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Review Article

Drug Dose Individualization in Patients with Hepatic Impairment: A Comprehensive Review of Pharmacokinetic and Pharmacodynamic Alterations and Their Implications for Therapeutic Management

J. S. Venkatesh, Vinuth Chikkamath, Linda Joy*, Sahana H. M., Sreejith S., Devika K. S.

S.C.S. College of Pharmacy, Harapanahalli-583131, Karnataka, India.

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ABSTRACT

The liver plays a vital role in drug metabolism, biotransformation, and elimination. Hepatic impairment resulting from chronic hepatitis, alcoholic liver disease, and cirrhosis can significantly alter drug disposition and therapeutic responses. These changes may affect drug absorption, distribution, metabolism, and elimination, increasing the risk of drug accumulation and adverse drug reactions. This review examines the pharmacokinetic and pharmacodynamic alterations associated with hepatic impairment, emphasizing their implications for individualized drug therapy. Altered cytochrome P450 enzyme activity, plasma protein binding, hepatic blood flow, and phase I and phase II metabolic pathways contribute to variations in drug clearance. Additionally, pharmacogenetic differences involving drug-metabolizing enzymes and transporters influence individual therapeutic responses. Changes in drug sensitivity further complicate treatment management. Appropriate dose modification, careful drug selection, assessment of hepatic function, and therapeutic drug monitoring are important strategies for improving medication safety and therapeutic effectiveness. This review highlights drug-related alterations in hepatic impairment and their implications for individualized dosing and safe therapeutic management. Clinical pharmacist involvement supports individualized treatment and minimizes medication-related complications.

***Corresponding Author:** Linda Joy
Address: S.C.S. College of Pharmacy, Harapanahalli-583131, Karnataka, India.
Email ✉: lindazara2002@gmail.com
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INTRODUCTION

The liver is a vital organ that plays a central role in maintaining physiological homeostasis and regulating the disposition of drugs and other foreign substances entering the human body. It is primarily responsible for drug metabolism, biotransformation, plasma protein synthesis, bile production, and the elimination of various endogenous and exogenous compounds. Most medications undergo hepatic metabolism before their elimination from the body, making normal liver function an important determinant of drug exposure and therapeutic response. However, several pathological conditions, including chronic viral hepatitis, alcoholic liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), cholestatic disorders, and liver cirrhosis, can progressively compromise hepatic function. Such conditions may significantly alter the pharmacokinetic and pharmacodynamic properties of medications, resulting in unpredictable therapeutic responses, increased drug exposure, reduced treatment effectiveness, and a greater risk of adverse drug reactions (ADRs). Therefore, appropriate drug dose individualization is essential when managing patients with hepatic impairment to achieve therapeutic benefits while minimizing medication-related complications [1,2].

Hepatic impairment affects the major pharmacokinetic processes of absorption, distribution, metabolism, and excretion (ADME). Changes in gastrointestinal function, portal hypertension, and portosystemic shunting can influence the absorption and bioavailability of orally administered medications. In particular, the reduced hepatic first-pass metabolism associated with portosystemic shunting may increase the systemic availability of certain drugs. Furthermore, reduced hepatic blood flow, loss of functional hepatocytes, and structural changes in the hepatic architecture can decrease drug clearance and prolong elimination half-life. Alterations in plasma protein synthesis, particularly reduced albumin production, may increase the unbound fraction of highly protein-bound medications. This can influence drug distribution, pharmacological activity, and the risk of toxicity. Similarly, changes in biliary secretion and hepatic transport mechanisms may interfere with the elimination of drugs and their metabolites. The extent of these alterations varies according to the underlying disease, its severity, and the metabolic characteristics of individual medications [1,3].

Drug metabolism is another important factor influencing medication safety in patients with impaired hepatic function. Hepatic biotransformation generally occurs through two major phases. Phase I reactions, including oxidation, reduction, and hydrolysis, are primarily mediated by enzymes belonging to the cytochrome P450 (CYP450) family. Phase II reactions involve conjugation processes such as glucuronidation, sulfation, acetylation, and glutathione conjugation, which generally facilitate the elimination of drugs and their metabolites. In patients with chronic liver disease, the expression and activity of these metabolic enzymes may be altered, leading to changes in drug clearance and systemic exposure. Although both phases can be affected, the extent of impairment differs depending on the specific enzyme, underlying liver condition, and severity of hepatic dysfunction. Changes in membrane transporters, including organic anion-transporting polypeptides (OATPs), organic anion transporters (OATs), and bile salt export pump (BSEP), may further influence hepatic drug uptake, intracellular transport, and biliary elimination [3,4].

In addition to disease-related changes in drug metabolism, pharmacogenetic variability is an important consideration in predicting individual drug responses. Genetic polymorphisms in genes encoding drug-metabolizing enzymes and transport proteins can produce differences in enzyme activity, resulting in variations in drug exposure, therapeutic effectiveness, and susceptibility to toxicity. Variations involving CYP2C9, CYP2C19, CYP2D6, and CYP3A5 may influence the metabolism of several clinically important medications. Depending on the genetic variation, individuals may demonstrate poor, intermediate, normal, or increased metabolic activity. However, the relationship between genotype and actual drug-metabolizing capacity is not always straightforward in patients with hepatic impairment. Liver inflammation, hepatocellular damage, altered enzyme expression, nutritional status, and concomitant medication use may independently modify metabolic activity. This phenomenon, sometimes referred to as phenoconversion,

demonstrates that a patient's observed metabolic phenotype may differ from that predicted by genetic testing alone. Therefore, pharmacogenetic information should be considered alongside hepatic functional status, clinical findings, and other patient-specific factors when planning individualized pharmacotherapy [4,5].

Apart from pharmacokinetic alterations, hepatic impairment can also produce clinically significant pharmacodynamic changes. Pharmacodynamic alterations refer to changes in the body's response to a drug, even when drug concentrations remain within the expected therapeutic range. Patients with advanced liver disease may exhibit increased sensitivity to medications such as benzodiazepines, opioids, sedatives, and certain cardiovascular agents. Alterations in neurotransmission, receptor responsiveness, physiological compensatory mechanisms, and electrolyte balance may contribute to these responses. For example, patients with cirrhosis may be particularly susceptible to central nervous system depression and the development or worsening of hepatic encephalopathy following exposure to sedative medications. Similarly, altered haemostatic balance and changes in coagulation factor synthesis can complicate the use of anticoagulant and antiplatelet medications. These observations indicate that dose adjustment should not depend exclusively on pharmacokinetic parameters, as changes in drug sensitivity and physiological responses also influence treatment outcomes [2,5].

Another important challenge in patients with hepatic impairment is the increased possibility of drug–drug interactions and medication-related complications. Patients with chronic liver disease frequently receive multiple medications for the management of underlying hepatic conditions and associated complications, including ascites, portal hypertension, diabetes mellitus, cardiovascular disorders, and infections. Concomitant administration of drugs that inhibit or induce hepatic metabolic enzymes may further modify drug exposure. Additionally, impaired renal function, nutritional deficiencies, altered fluid distribution, and changes in plasma protein binding can contribute to unpredictable pharmacological responses. These factors emphasize the importance of comprehensive medication review, identification of potentially inappropriate medications, and continuous monitoring for adverse drug reactions [2,6].

Assessment of hepatic functional status is an essential step in determining appropriate drug therapy. The Child–Pugh classification is commonly used to categorize hepatic impairment into three classes: Class A (mild), Class B (moderate), and Class C (severe). It considers five clinical and laboratory parameters, namely serum bilirubin, serum albumin, prothrombin time or international normalized ratio (INR), ascites, and hepatic encephalopathy. Although this classification is widely used in clinical practice and drug development, it has limitations in predicting the metabolic capacity of the liver and the clearance of individual medications. Two patients belonging to the same Child –Pugh category may demonstrate different drug-metabolizing capacities depending on their underlying disease, hepatic blood flow, enzyme activity, renal function, and other physiological characteristics. Consequently, additional clinical assessment and drug-specific pharmacokinetic information are necessary to support appropriate dose selection [1,7].

Drug dose individualization in hepatic impairment therefore requires an integrated approach that considers disease severity, pharmacokinetic and pharmacodynamic alterations, pharmacogenetic variability, therapeutic index, and concomitant medication use. Depending on the characteristics of the prescribed drug and the patient's clinical condition, appropriate strategies may include dose reduction, modification of dosing intervals, selection of alternative medications, or avoidance of drugs associated with an increased risk of toxicity. Therapeutic drug monitoring, where clinically indicated and available, can provide additional information for optimizing treatment, particularly for medications with a narrow therapeutic index. Clinical pharmacists also have an important role in evaluating prescriptions, identifying potential drug interactions, monitoring treatment outcomes, and educating patients regarding medication safety. Furthermore, physiologically based pharmacokinetic (PBPK) modelling and other individualized prediction approaches may offer opportunities to improve dose selection in patients with different degrees of hepatic dysfunction. In this context, the present review focuses on the pharmacokinetic

and pharmacodynamic alterations associated with hepatic impairment, the contribution of pharmacogenetic variability, and their implications for individualized drug dosing and effective therapeutic management

DISCUSSION

Drug dose individualization in patients with hepatic impairment remains a significant challenge in clinical practice because hepatic dysfunction produces considerable variability in drug disposition and therapeutic response. Reduced hepatic blood flow, impaired cytochrome P450 enzyme activity, altered phase I and phase II metabolic reactions, and changes in plasma protein binding may increase systemic drug exposure and prolong elimination half-life. However, the extent of these alterations differs depending on the severity of liver disease and the metabolic characteristics of individual medications [1,2].Pharmacogenetic variability further contributes to differences in drug metabolism and treatment outcomes. Polymorphisms in genes encoding CYP enzymes and drug transporters may influence individual metabolic capacity, although their effects can be modified by underlying hepatic disease. Simultaneously, pharmacodynamic alterations, including increased sensitivity to sedatives, opioids and anticoagulants, may increase the risk of adverse drug reactions even when conventional dosing is followed [3,4].Therapeutic management should therefore involve comprehensive assessment of hepatic function, renal status, concomitant medications and individual drug characteristics. Dose reduction, extension of dosing intervals, selection of alternative medications and therapeutic drug monitoring may be considered according to clinical requirements. Clinical pharmacists can contribute through medication review, identification of drug interactions, adverse drug reaction monitoring and patient education. Integrating pharmacokinetic, pharmacodynamic and pharmacogenetic information into clinical decision-making may improve treatment safety and therapeutic outcomes in this vulnerable population

CONCLUSION

Drug dose individualization is essential for ensuring safe and effective pharmacotherapy in patients with hepatic impairment. Alterations in drug absorption, distribution, metabolism, elimination, and pharmacodynamic responses can significantly influence therapeutic outcomes and increase the risk of adverse drug reactions. Pharmacogenetic variability further contributes to differences in individual drug responses, highlighting the importance of personalized therapeutic approaches. Appropriate dose adjustments, careful drug selection, assessment of hepatic function, and regular monitoring are necessary to minimize medication-related complications. The integration of clinical pharmacy services and individualized treatment strategies can improve medication safety, optimize therapeutic effectiveness, and enhance patient outcomes.

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