5 Pharmacokinetics and Pharmacodynamics of Drugs in Liver Disease

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5.1 Introduction

Any therapeutic substance that is administered to the body undergoes metabolism and elimination. Metabolism is the biotransformation of all the endogenous and exogenous compounds within our body which converts them into water soluble substances which may be readily eliminated.

Pharmacokinetics is a term used to denote the fate of the drug in the body. This refers to the absorption, distribution, metabolism, and elimination of a drug as it passes through the human body. All these factors influence the final available concentration of the drug at the site of action. To make it simpler, it is termed as "what the body does to the drug." Pharmacodynamics refers to the effect of the drug on the body which is affected by the drugs affinity and action at its receptors. In general, it refers to "what the drug does to the body." First-pass metabolism refers to the metabolism of the drug before its entry into the systemic circulation, thereby reducing its bioavailability. The liver is an important site for first-pass metabolism.

Understanding clinical pharmacokinetics is important to enhance the efficacy and reduce the toxicity of the drug therapy while pharmacodynamic principles would help in understanding the interplay between the concentration of the drug at its receptor site and its pharmacological effect.

5.2 The Normal Liver

The liver is an intraperitoneal organ located in the right upper quadrant of the abdomen. It consists of a right and a left lobe. The liver has a dual blood supply by the hepatic artery and the portal vein. The portal blood flow is the major regulator of the vascular tone of the hepatic artery—a phenomenon termed as the "Hepatic arterial Buffer response" [1]. The hepatic arteries and portal veins divide to supply each lobe of the liver and converge at the sinusoids of the liver to supply blood to the hepatocytes. The hepatic sinusoids are low pressure vascular channels which consist of fenestrated endothelium which is essential for influx and efflux of various molecules into the perisinusoidal space of Disse. After draining the liver, the blood enters a central vein via the hepatic lobule, which eventually drains into the hepatic vein.

5.3 Role of Liver in Drug Metabolism

Disposition of most of the drugs relies on the functioning of the liver, which may be altered to varying extent in hepatic dysfunction. In order to

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understand the effect of hepatic impairment on drug xenobiotics, it is prudent to understand the basic role of the liver in metabolism as well as the factors affecting liver metabolism. The liver is the most metabolically active tissue in the human body. At physiological pH, most of the therapeutic agents are non-ionized or partially ionized. They undergo reactions in a phased manner which converts them into polar substances, which may then be excreted from the body. The endoplasmic reticulum of the hepatocytes is the major site of this biotransformation of drugs. It is abundant in microsomes, which contains the enzymes necessary for this process. The cytochrome P450 (CYP) system is one such membrane-bound oxidative enzymatic system, which is essentially a heme-containing protein [2]. The iron in this heme protein is the active site for binding with the drugs, which then undergo a series of reactions ultimately leading to the metabolism of the therapeutic substance. The human genome sequencing revealed the presence of 58 genes coding for the CYP proteins, and these genes are polymorphic in nature. These genetic polymorphisms are responsible for significant variations in drug metabolisms between individuals [3]. Many isoenzymes of the cytochrome P-450 exist, which have different activities, different tissue distribution, and variable drug affinities [4, 5]. Drugs undergo phase 1 and phase 2 reactions, either sequentially or only one and subsequently are excreted by transporters which are present on the membranes of canaliculi or hepatic sinusoids. This transport via canaliculi is often termed as the phase 3 reactions of xenobiotics [6].

Phase 1 reactions are essentially functionalization reactions. Lipophilic molecules undergo oxidation, reduction, or hydrolysis reactions via the mixed function oxygenases and are converted into hydrophilic moieties. Oxidation reaction involves insertion of a single molecule of oxygen within the parent compound. Examples of oxidative reactions include deamination, hydroxylation, dealkylation, dehalogenation, and epoxidation. This phase is also responsible for the generation of electrophilic substances and toxic-free radicals which may lead to cellular injury.

In phase 2 reactions, a parent drug can undergo phase 2 reactions directly or after it has been processed via the phase 1 pathway. These reactions are popularly termed as the "conjugation" reactions. These are responsible for addition of a polar ligand such as glucuronide, sulfate, glutathione, methyl group, acetate etc. Conjugation reactions occur within the cytosol of the hepatocytes and are mediated by transferases—enzymes which transfer the conjugating polar ligand to the compound undergoing the biotransformation [7].

Phase 3 reactions are responsible for the transport of the end products of metabolism into the bile [7]. These transporters are termed as ATP-binding cassettes (ABCs) [8]. The drug transport is mediated by ATP-hydrolysis, hence the name. The clinically important ABCs include the P-glycoprotein, the Bile Salt Exporter protein (BSEP), and the Multidrug Resistant proteins (MRP). The genes encoding for these transporter proteins are also susceptible to genetic polymorphisms, and variations of these proteins may play a role in the development of adverse drugs reactions as well as drug-drug interactions [9]. Some drugs are excreted in the bile initially but are reabsorbed from the small intestine—a phenomenon termed as "enterohepatic circulation" [10]. Enterohepatic circulation may lead to prolonged duration of actions of some drugs. Enterohepatic circulation may alter the bioavailability, volume of distribution, and clearance of a given drug. Furthermore, the liver being one of the important sites of first-pass metabolism, the amount of drug available at the receptor site is ultimately dependent on the functioning of the liver in case of drugs which have a high first-pass metabolism [11].

Hepatic drug clearance is defined as the volume of blood from which a drug is removed entirely by the liver per unit time. This is depended on two factors—the hepatic blood flow and the hepatic extraction ratio (Clearance = Blood flow × Extraction ratio) [12, 13]. Hepatic extraction ratio is the fraction of the drug which is "extracted" or removed during one pass of blood through the liver [14]. This is governed by the amount of unbound drug available and the intrinsic clearance of the liver. The effect of the hepatic

blood flow on clearance of the drug depends on its hepatic extraction ratio. With increases in the blood flow to the liver, the extraction ratio declines for all drugs. Since the extraction ratio also depends on the amount of unbound drug available to the hepatocytes, the extraction ratio is also affected by the protein binding. Increasing hepatic blood flow causes a more rapid fall in the extraction ratios of drugs with low intrinsic clearance. On the basis of the efficiency of the liver in removing substances from the circulation, the extraction ratio is classified as high when it is more than 0.7 and low when it is less than 0.3. An extraction ratio of 0.3–0.7 is termed as intermediate. The hepatic clearance of drugs with high extraction ratios is limited by the blood flow and is indifferent to alterations in enzymatic activity or drug binding.

5.4 Consequences of Liver Disease on Pharmacokinetics

Pharmacokinetics of a drug broadly consists of drug absorption, distribution, and metabolism. The ability of the liver to metabolize a drug is dependent on both—hepatic blood flow and the enzymatic activity of the liver enzyme [15]. Hepatic dysfunction would impact both ultimately altering the drug disposition and its therapeutic effect. In hepatic dysfunction, both the hepatic blood flow and the activity of the cytochrome P-450 enzymes may be altered, and the effect of the two together may be synergistic. Acute liver insults primarily effect the hepatic blood flow while chronic liver diseases usually involve the enzymatic systems of the liver.

5.5 Drug Absorption

Patients with liver impairment have co-existing gastrointestinal dysfunction. Cirrhotic patients are known to have altered intestinal permeability which may have a bearing on the absorption of orally administered drugs [16]. Furthermore, patients with severe hepatic dysfunction also exhibit delayed gastric emptying and abnormal intestinal motility which may influence the absorption of drugs administered enterally [17, 18]. The liver being the major determinant of the pre-systemic metabolism, drugs which are subjected to a high first-pass metabolism are invariably affected. However, this would not be applicable to drugs with low extraction ratio as the fraction of these drugs that is taken up by the liver from the blood during a single pass is already insignificant. Liver cirrhosis may lead to reduced activity of the enzymes involved in the first-pass metabolism. This in conjunction with portosystemic shunts would lead to reduced first-pass metabolism, thereby increasing the bioavailability of the drugs. Furthermore, in cirrhosis, there would be a decline in the clearance of the "flow-limited" drugs, thereby increasing the concentration of these drugs substantially. Therefore, such drugs need to have their dose modified in patients with hepatic dysfunction [19]. A classic example of this would be reduced oral dosing of labetalol and carvedilol in patients with liver cirrhosis due to decreased first-pass metabolism and reduced clearance [20, 21]. Another example is midazolam which has an oral bioavailability ranging from 34% to 68% as it is dose-dependent [22]. It undergoes first-pass metabolism by CYP3A enzymes and is 95% plasma protein bound. In advanced liver disease, there is more unbound form of the drug available due to reduced protein binding, greater oral bioavailability due to reduced pre-systemic metabolism, and increased half-life due to reduced clearance [23]. Pre-systemic metabolism is the major determinant of the oral bioavailability of midazolam. Gorski et al. showed that interindividual variations in the first-pass extraction of drugs such as midazolam which have a very high affinity for the CYP3A enzyme are basically a function of the intestinal enzyme activity [24].

5.6 Plasma Protein Binding and Drug Distribution

The distribution of a therapeutic substance within the body depends on the fraction of unbound form available. This in turn depends upon the binding of the drug in a reversible fashion with various macromolecules like blood cells and plasma proteins. The unbound fraction of drugs which have a high plasma protein binding to albumin or alpha-1 glycoprotein may change in advanced hepatic impairment. The reduced plasma protein binding may be multifactorial in origin—due to reduced protein synthesis, due to synthesis of altered proteins in liver disease, and due to presence of endogenous inhibitors of plasma protein binding like elevated bilirubin [25]. Increased unbound fraction due to reduced binding to plasma proteins may in turn affect the volume of distribution of these drugs. Increased unbound fraction is also the fraction which being pharmacologically active is cleared more rapidly through the liver or kidney. Therefore, hypoproteinemic patients may have increased proportion of drug which distributes into the tissues and does not stay within the circulation, thereby decreasing its therapeutic levels.

Liver cirrhosis predisposes the patient to development of anasarca—particularly ascites. This would significantly increase the volume of distribution of hydrophilic agents. For these drugs, in case a rapid action is desired, it may be achieved by increasing the loading doses as is seen in the case of antimicrobials belonging to beta-lactam and aminoglycoside classes [26]. Simultaneously, the increased volume of distribution translates into increased elimination half-life of the drug [27]. This increased half-life predisposes to the development of drug toxicity due to accumulation [14].

All these factors help in understanding the possible influence of hepatic dysfunction on drug pharmacokinetics but, owing to the variable extent of liver impairment and change in the pharmacodynamics of the drug as well along with extrahepatic mechanisms, contribute to an unpredictable drug effect and complicate the drug dose adjustments in patients with liver dysfunction.

5.7 Metabolism

The intrinsic hepatic clearance is primarily regulated by two factors—the efficacy of the hepatic enzymatic systems and the activity of the transporter proteins present in hepatic sinusoidal and canalicular membranes. Intrinsic hepatic clearance could be defined as the capability of the liver to remove unbound fraction of a drug from the blood in the absence of any blood flow limitations [7, 13]. However, with the onset of liver cirrhosis, even the blood flow to the liver gets impeded. This results in reduced presentation of the drugs to the liver, and drugs which predominantly dependent on hepatic clearance would be prone to accumulation.

Of the various pathways of drug metabolism, some are more affected than the others in liver disease. With the loss of functionally intact hepatocytes in liver disease, the synthesis of enzymes is also reduced. The cytochrome (CYP) mixed function oxygenases are affected more than those involved in the phase 2 reactions of the metabolism in an inconsistent and nonuniform way not in correlation with the hepatic blood flow [28].

Caffeine being completely metabolized by the hepatic CYP1A2 is used as a probe to evaluate the decline in the activity of this enzyme in hepatic derangements [29]. Furthermore, it has been demonstrated that the extent of hepatic impairment correlates well with the degree of decline in the activity of this enzyme [30]. Similarly, coumarin is utilized as a metabolic probe for evaluating the activity of the CYP2A6 which hydroxylates the parent compound [31]. After oral administration of coumarin, decreased urinary concentration of the hydroxylated metabolite was observed in patients with liver cirrhosis, which inversely correlated with their Child-Pugh scores [32]. Four isoenzymes have been identified in the CYP2C class which include CYP2C8, CYP2C9, CYP2C10, and CYP2C19. Metabolic probes for

CYP2C9 and CYP2C10 include Irbesartan, tolbutamide, and mephenytoin [33]. The study with these probes revealed that CYP2C9 is not affected significantly in patients with hepatic impairment. Mephenytoin is a racemic drug—with R-enantiomer being metabolized by the CYP2C9 and the S-enantiomer being metabolized by the CYP2C19 [34]. After oral administration of mephenytoin to patients with liver cirrhosis, there was a simultaneous decrease in oral clearance of its S-enantiomer along with reduced urinary excretion of its hydroxylated metabolite [35]. Again, this decline was associated with the extent of liver disease with patients with moderate cirrhosis exhibiting greater reductions in their clearance. The specific probe for evaluating CYP2D6 is debrisoquine. When the same group of patients were administered debrisoquine per orally, the metabolism was not altered significantly in hepatic impairment [35]. This further corroborates the fact that various enzyme systems are altered to varying extent in hepatic impairment, and extrapolating this knowledge to clinical circumstances may be very intricate. CYP3A activity is also reduced to varying extents in patients with liver disease—reduction of up to 30–50% has been reported in patients with nonalcoholic fatty liver disease [36]. Many drugs have been used as probes for this particular enzyme—commonly used one being MEGX (monoethylglycinexylidide) [37]. Huang YS injected intravenous lignocaine to patients with liver cirrhosis and chronic hepatitis and measured the concentration of its metabolite—MEGX. They found that the serum MEGX concentrations were inversely proportional to the Child-Pugh severity [38].

Subsequently a "sequential progressive model of hepatic dysfunction" was suggested [14, 29]. This model used the activity of various CYP enzymes to assess qualitative hepatic impairment. This model suggests that in mild degrees of hepatic impairment, only the activity of CYP2C19 will be impaired and the metabolites of CYP1A2, CYP2D6, and CYP2E1 would remain unaltered. But with progressive hepatic dysfunction as seen in decompensated cirrhotics, the clearance of drugs by all of these would be hampered. With intermediate level of liver dysfunction, the clearances would be dependent upon the extent to which the enzyme systems are affected. It is also important to remember that most of the genes coding for these enzymes are polymorphic in nature, and interindividual variation would be present to varying extents in patients with liver disease as well as healthy individuals [3].

That the impact of liver disease is primarily on the mixed function oxygenases or the phase 1 reactions and phase 2 reactions are not affected significantly is demonstrated by the clearance of various benzodiazepines. Midazolam and diazepam undergo phase 1 metabolism and their clearance is affected, whereas oxazepam, temazepam, and lorazepam undergo glucuronidation directly (phase 2 metabolism) and their clearance is not decreased in patients with liver cirrhosis [22, 39, 40]. The selective sparing of glucuronidation in liver dysfunction may be partially explained by upregulation of this enzyme in patients with liver disease, or by increased extrahepatic glucuronidation [41, 42]. However, of late this theory has also been questioned as patients with end-stage liver disease demonstrated impaired glucuronidation of many drugs including morphine, oxazepam, mycophenolate among others [43]. But the plausible explanation of this is that genetic polymorphism is seen in genes coding for UDP-glucuronyltransferases and various isoforms of this enzyme have also been identified [44]. Another possibility is that different isoforms of this enzyme may be affected to different extents in liver injury [45, 46].

Apart from enzyme inhibition, even enzyme induction may be altered in patients with liver disease. However, the number of human studies performed in this regard is limited, and animal studies conclude that the inducibility of enzymes would be affected both by the type of isoform under question and the nuclear receptor being evaluated [47].

The effect of transporter proteins on the disposition of drugs metabolized by the liver has been researched recently. The transported proteins are responsible for substances within the hepatocytes, as well as their efflux against a concentration gradient into the bile by ATP hydrolysis [8]. Due to fibrosis occurring within the space of

Disse in liver cirrhosis, the microvascular bed of the liver is occluded which impairs the uptake of macromolecules and drugs into the hepatocytes. This would be more applicable to drugs which are highly plasma protein bound as is seen in the case of propranolol [48]. Liver biopsy samples of patients with nonalcoholic steatohepatitis revealed altered expression and internalization of some of the transporter proteins which can possibly impair elimination of drugs predisposing the patient to adverse drug reactions [49].

5.8 Biliary Excretion

Cholestasis may be intra- or extrahepatic in nature. Intrahepatic cholestasis occurs due to functional impairment of the canalicular transport mechanisms. This is seen in cases of drugs like erythromycin and phenothiazines [50, 51]. Due to reduced secretion of bile, the elimination of drugs by the hepatobiliary route will decline, which has been observed in patients undergoing surgery for common biliary duct obstruction [52]. These patients demonstrated decreased biliary secretion of beta-lactams antibiotics, clindamycin, cephalosporins, and ciprofloxacin. Cholestasis may predispose to drug accumulation of such drugs. Additionally, the accumulation of these drugs may also indirectly lead to hepatocyte injury further aggravating the liver damage [53]. Simultaneously, cholestasis also has an inhibitory effect on some liver enzymes like the CYP2C and CYP2E1—thereby necessitating dose modification of drugs metabolized by these pathways in patients with cholestasis [54]. Pharmacokinetics of antineoplastic agents has been studied extensively in patients with cholestasis and dose adjustment for vinca alkaloids and doxorubicin is suggested in accordance with the bilirubin levels [55].

5.9 Drugs Undergoing Renal Excretion

Hepatorenal syndrome is a type of functional renal failure complicating the course of disease of patients with end-stage liver disease. It occurs due to abnormal circulatory and neurohormonal mechanisms. Splanchnic vasodilation mediated by nitric oxide and other vasodilators leads to reduced effective blood volume. This reduced effective blood volume leads to activation of the renin-angiotensin-aldosterone system (RAAS), release of arginine vasopressin, and stimulation of sympathetic nervous system. These neurohormonal vasoconstrictors increase the renal vasomotor tone leading to a dramatic decline in the glomerular filtration rate which leads to the pathogenesis of the hepatorenal syndrome [56]. Reduced renal excretion of some drugs which are otherwise excreted in an unchanged form by the kidneys has been reported in patients with decompensated liver cirrhosis—examples include diuretics and levetiracetam [57, 58]. The creatinine clearance estimated by the Cockcroft-Gault equation is also inaccurate due to cachexia in patients with cirrhosis as well as due to impaired creatinine synthesis; and cystatin-c may be a better marker in this cohort of patients [59, 60]. Thus, it would be prudent to remember that even drugs undergoing renal elimination may require dose modifications while administering them to a patient with severe hepatic insufficiency.

5.10 Consequences of Liver Disease on Pharmacodynamics

Pharmacokinetics and pharmacodynamics are not isolated processes and in clinical practice, both are inter-related and influence each other. Plasma protein binding has a significant effect on the pharmacodynamics of any drug as ultimately it is the unbound fraction which exerts pharmacological effects. Nonetheless, a significant number of alterations in drug effects are observed in patients with cirrhosis which cannot be explained by changes in pharmacokinetics alone. This deviation in drug behavior may be explained by altered receptor interactions, altered receptor affinity, and transformed intrinsic activity in diseased states. However, this is insufficient research on pharmacodynamic deviations in hepatic insufficiency. Altered receptor sensitivity is com-

monly observed in patients with liver disease. The two organ systems specifically prone to pharmacodynamic alteration include the brain and the kidney [15]. Patients with moderate to severe degrees of hepatic insufficiency are more sensitive to the psychoactive actions of opioids and benzodiazepines [61, 62]. Benzodiazepines and opioids are common precipitating factors of hepatic encephalopathy in patients with severe liver disease [63]. The concurrent administration of more than one class of sedative agents may therefore be hazardous to patients with significant liver pathology. Increased number of GABA receptors, altered GABA-ergic tone, and increased permeability to the blood-brain barrier are the postulated mechanisms of increased sensitivity to these agents. Accumulation of endogenous GABA-mimetic agents in patients with hepatic decompensation may also play a role as patients with hepatic encephalopathy demonstrate neurological improvement with the administration of flumazenil [64].

The response to diuretics in a cirrhotic patient is not so well elucidated. Diuretic resistance has been observed commonly in patients with cirrhosis—more so with furosemide [65]. When compared to healthy population, cirrhotics require a greater diuretic concentration to excrete similar amount of sodium. This alteration in their natriuretic potency could be due to reduced number of nephrons as well as due to the extent of response of each nephron to diuretic [66, 67]. Diuretic use in patients of cirrhotic ascites has also been associated with the development of hepatorenal syndrome [56]. The nephrotoxicity of aminoglycoside group of antibiotics is also enhanced in patients with severe liver derangements—the plausible explanation of this phenomenon being altered pharmacodynamics [68]. Cirrhotics are more prone to the renal toxicity of nonsteroidal anti-inflammatory drugs than the usual population [69]. Not only can they precipitate acute renal failure in these patients, but they can also cause gastrointestinal bleed, thereby predisposing the patient to development of hepatic encephalopathy.

The therapeutic effect of beta blockers is attenuated in patients with ascites and cirrhosis. Cirrhotic patients exhibit downregulation of beta-adrenergic receptors which is also implicated in the development of cirrhotic cardiomyopathy [70]. It may be surmised that advanced liver disease results in reduced sensitivity of the beta-adrenergic receptors as is observed in the case of propranolol [71].

5.11 Assessment of Liver Function

The functional impairment of liver is difficult to assess. Various scores have been suggested to this effect [72]. The Child-Pugh scoring system is one such widely accepted tool which is used to assess the prognosis of chronic liver disease—specifically liver cirrhosis [73]. It incorporates five clinical variables which are assigned into three risk levels—and the final score is amalgamated into three clinical classes. The Child-Pugh score has been validated for prediction of mortality in patients with liver cirrhosis undergoing surgery [74]. It has also been validated as a prediction tool for survival in nonsurgical cirrhotic patients [75].

5.12 Child-Pugh Scoring System

Clinical/ biochemical indicator	Score 1	Score 2	Score 3
Serum bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/dL)	>3.5	3.5–2.8	<2.8
Prothrombin time (s > control)	<4	4–6	>6
Encephalopathy grade	Absent	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate

Total score according to severity is classified as:

- Group A—Mild—Total score of 5–6
- Group B—Moderate—Total score of 7–9
- Group C—Severe—Total score of 10–15

The MELD (Model for End-stage Liver Disease) score has also been used to prognosti-

cate patients with liver cirrhosis. It comprises bilirubin concentration, serum creatinine values, coagulation parameter in the form of INR (International Normalized Ratio), and the cause of cirrhosis. The original score was used to predict 3-month survival in cirrhotics [76]. Subsequently the etiology of liver disease was dropped from the score as it was spurious or multifactorial in many patients [77]. Due to its accuracy in predicting short-term survival in chronic liver disease, it was adopted for use in prioritizing patients awaiting orthotopic hepatic transplantation. Subsequently the MELD-Na or the MELD-sodium score was developed to include serum sodium which is a marker of the severity of liver cirrhosis [78].

Dynamic tests to assess the liver function to predict the effect of various drugs in liver disease have also been suggested [79]. These tests involve administration of an exogenous substance which depends solely on the liver for its elimination. The concentration of the exogenous substrate in blood or of its metabolite in urine, serum, or exhaled breath is measured. The exogenous substrates with high extraction ratios would be flow-limited and those with low extraction ratios would be capacity-limited. These test compounds with high extraction ratio include indocyanine green (ICG), sorbitol, and galactose [80–82]. Co-administration of indocyanine green and sorbitol helps in approximating the extent of hepatic sinusoidal shunting [83]. The metabolic elimination of caffeine, midazolam, and antipyrine is exclusively dependent on the CYP isoenzymes and is not affected by hepatic blood flow or portosystemic shunting. These tests constitute "Dynamic Liver Function" tests and can be used to evaluate the metabolic hepatocellular dysfunction. Caffeine being primarily metabolized by the CYP1A2, the ratio of caffeine metabolite paraxanthine to caffeine is reduced in patients with liver disease in linear correlation with Child-Pugh scores [28, 84].

Breath tests have been used to assess the hepatic mitochondrial function [85]. The test compound in these tests incorporates isotopes of carbon—a ^{14}C atom or a ^{13}C atom which undergoes metabolism and the amount of the isotope is measured in the exhaled breath [86]. The ^{14}C-erythromycin breath test and ^{13}C-Methacetin breath tests are a few tests which have been used in research practice for this purpose [87–89]. More recently, nuclear imaging techniques have been suggested for the assessment of dynamic liver function [90]. ^{99m}Technetium labeled iminodiacetic acid (IDA) is frequently employed for this technique. These scintigraphic techniques provide information about global and regional hepatic blood flow and functioning. The liver is the sole site for ^{99m}Tc galactosyl human albumin (GSA), thereby making it a suitable agent to assess hepatic function [91]. Its uptake is not influence by elevated bilirubin concentration further promoting its applicability in cholestatic liver pathologies also.

The results of dynamic tests for liver function exhibit a linear correlation with the severity of Child-Pugh classification. However, these tests are not widely used in clinical practice owing to cost implications and requirement of specialized assessment techniques which may not be available in out of research situation. Furthermore, no test has been designated as the "gold standard" of dynamic liver function which is analogous to creatinine clearance in renal pathologies. The need of the hour is to develop such a dynamic test which measures the residual eliminating capacity of the diseased liver so that the drug dose modification could be done accordingly. Hence, clinical methods rely on the more readily available scoring systems like the Child-Pugh system to decide the dosage of drugs in hepatic disease. In such circumstances, due to lack of a model predicting dose modifications in hepatic insufficiency, therapeutic drug monitoring may be suggested for drugs with narrow therapeutic index [92]. This would be beneficial particularly when sicker patients may be exposed to a number of drugs, thereby increasing the potential for drug-drug interactions as well which cannot be predicted by a simplified pharmacokinetic-pharmacodynamic interaction model in diseased state [93]. Furthermore, despite recommendation by the US-FDA (Food and Drugs Administration) and the EMA (European Medical Agency), information about altered pharmacokinetics in liver disease is lacking [94]. Therefore, safe administration

and optimal usage of drugs in hepatic insufficiency may be guided by therapeutic drug monitoring.

5.13 Conclusion

- Liver cirrhosis is characterized by reduced hepatic blood flow, portosystemic shunting of blood, decreased number and activity of functional hepatocytes, and hepatic sinusoidal capillarization.
- Liver disease reduces the pre-systemic metabolism, thereby warranting a dose reduction of drugs administered orally.
- Reduced uptake of drugs may occur into the liver due to reduced hepatic blood flow in patients with liver cirrhosis.
- Drugs with high extraction ratios are blood flow-limited and are insensitive to plasma protein binding or enzyme activity.
- Drugs with low extraction ratios are enzyme activity-limited and are dependent on protein binding along with intrinsic hepatic clearance.
- Drug metabolizing enzymes are not only polymorphic in nature accounting for the interindividual variations but are also affected differentially in liver disease.
- Volume of distribution of polar drugs may be altered in liver disease due to ascites and anasarca. This should be accounted for, particularly while administering loading doses of drugs like antimicrobials.
- Creatinine clearance is not a reliable marker for glomerular filtration in patients with hepatic pathologies as it overestimates the GFR.
- End-stage liver disease patients may be suffering from hepatorenal syndrome in which the excretion of the renally eliminated drugs will also be hampered, thereby necessitating appropriate dose adjustments for this phenomenon.
- The interplay between pharmacokinetic and pharmacodynamic interactions is complex, heterogenous, unpredictable, and drug specific; hence estimation of drug dose modification becomes difficult.
- Extreme vigilance is warranted while prescribing drugs with narrow therapeutic index to patients with severe degrees of hepatic insufficiency.
- Therapeutic drug monitoring could be utilized in patients with severe liver disease to ensure adequate drug exposure along with avoidance of drug toxicity.

Key Points

- Drug disposition depends on adequate functioning of the liver as it is the major site for metabolism of endogenous as well as exogenous substrates.
- Pharmacokinetics refers to the series of processes that a drug undergoes to reach its fate in the body. Pharmacodynamics is the effect of the drug on the body.
- Various steps of drug metabolism include uptake of drugs in the liver, phase 1 and 2 reactions, and transport into the bile followed by elimination.
- The impairment of drug metabolism usually correlates well with the extent of hepatocellular damage.
- Liver disease may lead to reduced hepatic blood flow, flow diversion in the form of portosystemic anastomosis, reduced first-pass metabolism, reduced metabolism and clearance, altered secretion, and prolonged half-life of drugs.
- Liver diseases are associated with varied and nonuniform reductions in activities of drug-metabolizing enzymes. Some enzymes are more affected than others.
- Pharmacodynamic alterations in liver disease are commonly manifested in the central nervous system and the kidney.
- Patients with end-stage liver disease may have concomitant renal dysfunction, necessitating dose adjustments for renally eliminated drugs as well.
- The complexities of the pharmacokinetic and pharmacodynamic interactions make it difficult to predict the therapeutic effect of drugs in diseased states.

References

1. Lautt WW. Mechanism and role of intrinsic regulation of hepatic arterial blood flow: hepatic arterial buffer response. Am J Physiol Gastrointest Liver Physiol. 1985;249(5):G549–56.
2. Nelson DR. The cytochrome P450 homepage. Hum Genomics. 2009;4(1):59–65.
3. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, Preissner S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS One. 2013;8(12):e82562.
4. Rendic S, Carlo FJD. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. Drug Metab Rev. 1997;29(1–2):413–580.
5. Guengerich FP. Human cytochrome P450 enzymes. In: Ortiz Montellano PR, editor. Cytochrome P450. Springer; 1995. p. 473–535.
6. Testa B, Krämer SD. The biochemistry of drug metabolism–an introduction: part 1. principles and overview. Chem Biodivers. 2006;3(10):1053–101.
7. Almazroo OA, Miah MK, Venkataramanan R. Drug metabolism in the liver. Clin Liver Dis. 2017;21(1):1–20.
8. Faber KN, Müller M, Jansen PL. Drug transport proteins in the liver. Adv Drug Deliv Rev. 2003;55(1):107–24.
9. Chandra P, Brouwer KL. The complexities of hepatic drug transport: current knowledge and emerging concepts. Pharm Res. 2004;21(5):719–35.
10. Roberts MS, Magnusson BM, Burczynski FJ, Weiss M. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. Clin Pharmacokinet. 2002;41(10):751–90.
11. Blaschke TF, Rubin PC. Hepatic first-pass metabolism in liver disease. Clin Pharmacokinet. 1979;4(6):423–32.
12. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. Clin Pharmacol Ther. 1975;18(4):377–90.
13. Rowland M, Benet LZ, Graham GG. Clearance concepts in pharmacokinetics. J Pharmacokinet Biopharm. 1973;1(2):123–36.
14. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147–61.
15. Blaschke TF. Effect of liver disease on dose optimization. International congress series. Amsterdam: Elsevier; 2001. p. 247–58.
16. Zuckerman MJ, Menzies IS, Ho H, Gregory GG, Casner NA, Crane RS, et al. Assessment of intestinal permeability and absorption in cirrhotic patients with ascites using combined sugar probes. Dig Dis Sci. 2004;49(4):621–6.
17. Verne GN, Soldevia-Pico C, Robinson ME, Spicer KM, Reuben A. Autonomic dysfunction and gastroparesis in cirrhosis. J Clin Gastroenterol. 2004;38(1):72–6.
18. Roland BC, Garcia-Tsao G, Ciarleglio MM, Deng Y, Sheth A. Decompensated cirrhotics have slower intestinal transit times as compared with compensated cirrhotics and healthy controls. J Clin Gastroenterol. 2013;47(10):888–93.
19. Delco F, Tchambaz L, Schlienger R, Drewe J, Krahenbuhl S. Dose adjustment in patients with liver disease. Drug Saf. 2005;28(6):529–45.
20. Homeida M, Jackson L, Roberts CJ. Decreased first-pass metabolism of labetalol in chronic liver disease. Br Med J. 1978;2(6144):1048–50.
21. Neugebauer G, Gabor M, Reiff K. Pharmacokinetics and bioavailability of carvedilol in patients with liver cirrhosis. Drugs. 1988;36(6):148–54.
22. Pentikäinen PJ, Välisalmi L, Himberg J-J, Crevoisier C. Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol. 1989;29(3):272–7.
23. Trouvin J-H, Farinotti R, Haberer JP, Servin F, Chauvin M, Duvaldestin P. Pharmacokinetics of midazolam in anaesthetized cirrhotic patients. Br J Anaesth. 1988;60(7):762–7.
24. Gorski JC, Jones DR, Haehner-Daniels BD, Hamman MA, O'Mara EM Jr, Hall SD. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. Clin Pharmacol Ther. 1998;64(2):133–43.
25. Delco F, Tchambaz L, Schlienger R, Drewe J, Krähenbühl S. Dose adjustment in patients with liver disease. Drug Saf. 2005;28(6):529–45.
26. Bartoletti M, Giannella M, Lewis RE, Viale P. Bloodstream infections in patients with liver cirrhosis. Virulence. 2016;7(3):309–19.
27. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840–51.
28. Villeneuve J-P, Pichette V. Cytochrome P450 and liver diseases. Curr Drug Metab. 2004;5(3):273–82.
29. Frye RF, Zgheib NK, Matzke GR, Chaves-Gnecco D, Rabinovitz M, Shaikh OS, et al. Liver disease selectively modulates cytochrome P450–mediated metabolism. Clin Pharmacol Ther. 2006;80(3):235–45.
30. Jodynis-Liebert J, Flieger J, Matuszewska A, Juszczyk J. Serum metabolite/caffeine ratios as a test for liver function. J Clin Pharmacol. 2004;44(4):338–47.
31. Pelkonen O, Rautio A, Raunio H, Pasanen M. CYP2A6: a human coumarin 7-hydroxylase. Toxicology. 2000;144(1–3):139–47.
32. Sotaniemi EA, Rautio A, Backstrom M, Arvela P, Pelkonen O. CYP3A4 and CYP2A6 activities marked by the metabolism of lignocaine and coumarin in patients with liver and kidney diseases and epileptic patients. Br J Clin Pharmacol. 1995;39(1):71–6.
33. Relling MV, Aoyama T, Gonzalez FJ, Meyer UA. Tolbutamide and mephenytoin hydroxylation by human cytochrome P450s in the CYP2C subfamily. J Pharmacol Exp Ther. 1990;252(1):442–7.

34. Brøsen K, Meyer UA, Goldstein JA. A multifamily study on the relationship between CYP2C19 genotype and s-mephenytoin oxidation phenotype. Pharmacogenetics. 1995;5(5):312–7.
35. Adedoyin A, Arns PA, Richards WO, Wilkinson GR, Branch RA. Selective effect of liver disease on the activities of specific metabolizing enzymes: investigation of cytochromes P450 2C19 and 2D6. Clin Pharmacol Ther. 1998;64(1):8–17.
36. Woolsey SJ, Mansell SE, Kim RB, Tirona RG, Beaton MD. CYP3A activity and expression in nonalcoholic fatty liver disease. Drug Metab Dispos. 2015;43(10):1484–90.
37. Oellerich M, Armstrong VW. The MEGX test: a tool for the real-time assessment of hepatic function. Ther Drug Monit. 2001;23(2):81–92.
38. Huang Y-S, Lee S-D, Deng J-F, Wu J-C, Lu R-H, Lin Y-F, et al. Measuring lidocaine metabolite—monoethylglycinexylidide as a quantitative index of hepatic function in adults with chronic hepatitis and cirrhosis. J Hepatol. 1993;19(1):140–7.
39. Ochs HR, Greenblatt DJ, Verburg-Ochs B, Matlis R. Temazepam clearance unaltered in cirrhosis. Am J Gastroenterol. 1986;81(1):80–4.
40. Kim JW, Phongsamran PV. Drug-induced liver disease and drug use considerations in liver disease. J Pharm Pract. 2009;22(3):278–89.
41. George J. Elevated serum β-glucuronidase reflects hepatic lysosomal fragility following toxic liver injury in rats. Biochem Cell Biol. 2008;86(3):235–43.
42. Tanaka Y, Kobayashi Y, Gabazza EC, Higuchi K, Kamisako T, Kuroda M, et al. Increased renal expression of bilirubin glucuronide transporters in a rat model of obstructive jaundice. Am J Physiol Gastrointest Liver Physiol. 2002;282(4):G656–62.
43. Hoyumpa AM, Schenker S. Is glucuronidation truly preserved in patients with liver disease? Hepatology. 1991;13(4):786–95.
44. Sugatani J. Function, genetic polymorphism, and transcriptional regulation of human UDP-glucuronosyltransferase (UGT) 1A1. Drug Metab Pharmacokinet. 2013;28:83.
45. Lin JH, Wong BK. Complexities of glucuronidation affecting in vitro-in vivo extrapolation. Curr Drug Metab. 2002;3(6):623–46.
46. Furlan V, Demirdjian S, Bourdon O, Magdalou J, Taburet A-M. Glucuronidation of drugs by hepatic microsomes derived from healthy and cirrhotic human livers. J Pharmacol Exp Ther. 1999;289(2):1169–75.
47. Palatini P, De Martin S, Pegoraro P, Orlando R. Enzyme inhibition and induction in liver disease. Curr Clin Pharmacol. 2008;3(1):56–69.
48. Gariépy L, Fenyves D, Kassissia I, Villeneuve J-P. Clearance by the liver in cirrhosis. II. Characterization of propranolol uptake with the multiple-indicator dilution technique. Hepatology. 1993;18(4):823–31.
49. Hardwick RN, Fisher CD, Canet MJ, Scheffer GL, Cherrington NJ. Variations in ATP-binding cassette transporter regulation during the progression of human nonalcoholic fatty liver disease. Drug Metab Dispos. 2011;39(12):2395–402.
50. Klaassen CD, Watkins JB. Mechanisms of bile formation, hepatic uptake, and biliary excretion. Pharmacol Rev. 1984;36(1):1–67.
51. Elferink RPO, Meijer DK, Kuipers F, Jansen PL, Groen AK, Groothuis GM. Hepatobiliary secretion of organic compounds; molecular mechanisms of membrane transport. Biochim Biophys Acta Rev Biomembr. 1995;1241(2):215–68.
52. Padda MS, Sanchez M, Akhtar AJ, Boyer JL. Drug-induced cholestasis. Hepatology. 2011;53(4):1377–87.
53. Pauli-Magnus C, Meier PJ. Hepatobiliary transporters and drug-induced cholestasis. Hepatology. 2006;44(4):778–87.
54. Bramow S, Ott P, Thomsen Nielsen F, Bangert K, Tygstrup N, Dalhoff K. Cholestasis and regulation of genes related to drug metabolism and biliary transport in rat liver following treatment with cyclosporine A and sirolimus (Rapamycin). Pharmacol Toxicol. 2001;89(3):133–9.
55. Tchambaz L, Schlatter C, Jakob M, Krâhenbûhl A, Wolf P, Krahenbuhl S. Dose adaptation of antineoplastic drugs in patients with liver disease. Drug Saf. 2006;29(6):509–22.
56. Erly B, Carey W, Kapoor B, McKinney J, Tam M, Wang W. Hepatorenal syndrome: a review of pathophysiology and current treatment options. Semin Interv Radiol. 2015;32(4):445–54.
57. Brockmöller J, Thomsen T, Wittstock M, Coupez R, Lochs H, Roots I. Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. Clin Pharmacol Ther. 2005;77(6):529–41.
58. Brater DC. Update in diuretic therapy: clinical pharmacology. Seminars in nephrology. Amsterdam: Elsevier; 2011. p. 483–94.
59. Woitas RP, Stoffel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr H-U, et al. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. Clin Chem. 2000;46(5):712–5.
60. Caregaro L, Menon F, Angeli P, Amodio P, Merkel C, Bortoluzzi A, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. Arch Intern Med. 1994;154(2):201–5.
61. Bergasa NV, Rothman RB, Mukerjee E, Vergalla J, Jones EA. Up-regulation of central mu–opioid receptors in a model of hepatic encephalopathy: a potential mechanism for increased sensitivity to morphine in liver failure. Life Sci. 2002;70(14):1701–8.
62. Hasselstrom J, Eriksson S, Persson A, Rane A, Svensson JO, Sawe J. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. Br J Clin Pharmacol. 1990;29(3):289–97.
63. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases

and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715–35.
64. Laccetti M, Manes G, Uomo G, Lioniello M, Rabitti PG, Balzano A. Flumazenil in the treatment of acute hepatic encephalopathy in cirrhotic patients: a double blind randomized placebo controlled study. Dig Liver Dis. 2000;32(4):335–8.
65. Keller E, Hoppe-Seyler G, Mumm R, Schollmeyer P. Influence of hepatic cirrhosis and end-stage renal disease on pharmacokinetics and pharmacodynamics of furosemide. Eur J Clin Pharmacol. 1981;20(1):27–33.
66. Schwartz S, Brater DC, Pound D, Green PK, Kramer WG, Rudy D. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide in patients with cirrhosis. Clin Pharmacol Ther. 1993;54(1):90–7.
67. Gentilini P, La Villa G, Marra F, Carloni V, Melani L, Foschi M, et al. Pharmacokinetics and pharmacodynamics of torasemide and furosemide in patients with diuretic resistant ascites. J Hepatol. 1996;25(4):481–90.
68. Moore RD, Smith CR, Lietman PS. Increased risk of renal dysfunction due to interaction of liver disease and aminoglycosides. Am J Med. 1986;80(6):1093–7.
69. Imani F, Motavaf M, Safari S, Alavian SM. The therapeutic use of analgesics in patients with liver cirrhosis: a literature review and evidence-based recommendations. Hepat Mon. 2014;14(10):e23539.
70. Møller S, Henriksen JH. Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease. Heart. 2002;87(1):9–15.
71. Caujolle B, Ballet F, Poupon R. Relationship among beta-adrenergic blockade, propranolol concentration, and liver function in patients with cirrhosis. Scand J Gastroenterol. 1988;23(8):925–30.
72. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from Child to MELD. Hepatology. 2001;33(2):473–5.
73. Child CG. The liver and portal hypertension. Philadelphia, PA: Saunders; 1967.
74. Garrison RN, Cryer HM, Howard DA, Polk HC. Clarification of risk factors for abdominal operations in patients with hepatic cirrhosis. Ann Surg. 1984;199(6):648–55.
75. Albers I, Hartmann H, Bircher J, Creutzfeldt W. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. Scand J Gastroenterol. 1989;24(3):269–76.
76. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864–71.
77. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl. 2001;7(7):567–80.
78. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. Gastroenterology. 2011;140(7):1952–60.
79. Rassam F, Olthof PB, Bennink RJ, van Gulik TM. Current modalities for the assessment of future remnant liver function. Visc Med. 2017;33(6):442–8.
80. Herold C, Heinz R, Niedobitek G, Schneider T, Hahn EG, Schuppan D. Quantitative testing of liver function in relation to fibrosis in patients with chronic hepatitis B and C. Liver. 2001;21(4):260–5.
81. Clemmesen JO, Tygstrup N, Ott P. Hepatic plasma flow estimated according to Fick's principle in patients with hepatic encephalopathy: evaluation of indocyanine green and d-sorbitol as test substances. Hepatology. 1998;27(3):666–73.
82. Marchesini G, Bua V, Brunori A, Bianchi G, Pisi P, Fabbri A, et al. Galactose elimination capacity and liver volume in aging man. Hepatology. 1988;8(5):1079–83.
83. Molino G, Avagnina P, Ballarè M, Torchio M, Niro AG, Aurucci PE, et al. Combined evaluation of total and functional liver plasma flows and intrahepatic shunting. Dig Dis Sci. 1991;36(9):1189–96.
84. Fuhr U, Rost KL. Simple and reliable CYP1A2 phenotyping by the paraxanthine/caffeine ratio in plasma and in saliva. Pharmacogenetics. 1994;4(3):109–16.
85. Wagner DA, Woolf GM. Breath test for assessing hepatic function. 1999.
86. Bonfrate L, Grattagliano I, Palasciano G, Portincasa P. Dynamic carbon 13 breath tests for the study of liver function and gastric emptying. Gastroenterol Rep. 2015;3(1):12–21.
87. Schmidt LE, Olsen AK, Stentoft K, Rasmussen A, Kirkegaard P, Dalhoff K. Early postoperative erythromycin breath test correlates with hepatic cytochrome P4503A activity in liver transplant recipients. Clin Pharmacol Ther. 2001;70(5):446–54.
88. Braden B, Lembcke B, Kuker W, Caspary WF. 13C-breath tests: current state of the art and future directions. Dig Liver Dis. 2007;39(9):795–805.
89. Petrolati A, Festi D, De Berardinis G, Colaiocco-Ferrante L, Di Paolo D, Tisone G, et al. 13C-methacetin breath test for monitoring hepatic function in cirrhotic patients before and after liver transplantation. Aliment Pharmacol Ther. 2003;18(8):785–90.
90. de Graaf W, Bennink RJ, Vetelainen R, van Gulik TM. Nuclear imaging techniques for the assessment of hepatic function in liver surgery and transplantation. J Nucl Med. 2010;51(5):742–52.
91. Kokudo N, Vera DR, Makuuchi M. Clinical application of TcGSA. Nucl Med Biol. 2003;30(8):845–9.
92. Sonne J. Drug metabolism in liver disease: implications for therapeutic drug monitoring. Ther Drug Monit. 1996;18(4):397–401.
93. Guaraldi G, Cocchi S, Codeluppi M, Di Benedetto F, Bonora S, Pecorari M, et al. Role of therapeutic drug monitoring in a patient with human immunodeficiency virus infection and end-stage liver disease undergoing orthotopic liver transplantation. Transplant Proc. 2005;37(6):2609–10.
94. Weersink RA, Bouma M, Burger DM, Drenth JPH, Hunfeld NGM, Kranenborg M, et al. Evaluating the safety and dosing of drugs in patients with liver cirrhosis by literature review and expert opinion. BMJ Open. 2016;6(10):e012991.