

# The Role of Inhalational Anesthetic Drugs in Patients With Hepatic Dysfunction: A Review Article

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**Context:** Anesthetic drugs including halogenated anesthetics have been common for many years. Consequent hepatic injury has been reported in the literature. The mechanism of injury is immunoallergic. The first generation drug was halothane; it had the most toxicity when compared to other drugs. The issue becomes more important when the patient has an underlying hepatic dysfunction.

**Evidence Acquisition:** In this paper, reputable internet databases from 1957–2014 were analyzed and 43 original articles, 3 case reports, and 3 books were studied. A search was performed based on the following keywords: inhalational anesthesia, hepatic dysfunction, halogenated anesthetics, general anesthesia in patients with hepatic diseases, and side effects of halogenated anesthetics from reliable databases. Reputable websites like PubMed and Cochrane were used for the searches.

**Results:** In patients with hepatic dysfunction in addition to hepatic system and dramatic hemostatic dysfunction, dysfunction of cardiovascular, renal, respiratory, gastrointestinal, and central nervous systems may occur. On the other hand, exposure to inhalational halogenated anesthetics may have a negative impact (similar to hepatitis) on all aforementioned systems in addition to direct effects on liver function as well as the effects are more pronounced in halothane.

**Conclusions:** Despite the adverse effects of inhalational halogenated anesthetics (especially halothane) on hepatic patients when necessary. The effects on all systems must be considered and the necessary preparations must be provided. These drugs are still used, if necessary, due to the presence of positive effects and advantages mentioned in other studies as well as the adverse effects of other drugs.

**Keywords:** Inhalational Anesthetics; Hepatitis; Halothane

## 1. Context

### 1.1. Liver Dysfunction

The liver as an important organ in the human body, which is responsible for several functions as follows: metabolism of carbohydrates (to control and store glycogen), protein metabolism (metabolism of albumin and other proteins that play a pivotal role in the homeostasis of the body and the immune system), the metabolism of drugs and toxins (based on the activity of cytochrome enzyme), metabolism of fats and cholesterol, and many other biological processes some of which remain unknown (1, 2).

Given the enormous scope of activity of the liver and its anatomic position, it is one of the largest organs of the body and requires a larger and more complicated circulatory system as well as passes a large part of circulating blood through it (via the portal system and hepatic artery) and accounts for the extent of damages as much as it is effective on its activity (3).

Liver diseases are classified into acute and chronic types. The most common cause of the acute type worldwide are viral infections, alcohol, and drug toxicity, a common cause in developed countries, so much so that 70% of patients in the UK are related to acetaminophen toxicity (4–6). Viral hepatitis type(s) B and C, alcohol consumption, autoimmune hepatitis, and genetic disorders are among the major causes of chronic liver dysfunction (7).

Hepatic dysfunction can cause symptoms in the digestive system (impaired metabolism of carbohydrates, cholesterol, bile salts, esophageal varices, and gastrointestinal bleeding, among others), cardiovascular system (portal hypertension leading to right-side heart failure and in addition, ascites creating the third space ultimately, can severely reduce cardiac function and through different ways cause cardiomyopathy, blood pressure disorders especially hypotension are common in hepatic patients) (8, 9), respiratory system (ascites can be directly

and through pressure to diaphragm can cause alveolar dysfunction, portal hypertension can lead to portopulmonary hypertension, in these patients the risk of aspiration is high) (10), the hematology system (anemia due to gastrointestinal bleeding, hypersplenism and hemolysis, malnutrition, disorders of coagulation and homeostasis due to decreased production of critical proteins in the liver) (11, 12), adrenal system (pre-renal azotemia and severe electrolyte disorder due to ascites) (9, 10), and central nervous system (hepatic encephalopathy). Additionally, patients with liver dysfunction have a significant risk of morbidity and mortality after anesthesia and surgery (12).

Therefore, for general anesthesia in patients with hepatic dysfunction (especially chronic types) the aforementioned set of rules should be considered and treated as a complex system.

### 1.2. Halogenated Inhalational Anesthetics

Anesthesia is a modern intervention that was first introduced in 1846 (13-16). Ether and chloroform were used as anesthetic agents before the 1950s, despite awareness of numerous side effects. However, with the introduction of halothane (by the British chemist Dr. Charles Suckling), as the first halogenated anesthetic, at this point previous agents were quickly replaced with this class of drugs and now these drugs are used as the most common agents for general anesthesia (4, 17).

This class of drugs includes halothane, Enflurane, Isoflurane, Methoxyflurane, Desflurane, Sevoflurane, and many other isoforms. They enter the body through the respiratory system and excrete in the same way (over 80%). This is regarded as the ideal factor; however, due to the lipophilic properties of the drugs, some is absorbed and requires cellular metabolism (usually hepatic) for detoxification and excretion (18-20).

Enzymes that are involved in the metabolism of the absorbed portion of these drugs are accumulated mainly in the liver and less so in the kidney and other tissues. They act via two oxidative (by the enzyme cytochrome oxidase 2E1 and 2A6) and reductase (by the enzyme cytochrome 3A4) pathways causing Fluoroacetylate TFA and its components (a large part is changed in the oxidative pathway and through reaction with the enzyme 2E1) (17).

This agent and the decomposition resultant products bind to specific proteins of hepatic cells and give rise to a complex (Hoptun theory) and stimulate T-helper as well as via another pathway, T-Cytotoxic cells, and, eventually, leads to liver cell damage (19-22).

It is expected that autoimmune reactions are more severe in subsequent stimulations, which is consistent with the findings of researchers as well given the above immunoallergic process (4).

In addition to the damages that were discussed at length, the side effects of inhalational halogenated anesthetics are important and enormous including arrhythmia and bradycardia; attenuation myocardium and

reduced cardiac output; decreased mean arterial pressure; peripheral vasodilatation; decreased tidal volume, increased pulmonary arterial pressure, and reduced hypoxic ventilatory response; increased intracranial pressure; cerebral metabolic rate reduction; malignant hyperthermia; and renal failure (23-28).

## 2. Evidence Acquisition

This study was carried out as a review article using published research literature from 1957-2014 on various reputable websites (PubMed, Cochrane) with 45 original articles, three case reports, and three books.

The searches were conducted with the following keywords: inhalational anesthesia, liver dysfunction, halogenated anesthetics, general anesthesia in hepatic patients, side effects of halogenated anesthetics, and other similar words. Reputable websites like PubMed, Cochrane, and other databases were used to search. The references include articles on interventional research, case-control, descriptive, case reports, review articles, and abstracts. We excluded all unpublished articles (74 articles).

## 3. Results

In recent years, a significant increase occurred in the number of patients with hepatic dysfunction or end stage liver disease (ESLD) that require surgery. Anesthesiologists should have sufficient knowledge about the underlying disease and its impact on the performance of other organs, the risks of anesthesia, and anesthetic effect on the underlying disease as well as when evaluating these patients. In a preoperative evaluation of these patients, the possibility of hepatic encephalopathy, pleural effusion, cirrhotic cardiomyopathy, and coagulation disorders should be considered. Using the Child-Turcotte-Pugh classification and the model for end stage liver disease options can help anesthesiologists assess the risks of surgery. Enflurane and halothane are not recommended to maintain anesthesia in these patients and it is advised to use other inhalational anesthetic agents (26, 29).

Based on the literature, halothane and sevoflurane have been reported as volatiles with the most and least associated complications, respectively (13, 30).

In a survey conducted by NIH (National Institutes of Health) on 250000 subjects who have received halothane, the incidence of halothane-induced necrotizing hepatitis is 1 in 35000. However, there is another type of acute liver damage following halothane usage in the form of dose-independent severe necrotizing hepatitis whose incidence is 1 in 15000, which could reach to 1 in 1000 in the following exposures (31).

Common complications secondary to hepatic dysfunction in these patients include acute coagulopathy, encephalopathy, adult respiratory distress syndrome (ARDS), acute renal failure, and sepsis. The severity of malnutrition, managing patient ascites, encephalopathy level, prothrombin time, bilirubin, and albumin concen-

trations of serum are good predictors of postoperative complications and death. Other factors associated with adverse outcomes, including emergency surgery, old age, and underlying heart disease. The dominant manifestation of advanced liver disease is portal hypertension makes patients prone to bleeding, hepatorenal or hepatopulmonary syndrome, and uncontrolled ascites. Portal hypertension can be reduced by using embedded portosystemic or cutaneous shunt (32).

### 3.1. Hepatic System

In patients with liver dysfunction, with any underlying cause, tissue damage to hepatocytes results in releasing liver enzymes and increasing amino esterases, liver enzymes (AST, ALT, ALP), and bilirubin (in most cases of more severe injury). Research shows that after exposure to halogenated anesthetics, the AST and ALT levels increase 5-50 times. In the incidence of drug-induced hepatitis, by these drugs, bilirubin rises to the extent that is clinically diagnosed. In an extensive study on 86515 patients from 1959-1962, who were under general anesthesia with different anesthetics, acute liver failure was reported in 9 cases, of which 7 patients had received halothane and 4 were exposed more than once during 6 weeks. Further investigations showed that the prevalence to the exposure at the first time was 1 in 15000 and with repeated exposures was 1 in 1000 cases) (4, 5, 16, 33). Patient liver function plays an important role as the underlying factor. Therefore, the presence of an underlying problem such as viral hepatitis, cirrhosis, heart failure (reduced blood supply to the liver up to 50% in extreme cases), and most of all using drugs affecting the activity of hepatic cytochrome enzymes (such as barbiturates, benzodiazepines, and insecticides, among others, as stimulators and amiodarone, macrolides and inhibitors) can have a significant effect (16). Hepatitis and liver injury can have many different causes, including viral agents, hypoxia, autoimmunity, alcohol, fatty liver, and a wide variety of drugs. In fact, hepatitis induced by halogenated anesthetics is a small part of the total cases. Therefore, understanding its characteristics is important for differential diagnosis (4, 8, 16, 34-38).

### 3.2. Cardiovascular System

As noted, in patients with liver dysfunction (in advanced stages) followed by portal hypertension, ascites (and third space) production and hemodynamic impairment due to reduced albumin, anemia, renal dysfunction, cardiac contractility, and the blood pressure of the patient are reduced. In some studies, it was shown that there is a disorder of the heart conduction system and QT increases. In patients exposed to halogenated agents, especially Enflurane and halothane, myocardium is attenuated and cardiac output is reduced. In addition, in these patients bradycardia is a common finding. Isoflurane consumption leads to peripheral vascular resistance. In general,

studies show that in most cases the use of inhalational anesthetics reduced blood pressure (25, 34, 35, 39-42).

### 3.3. The Respiratory System

In patients with severe liver dysfunction, ascites, either directly or through pressure effects (indirect) may reduce the ability of alveolar ventilation. In patients who were exposed to halogenated anesthetic, tidal volume ventilation reduced and pulmonary arterial pressure increased. Additionally, in these patients respiratory control center response to hypoxia (for more ventilation) was suppressed (25, 39, 43-45)

### 3.4. Central Nervous System

Hepatic encephalopathy is one of the signs of severe liver dysfunction. Any kind of anesthesia will be accompanied by a decreased level (and content) of consciousness (though temporarily) for patients (46-48).

### 3.5. Hematologic System

In these patients, anemia is secondary to chronic blood loss from gastrointestinal tract, hemolysis in enlarged spleen, chronic disease, and malnutrition. Impaired production of coagulation factors, particularly factors related to vitamin K (factors II, VII, IX, and X) lead to an increase in prothrombin time and activated partial thromboplastin time. In these patients, the platelet dysfunction and thrombocytopenia are also common (12, 49).

### 3.6. Cross Reaction Between Volatile Halogenated Anesthetics

Cross-reaction between volatile halogenated anesthetics is well studied. Oxidative metabolism of isoflurane and enflurane through P450 cytochrome can lead to the production of immunoreactive protein metabolites causing hepatitis similar to the halothane-induced necrotizing hepatitis. Microsomal compounds have been detected in the rat liver following halothane, isoflurane, and enflurane administration for whose identification specific IgG antibodies against TFA hapten has been utilized. These compounds are more frequently found following halothane, enflurane, and isoflurane, respectively. Although these reactions are more frequent after multiple-encounters with these volatiles, cases following single administration have also been reported. TFA metabolites of these volatiles might bind with liver proteins acting as antigens. This theory has been hypothesized for explaining the idiosyncratic hepatotoxicity and cross-reaction of volatile agents. In some studies, microsomal antigenic compounds have been detected in the rat liver of those having received halothane or enflurane. However, these compounds were traced in extremely low concentrations in rats having received isoflurane or sesame oil. These findings suggest that isoflurane has low (Not null) immunologic properties. Some concerns have arisen fol-

lowing reports following isoflurane administration in those who had previously received halothane or enflurane (50).

#### 4. Conclusions

One of the factors that should be considered in anesthesia of patients with impaired liver function is to maintain the supply-demand balance of oxygen to the liver. Therefore, during anesthesia of the patients keeping pulmonary ventilation and cardiovascular function including cardiac output, the amount of blood, and perfusion adequate is necessary. In addition, hypotension must be prevented during anesthesia induction or due to excessive administration of inhalational anesthetics, or bleeding during surgery. In patients with advanced liver disease, auto-regulation to maintain proper blood flow is interrupted. Therefore, it should always be kept in mind that in these patients, halothane should not be used, as it caused a loss of blood flow to the liver and the supply of oxygen to the tissues of liver in which the result is an exacerbation of liver injury (51).

The same clinical signs and disorders in patients with ESLD on major physiological systems as described along with the side effects of halogenated inhalational anesthetics certainly will be aggravated and remedying the situation in patients is certainly more difficult than for normal patients.

Although evidence suggests that the use of halogenated anesthetics results in liver damage, the impact of a new generation drugs is less and in some cases it has been observed that for damages of ischemia/reperfusion, the liver and the kidney play a protective role (19-21).

Therefore, it is recommended to further study this with a broader perspective. We certainly can opt to use these drugs except for halothane that according to the evidence it does not seem reasonable to use it. This is more evident when the drawbacks of other anesthetics were also evaluated based on scientific and careful rationality.

#### Author's Contributions

Study concept and design: Seyed Moayed Alavian, Hassan Soleimanpour and Saeid Safari; Drafting of the manuscript: Saeid Safari, Farzad Rahmani and Hoorolnesa Ameli.

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