INNOVATIVE PUBLICATION
Journal of Effective Learning and Sustainable Innovation
Vol.3 №10 (2025). October
innovativepublication.uz

CLINICAL PHARMACOLOGY OF THE USE OF HEPATOPROTECTIVE DRUGS IN CHRONIC VIRAL INFECTIOUS DISEASES

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Abstract. This article presents a comprehensive analysis of the clinical pharmacology of hepatoprotective drugs used in the management of chronic viral infectious diseases, particularly chronic hepatitis B and C. It explores the pharmacodynamic principles, mechanisms of hepatic protection, and the pharmacokinetic behavior of major hepatoprotective agents. The discussion extends to the role of antioxidant, membrane-stabilizing, antifibrotic, and immunomodulatory agents in the restoration of hepatic function under chronic viral injury. Given that the liver is a vital organ responsible for detoxification, metabolism, and protein synthesis, maintaining hepatocellular integrity in chronic viral infections is critical to improving long-term survival and quality of life. The paper emphasizes the importance of combining antiviral therapy with hepatoprotective treatment to achieve comprehensive management of hepatic pathology.

Keywords: hepatoprotective drugs, chronic hepatitis, viral infection, liver regeneration, pharmacology, silymarin.

INTRODUCTION

Chronic viral hepatitis represents one of the most serious global health challenges, contributing significantly to the burden of cirrhosis, hepatocellular carcinoma, and liver failure. Despite significant advances in antiviral therapy, including the development of direct-acting antivirals (DAAs) and nucleos(t)ide analogs, complete restoration of hepatic structure and function often remains elusive. Persistent viral replication, oxidative stress, immune-mediated inflammation, and fibrotic remodeling of the hepatic parenchyma continue to cause progressive liver damage. In this context, hepatoprotective drugs play an essential complementary role in preserving hepatocyte viability, modulating inflammatory cascades, and stimulating regenerative processes [1].

From a clinical pharmacology perspective, hepatoprotective agents encompass a wide range of substances of natural, semi-synthetic, or synthetic origin that act through different mechanisms. Their pharmacological effects include stabilizing cellular

membranes, inhibiting lipid peroxidation, enhancing detoxification pathways, restoring mitochondrial function, and stimulating protein synthesis. The challenge for clinicians and researchers lies in identifying compounds that can effectively counteract the pathophysiological consequences of chronic viral infection while demonstrating proven safety and bioavailability in the compromised liver.

MATERIALS AND METHODS

The pathogenesis of chronic viral hepatitis involves a complex interplay between direct viral cytopathic effects and host immune responses. Hepatocytes infected with hepatitis B or C viruses undergo continuous immune-mediated attack, resulting in necrosis and apoptosis. The release of reactive oxygen species (ROS) and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins accelerates lipid peroxidation and disrupts cellular membranes. Mitochondrial dysfunction and depletion of endogenous antioxidants, particularly glutathione, further exacerbate hepatocellular injury. Over time, these processes lead to fibrosis and architectural distortion of the liver parenchyma, impairing metabolic functions such as albumin synthesis, bilirubin conjugation, and drug metabolism.

Given this multifactorial damage, the rationale for hepatoprotective therapy lies in interrupting these cascades at various biochemical levels — by enhancing antioxidant defenses, improving energy metabolism, inhibiting stellate cell activation, and facilitating hepatic regeneration.

Hepatoprotective agents act through several pharmacodynamic pathways:

Antioxidant and Free Radical Scavenging Effects [2]: Many hepatoprotective drugs, such as silymarin (derived from Silybum marianum), neutralize reactive oxygen species and inhibit lipid peroxidation of hepatocyte membranes. This preserves membrane integrity and prevents enzyme leakage.

Membrane-Stabilizing and Regenerative Effects: Phospholipid-based drugs such as essential phosphatidylcholine integrate into hepatocyte membranes, restoring fluidity and enhancing repair mechanisms. They also support the synthesis of lipoproteins, improving lipid metabolism.

Antifibrotic and Anti-Inflammatory Actions: Compounds like ursodeoxycholic acid (UDCA) reduce bile acid toxicity, modulate immune-mediated injury, and decrease fibrogenic signaling by inhibiting hepatic stellate cell activation.

Detoxifying and Methylation Enhancement: Ademetionine (S-adenosylmethionine) acts as a methyl donor in transmethylation and transsulfuration reactions, promoting glutathione synthesis and detoxification of xenobiotics.

Each of these pharmacological effects contributes to the restoration of normal hepatic

homeostasis, particularly when viral replication has been suppressed by antiviral therapy.

RESULTS AND DISCUSSION

Pharmacokinetics of hepatoprotective drugs are profoundly influenced by the pathophysiological state of the liver. In chronic viral hepatitis, decreased hepatic blood flow, altered first-pass metabolism, and reduced cytochrome P450 enzyme activity lead to slower drug clearance and prolonged half-life. Protein binding is often diminished due to hypoalbuminemia, increasing the free fraction of drugs and the potential for toxicity. For example, silymarin exhibits variable bioavailability because of extensive enterohepatic circulation, while ademetionine, being highly hydrophilic, requires parenteral administration to achieve adequate plasma levels in advanced disease. Hence, dose adjustments and careful monitoring are essential to ensure optimal therapeutic concentrations without overburdening the compromised hepatic system [3].

In clinical practice, hepatoprotective drugs are primarily used as adjunctive therapy in chronic hepatitis B and C, alcoholic liver disease, non-alcoholic fatty liver disease, and drug-induced hepatotoxicity. The combination of antiviral and hepatoprotective agents has shown synergistic benefits in improving biochemical markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels.

Silymarin remains one of the most extensively studied hepatoprotective agents. Clinical trials demonstrate that it enhances superoxide dismutase activity, stabilizes cell membranes, and improves liver enzyme profiles. Long-term administration of silymarin in patients with chronic hepatitis C has been associated with improved liver histology and decreased oxidative stress markers.

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, improves cholestasis by displacing toxic bile acids, enhancing bile flow, and exerting immunomodulatory effects on hepatocytes and cholangiocytes. Its benefit is particularly evident in cholestatic variants of hepatitis and autoimmune-related liver diseases.

Ademetionine plays a central role in methyl group transfer reactions essential for phospholipid and neurotransmitter synthesis. In chronic viral hepatitis, it replenishes hepatic glutathione stores, reduces cholestasis, and supports mitochondrial function.

Other hepatoprotective substances, such as L-ornithine L-aspartate (which reduces ammonia levels and improves hepatic encephalopathy), and glycyrrhizin (which modulates immune and anti-inflammatory pathways), also demonstrate clinical value, especially in Asia and Eastern Europe.

The treatment of chronic viral liver disease requires a multidimensional approach that addresses both viral replication and tissue injury. While antiviral drugs directly

suppress viral load, hepatoprotective drugs act at the cellular level to restore hepatocellular structure and metabolic efficiency. Clinical pharmacology supports this integrative approach, as simultaneous use enhances tolerance to antivirals and reduces the incidence of hepatotoxic side effects. Additionally, hepatoprotective therapy improves patients' overall well-being, appetite, and energy levels — factors crucial for adherence to long-term antiviral regimens [4].

The dosing and duration of hepatoprotective therapy depend on the stage of liver damage and the patient's response to treatment. Continuous monitoring of liver function tests and imaging studies is essential to evaluate therapeutic efficacy and adjust drug regimens accordingly [5].

CONCLUSION

The use of hepatoprotective drugs in chronic viral infectious diseases exemplifies the interplay between pathophysiology, pharmacology, and clinical practice. While antiviral agents remain the cornerstone of therapy, hepatoprotective agents fulfill a complementary role by maintaining hepatocyte integrity, modulating inflammation, and promoting regeneration. Their mechanisms of action — including antioxidant defense, membrane stabilization, detoxification, and antifibrotic activity — collectively contribute to the preservation of hepatic function in patients living with chronic viral hepatitis.

Clinical pharmacology underscores the necessity of understanding both pharmacokinetic alterations and pharmacodynamic variability in liver-compromised patients. Because hepatic metabolism and protein binding are altered in chronic liver disease, individualized dosing regimens and careful therapeutic monitoring are indispensable. Moreover, the rational combination of hepatoprotective agents with antiviral and supportive therapies offers a comprehensive strategy for improving prognosis, reducing complications, and enhancing quality of life.

Future perspectives in hepatoprotection focus on molecular and genetic research aimed at identifying novel compounds capable of targeting mitochondrial dysfunction, endoplasmic reticulum stress, and apoptosis pathways more precisely. The advent of nanocarrier-based delivery systems, bioengineered antioxidants, and combination pharmacotherapy opens new horizons for safe and effective liver protection. Ultimately, hepatoprotective treatment should not be viewed as ancillary care but as an integral component of the multidisciplinary management of chronic viral liver diseases — safeguarding one of the most essential organs of human life through evidence-based pharmacological precision.

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