Hepatitis: Sedation and Anesthesia Implications

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Hepatitis is an inflammation of the liver with a variety of causes that include 5 hepatotropic viruses (HAV, HBV, HCV, HDV, HEV), nonhepatotropic viruses (cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella virus), infectious agents other than viruses (bacteria, fungi, parasites), drugs and toxic agents, autoimmune conditions, and metabolic disorders such as Wilson disease and α_1 -antitrypsin deficiency.¹⁻³ Hepatitis can be self-limiting, resolving on its own, or it can progress to cirrhosis or hepatocellular carcinoma. In the United States, viral hepatitis accounts for more than 50% of the acute hepatitis, with HAV, HBV, and HCV being the most common types.⁴ Acute manifestations include nausea and vomiting, fatigue, malaise, abdominal pain, and jaundice. In addition, HBV and HCV can lead to chronic infection that renders the patients infectious carriers for many years.^{2,4} Patients with hepatitis are at high risk for morbidity and mortality postoperatively because of both surgical stress and the effects of anesthesia. Assessing and identifying surgical and anesthesia risks in these patients is imperative to minimize postoperative complications.

LIVER ANATOMY AND PHYSIOLOGY: OVERVIEW

The liver is the largest internal organ and gland in the body and sits right below the diaphragm, occupying most of the right hypochondrium. It is an interface between the digestive system and the blood, in which nutrients and substances absorbed and transported to the liver through the portal vein are processed for use by other parts of the body. The liver is vital for plasma protein synthesis (such as albumin, clotting factors, and carrier proteins), hormone production, coagulation,

glucose homeostasis, drug metabolism and detoxification, protein metabolism, as well as the production of enzymes that aid in digestion. The diverse functions of the liver have an impact on all other parts of the body. A fundamental knowledge of the hepatic anatomy and physiology is thus imperative in understanding the pathophysiology of liver diseases and its therapeutic challenges.

Anatomy

The liver is wrapped in a connective tissue capsule and covered by a layer of visceral peritoneum that protects and holds it in place in the abdominal cavity. It is composed of 4 anatomical lobes: left and right lobe on the anterior surface marked by the falciform ligament and caudate and quadrate lobe on the posterior surface.^{5,6} Arteries, portal veins, and ducts enter and leave the liver at the hilus, a region known as the porta hepatis. After ascending to the porta hepatis, the portal vein and proper hepatic artery divide into the left and right portal veins and hepatic arteries. Their terminal branches drain into the liver sinusoids, which are tiny capillaries that supply the hepatocytes.^{5,7}

From a surgical standpoint, the four lobes can be further divided into 8 independent segments, with each segment having its own specific blood supply and biliary drainage, allowing for intact functionality of neighboring segments after surgical resection. Because of the anatomical variations in human livers, an individual's real physiologic anatomy requires advanced imaging techniques such as contrast-enhanced computed tomography (CT) scan.⁵

Microanatomy

Lobule. The structural organization of the liver is traditionally described in terms of the hepatic lobules,

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Figure 1. Anatomy of the liver. (A) Anterior view. (B) Posteroinferior view. (Source: Figure 26.18 in McKinley & O’Loughlin’s *Human Anatomy*, 2nd ed.)

which are a hexagon composed of portal triads (bile duct, hepatic artery, and hepatic portal vein) at each corner with cylindrically arranged plates of hepatocytes inside the hexagon around a central vein (Figure 2).^{6,8}

Liver Sinusoids. The plates of hepatocytes are separated by sinusoids in which blood flows from the hepatic artery and portal vein. The sinusoids are dilated capillaries composed of a layer of fenestrated endothelial cells.^{5,6} Blood percolates through the endothelial wall to make contact with the hepatocytes. Hepatocytes perform most of the liver’s functions: metabolism, storage, digestion, and bile production. The branches of hepatic arteries and portal veins send blood to the sinusoids toward the central vein. There is thus a mixing of the oxygenated blood from hepatic artery and

deoxygenated, nutrient-rich blood from the portal vein within the sinusoids.^{6,7} The sinusoids run radially and converge in the center to form the central veins. The central veins coalesce into hepatic veins that eventually empty into the inferior vena cava.⁶

Acinus. A hepatic acinus, the functional unit of the liver, has at its center the portal tract (portal axis) that carries blood supply to the liver parenchyma and central veins at the periphery. Hepatocytes in the liver acinus are arranged into 3 zones defined by the proximity to the portal axis.^{6–8} Cells in zone 1, the periportal cells, are closest to the portal triad and receive oxygen and nutrient-rich blood. During impaired circulation, they are the last to show ischemic changes and the first to regenerate. Cells in zone 3, the centrilobular cells, are

Figure 2. Hepatic lobule. (A) Depiction of the hepatic lobules. (B) Arrangement of hepatocytes and hepatic sinusoids. (C) Histology of a portal tract. (Source: Figure 26.19 in McKinley & O’Loughlin’s *Human Anatomy*, 2nd ed.)

Figure 3. Blood supply of a liver acinus. Oxygen tensions and nutrient levels within sinusoids continuously decrease as blood flows from zone 1 through zone 3. BD, bile ductule; CV, central vein; HA, hepatic artery; PV, portal vein. (Source: Jones AL. *Anatomy of the normal liver*. In: Zakim D, Boyer T, eds. *Hepatology: A Textbook of Liver Disease*. 3rd ed. 1996.)

farthest from the portal triad and are the first to show ischemic necrosis. They have the highest density of cytochrome P450 and are the most susceptible to injuries caused by toxins, drugs, oxidative stress, and hypotension.^{6,7}

Hepatic Blood Flow. The liver receives about 25–30% of the cardiac output. Roughly 25% of the blood flow to the liver is oxygenated blood from the hepatic artery proper, which arises from the celiac trunk of the abdominal aorta. The remaining 75% consists of venous blood from the hepatic portal vein formed by the union of superior mesenteric and splenic veins.^{7,9} The hepatic portal circulation carries nutrient-rich, oxygen-poor blood from the esophagus, stomach, small intestine, most of the large intestine, and spleen to the liver. Approximately half of the liver's oxygen demand is supplied by the portal vein, and the other half supplied by hepatic arteries.⁶ In general, the liver has substantial functional reserve because of its dual blood supply from the hepatic artery and portal vein. Hence, clinical manifestations of liver damage occur only after considerable injury.^{6,7,9}

Enterohepatic Circulation. Certain substances circulate continuously between the liver and small intestine in a circuit known as the enterohepatic circulation. The requirement for a substance to enter into the enterohepatic circulation is that it can be transported into hepatocytes and secreted into bile, which is then reabsorbed from the small intestine.^{7–9} Certain drugs

Figure 4. Splanchnic circulation under fasting conditions. The liver receives most of its blood supply via the portal vein under fasting conditions. (Source: Barrett KE. Chapter 10. Functional anatomy of the liver and biliary system. In: Barrett KE, ed. *Gastrointestinal Physiology*, 2nd ed. 2014.)

and their metabolites may circulate through this route, altering their pharmacokinetics. A classic anesthetic example of enterohepatic circulation is associated with the benzodiazepine diazepam. This drug undergoes biliary excretion and can result in intestinal absorption from bile after ingestion of a fatty meal leading to re-sedation, often known as the so-called “sundowner effect.” However, some evidence refutes the significance

Figure 5. Enterohepatic circulation. Bile secreted by hepatocytes enters the bile duct and flows through the biliary system to the duodenum. Conjugated bile acids are reabsorbed in the terminal ileum and recirculated through the portal vein back to the liver. (Source: Barrett KE. Chapter 10. Functional anatomy of the liver and biliary system. In: Barrett KE, ed. *Gastrointestinal Physiology*, 2nd ed. 2014.)

of clinically significant biliary excretion.¹⁰ In contrast, the extensive enterohepatic circulation of low-dose ethinylestradiol, the most commonly used oral synthetic estrogen birth control medication, is clinically relevant in terms of duration of action in affecting human female fertility.

Blood Reservoir Function. The liver is capable of acting as a blood reservoir that stores and releases blood. The hepatic blood volume accounts for 10–15% of the total blood volume.³ The relatively low resistance and high compliance of the hepatic vessels and sinusoids allow for large blood flow into the liver. Consequently, minor changes in hepatic venous tone and pressure can lead to substantial changes in hepatic blood volume. When intravascular volume is acutely increased, as occurs in rapid fluid infusion, the hepatic blood volume expands to buffer against the drastic increase in systemic blood volume. A decrease in hepatic venous pressure, as occurs in hemorrhage, prompts the release of blood from sinusoids into the systemic circulation. The postsinusoidal blood vessels are the major contribution to total hepatic vascular resistance.³ An increase in vascular resistance within the postsinusoidal veins can promote transudation of plasma into lymphatic vessels and the peritoneal cavity and result in edema, ascites, and hypovolemia.¹¹

Regulation of Blood Flow. The hepatic blood flow is regulated by intrinsic (regional microvascular) and extrinsic (neurohumoral) mechanisms.

Intrinsic Regulation. Because of the lack of ability to control portal venous flow, the regional vascular system regulates blood flow exclusively through controlling the hepatic arteriolar tone by the hepatic arterial buffer response (HABR) and pressure-flow autoregulation.³ The most important mechanism is HABR, in which the hepatic arterial blood flow changes reciprocally in response to changes in portal venous flow and decreases in blood pH. The HABR increases arterial blood flow to compensate for a reduction in portal venous flow and acidosis to a limited extent to protect the liver from ischemic injuries. The HABR appears to be modulated by the following mechanism: Adenosine, a potent vasodilator that inhibits sympathetic nervous stimulation, norepinephrine, and angiotensin, is constantly secreted into the portal triad and can be carried into the bloodstream of the portal vein or hepatic artery. The breakdown of S-adenyl-homocysteine stimulates adenosine release into the periportal space. A reduced portal blood flow leads to adenosine accumulation in the area, resulting in hepatic artery dilation.¹² The maximum buffer response is doubling the arterial blood flow to compensate for a 50% reduction in the portal venous flow.¹¹ Even though the buffer capacity is limited, the

HABR is typically an effective mechanism because of the hepatic artery's carrying higher oxygen content.^{3,11}

The hepatic artery also undergoes pressure-flow autoregulation. The pressure-flow mechanism involves responses of the vascular smooth muscle to stretch when there is a change in the transmural pressure.^{3,11} An increase in the transmural pressure stretches the arterial smooth muscle and thereby prompts vasoconstriction to prevent excess blood flow. Conversely, transient hypotension lowers transmural pressure and causes vasodilation to sustain proper organ perfusion. The pressure-flow autoregulation appears to be inactive in the fasting state and nonexistent in the portal system and has a little role as an intraoperative regulatory mechanism of hepatic blood flow with the exception of emergency surgeries on patients in the nonfasting state.^{3,9} Liver cirrhosis and volatile anesthetics reduce the HABR buffering capacity and may subject the liver to an increased risk of ischemia.

Extrinsic Regulation. The extrinsic regulation of hepatic blood flow consists of various neural and humoral mechanisms.

Neural Mechanism. The liver is innervated by the sympathetic nerve fibers of the splanchnic nerves from T6–T12 and parasympathetic nerve fibers of the vagus nerves bilaterally.¹³ These nerve fibers function to control metabolism through sensing glucose, protein, lipid, and hormone level. The sympathetic nerve fiber alters hemodynamics and metabolism of the liver by increasing the hepatic vascular resistance, decreasing the blood volume, and increasing the blood glucose level through gluconeogenesis and glycogenolysis.¹³ A reduced sympathetic tone causes an increase in the liver reservoir volume, whereas a sympathetic stimulation causes release of blood from liver to the systemic circulation.^{3,14} Vagal stimulation changes the intrahepatic distribution of blood volume through altering the perisinusoidal sphincters but has no direct effect on total hepatic blood flow.^{3,14}

Humoral Mechanism. A variety of humoral substances can alter hepatic blood flow, including catecholamines, vasopressin, angiotensin II, and glucagon. The hepatic arterial system contains both α and β adrenergic receptors, whereas the portal system has only α receptors.^{3,14} Therefore, administering exogenous catecholamines such as epinephrine causes initially vasoconstriction via α_1 adrenergic effect, compensated partially by vasodilation at a later phase through β_2 receptors. In contrast, epinephrine administration into the portal vessels causes only vasoconstriction. Dopamine has little effect on the liver because of the lack of dopamine receptors. Vasopressin increases hepatic arterial resistance and markedly reduces portal venous resistance. For that reason, high-dose vasopressin may

have efficacy in alleviating portal hypertension.^{3,14} Angiotensin II constricts both the hepatic and portal vasculatures and can cause a sudden drop in total hepatic blood flow. Glucagon induces hepatic arteriolar dilation, which antagonizes the effect of vasoconstrictors.^{3,14}

Effects of Anesthesia on Hepatic Blood Flow. Anesthesia alters hepatic blood flow by way of changing the hepatic perfusion pressure or splanchnic vascular resistance.^{3,14} This alteration is due to a variety of factors that include the effect of individual anesthetics, type of anesthesia, ventilation mode, and type of surgery.¹¹ Most anesthetic agents that cause hypotension and decrease cardiac output also decrease the hepatic blood flow. During general anesthesia, as the splanchnic vascular resistance increases, the liver blood flow decreases. Application of positive end-expiratory pressure decreases the hepatic blood flow by increasing the hepatic portal venous pressure.

There is no significant change in hepatic blood flow with up to a 40% reduction in mean arterial pressure due to the dual contribution of blood flow from the portal and hepatic arterial vasculature.³ The simultaneous decrease in oxygen requirements by the liver makes ischemic liver injury a rare phenomenon during anesthesia.

Physiological Function of the Liver. By virtue of its relationship to the rest of the gastrointestinal (GI) organs, the liver plays a pivotal role in the physiology of the many systems by processing ingested substances entering via the GI tract, metabolism and detoxification of drugs, and synthesis of hormones and plasma proteins. This section will focus on the broad category of liver functions relevant to anesthesia as it is beyond the scope of this review to provide a comprehensive analysis of all the metabolic functions of the liver.

Regulation of Glucose Level. The liver is the main organ for glucose homeostasis. It does so by storing excess glucose as glycogen and releasing glucose as needed through glycogenolysis and gluconeogenesis. The liver is the dominant site of glucose deposition, while muscle and adipose tissue are minor sites.⁹ Surgical stress causes an increase in sympathetic tone, which stimulates glycogen breakdown, frequently leading to perioperative hyperglycemia.

Coagulation. All of the procoagulants are synthesized in the liver except von Willebrand factors, which are synthesized in megakaryocytes and endothelial cells, and some factor VIII, which is produced by endothelial cells.¹⁵ The only other plasma protein not synthesized in the liver is immunoglobulin, which is produced by lymphocytes and plasma cells. Therefore, a reduction in the level of circulating procoagulants and anticoagulants ensues in the presence of liver disease. The extent of coagulation abnormality greatly depends on the degree

of liver disease and dysfunction. Changes may be minor in patients with minor liver dysfunction but can be severe in those with cirrhosis and liver failure. Platelets are also altered quantitatively and qualitatively in these patients, with the development of disseminated intravascular coagulation.¹⁶

The clotting function is evaluated by measuring prothrombin time/international normalized ratio (INR), partial thromboplastin time, and fibrinogen levels. Prothrombin time is the most useful diagnostic tool for acute liver dysfunction as the vitamin K-dependent factors (factor II, VII, IX, X) have short half-lives^{16,17} and thus, alterations in the synthesis of these procoagulants are observed faster than others. In general, hepatic synthetic function needs to be sufficiently depressed before impaired coagulation occurs because many factors require only 20–30% of their normal level to prevent bleeding.¹⁶

Detoxification and Drug Metabolism. The liver is highly active in removing particulates from the blood. Kupffer cells (specialized macrophages found in the sinusoid lumen) exhibit a blood-cleansing property that filters debris, bacteria, and their toxins. Other detoxification functions are biochemical in nature through cytochrome P450 and other enzymes that can convert drugs and toxins into inactive, less lipophilic metabolites that can be excreted through the kidneys and other parts of the body. The bioavailability of many drugs is highly regulated through the first-pass mechanism, in which the metabolism of the ingested drugs undergoes metabolism before entry into the systemic circulation. In general, the hepatic metabolism of drugs is divided into phase I reaction (oxidation, hydroxylation, and other reactions mediated by CYP450s) and phase II reaction (esterification with addition of sulfate, glucuronic acid, amino acids, or glutathione).⁹ Occasionally, metabolism of specific drugs (such as acetaminophen) can produce toxic intermediates, particularly in an overdose.^{9,18}

Chronic liver disease such as cirrhosis may interfere with the metabolic function of the liver by decreasing hepatic blood flow as well as decreased number of hepatocytes.^{11,19,20} Prolonged elimination half-life for many anesthetic drugs is expected in these patients.

Liver Function Tests

A variety of laboratory diagnostic assays are available to examine and provide differential diagnoses of hepatic function. Table 1 describes the more commonly employed tests used in liver function tests and panels. A global interpretation of abnormal liver function tests can help deduce if the underlying condition is likely

Table 1. Commonly Used Liver Function Tests

<i>Test</i>	<i>Function</i>	<i>Reference Range</i>	<i>Differential Diagnoses</i>
Albumin	Biosynthetic capacity	3.5–5.5 g/dL	Hypoalbuminemia: cirrhosis, chronic hepatitis
Alanine transaminase (ALT)	Hepatocellular injury	7–40 U/L	Acute hepatitis, acetaminophen toxicity
Aspartate transaminase (AST)	Hepatocellular injury (nonspecific)	7–40 U/L	Acute hepatitis, acetaminophen toxicity
AST/ALT ratio	Alcoholic liver disease	0.8–1:1	Alcoholic liver disease
Alkaline phosphatase (ALP)	Cholestatic abnormality	M: 38–126, F: 70–230 U/L	Chronic cholestatic disease, cholelithiasis, neoplasm
Total bilirubin	Transport and metabolic capacity, prehepatic abnormality	0.2–1.0 mg/dL	Anemia, trauma
Conjugated (direct) bilirubin	Hepatobiliary disease	0–0.2 mg/dL	Chronic cholestatic disease, cholelithiasis, hepatocellular injury
Gamma glutamyl transpeptidase (GGT)	Cholestatic abnormality	M: 9–50, F: 8–40 U/L	With increased ALP: chronic cholestatic disease, cholelithiasis In isolation: alcohol abuse, chronic barbiturate use
Lactate dehydrogenase	Hepatic ischemia	90–190 U/L	

prehepatic, intrahepatic, or posthepatic in nature and can help determine if further workup is required.

Bilirubin is the by-product of red blood cell degradation and is insoluble in its free form. The liver is responsible for the conjugation of free bilirubin so that it can be secreted in bile and ultimately excreted in the feces. Increases in unconjugated bilirubin, or increases in

total bilirubin in the setting of normal levels of conjugated bilirubin, can be indicative of prehepatic conditions such as overproduction of bilirubin (hemolysis, anemia) or impaired uptake of bilirubin (decreased hepatic flow, Gilbert syndrome). Abnormal levels of conjugated bilirubin, however, are more indicative of hepatocellular dysfunction or posthepatic biliary obstruction.^{21,22}

Alkaline phosphatase (ALP) is an enzyme responsible for the hydrolysis of organic phosphate esters and is

Table 2. Differential Diagnosis of Acute Hepatitis^{1,2,44}

Hepatotropic viruses	HAV HBV HCV HDV HEV
Nonhepatotropic viruses	Herpes simplex virus (HSV) Cytomegalovirus (CMV) HIV Epstein-Barr virus (EBV) Varicella-zoster virus (VZV) Parvovirus Coxsackievirus Adenovirus
Noninfectious	Toxin- or drug-induced (including alcohol) Ischemic hepatitis/vascular disease Autoimmune hepatitis Wilson disease Acute biliary obstruction
Other infections	Legionella Leptospirosis Rocky mountain spotted fever Q fever Secondary syphilis Toxocariasis

Table 3. Differential Diagnosis of Chronic Hepatitis and Cirrhosis^{1,2,25,26}

Hepatotropic viruses	HBV HCV HDV HEV (rare)
Cholestatic diseases	Primary sclerosing cholangitis Primary biliary cirrhosis Vanishing bile duct syndrome AIDS cholangiopathy
Noninfectious	Alcoholic steatohepatitis Nonalcoholic steatohepatitis Autoimmune hepatitis Hereditary hemochromatosis Wilson disease Drug-induced chronic hepatitis α 1-antitrypsin deficiency Celiac disease Hyperthyroidism Sarcoidosis Granulomatous hepatitis Cryptogenic

Table 4. Characteristics of Viral Hepatitis^{2,5,25,26,27,44}

<i>Virus</i>	<i>HAV</i>	<i>HBV</i>	<i>HCV</i>	<i>HDV</i>	<i>HEV</i>
Viral genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Transmission	Fecal-oral	Parenteral Perinatal Sexual	Parenteral Sexual	Parenteral Perinatal Sexual	Fecal-oral
Incubation period (days)	15–45	30–180	15–150	30–180	14–60
Carrier state	No	Yes	Yes	Yes	Rare
Progression to chronicity	None	<5% in adult ⁵ Common before age 5	Common 75–85% ⁵	Common with superinfection of HBV; rare with HBV/HDV coinfection	Rare
Hepatocellular carcinoma	No	Yes	Yes	Yes	No
Vaccine availability	Yes	Yes	No	No	Not currently available in the United States
Prevention	Vaccine	Vaccine	Behavioral modification	HBV vaccine; behavioral modification	Vaccine
Treatment	Supportive	Interferon Pegylated IFN; nucleoside/ nucleotide inhibitor	Interferon Pegylated IFN; protease inhibitor	Interferon Pegylated interferon	Supportive

present in high concentrations in the liver and bone. ALP concentrations greater than 4 times the limit of normal are often seen in the setting of posthepatic cholestasis, although the magnitude of ALP elevation is not indicative of the degree of cholestasis. To confirm the elevated ALP is hepatobiliary in nature, it is important to compare other markers of biliary obstruction, such as gamma glutamyl transpeptidase (GGT).²³

Aminotransferases, aspartate transaminase (AST) and alanine transaminase (ALT), are enzymes normally present in the liver and other organs. Increased “liver enzyme” levels can be indicative of hepatocellular injury. AST is found in the liver, cardiac and skeletal muscle, kidney, and brain and is therefore nonspecific to hepatocellular injury. ALT, however, is found predominantly in the liver and is considered more specific to hepatocellular injury. Disproportionately elevated AST and ALT relative to ALP levels suggests hepatocellular injury rather than hepatobiliary dysfunction. AST/ALT levels can also be increased 3–8 times the normal limit in cholestasis, while levels greater than 25 times the limit of normal are highly specific to hepatocellular injury. AST levels are lower than ALT for most causes of hepatocellular injury. The exception to this rule is in the setting of alcoholic liver disease, which presents with an AST:ALT ratio greater than 2:1. Alcoholic liver disease often also presents with elevated GGT.²⁴

Albumin as well as coagulation factors are produced by hepatocytes, and therefore albumin concentrations

and INR are good indicators of the liver’s biosynthetic capacity. Because of albumin’s long elimination half-life, it is not a good indicator of acute hepatic disease.

Hepatitis. Hepatitis (inflammation of the liver), whether acute or chronic, is brought about by a wide variety of different causes (Tables 2 and 3). The condition is generally self-limiting but can progress to cirrhosis and hepatocellular carcinoma.

Viral Hepatitis. *Viral hepatitis* is a term referring to inflammation of the liver caused by viral infection. In the United States, viral hepatitis affects roughly 1–2% of the population and is most commonly caused by HAV, HBV, and HCV.²⁵ The diagnosis of viral hepatitis relies on clinical signs and symptoms, lab findings, serological and molecular assays, and, occasionally, liver biopsy.^{4,25} All types of viral hepatitis share similar clinical and laboratory features.

Acute infection may result in clinical presentations ranging from subclinical (asymptomatic) or mild symptoms to fulminant hepatic failure. Typical manifestations of acute hepatitis are flu-like symptoms, fatigue, nausea and vomiting, anorexia, and often fever and jaundice.⁴ Most cases resolve spontaneously, but some (HBV, HCV, HDV) can progress to chronic hepatitis that eventually leads to cirrhosis and hepatocellular carcinoma (see Table 4). Available testing includes immunoassays for viral-specific antigen and antibodies, nucleic acid-based tests such as real-time polymerase chain reaction to detect viral load, viral genotyping tests

Table 5. List of Common Hepatotoxic Drugs^{1,18,30,31,32,44}

<i>Drug</i>	<i>Mechanism of Injury</i>
Acetaminophen	Direct toxin
Isoniazid	Toxic and idiosyncratic
Valproic acid	Toxic and idiosyncratic
Amoxicillin-clavulanic acid	Idiosyncratic
Phenytoin	Idiosyncratic
Amiodarone	Toxic and idiosyncratic
Erythromycin	Cholestatic idiosyncratic
Oral contraceptives	Cholestatic reaction
Anabolic steroids	Cholestatic reaction
Trimethoprim-sulfamethoxazole	Idiosyncratic
Statins	Idiosyncratic and cholestatic
Highly active antiretroviral therapy (HAART) for HIV infection	Toxic, idiosyncratic, cholestatic

to determine HBV and HCV genotype to assess prognosis, and routine blood test (liver function test, complete blood cell count, and INR) to assess the extent of liver damage and monitor antiviral therapy.^{2,4,25} Four initial serological tests are generally used to diagnose acute viral hepatitis in symptomatic patients: HAV IgM, HBsAg, HBcAb IgM, and HCV antibody. Elevated ALT and AST levels generally provide the initial clues to viral hepatitis infection, although definitive diagnoses depend on serological testing.^{4,25}

According to Centers for Disease Control and Prevention statistics, an estimated 2 billion of the world's population has been infected with HBV, and more than 350 million have lifelong, chronic infections.²⁶ With HCV, however, an estimated 2.7–3.9 people in the United States are infected with the virus, and 75–85% of these individuals will go on to develop chronic infection and 60–70% will develop chronic liver disease.²⁷

Management of viral hepatitis varies depending on the type and severity of the disease. Acute viral hepatitis usually involves supportive care such as intravenous (IV) rehydration and does not require hospitalization unless clinical presentations suggest severe complications such as fulminant hepatic failure.^{2,25} Some of the admission criteria include altered mental status, marked coagulopathy (elevated INR), and significant electrolyte or fluid disturbance. The approach to managing chronic viral hepatitis includes minimizing future liver injury and monitoring for cirrhosis and hepatocellular carcinoma. Antiviral therapy may be beneficial for patients with chronic HBV and HCV patients.² Patients should be advised against alcohol consumption and potentially hepatotoxic medications (especially over-the-counter nonsteroidal anti-inflammatory drugs and acetamino-

phen, statins) and supplements. Liver transplant may be an option for people whose hepatitis progresses to end-stage liver failure and fails to respond to standard treatment.

Nonviral Hepatitis. Acute nonviral hepatitis is typically caused by the ingestion of toxin (primarily alcohol), chemicals, or drugs. Other causes of nonviral hepatitis include metabolic diseases (Wilson disease, hemochromatosis, steatosis), autoimmune disorders, and bacterial or parasitic infections. This section focuses on toxin and drug-induced hepatitis, which is the most common form of nonviral hepatitis.

Toxin- and Drug-Induced Hepatitis. Acute liver injury may follow ingestion, inhalation, and parenteral intake of pharmacologic agents and toxic substances. Drug-induced liver injury is the most common cause of acute liver failure. Hepatotoxic drugs can cause injury to the hepatocytes directly via free-radical production or idiosyncratically via activation of the immune system or apoptotic pathways.^{1,28,29} Alternatively, a drug or its metabolite can initiate damage to the bile duct system with accumulation of the bile acids in the liver, leading to necrosis of hepatocytes. Other mechanisms include cholestasis, inhibition of protein synthesis, blockage of lipid movement, and intracellular triglyceride accumulation.^{30–33} See Table 5 for a list of common hepatotoxic drugs and their mechanism of injury.

Liver injury is usually short onset (several hours to 24–48 hours).^{32,33} Agents producing hepatitis are generally toxins and poisons that are converted to toxic metabolites.^{33,34,36} Clinical manifestations are highly variable, ranging from asymptomatic with elevated liver enzymes to fulminant hepatic failure. Acetaminophen can cause fulminant hepatic failure after an overdose and can also induce chronic hepatic injury in analgesic doses to those who have chronic alcoholism and existing impaired liver function/liver damage.^{33,34} Ethanol has been shown to induce the CYP 2E1 isoenzyme, which is primarily responsible for production of the toxic metabolite of acetaminophen, N-acetyl-*p*-benzoquinone imine. Studies have shown up to a 22% increase in the toxic metabolite after administration of 500 mg acetaminophen in healthy adults. This result is likely potentiated in the setting of existing liver damage or impaired function.³³

A rare, but life-threatening form of hepatitis may reflect an immune-mediated hepatotoxicity caused by volatile anesthetics, notably the older agent, halothane. The most compelling evidence for an immune-mediated mechanism is the presence of circulating IgG antibodies in most patients with halothane hepatitis. Initial exposure to halothane produces trifluoroacetyl metabolites that change the structure of liver microsomal surface proteins and turns them from self to nonself.

Subsequent antigen-antibody reaction is responsible for liver injury (1 in 10,000 to 30,000 patients).^{3,34} Isoflurane and desflurane are also capable of producing trifluoroacetyl metabolites, but the incidence of drug-induced hepatitis after exposure to these drugs is less because of the decreased magnitude of metabolism compared with halothane.^{3,38}

Preoperative Considerations

Among the most common adverse events of surgery, including oral and maxillofacial surgery in the setting of hepatitis and liver disease, is excessive intraoperative and postoperative bleeding. Impaired synthesis of clotting factors and concomitant thrombocytopenia can result in severe bleeding after routine procedures despite usual hemostatic measures.³⁵ Screening for selected patients previously undiagnosed with liver disease, assessing the severity of known conditions, and using sound clinical judgment to postpone or cancel elective outpatient procedures in conjunction with a patient's primary care provider is vital to minimizing the risk of excessive bleeding in this patient population.

Patients with known histories of hepatitis, liver disease, jaundice, or suspected alcohol abuse may benefit from being referred to their physician to access hepatic function prior to elective surgery.³⁶ In addition, patients with a history of persistent bleeding or frequent bruising should also receive screening if clinically relevant. It is important to ascertain the depth and acuity of care and monitoring a patient is receiving in regard to his or her hepatic functional status. A collaborative effort with a patient's primary care physician or gastroenterologist can provide valuable information regarding liver function testing trends and presentation of symptoms to better assess hepatic function and determine the need for repeat laboratory assays or additional workup.

Patients should be assessed at the initial consultation for any signs and symptoms of acute liver disease, often presenting as a mild prodromal illness (low-grade fever, nausea, vomiting, fatigue, and/or abdominal pain) with or without subsequent jaundicing of the skin.² Patients exhibiting these signs and symptoms should be referred to their physician for serologic testing. Any patients with a diagnosis of acute hepatitis should have all elective surgeries postponed until current illness is resolved due to the increased perioperative and postoperative risks involved.¹⁹

Routine serologic testing of hepatic function in the absence of symptoms or relevant medical history is not currently recommended. Unexpected liver enzyme ab-

normalities occurred in as little as 0.3% of healthy individuals,³⁷ and mild abnormalities in liver enzyme tests in patients with no known liver disease have not been linked to increases in surgical morbidity and mortality.⁴¹

Asymptomatic patients with mild to moderate chronic hepatitis are at low risk for complications.⁴¹ Prothrombin time (INR) is one of the best indicators of hepatic synthetic function¹⁹ and, along with platelet count, is a valuable screening tool for possible hemostatic complications. A recent study of 1135 patients with end-stage liver disease undergoing tooth extraction revealed a bleeding risk comparable to healthy individuals if INR <2.5 and platelet count >40 × 10³/μL. Patients with coagulation tests beyond these benchmarks showed up to a 40% increase in bleeding risk requiring surgical intervention.⁴⁰

Perioperative Considerations

Liver disease is often associated with reduced portal venous flow and therefore decreases a patient's tolerance to acute changes in hepatic arterial perfusion.¹⁹ The effects of anesthetic medications on liver function vary with severity of liver disease and comorbid conditions and can have a profound effect on hepatic blood flow. Inhaled anesthetics and many IV anesthetic medications routinely cause hypotension and decreased cardiac output, thereby decreasing hepatic blood flow. Vasoactive medications should be readily available in the event of pharmacologically induced hypotension. Drugs with high extraction ratios are dependent on hepatic blood flow for metabolism and can see extensive changes in their pharmacokinetics in the setting of reduced hepatic perfusion. Drugs with lower extraction ratios, while not as sensitive to acute changes in hemodynamics, can be greatly affected by changes in protein binding and hepatocellular dysfunction. Hepatocytes are responsible for producing the primary plasma binding proteins, albumin, and α₁ acidic glycoprotein. Decreased protein binding leads to increased concentrations of unbound, active medications. Increased active medication concentrations, when coupled with diminished metabolic capacity, can lead to prolonged durations of action. The potential for oversedation and delayed awakening increases with infusions or repeat bolus doses.

Volatile Anesthetics. Halothane, although no longer commercially available in the United States, has a well-documented history of hepatotoxicity likely due to the active metabolite trifluoroacetylchloride (TFA).³⁸ Current volatile anesthetics, isoflurane and desflurane,

undergo significantly less metabolism to TFA and rarely, if ever, cause hepatic injury. Sevoflurane is metabolized to hexafluoroisopropanol, which has not been associated with hepatic injury.

Isoflurane and sevoflurane largely preserve hepatic blood flow at 1.0 MAC, while desflurane can reduce hepatic blood flow by up to 30% at 1.0 MAC.⁴³ Nitrous oxide at high concentrations may decrease hepatic blood flow secondary to a reduction in sympathetic innervation.

Sedative Hypnotics. IV anesthetics such as propofol, etomidate, and ketamine are usually well tolerated in clinical induction doses in patients with mild to moderate liver disease as long as cardiac output and blood pressure are maintained. Offset of action from bolus induction dosing is based more on redistribution than metabolism. Benzodiazepines have low hepatic extraction ratios, and elimination half-life and duration of action can expect to increase as liver disease progresses. Initial doses should be reduced and titrated to effect.^{3,19}

Opioids. Opioids, similar to benzodiazepines, exhibit increasing elimination half-lives and durations of action with decreasing liver function. Drug accumulation is more profound with continuous infusions or serial boluses. Dosing should be titrated to effect with longer dosing intervals,³⁹ and opioids with shorter durations of action should be considered to minimize risk of prolonged effects. Fentanyl is well tolerated in patients with moderate liver dysfunction with pharmacokinetics properties remaining largely intact.⁴⁴ Remifentanyl is the exception in this class of medications as it is rapidly hydrolyzed in blood by tissue esterases, and therefore is not affected by liver function.

Neuromuscular Blocking Agents

Succinylcholine is rapidly metabolized by plasma pseudocholinesterase. Pseudocholinesterase levels may be decreased by advanced liver disease leading to prolonged neuromuscular blockade. However, this increase in duration is rarely of clinical significance.⁴³ Pancuronium and vecuronium are both metabolized by the liver, while rocuronium is predominantly excreted in bile. In contrast, the neuromuscular blocking agent cisatracurium is metabolized by exhaustive methylation, otherwise known as the Hofman elimination process, and is independent of hepatic function. Advanced liver disease can have varying effects on the durations of action on many nondepolarizing neuromuscular blocking agents. There are no current guidelines for specific dose adjustments in the setting of liver disease, although close monitoring with nerve stimulation and titration to desired effect is recommended.^{3,19,43}

Postoperative Pain Control. Patients with mild to moderate hepatic dysfunctions typically tolerate oral analgesics similarly to healthy patients with the likelihood of adverse effects increasing as liver function decreases. An exact degree of compromised liver function at which drug selection and dosing must be considered is not currently available.

Acetaminophen is considered front-line treatment for mild to moderate pain despite the well-documented risk for acute hepatotoxicity. Hepatotoxicity can occur in the general population at doses approaching 10 g per day. Doses below 6 g per day are considered nontoxic unless continued for extended periods of time, leading to the current recommendations stating a 24-hour maximum dose of 4 g. Previous studies of patients with confirmed cirrhosis showed no evidence of hepatotoxicity or drug accumulation after administration of 4 g per day for up to 14 days.⁴⁴ The general recommendation for patients with known liver disease is to limit acetaminophen to 2 g per day. Special precaution should be taken with those patients who actively consume alcohol as this may induce the CYP-450 enzyme system and increase production of toxic metabolites.⁴⁴ This is especially of concern when the chronic alcoholic abstains from alcohol, as may occur perioperatively. Acetaminophen is contraindicated in those patients with severe alcoholic hepatitis or acute liver injury.

Nonsteroidal anti-inflammatory drugs have been associated with increased variceal bleeding, decreased renal function, and development of diuretic-resistant ascites in patients with advanced hepatic disease. Given the potential to worsen existing ascites, edema, and coagulopathies seen with decreased liver function, nonsteroidal anti-inflammatory drugs should be used with caution in those with moderate liver disease and are contraindicated in patients with advanced liver disease and cirrhosis.⁴⁴

Codeine, a prodrug extensively metabolized by CYP2D6 enzyme into morphine, requires the oxidative enzyme capacity of the liver to produce active metabolites. The effectiveness of codeine can be unpredictable in the setting of decreased liver function, and alternative methods of analgesia should be considered.⁴⁴

Both hydromorphone and oxycodone depend on hepatic metabolism and show increases in peak plasma concentration and duration of action in patients with even mild to moderate liver disease. As such, it is recommended that these medications be administered at decreased doses and increased intervals compared with healthy individuals.⁴⁴

CONCLUSION

A thorough preoperative evaluation is critical for patients with hepatic concerns. A proper anesthetic plan

will attempt to preserve hepatic blood flow, ensure adequate clotting function, and take into account the potentially impaired metabolism and hepatotoxicity of various anesthetic agents. Postoperative analgesics may also need to be modified because of metabolic concerns.

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CONTINUING EDUCATION QUESTIONS

1. The liver receives approximately which percentage of total oxygenated blood flow from the hepatic artery?
 - A. 15%
 - B. 25%
 - C. 35%
 - D. 45%
2. Which of the following drugs can circulate continuously between the liver and the small intestine by being secreted into bile and then being reabsorbed (enterohepatic circulation)?
 - A. Diazepam
 - B. Methohexital
 - C. Propofol
 - D. Sufentanil
3. Which of the following liver function tests is specific for hepatocellular injury such as acute hepatitis or acetaminophen toxicity?
 - A. Alanine transaminase (ALT)
 - B. Aspartate transaminase (AST)
 - C. Alkaline phosphatase (ALP)
 - D. Gamma glutamyl transpeptidase (GGT)
4. Of those infected with hepatitis C virus (HCV) in the United States, how many will develop chronic liver disease?
 - A. 10–20%
 - B. 20–30%
 - C. 40–50%
 - D. 60–70%