Pharmacologic Issues in Liver Disease

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KEYWORDS

• Pharmacology • Liver disease • Drug dosing • Pharmacokinetics • Critical illness

KEY POINTS

- The liver is a major site for drug metabolism and clearance, and any changes in liver function can subsequently affect drug disposition.
- Very few medications have recommendations for dose adjustments in liver dysfunction; however, most available recommendations are based on severity of liver disease assessed by Child-Pugh score.
- Most pharmacokinetic studies are in patients with end-stage liver disease (ESLD) with almost none in patients with acute liver failure. Dose adjustment recommendations for these patients are extrapolated from ESLD data.
- Concomitant renal dysfunction is common in patients with ESLD, so dose adjustments based on renal function should also be considered.

INTRODUCTION

The liver plays a vital role in drug disposition because it is a major site for drug metabolism and clearance; consequently, alterations in liver function cause alterations in drug disposition. However, there are no endogenous markers of hepatic clearance and traditional scoring systems such as the Child-Pugh classification (**Table 1**) do not correlate well with hepatic clearance and drug metabolism in liver disease.[1] Thus, the effect of liver dysfunction on drug disposition may be hard to determine. However, there are known changes in pharmacokinetics that occur in liver disease, particularly end-stage liver disease (ESLD), that can aide clinicians in drug dosing, and these are reviewed in this article. In addition, there are pharmacokinetic data

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Table 1
Child-Pugh score

Clinical and Laboratory Criteria	Points 1	2	3
Ascites	None	Slight	Moderate to severe
Hepatic encephalopathy	None	Grade 1–2	Grade 3–4
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin Time			
Time prolonged (s)	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3

Points	Grade	Description
5–6	A	Mild; well compensated
7–9	B	Moderate; significant functional compromise
10–15	C	Severe; decompensated disease

Abbreviation: INR, International Normalized Ratio.

available for select medications that are also included. Unless otherwise noted, recommendations included here are for both ESLD and acute liver failure (ALF).

PHARMACOKINETIC AND PHARMACODYNAMIC ALTERATIONS

Absorption

Little is known about the changes in the absorption of orally administered medications in patients with liver dysfunction and how these affect drug dosing. However, delayed gastric emptying can be present in patients with cirrhosis, which delays the absorption of medications by the small intestine.[2,3] Although delayed absorption of medications can occur, it does not seem to affect the extent of absorption.[3] In addition, the bioavailability of orally administered medications can be significantly increased in patients with liver dysfunction because of a reduction in first-pass metabolism. First-pass metabolism refers to the metabolism of an orally administered medication after absorption and before distribution into the systemic circulation.[2,4] The liver plays a large role in first-pass metabolism because the small intestine, where most orally administered medications are absorbed, empties into the hepatic portal circulation.[5] First-pass metabolism is avoided when medications are administered intravenously. The effect of liver dysfunction on first-pass metabolism is discussed in detail later.

Distribution

Often, patients with cirrhosis experience fluid retention and/or ascites causing an increase in volume of distribution (Vd). This increase in volume mainly affects medications that are water soluble, or hydrophilic, because they reside in serum.[2] Consequently, the dose of hydrophilic medications may need to be increased to achieve therapeutic efficacy.[3] Medications that are bound to plasma proteins can have an increased free plasma concentration in chronic liver disease. This process is multifactorial, including a reduction in the synthesis of plasma proteins, namely albumin and α_1-acid glycoprotein, as well as an increase in substances that can displace protein-bound medications, such as bilirubin.[6] Therapeutic drug monitoring of drugs that are highly protein bound should be considered, particularly for medications with a narrow therapeutic index.