This article provides an overview of the physiological changes found in patients who have alcoholic liver disease. The pharmacological interactions and anesthetic considerations necessary for the management of these patients are explored.

In a report by the United States Congress on alcohol and health it has been determined that alcohol is the most abused drug in America today. This fact is not so unusual considering that it is the most widely available, easily produced and widely consumed beverage in the U.S. today. It is estimated that two out of every three people drink alcohol, with beer accounting for 49% of the ethanol consumed, and distilled spirits and wine accounting for the other 51%.

At least one-half of the automobile fatalities, fire-related deaths and drownings in the U.S. involve alcohol. It is also implicated in three-fourths of all stabbings, two out of three beatings and more than one-half of all shootings. The abuse of alcohol is a major health problem; and for nurse anesthetists, an awareness of this problem and its potential impact on their patients is essential.

After alcohol is consumed it is quickly absorbed in the stomach and the upper portion of the small intestines. Measurable amounts of alcohol are present in the bloodstream within 0.5 to 20 minutes. The greater the concentration of alcohol, the faster it is absorbed.

Clinical recognition

Central nervous system. The primary pharmacological actions of alcohol are manifested through the central nervous system. Ethanol can be described as a primary, functional, irregularly descending central nervous system (CNS) depressant. The first effects are prominent in the parts of the CNS involved with highly integrated functions such as the reticular activating system and the cortex. As the cortex loses its control from the effect of alcohol, the drinker experiences euphoria. As the cerebellum becomes depressed from its effects, a loss of motor coordination also occurs. When depression of the midbrain ensues, interference with spinal reflexes and temperature regulation becomes apparent, however, the vital centers of the medulla are bypassed. The progression from ataxia, stupor and coma can then occur, and, with further consumption the drinker is now essentially "anesthetized." Ultimately the medulla will succumb to effects of alcohol, and death can occur from a paralysis of the medullary centers.

Gastrointestinal tract. Alcohol can damage tissues both directly and indirectly through metabolic and nutritional effects. Even acute exposure causes mitochondrial changes, though these are more apparent in chronic consumption, particularly in the liver, the organ most exposed. These changes are characterized by mitochondrial swelling and distortion which may culminate in total disintegration with associated lipid deposition.

In the gastrointestinal (GI) tract, ethanol
stimulates the secretion of gastric juices by complex mechanisms that may involve psychic, neural and humoral factors. A significant delay in gastric emptying caused by alcoholic beverages is of major importance to the anesthetist. Reflux esophagitis, gastritis and acute or chronic pancreatitis are common in the chronic alcohol abuser. The pancreatitis seen in these patients may produce elevated serum and urinary amylase levels, hyperglycemia and glucosuria. Leukocytosis may also be present.

The heart. There is substantial evidence available associating the chronic use of alcohol and heart muscle failure. This "cardiomyopathy" is manifested by increases in heart rate, a decreased peripheral vascular resistance, decreased ventricular contractility and an increased cardiac output. Rhythm disturbances have also been associated with the use of alcohol. However, it has also been shown that abstinence can produce a marked degree of recovery even with advanced disease.

In recent literature observations have been made that small amounts of alcohol may have a protective effect in coronary artery disease. This is substantiated by evidence showing that alcohol raises high density lipoprotein cholesterol (HDL-C) levels in the blood. These studies have shown that elevated HDL-C is inversely related to coronary artery disease and may provide a protective role by aiding in removal of cholesterol from the body by retarding the formation of atherosclerotic plaques. However, while evidence for this is mounting, the hypothesis is not yet firmly established.

Ethanol, while having only mild cardiovascular effects when taken acutely, has been shown to enhance cutaneous blood flow. However, this effect also increases heat loss. The heat loss along with the impaired thermoregulatory center can lead to hypothermia.

It has been established that there is an association between alcohol use and an increase in blood pressure. The possibility exists that the association could be influenced in part by such elements as: (1) psychosocial stress as being an underlying factor for both hypertension and consumption of alcohol, (2) there being a common hereditary predilection for both alcohol use and hypertension, (3) environmental factors such as dietary habits, and (4) alcohol withdrawal leading to increases in blood pressure.

The lung. Many alcoholics smoke large numbers of cigarettes and have associated chronic obstructive lung disease. Pulmonary infections and pneumonia also tend to be common in these patients. Alcohol as a CNS depressant can depress the cough reflexes leading to aspiration. Tuberculosis is so common in alcoholic patients that yearly chest x-rays and skin tests should be routine in these patients.

Hematologic changes. The most common red cell abnormality seen in chronic alcoholics is a megaloblastic anemia caused by folate deficiency resulting from a poor diet. Thrombocytopenia has been observed frequently in alcoholic patients and is usually attributed to hypersplenism associated with cirrhosis. It may also be attributed to suppression of platelet production and reduction platelet survival by ethanol. Little is known about the effects of alcohol on leukocytes but there is evidence to suggest that alcohol decreases bone marrow reserve and leukocyte mobilization, leading to a greater susceptibility to infection.

Renal changes. Some diuretic effects of alcohol may be due to the increased fluid intake associated with drinking, however the major mechanism for diuresis is a suppression of the release of the antidiuretic hormone from the posterior pituitary by ethanol.

The liver. Alcohol has major effects on the liver where protein synthesis occurs. Clotting factors especially fibrinogen, prothrombin, and factors V, VII, IX, and X may be deficient. Pseudocholinesterase may also be deficient in alcoholics with severe liver disease. Albumin levels are typically lower in patients with alcoholic liver disease, leading to fewer sites for drug binding. An enhanced pharmacological effect of some drugs such as thiopental may be seen. In contrast, resistance to the effects of d-Tubocurarine (DTC) have been observed in these patients. This resistance may reflect increased binding of DTC to gamma globulins and/or an increased drug distribution volume due to circulatory changes associated with liver disease.

Recent data have demonstrated a decreased plasma clearance and increased distribution volume for pancuronium in patients with alcoholic liver disease. Given these observations, the initial dose of pancuronium may need to be increased to produce adequate surgical relaxation in a patient with a large distribution volume; however, the duration of relaxation may be prolonged due to a slowed plasma clearance.

Severe liver disease may also result in decreased microsomal enzyme activity and slowed drug metabolism. Increased plasma half-lives for diazepam, meperidine, lidocaine, and barbitur-
rates have been demonstrated in these patients. In contrast, the same patient may exhibit resistance to drugs metabolized in the liver reflecting microsomal enzyme induction from chronic alcohol ingestion.

The liver plays a major role in the metabolism of carbohydrates. A significant clinical effect of the ingestion of alcohol is hypoglycemia. This effect is due in part to the block of hepatic gluconeogenesis by alcohol which is a result of an NADH:NAD (nicotinamide adenine dinucleotide) ratio which decreases the conversion of pyruvate to oxaloacetate, a key step in gluconeogenesis.

Another problem encountered with these patients, dependent upon the extent of their disease, is the synthesis of bile salts or obstruction of their excretion into the bile duct. Intestinal absorption of vitamin K which requires bile salts, will decrease and therefore impair the synthesis of clotting factors.

Portal hypertension is a serious and late complication of alcoholic liver disease. Increased pressures in the portal system as well as clotting abnormalities can lead to severe and fatal hemorrhage. Congestive splenomegaly may occur, leading to sequestration of platelets. The presence of ascites can raise the diaphragm and decrease the lungs’ functional residual capacity.

Metabolism of alcohol. The first stage of alcohol metabolism takes place almost exclusively in the liver. This first step of converting alcohol to acetaldehyde is mediated by an enzyme found in the cytoplasm of the hepatocyte called alcohol dehydrogenase (ADH). This conversion requires NAD+ as a co-factor. The next step is oxidation of acetaldehyde mediated by aldehyde dehydrogenase which also requires NAD+ as a co-factor. The products are NADH and acetate. Acetate is metabolized in the liver and elsewhere via the citric acid cycle to CO₂ and NADH with production of adenosine triphosphate (ATP). The NADH is then oxidized by the mitochondrial respiratory chain to H₂O with production of additional ATP. Thus, it can be demonstrated that alcohol is converted to energy which has no other nutritional value to the body.

In addition to alcohol dehydrogenase, another enzyme system is thought to be responsible for metabolizing alcohol in the body. This system is referred to as the cytochrome P₄₅₀ system or a microsomal ethanol oxidizing system (MEDS) localized in the smooth endoplasmic reticulum of the hepatocyte.

As mentioned earlier, many alcoholics have accompanying hypertension. It has been found that acetaldehyde functions as a norepinephrine-releasing agent at adrenergic nerve terminals. It gets into the nerve terminal and displaces norepinephrine so that the observed hypertensive response is due to an increase in norepinephrine release. With large doses of acetaldehyde, the reflex effect on heart rate results in a bradycardia. This response masks a weaker direct vasodilation induced by acetaldehyde.

Anesthetic considerations

Three major complications may occur in a patient with liver disease: (1) encephalopathy, (2) ascites, and (3) gastrointestinal hemorrhage.

Encephalopathy is associated with a very high mortality. Mental obtundation, asterixis, and fetor hepaticus are present due to nitrogenous waste products accumulating in the bloodstream. Lactulose may be given to these patients to decrease the concentration of ammonia.

Ascites, commonly found in association with alcoholic liver disease, can elevate the diaphragm. This can, in turn, lead to a compression of the lungs with a concomitant decrease in the ventilation/perfusion ratio or hypoxemia. Ascites may also contribute to the anesthetic risk of these patients due to obstruction of venous return to the heart by way of the inferior vena cava; hypotension is the end result. Finally, ascites can increase anesthetic risk by altering the distribution and disposition of drugs, especially intravenous agents. The ascitic fluid significantly increases the volume of distribution of drugs used in anesthesia. Therefore the onset of action may be delayed and the duration of action may be prolonged since ascitic fluid is relatively isolated from circulation. Paracentesis is often performed 5-10 hours prior to surgery, when possible, to allow for lung re-expansion and cardiovascular stability.

Bleeding esophageal varices represent the most important of all anesthetic risk factors in these patients. The two major complications of this problem are aspiration of blood and hypovolemia. The problems encountered here cannot be resolved by removal of blood prior to surgery. This is because blood in the stomach usually contains massive clots that cannot be removed regardless of the size of gastric tube used. These tubes are also contraindicated because they may traumatize the varices within the esophagus, leading to further bleeding. A Senstaken™ tube used to tamponade bleeding varices does not always prevent pulmonary aspiration, since all too often such tubes are vomited up into the airway during induction.
It is recommended that in these patients an awake intubation be performed using a topical anesthesia applied to the mouth and at the base of tongue. Topical anesthesia should not be applied to the larynx or epiglottis. Anesthetizing these areas can lead to a block of reflexes and increase the chance of aspiration. The hypovolemia associated with bleeding varices should be treated as any other blood loss would be. The sympathetic nervous system must be kept intact and therefore spinal or epidural anesthesia is usually contraindicated in these patients. Stabilization of the patient’s pressure and pulse is the objective, not restoration to normal values.

The liver receives 25% of the cardiac output by way of the hepatic artery and portal vein. This blood flow is determined by the perfusion pressure (mean arterial pressure and splanchnic vascular resistance). The idea of autoregulation of hepatic blood flow is controversial, and if performed would probably be limited to the hepatic artery.

It is well known that anesthetics and surgical stimulation decrease hepatic blood flow. A potential adverse effect produced by decreased hepatic blood flow is decreasing oxygen delivery, resulting in hepatic hypoxia. The implications of the hypoxia may favor reductive (anaerobic) metabolism. However, to date, this has only been shown with halothane. Since the reductive metabolites of halothane are virtually hepatotoxic, maintenance of adequate hepatic blood flow is essential during an anesthetic. A reduction in hepatic blood flow may also reduce drug delivery to the liver resulting in increased drug effects. Therefore, requirements of drugs with high hepatic extraction ratios such as lidocaine or propranolol may be reduced.

There is evidence that alcohol abuse increases anesthetic requirements (MAC) for halothane and isoflurane. Cellular tolerance and increased microsomal enzyme induction are thought to be the mechanisms for this effect.

The use of muscle relaxants such as succinylcholine is acceptable in patients with alcoholic liver disease, but the dosage should be adjusted accordingly if the patient exhibits abnormal pseudocholinesterase activity. As stated earlier, resistance to the effects of curare may be seen as a result of increased d-Tubocurarine binding to gamma globulin and increased drug distribution volume. With the use of pancuronium the distribution may be increased and the plasma clearance decreased. Therefore the initial dose of pancuronium may need to be increased while the duration of paralysis may be prolonged due to a slowed plasma clearance. Atracurium may be used since its inactivation is accomplished through the Hoffman elimination and ester hydrolysis. The liver does not play a role in atracurium’s elimination.

In a study by Durant and associates, vecuronium produced a neuromuscular blockade similar to that of pancuronium whereby the absence of hepatic function did increase the time course in cats.

The use of most hypnotics, tranquilizers, local anesthetics and narcotics may also have an increased duration of action due to free intrinsic hepatic clearance.

A thorough preoperative visit is a must in the preparation of the anesthetic management of these patients. An adequate history of alcohol abuse may be difficult to obtain but a physical examination and laboratory tests may lead to the suspicion of alcohol abuse. The alcohol abuser can be categorized into two different classifications: (1) the acutely intoxicated patient in need of emergency surgery, or (2) the chronic alcohol abuser admitted for elective surgery.

In managing the patient who is acutely intoxicated, the anesthetic requirement may be decreased due to the additive depressant effect between alcohol and anesthetics. This patient also has less tolerance for stress, blood loss, brain hypoxia and hypothermia. This patient also may be more vulnerable to regurgitation of gastric contents due to a loss of lower esophageal sphincter tone. It is suggested that the alcoholic patient be treated with minimal anesthetics and a rapid sequence intubation should be performed only after the patient is fully awake and with all reflexes present.

In anesthetizing the chronic alcohol abuser the best choice of drugs is unknown. However, it must be remembered that a decreased hepatic blood flow and reduced perfusion of the liver can lead to postoperative hepatic dysfunction. With these considerations in mind it would seem prudent to select drugs that will not increase splanchnic vascular resistance and which undergo minimal biotransformation. Therefore nitrous oxide, enflurane and isoflurane are the preferred choices. In a study by McClain and Hug, the pharmacokinetics of fentanyl were not altered in surgical patients with alcoholic liver disease. Therefore, fentanyl may also be used in conjunction with nitrous oxide and oxygen. Another study by Pandele and associates, indicated that, despite its hepatic-dependent elimination, the risk of a prolonged effect following thiopental administration
appears unlikely. This is true even though a single induction dose may have enhanced pharmacologic activity due to the unbound fraction observed in patients with cirrhosis.

In administering fluids, an intravenous infusion of glucose is important not only to prevent hypoglycemia but to reduce the likelihood of deposition of potentially harmful lipid soluble metabolic products of volatile anesthetics in hepatocytes. Intraoperative maintenance of urine output, particularly in those patients with co-existing jaundice is important in reducing the chances of postoperative renal failure. Mannitol may be necessary to maintain a diuresis.24

An alcoholic patient undergoing surgery—whether it be emergency or elective—may exhibit withdrawal symptoms. Minor symptoms may occur 6-8 hours following abstinence from alcohol due to a compensatory neuronal excitability and catecholamine release. These include tremulousness, insomnia, and irritability. An autonomic nervous system imbalance may be reflected by hypertension, tachycardia, and cardiac dysrhythmias.24

A severe alcohol withdrawal syndrome occurs in approximately 5% of alcoholic patients. This represents a medical emergency and mortality may reach 15%. Severe alcohol withdrawal syndrome occurs usually between 48-72 hours after cessation of drinking.4 Signs and symptoms include tremulousness, disorientation and hallucinations, diaphoresis, hyperpyrexia, tachycardia, hypotension, and seizures. Treatment would include prompt sedation, vitamin replacement (especially thiamine) and correction of electrolyte imbalance. Propranolol may be effective in suppressing the sympathetic nervous system activity.

On occasion, profound hypotension may be observed in the chronic alcoholic patient who is receiving disulfiram.86 This may reflect depletion of the sympathetic nervous system neurotransmitter, as disulfiram inhibits the enzyme (dopamine beta-oxidase) necessary for the conversion of dopamine to norepinephrine.

Laboratory tests that may be of benefit to the anesthetist include the blood alcohol level (20-100 mg % = muscular incoordination, 300-400 mg % represent the early stages of anesthesia and over 400 mg % can prove fatal). It must be kept in mind that the liver function tests are rarely specific. In view of the liver's large reserve, a considerable amount of damage must be present before these tests are altered. Such tests include: (1) serum bilirubin (normal serum concentration 0.5-1.1 mg/100 ml); (2) Bromsulphalein® excretion (less than 5% retention 45 minutes after injection of 5 mg/kg dye); and (3) serum transaminases including SGOT, SGPT and LDH. These also may be elevated in other diseases, including instances of heart muscle damage, skeletal muscle damage and lung disease. Consequently, such tests' diagnostic value must be supplemented by other findings.

Alkaline phosphatase is another test used to help differentiate hepatocyte dysfunction from biliary obstruction. Skeletal muscle also contains large amounts of this enzyme. Hepatocytes are responsible for the synthesis of most clotting factors including prothrombin, fibrinogen, and factors VI, VII, IX, X. Factor VIII is the only procoagulant not synthesized in the liver. A decreased prothrombin production may reflect severe hepatocellular disease or impaired vitamin K absorption. Clotting abnormalities must be suspected in any patient with liver disease and may be measured by the prothrombin time, partial thromboplastin time and bleeding time.

Serum albumin is produced by the liver and decreased concentrations of this protein may reflect hepatocellular disease. Normal values are 3.5-5.5 gm/100 ml. Altered responses to drugs due to decreased drug binding occurs when the albumin concentration is less than 2.5 gm/100 ml.

**Summary**

Although there are not “hard fast” rules dictating the anesthetic management of the patient with alcoholic liver disease, knowledge of the physiological effects of alcohol and its resultant pharmacokinetic effects will help prepare the anesthetist for the alcohol abuser.

**REFERENCES**


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