EFFECTS OF LIVER DISEASE ON PHARMACOKINETICS

- Liver disease in humans encompasses a wide range of pathological disturbances that can lead to a reduction in liver blood flow, extrahepatic or intrahepatic shunting of blood, hepatocyte dysfunction, quantitative and qualitative changes in serum proteins, and changes in bile flow.

- Different forms of hepatic disease may produce different alterations in drug absorption, disposition, and pharmacologic effect.

- The pharmacokinetic or pharmacodynamic consequences of a specific hepatic disease may differ among individuals or even within a single individual over time.

Hepatitis

- **Acute hepatitis** is an inflammatory condition of the liver that is caused by viruses or hepatotoxins.

- In acute viral hepatitis, inflammatory changes in the hepatocyte are generally mild and transient, although they can be chronic (chronic active hepatitis) and severe, resulting in cirrhosis or death.

Hepatitis

- In general, drug elimination during acute viral hepatitis is either normal or only moderately impaired.

- If the acute hepatitis resolves, drug disposition returns to normal. Drug elimination is likely to be impaired most significantly in patients who **develop chronic hepatitis B virus**-related liver disease, but even then only late in the evolution of this disease.

- Example: the plasma protein binding of both phenytoin and tolbutamide was reduced during acute hepatitis. For both drugs, this was partly attributed to drug displacement from protein binding sites by elevated bilirubin levels.

Pharmacokinetic Consequences of Liver Cirrhosis

- The net result of chronic hepatic disease that leads to cirrhosis is that pathophysiologic alterations may result in
- Decreased hepatocyte function, with as much as a 50% decrease in cytochrome P450 content,
- And/or shunting of blood away from optimally functioning hepatocytes.

Accordingly, cirrhosis affects drug metabolism more than does any other form of liver disease.

Chronic Liver Disease and Cirrhosis

- **Chronic liver disease** is usually secondary to chronic alcohol abuse or chronic viral hepatitis. Alcoholic liver disease is most common and begins with the accumulation of fat vacuoles within hepatocytes and hepatic enlargement.
- There is a decrease in cytochrome P450 content per weight of tissue, but this is compensated for by the increase in liver size so that drug metabolism is not impaired.

- Alcoholic fatty liver may be accompanied or followed by alcoholic hepatitis, in which hepatocyte degeneration and necrosis become evident. In neither of these conditions is there significant diversion of blood flow past functioning hepatocytes by functional or anatomic shunts.

Chronic Liver Disease and Cirrhosis

1. ***Influence of Portosystemic Shunting.***
2. ***Consequences of Decreased Protein Binding***
3. ***Consequences of Hepatocellular Changes.***
4. ***Enterohepatic Circulation.***

$$ER = \frac{f_u CL_{int}}{Q + f_u CL_{int}}$$

Use Of Therapeutic Drugs In Patients With Liver Disease

- A number of clinical classification schemes and laboratory measures have been proposed as a means of guiding dose adjustments in patients with liver disease, much as creatinine clearance has been used to guide dose adjustments in patients with impaired renal function.

TABLE 7.4 Pugh Modification of Child's Classification of Liver Disease Severity[a]

Assessment parameters	Assigned score		
	1 Point	**2 Points**	**3 Points**
Encephalopathy grade	0	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1–2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin Time (seconds > control)	1–4	4–10	>10
Classification of clinical severity			
Clinical severity	Mild	Moderate	Severe
Total points	5–6	7–9	>9

Encephalopathy grade

Grade 0: Normal consciousness, personality, neurological examination, EEG

Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5-cps waves on EEG

Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG

Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG

Grade 4: Unrousable coma, no personality/behavior, decerebrate, slow (2–3 cps) delta waves on EEG

Effects of Liver Disease on the Renal Elimination of Drugs

- Drug therapy in patients with **advanced cirrhosis** is further complicated by the fact that **renal blood flow** and **glomerular filtration rate** are frequently depressed in these patients in the absence of other known causes of renal failure.
- This condition, termed the ***hepatorenal syndrome***, occurs in a setting of **vasodilation** of the splanchnic circulation that results in underfilling of the systemic circulation.
- This activates pressor responses, causing marked **vasoconstriction** of the renal circulation.

Effects of Liver Disease on Patient Response

- The relationship between drug concentration and response also can be **altered** in patients with advanced liver disease.

- Of greatest concern is the fact that customary doses of sedatives may precipitate the disorientation and coma that are characteristic of portal systemic or hepatic encephalopathy.

- This provides a theoretical basis for the finding **that brain hypersensitivity**, as well as **impaired drug elimination**, is responsible for the exaggerated sedative response to **diazepam** that is exhibited by some patients with chronic liver disease

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