increased kidney side effects from nonsteroidal anti-inflammatory drugs.

# IMPLICATIONS OF HEPATIC DISEASE ON SERUM DRUG CONCENTRATION MONITORING AND DRUG EFFECTS

- An extremely important point for clinicians to understand is that the factors that are **important determinants of hepatic clearance** are different depending on the liver **extraction ratio** for the drug.
- In order to illustrate the differences that may occur in steady-state drug concentrations and pharmacologic effects for patients with liver disease, a graphical technique is used
- The next example assumes that a low hepatic extraction ratio drug (**100% liver metabolized**) is being given to a patient as a continuous intravenous infusion and that all **physiologic, pharmacokinetic, and drug effect parameters** (shown on the y-axis) **are initially stable**

# IMPLICATIONS OF HEPATIC DISEASE ON SERUM DRUG CONCENTRATION MONITORING AND DRUG EFFECTS

- On the x-axis of the first diagram, an arrow indicates that intrinsic clearance decreases due to the development of hepatic cirrhosis in the patient; an assumption made for this illustration is that any **changes in the parameters are instantaneous**.
- An increase in the parameter is denoted as an uptick in the line while a decrease in the parameter is shown as a downtick in the line.
- The first three parameters are physiologic values (LBF (Q)), $F_b$ (fraction unbound), and $Cl_{int}$ that will change in response to the development of hepatic dysfunction

# IMPLICATIONS OF HEPATIC DISEASE ON SERUM DRUG CONCENTRATION MONITORING AND DRUG EFFECTS

- In the next slide, only intrinsic clearance decreased due to the destruction of hepatocytes, and liver blood flow and free fraction of drug in the blood was not altered
- This change will decrease the hepatic clearance of the drug, volume of distribution will not be modified because blood and tissue volume or plasma protein and tissue binding did not change, and half-life will increase because of the decrease in clearance [$t_{1/2} = (0.693 \cdot V)/Cl$, where $t_{1/2}$ is half-life, Cl is clearance, and V is volume of distribution].
- Total and unbound steady-state drug concentrations will increase in tandem, and the pharmacologic response will increase because of the increase in unbound serum concentration.

Diagram 1: low hepatic extraction ratio drug

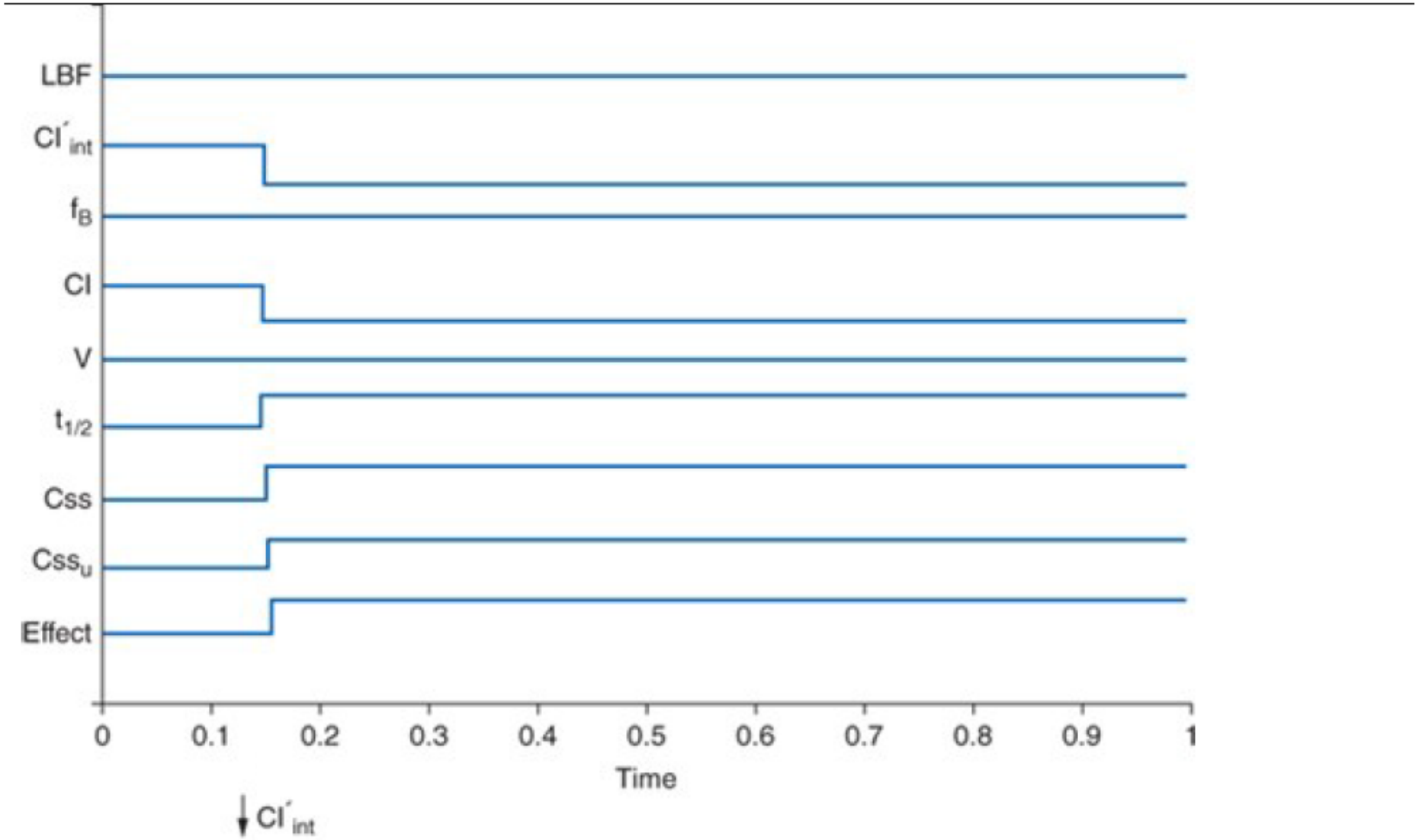
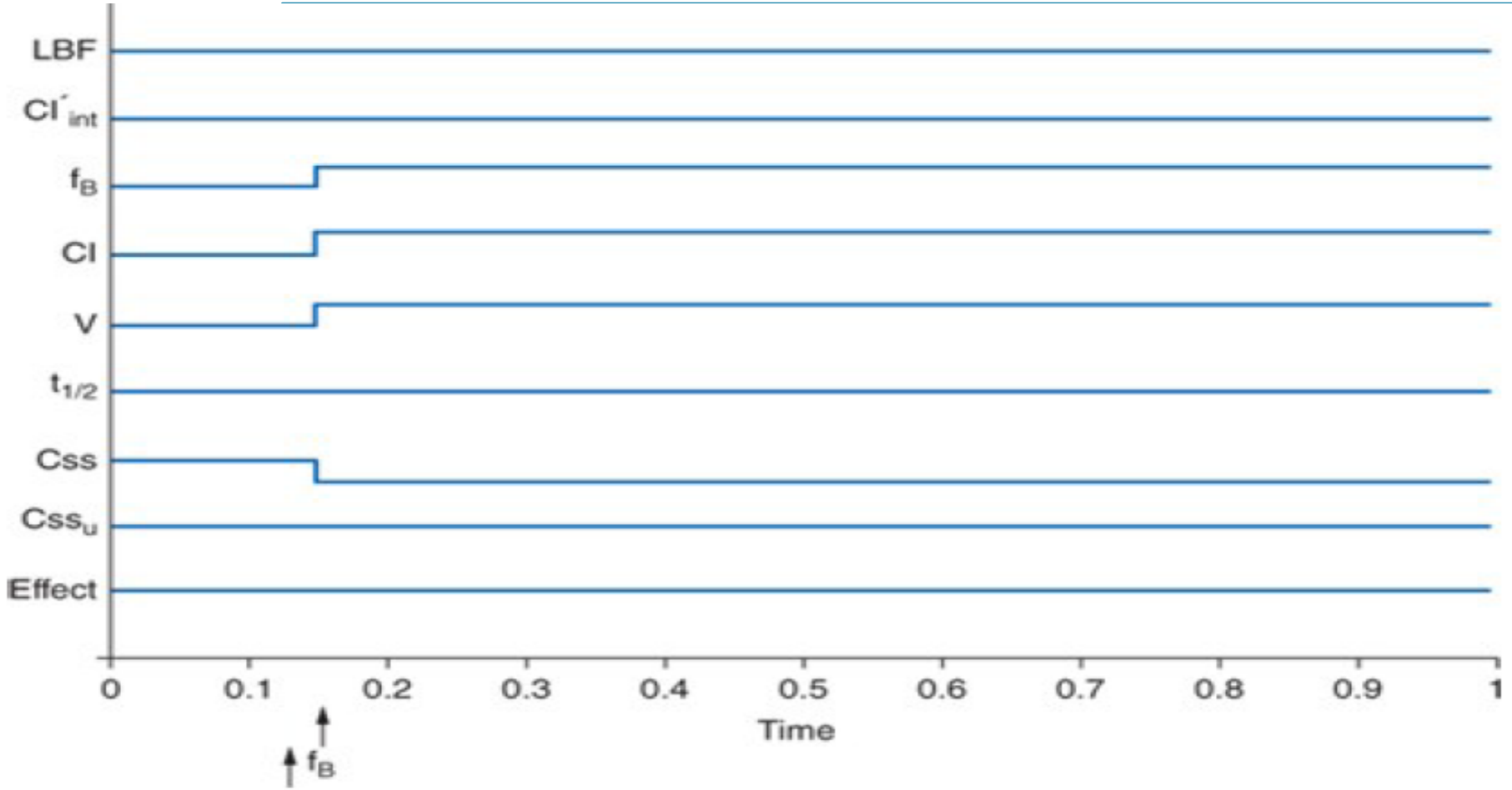
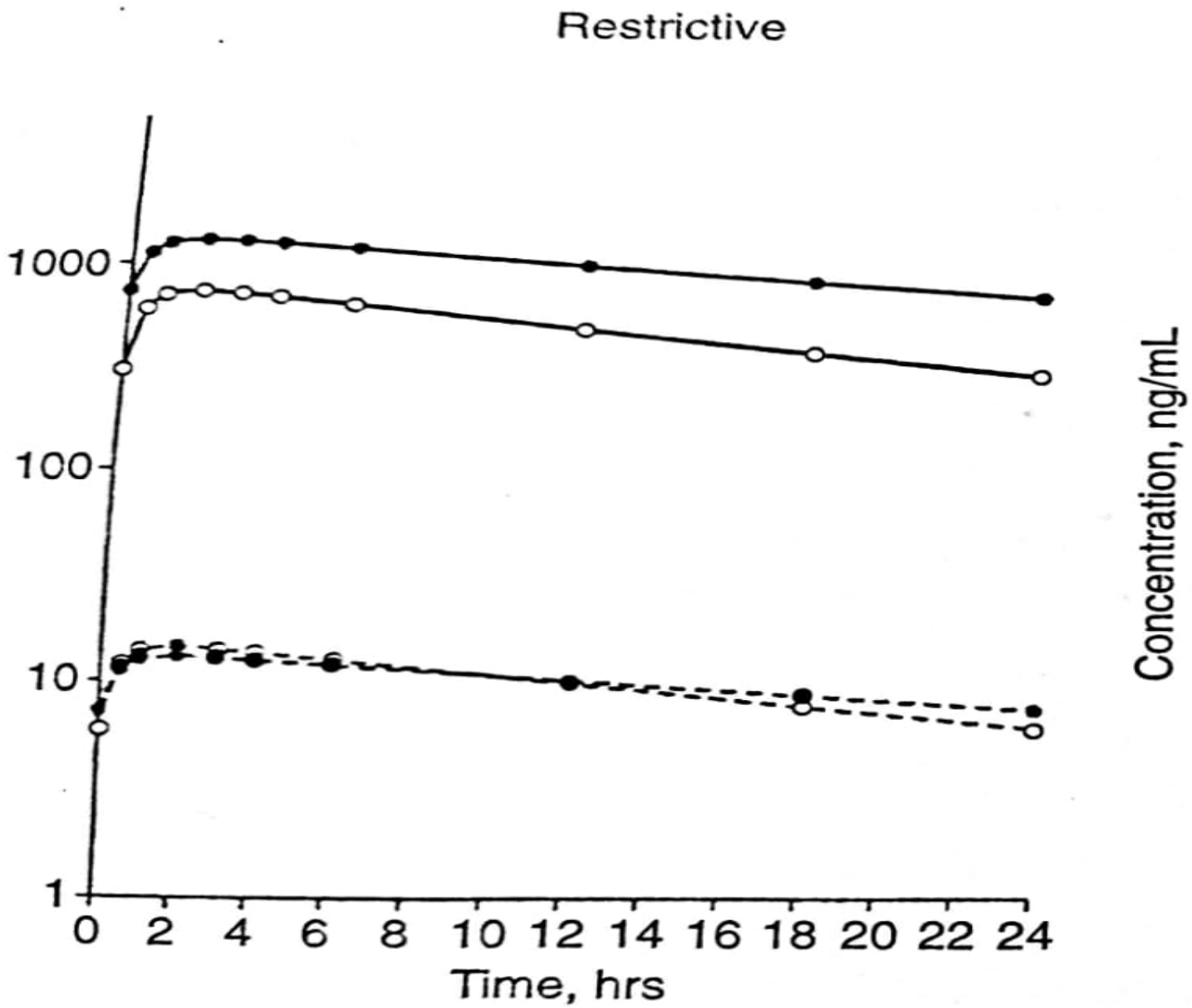


Diagram 2: Low hepatic extraction ratio drug, increase in unbound fraction






Effects of plasma protein binding, displacement on simulated steady state concentration time profiles. For restrictively cleared drug with a small volume of distribution.

Upper curves are total drug concentration. Lower curves are unbound drug concentration. Close circle is before displacement.

Open circle is after displacement.

Diagram 3: High hepatic extraction ratio drug increase in unbound fraction

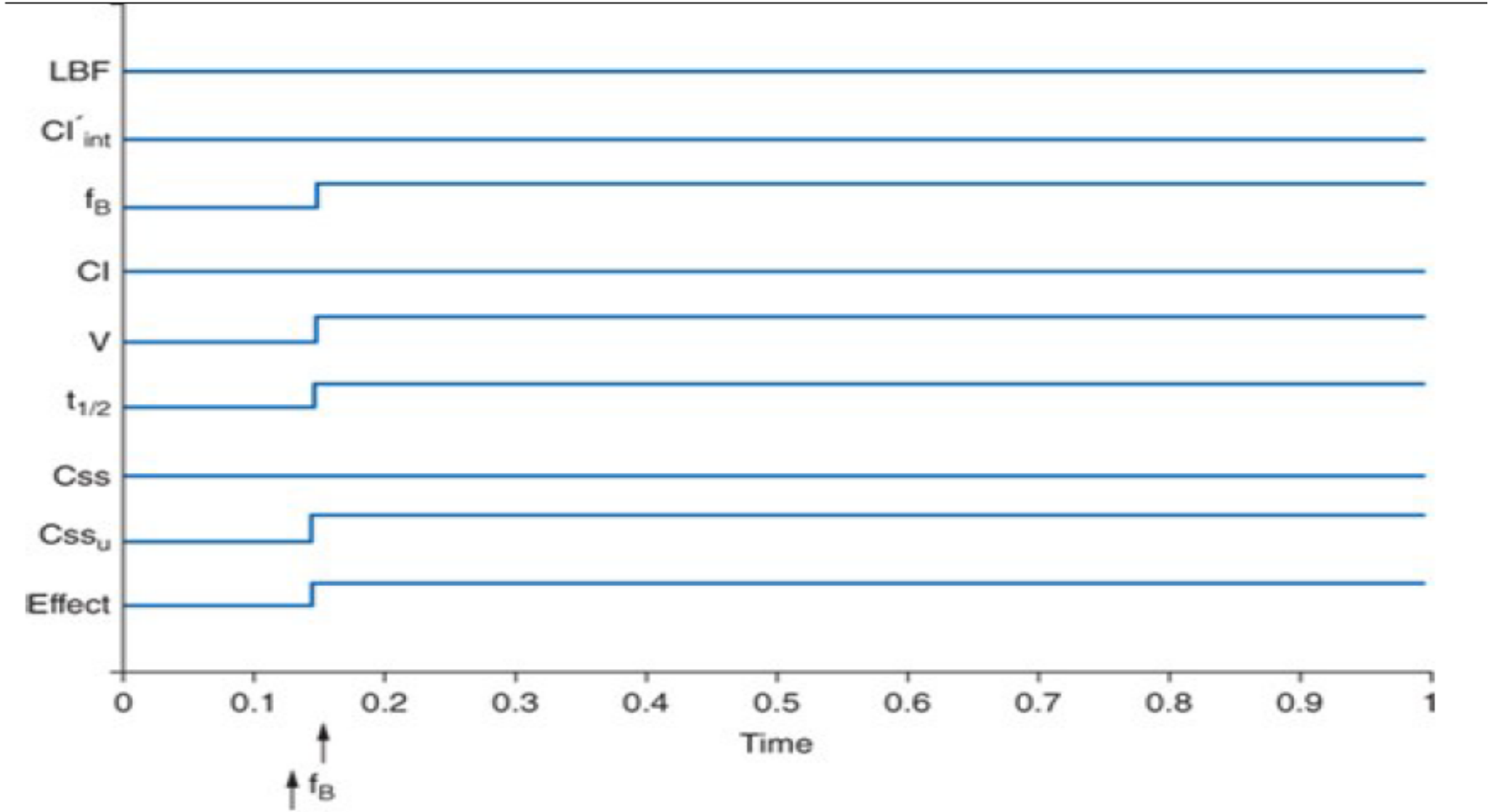
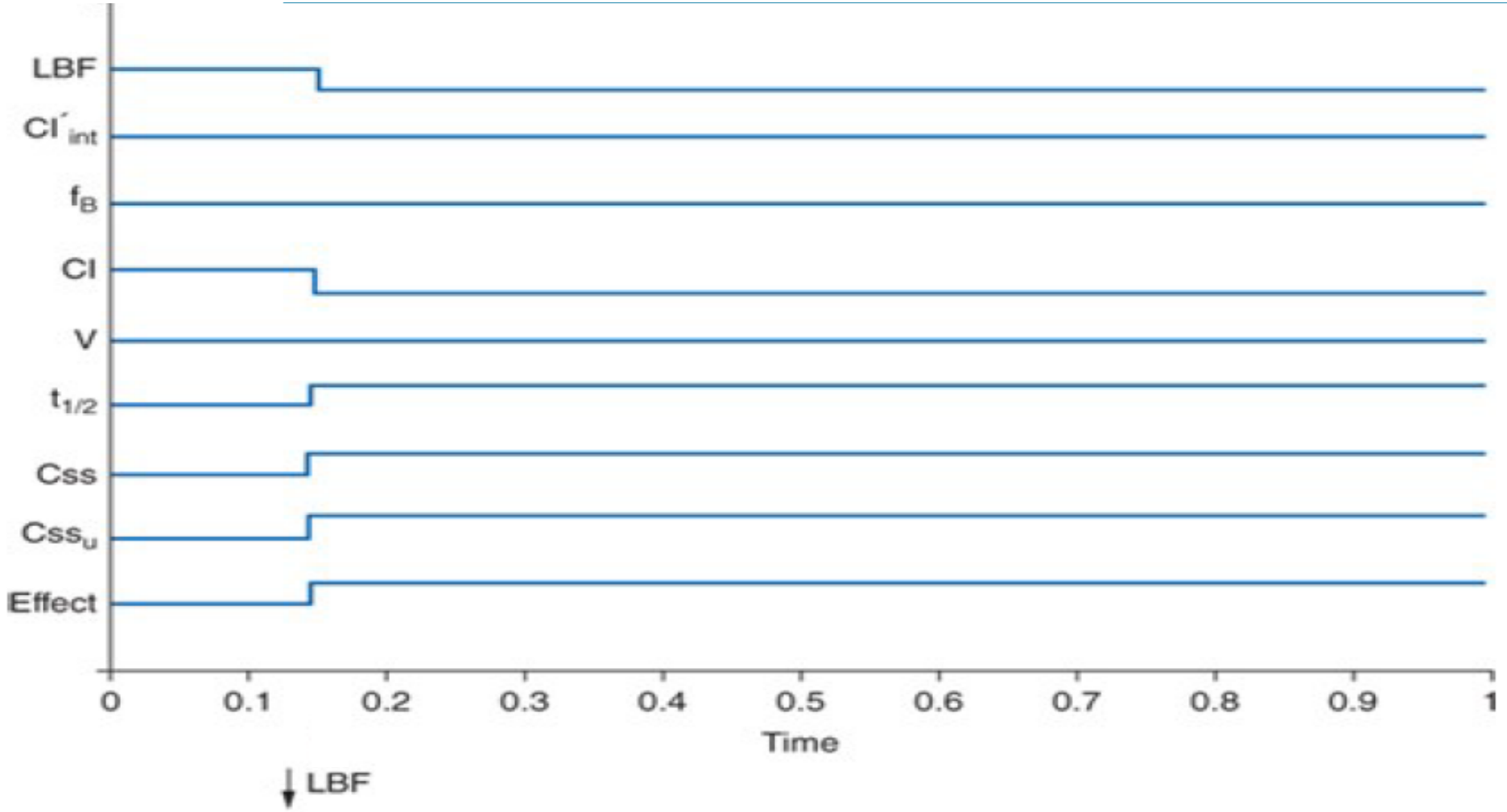
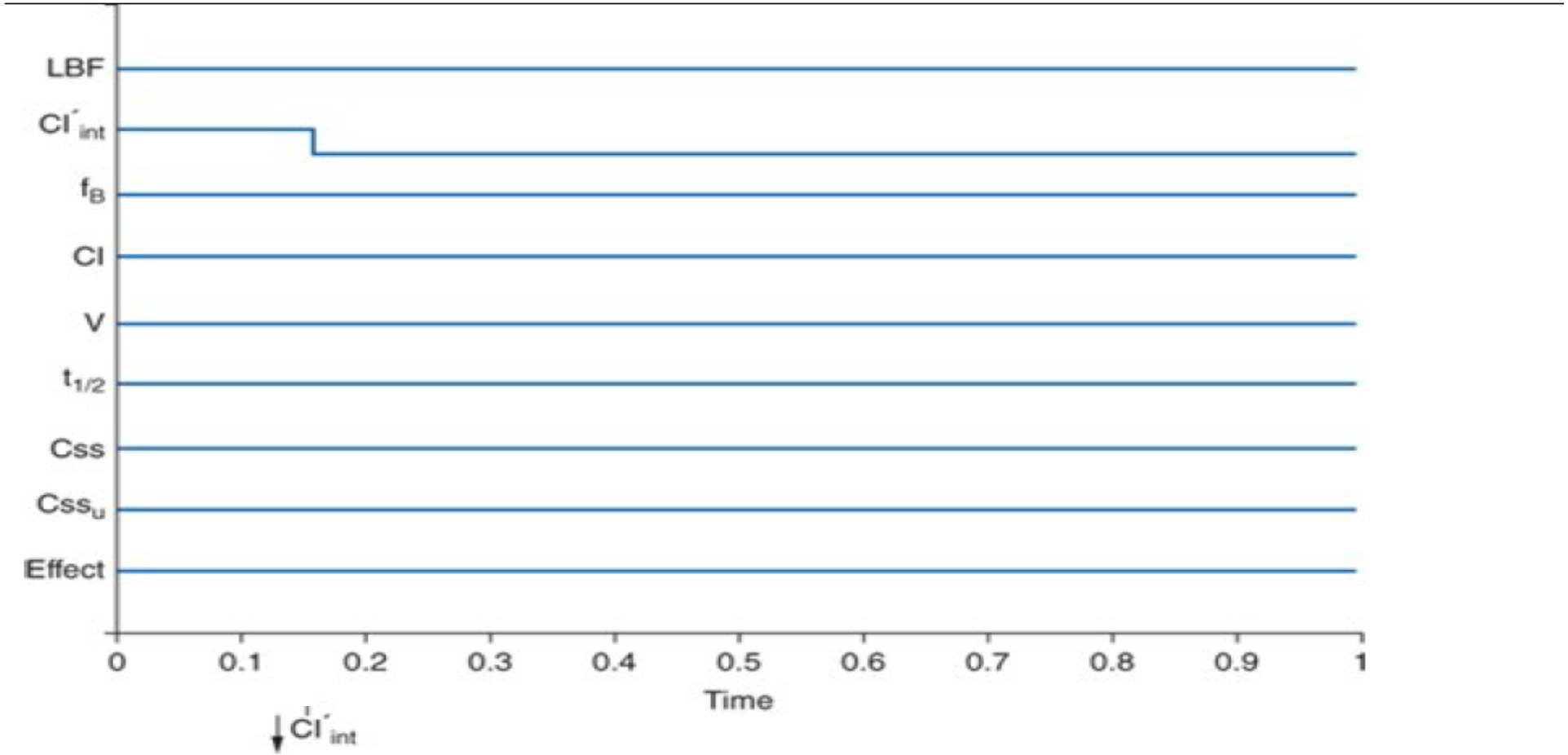


Diagram 4: High hepatic extraction ratio drug, reduced hepatic blood flow




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

Diagram 5: High hepatic extraction ratio drug reduction in intrinsic clearance



## TABLE 24-10 Considerations in Dosing Patients with Hepatic Impairment

| Item | Comments |
|---|---|
| Nature and severity of liver disease | Not all liver diseases affect the pharmacokinetics of the drugs to the same extent. |
| Drug elimination | Drugs eliminated by the liver >20% are less likely to be affected by liver disease. Drugs that are eliminated mainly via renal route will be least affected by liver disease. |
| Route of drug administration | Oral drug bioavailability may be increased by liver disease due to decreased first-pass effects. |
| Protein binding | Drug–protein binding may be altered due to alteration in hepatic synthesis of albumin. |
| Hepatic blood flow | Drugs with flow-dependent hepatic clearance will be more affected by change in hepatic blood flow. |
| Intrinsic clearance | Metabolism of drugs with high intrinsic clearance may be impaired. |
| Biliary obstruction | Biliary excretion of some drugs and metabolites, particularly glucuronide metabolites, may be impaired. |
| Pharmacodynamic changes | Tissue sensitivity to drug may be altered. |
| Therapeutic range | Drugs with a wide therapeutic range will be less affected by moderate hepatic impairment. |

# EXAMPLE

A 61-year-old female patient, weight 56 kg , height, 162 cm, suffering from tonic-clonic seizures received 100 mg tid of extended phenytoin sodium (Dilantin Kapseals capsules) by mouth (F=1, S=0.92) for 1 month to start therapy. She had normal liver and renal functions after routine laboratory tests (total bilirubin, 0.8 mg/dl; albumin, 5.1 g/dl; serum creatinine, 0.4 mg/dl). Steady-state total concentration of phenytoin was 8.7 mcg/mL at the time of that visit. The dosage was then increased to 400 mg daily for an additional month to adjust to individual patient response, and the resulting drug concentration at steady-state was then 12.3 mcg/mL. Nonetheless, the patient complained about this regimen because optimal seizure control was lacking so the **clinician added valproic acid (**Depakene, 1000 mg twice daily by mouth) to the regimen.

# EXAMPLE

The valproate-phenytoin interaction involves displacement of phenytoin binding to albumin and inhibition of phenytoin intrinsic clearance by valproate.

- Explain how these interaction can effect the total concentration, free concentration and drug effects.
- As a clinician what considerations would you take into account before changing the dose

# QUANTIFICATION OF LIVER FUNCTION

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 include **serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy**. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal) 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

Child-Pugh Scores for Patients With Liver Disease[37]

| 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 |

A total Child-Turcotte-Pugh score of **5 to 6** is considered Child-Pugh class A (mild dysfunction), 7 to 9 is class B (moderte dysfunction), and 10 to 15 is class C (severe dysfunction).

# EXAMPLE

Compute the Child-Pugh score for a 62-year-old, 65-kg male with hepatic cirrhosis, knowing that:

- Total bilirubin = 3.2 mg/dl
- Serum albumin = 3 mg/dl
- Prothrombin time prolonged over normal by 3.5 seconds
- Moderate amount of ascitic fluid
- Moderate hepatic encephalopathy

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REVIEW ARTICLE | Open Access

# Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment

Eman El-Khateeb, Adam S. Darwich, Brahim Achour, Varinder Athwal, Amin Rostami-Hodjegan,

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REVIEW ARTICLE

# Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction

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Amprenavir is extensively metabolized by P450 cytochromes, specifically, CYP3A4

Although there is a considerable variability in patients with hepatic disease, there appears to be a trend toward an increased AUC and reduced clearance in those with more severe hepatic disease

Note: No subjects with a Child-Pugh score of 12 were enrolled; therefore, extrapolation of results to subjects with higher Child-Pugh scores should be made with caution.

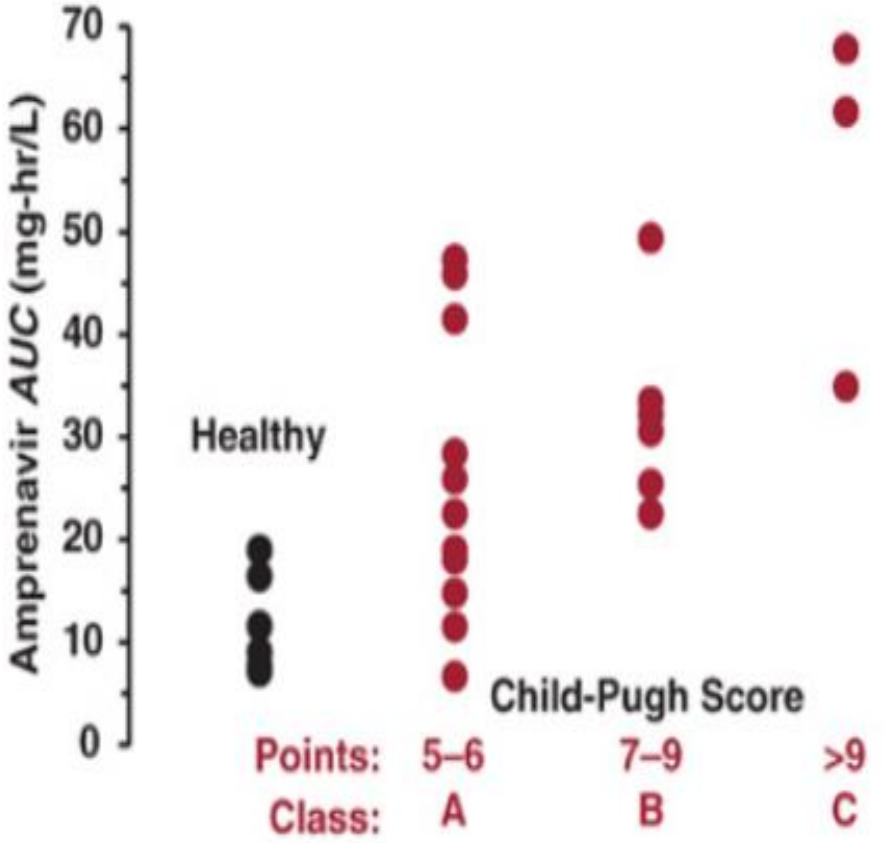



**FIGURE 15-2.** Relationship between amprenavir area under the curve (*AUC*) and the Child-Pugh score.

# DRUG DOSING IN HEPATIC DISEASE

- For drugs that are primarily liver metabolized, pharmacokinetic parameters are assigned to patients with liver disease **by assessing values previously measured in patients with the same type of liver disease and a similar degree of liver dysfunction**.

- For example theophylline clearance in patients with cirrhosis was found to be 0.35 **ml/min/kg**, the dosing rate of theophylline for a cirrhosis patient (non smoker, 65 kg) required to achieve a target steady state concentration of 10 mg/L can be calculated as ➔ $CL*C_{SS}$ ➔(0.35*65*0.06)*10=14 mg/h

# DRUG DOSING IN HEPATIC DISEASE

When prescribing medications that are principally eliminated by the liver in patients with liver dysfunction, it is possible to

A) Decrease the dose while retaining the normal dosage interval

B) Retain the normal dose and prolong the dosage interval

C) Modify both the dose and dosage interval.

# DRUG DOSING IN HEPATIC DISEASE

Compared to individuals with normal liver function receiving a drug at the usual dose and dosage interval, patients with hepatic disease who receive a normal dose but a prolonged dosage interval will have ***similar maximum and minimum steady-state serum concentrations***

However, if the **dose is decreased** but the dosage interval kept at the usual frequency, maximum steady-state concentrations will be **lower and minimum steady-state concentrations will be higher for patients with liver disease t**han for patients with normal hepatic function.

# DRUG DOSING IN HEPATIC DISEASE

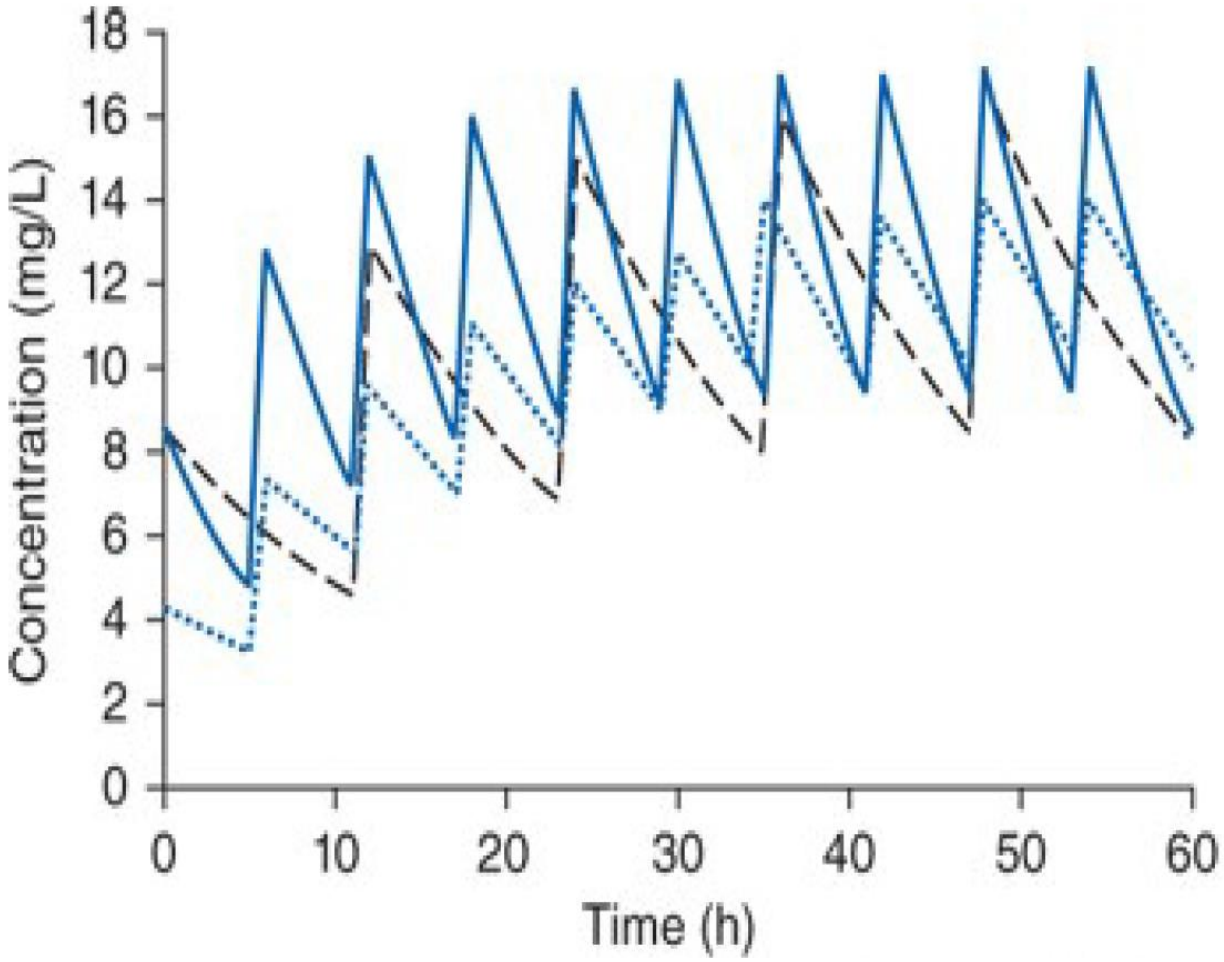
The actual method used to reduce the dose for patients with liver dysfunction will depend on the **route of administration and the available dosage forms**

For example, if the medication is only available as an oral capsule, it is likely that the usual dose will be given to a patient with liver disease, but the dosage interval will be prolonged.

However, if the drug is given parenterally, it may be possible to simultaneously modify the dose and dosage interval to attain the same maximum and minimum steady-state concentrations in patients with hepatic dysfunction as those encountered in patients with normal liver function.

Serum concentration versus time profile for a patient with normal liver function receiving hepatically eliminated drug at the dose of 300 mg every 6 hours (solid line).

In a patient with hepatic dysfunction, it is possible to give the same dose and **prolong t**he 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).



# DRUG DOSING IN HEPATIC DISEASE

**Drugs with a relatively high hepatic extraction ratio:**

The oral bioavailability of these drugs can be drastically increased in patients with chronic liver disease, and the **maintenance dosage** should be reduced accordingly.

Drugs with flow-dependent clearance are **avoided, if possible,** in patients with liver failure. When necessary, doses of these drugs **may** need to be reduced **to as low as one-tenth of the conventional dose, for an orally administered agent**.

The initial and maintenance doses in patients with cirrhosis **need to be reduced** because of the significant decrease in first-pass effect caused by portosystemic shunting and decreased hepatic blood flow across the liver.

The extent of this reduction cannot be predicted accurately

# DRUG DOSING IN HEPATIC DISEASE

**Drugs with a relatively high hepatic extraction ratio:**

- One approach is to assume 100% bioavailability unless there is specific bioavailability data or specific dosage adjustment guidelines, and estimate the reduced maintenance dose proportionally by the following mathematical expression:

$$D_H = D_N \cdot F/100$$

where F is the known bioavailability of the drug available from the literature or the manufacturer, and $D_H$ and $D_N$ are the doses used in patients with liver dysfunction and normal liver function, respectively.

The maintenance dose should be adjusted, taking into account the desired pharmacological effect and toxicity of the drug used

# DRUG DOSING IN HEPATIC DISEASE

**Drugs with intermediate hepatic extraction ratio:**

- The hepatic clearance of these drugs is determined by both the blood flow across the liver and ($f_B$ * $Cl_{int}$)
- In general, the hepatic clearance of these drugs is reduced, which necessitates the adjustment of their maintenance dose
- Treatment should be started with an initial dose in the low range of normal and maintenance doses should be adjusted as described for low extraction drugs with low protein binding (Table 1)

# DRUG DOSING IN HEPATIC DISEASE

**Drugs with a low hepatic extraction and high plasma protein binding (>90%):**

- The oral and intravenous clearance of these drugs is determined by the intrinsic capacity of the hepatic elimination mechanisms and the unbound drug fraction in blood or plasma.
- Because the unbound fraction of drug in blood or plasma may be significantly increased in patients with chronic liver disease, pharmacokinetic evaluation should be **based on unbound blood/plasma concentrations.** Unbound drug concentrations are available for several agents that are highly plasma protein bound, such as phenytoin, valproic acid and are valuable tools to guide drug dosage in liver disease patients.

# DRUG DOSING IN HEPATIC DISEASE

**Drugs with a low hepatic extraction ratio and low plasma protein binding (<90%):**

- The intrinsic clearance will be reduced to a degree determined by the functional status of the liver and the specific metabolic pathway(s) involved in the elimination of the drug
- Fluctuations in the **unbound drug fraction** in blood or plasma are rather small and will **not significantly affect blood/plasma clearance** of the drug
- The maintenance dose of these drugs should be reduced, whereas therapy can be started with a normal dose
- The maintenance dose can be adjusted based on the Child-Pugh score as shown in Table 1

# DRUG DOSING IN HEPATIC DISEASE

- The elimination of drugs that **are partly excreted in unchanged form by the kidneys** will be impaired in patients with the hepato-renal syndrome. It should be taken into account that **creatinine clearance significantly overestimates glomerular filtration rate in these patients**
- The volume of distribution of hydrophilic drugs may **be increased** in patients with chronic liver disease who have oedema or ascites. As a consequence, the loading dose may have to be increased in these patients if a rapid and complete effect of the drug is required. Since many hydrophilic drugs are eliminated primarily in unchanged form by the kidneys, **renal function should be taken into consideration**.
- Extreme caution is recommended when using drugs with a narrow therapeutic index in patients with liver disease and when administering any drug to patients with severe liver dysfunction (Child-Pugh class C)

**Table I. Categorization and dose recommendation in IH patients. Categorization based on Huet et al. (11) and Krähenbühl et al. (12). Recommendation for initial dose adjustment and maintenance adapted from Delcò et al. (1)**

| *Category* | *$E_H$* | *F* | *PB* | *General recommendation* |
|---|---|---|---|---|
| 1 | High (≥ 60%) | ≤ 40% | Any | Reduction Id and Md by: dose reduction = (Nd x F)/100 |
| 2 | Intermediate (30 - 60%) | 40-70% | Any | Id: start in the low range of normal<br>Md: should be adjusted as described in low $E_H$ and low PB |
| 3 | Low (≤ 30%) | ≥ 70% | ≥ 90%<br>< 90% | Drug monitoring<br>Md:<br>CP A: 50% of Nd<br>CP B: 25% of Nd<br>CP C: drug monitoring |
| 4 | Unknown | | | |

Id: initial dose. Md: maintenance dose. Nd: normal dose without liver disease. EH: hepatic extraction ratio. F: bioavailability. BP: fraction bounds to proteins. CP: Child-Pugh index.