Halothane Induced Hepatitis (CME).

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Abstract:
Halothane is a halogenated inhalation anesthetic. Its three trace elements are fluoride, chloride and bromide. Fluoride is well known by biochemists to be an inhibitor of enzymes. Fluoride forms a strong hydrogen bond with the amide group, and thus has the potential to interfere with fundamental life-processes involving the shape and function of both proteins and nucleic acids. Patients with halothane hepatitis or severe hepatic damage due to other halogenated anesthetics produce antibodies against several liver trifluoroacetylated microsomal proteins. Other studies suggest that molecular mimicry of N6-trifluoroacetyl-L-lysine by lipoic acid, or the impairment thereof, might play a role in the susceptibility of individuals for the development of halothane hepatitis. The spectrum of disease differs from aminotransferase elevation either without symptoms or with mild, self-limited symptoms to severe hepatitis or acute liver failure. More investigation is needed to understand the mechanisms of halothane hepatotoxicity. The aim of our report is to prevent, recognize and manage the complications of hepatitis associated with halothane administration.

Keywords: Halothane, Hepatitis, Anesthetic cares
Learning Objectives:

By completing this medical continuing education course, participants should be able to:

1. Describe the symptoms, signs, susceptibility factors, and pathogenesis of halothane induced hepatitis.
2. Describe prevention strategies for halothane induced hepatitis
3. Identify the complications associated with halothane induced hepatitis and how to manage them.

Background:

Halogenated inhalational anesthetic agents- Halothane was introduced into use as an anesthetic in 1956, and replaced ether as the anesthetic of choice. Within two years, isolated case reports of severe hepatitis were being reported.(1, 2) In 1969, a review of 250,000 cases of halothane use revealed an incidence of fatal hepatic necrosis of about 1 in 35,000 exposures.(3) Whether, and the extent to which each haloalkaline anesthetic causes liver injury is related to the amount they are metabolized by hepatic CYP enzymes: 20% to 30% for halothane, greater than 30% for methoxyfluorane, 2% for enflurane, 1% for sevoflurane, and 0.2% or less for isoflurane and desflurane.(4) The halogenated inhalational anesthetics halothane, enflurane, isoflurane and desflurane can produce metabolic hepatocellular injury in humans to a variable extent. Plasma inorganic fluoride concentrations are regularly increased after sevoflurane.(5)

Risk factors for Halothane hepatitis

Older age (> 40 years), female gender, two or more exposures, familial predisposition, obesity, induction of cytochrome P4502E1 (CYP2E1) by phenobarbital, alcohol, and isoniazid are all risk factors for halothane hepatitis.(6,7) Preexisting liver disease itself is not a risk factor for halothane hepatitis.

Mechanisms of hepatotoxicity

Mechanisms of halothane toxicity are idiosyncratic reaction, immunoallergic type, and the protein adducts formed in the initial toxic reaction provide the hapten for the formation of antibodies which augments damage on re-exposure. Covalent binding of halothane metabolites to tissue proteins has been well described. Up to one-third of inhaled halothane may be oxidatively metabolized by cytochrome P450 2E1 and 2A6. Trifluoroacetyl chloride, which has a strong ability to acetylate liver proteins, is formed during the synthesis of trifluoroacetic acid. Only a small amount (~%1) of halothane is metabolized through the reductive pathway by cytochrome P450 2A6 and 3A4. This pathway is favored under hypoxic conditions, resulting in the release of bromide and fluoride ions and in the formation of other volatile organic metabolites.(8) Several drugs or chemicals were shown to induce hepatitis with autoimmune involvement. Adduct formation of an activated metabolite is believed to act as a trigger and to induce a specific immune response.(9) Two types of halothane mediated hepatotoxicity have been defined. The first type, type I, is a mild,
self-limited postoperative hepatotoxicity, with a mild form of hepatocellular injury that can be observed in about 20% of halothane –treated patients. The mild hepatic injury is assumed to result from the direct action of halothane on the liver cells. Two clinically detectable factors appear to contribute to the mild form of hepatic injury. The first is a transient elevation of liver enzymes and the second is alteration of cellular integrity, which can be detected by electron microscopy. Lesions result from intracellular degradation of halothane via its anaerobic and aerobic pathways in combination with local hypoxia caused by an alteration of the hepatic oxygen demand and supply relationship. The second type of halothane-mediated hepatotoxicity is type II-halothane hepatitis. The incidence of this type of hepatotoxicity after halothane administration is one case per 10000-30000 adult patients. The probable mechanism is most likely an immune-mediated hepatotoxicity; antibodies are against modified liver microsomal proteins on hepatocyte surfaces. There is strong evidence that the fulminating form of halothane hepatitis is mediated by the patient’s own immune system. Besides signs of mild cellular injury, tissue acetylation is usually found due to the generation of reactive intermediates from halothane metabolism. The acetylation of intacellular proteins is considered the first step in the pathogenesis of the severe type of hepatic injury. The second step then involves the formation of antibodies directed towards these acetylated neo-antigens. The consequence of the immune response with regard to hepatic injury is severe and sometimes even fatal. Cytochrome P450 2E1 (CYP2E1) is a major catalyst in the formation of trifluoroacetylated proteins, which have been implicated as target antigens in the mechanism of halothane hepatitis. Patients with halothane hepatitis or severe hepatic damage to other halogenated anesthetics produce metabolites against several liver trifluoroacetylated microsomal proteins.

Reducive pathway: Halothane has the potential to decrease both portal venous and hepatic arterial blood flow in proportion to the degree of anesthesia. Clinical manifestations, course and outcome: Halothane is associated with two clinical patterns of hepatotoxicity. Type 1: Serum aminotransferase elevation either without symptoms or with mild, self-limited symptoms; and Type 2: Severe hepatitis or acute liver failure. Symptoms generally occur about two days to three weeks after exposure. Patients present with a fever (75 percent) and complain of anorexia, nausea, myalgias, arthralgias, and rash. Eosinophilia occurs in approximately 40 percent of cases, suggesting that toxicity is immunooallergic. Tender hepatomegaly and jaundice are common. Some patients present with acute liver failure, markedly elevated serum aminotransferases and prothrombin time, and possibly hepatic encephalopathy.

Surgery is a stressful condition for the liver. Approximately 25% to 75% of patients undergoing surgery experience postoperative hepatic dysfunction, ranging from mild elevations in liver tests to hepatic failure. Halothane hepatitis must be considered whenever postopera-
Adverse reverse prognostic factors include: serum bilirubin >20 mg/dL, coagulopathy, older age (> 40 years), obesity, and short duration interval to onset of jaundice.\(^{(6, 7)}\)

**Example of supposed to halothane induced hepatitis.**

The first three cases occurred in Iranian patients and the rest in other countries.

Case 1: A 38 year old woman with a history of hypothyroidism, abnormal uterine bleeding and iron deficiency anemia underwent surgery. One month later she was admitted to our hospital because of fever (38 centigrade), nausea, vomiting, and progressive jaundice.

Case 2: A 41 year old woman underwent uterine myomectomy. She had a history of surgery 10 years before. She had postoperative unexplained hepatitis after each surgery. Viral hepatitis A antibody, hepatitis B surface antigen, hepatitis E virus antibody, and also markers of autoimmune hepatitis were negative. There was no evidence of other causes of postsurgery hepatitis. Anesthesia in both two cases had been performed with halothane. Both patients received supportive cares for hepatic insufficiency.

Case 3: A 44 year old woman with a history of unexplained jaundice following her previous surgery was admitted for fulminant hepatitis and encephalopathy five days after surgery. There was no evidence of viral or metabolic markers of hepatitis. Liver biopsy was not performed because of coagulopathy. She did not respond to supportive therapy.

These three Iranian patients presented with approval of the ethical committee of the local hospital.

A study \(^{(23)}\), presented a case report wherein a person having undergone six operations under general anesthesia with halothane during his stay in the hospital died due to fulminant hepatitis, hepatic encephalopathy and acute renal failure.

In a study \(^{(24)}\), halothane was mentioned as a rare cause of hepatitis and the authors warned that it may be overlooked when evaluating a patient with sudden onset jaundice. This article includes reports from a 34-year-old nurse who presented to the liver clinic with sudden onset non-pruritic jaundice. Viral and collagen serological tests were all normal, malaria and sickling tests were negative, but transaminases were elevated. She reported inadvertent exposure to halothane in the surgical theatre where she works.

In another study \(^{(25)}\), it was stated that the adverse effects of halothane (Fluothane) are generally moderate with the exception of hepatitis that is usually severe and sometimes fatal. They analyzed eight cases of halothane-induced hepatitis: the injury was cytolytic in six cases and cholestatic in the two others. It was
fulminant in three cases of which two lead to death. These injuries are usually graves, with an unforeseeable appearance and a hypothetical mechanism.

Another study (26) presented a 68-year-old man who developed fulminant and fatal hepatic necrosis two days after surgery was performed under isoflurane anesthesia. Postmortem examination demonstrated centrilobular necrosis of the liver.

A case of acute cholestatic hepatitis following exposure to the inhalational anesthetic isoflurane three weeks following surgery under general anesthesia was reported. (27) There was no evidence for viral, autoimmune, or metabolic causes of hepatitis. Another study (28) stated that environmental exposure of anesthesia personnel to certain inhaled anesthetics can induce the formation of autoantibodies that are associated with anesthetic hepatitis. However, the majority of these individuals do not develop hepatitis, suggesting that autoantibodies may not have a pathological role in volatile anesthetic-induced hepatitis.

Differential diagnosis

Causes of postoperative hepatic dysfunction are as followed (29):

- Hepatocellular injury (Serum ALT elevation, with or without hyperbilirubinemia):
  - Inhalational anesthesia
  - Ischemic hepatitis
  - Acute post-transfusion hepatitis
  - Unrecognized liver disease, nonalcoholic steatohepatitis (NASH), hepatitis C,
  - Drugs
- Hepatic allograft rejection
- Hepatic artery thrombosis
- Other diagnosis
- Cholestatic jaundice (Elevated serum alkaline phophatase, with or without ALT, direct hyperbilirubinemia):
  - Benign postoperative cholestasis
  - Sepsis
  - Cardiac bypass of long duration
  - Acalculous cholecystitis
  - Common bile duct obstruction/ injury/microlithiasis
  - Hemobilia
  - Prolonged total parenteral nutrition
  - Drugs
  - Indirect hyperbilirubinemia (Elevated serum alkaline phophatase, normal ALT):
    - Resorbing hematoma
    - Hemolytic anemia
    - G6PD deficient
    - Gilbert s syndrome
    - Multiple transfusions

Prevention

The most effective preventive tool is to avoid the use of halothane in adults. This is particularly true in patients with prior exposure to the drug since the overall incidence of hepatic necrosis rises to as high as 1:1,400 after multiple exposures. (30)

Prevention of halothane hepatitis may be difficult, and the only clear way of reducing the incidence is to avoid re-exposure to halothane in those patients who have had a previous adverse reaction to the drug, demonstrated either by unexplained pyrexia or by jaundice. Halothane should also be avoided in those patients where there is a family history of sensiti-
zation to the drug. In such cases, halothane-free equipment should be used, and exposure to other volatile non-halogenated anaesthetics should be avoided.\(^6\) Recent exposure is the most important risk factor for type II fulminant hepatotoxicity. In patients with a history of jaundice and fever following previous halothane exposure, all volatile anesthetics (halothane, enflurane, isoflurane, sevoflurane, desflurane) should be used with caution. Patients with unexplained elevations of liver functions should not undergo anesthesia until a diagnosis has been confirmed. Ether, nitrous oxide, or cyclopropane are devoid of significant hepatotoxic potential, owing to their lack of halogen moieties.\(^{31}\)

**Treatment**

Because halothane hepatitis is a diagnosis of exclusion, ruling out other causes is essential. The treatment of halothane hepatitis is supportive. Hospitalized patients may be discharged after significant improvement of symptoms, normalization of prothrombin time, and after decreases of serum aminotransferase and bilirubin values are observed. In acute liver failure, the case fatality rate is about 50 percent, but can be as high as 80 percent in those who develop hepatic encephalopathy.\(^{32, 33}\) Severe, progressive cases may require emergent orthotopic liver transplantation.

Management of fulminant hepatic failure:

Fulminant hepatic failure (FHF) refers to the rapid development of severe acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver or had well compensated liver disease. Managing patients with FHF requires an understanding of all complications that can be present, including encephalopathy, cerebral edema, sepsis, renal failure, circulatory dysfunction, coagulopathy, gastrointestinal bleeding, and metabolic derangements. Because of the complexities involved, patients with FHF should be managed in an intensive care unit in centers with an active liver transplant program.\(^{34}\) Patients admitted to hospitals without a transplant program should be transferred as soon as possible since it can be hazardous to transfer patients later in the disease course because of severe coagulopathy and increased intracranial pressure.\(^{35}\)

Hepatic encephalopathy is a major complication of FHF, although the precise mechanism remains unclear.\(^{36}\) Cerebral edema develops in 75 to 80 percent of patients with grade IV encephalopathy.\(^{35}\) The classic signs of elevated ICP include systemic hypertension, bradycardia, and irregular respirations (referred to as Cushing’s triad). Neurologic manifestations may include increased muscle tone, hyperreflexia, and altered pupillary responses. However, early in the course of FHF, these signs and symptoms may be absent or difficult to detect.\(^{35}\)

Three parameters should be followed during intracranial pressure monitoring: intracranial pressure, cerebral perfusion pressure (CPP), and cerebral oxygen consumption. Cerebral perfusion pressure is the difference between mean arterial pressure and intracranial pressure. Cerebral oxygen consumption is a function of
cerebral blood flow and the oxygen gradient between arterial and jugular venous blood. The goals of therapy are to maintain the ICP below 20 mmHg and the CPP above 50 mmHg.\(^{37}\)

These goals can be accomplished using a combination of interventions: Patients should be placed in an environment with minimal sensory stimulation since stimulation can raise ICP. For the same reasons, attempts should be made to keep the patient from becoming agitated. Placement of a nasogastric tube can cause gagging and thus their use should be minimized. Similarly, endotracheal suction should be minimized. Overhydration can elevate ICP. Thus, the fluid status of patients with FHF should be closely monitored, which often requires placement of a pulmonary artery catheter. The head of the patient's bed should be elevated to 30 degrees.

However, patients with FHF commonly have compromised renal function and oliguria. In this setting, fluid should be removed via ultrafiltration or other continuous venous hemofiltration methods with a goal to remove three to five times the fluid volume of the infused mannitol.\(^{38, 39}\) If no response or relapse is noted after mannitol administration, pentobarbital coma should be induced using a bolus of 3 to 5 mg/kg intravenously. Dexamethasone has not proven to be effective in the treatment of cerebral edema caused by FHF and should not be administered.\(^{40, 41}\) Acute renal failure complicates FHF in approximately 30 to 50 percent of patients.\(^{38, 39}\) Continuous renal replacement therapies, such as continuous venovenous hemofiltration, are well tolerated and may be indicated for fluid control even before conventional indications for hemodialysis become apparent.\(^{38}\) Patients with FHF are at an increased risk of infection and sepsis from a wide variety of causes. Common metabolic disturbances in FHF include acid-base and electrolyte disorders, hypophosphatemia, and hypoglycemia. Among the acid-base disorders, alkalosis is more frequently encountered than acidosis in the early stages of FHF, and is frequently a mixed respiratory and metabolic abnormality.\(^{42}\) The most common electrolyte disturbances are hypokalemia, hyponatremia, and hypophosphatemia. Hypoglycemia, which occurs in more than 40 percent of the patients with FHF, results from both depletion of hepatic glycogen stores and impaired gluconeogenesis.\(^{43}\) The plasma glucose concentration should be monitored closely and hypertonic glucose solutions should be administered as needed to keep the values above 65 mg/dL.\(^{39}\)

Nutrition is a vital component in the treatment of FHF. In patients with grade I or II encephalopathy, oral or enteral feeding with a low protein diet is usually sufficient to meet metabolic requirements.\(^{39}\) Placement of a nasogastric tube can increase intracranial pressure (because of gagging) and thus should generally be performed only in patients who are intubated and sedated. In patients with advanced encephalopathy, parenteral nutrition should be considered early to prevent catabolism of body stores of proteins. Branched chain amino acids have been advocated as a source of protein, but compared with other protein preparations, superior efficacy has not
been clearly established in clinical trials.\(^{(42)}\) Patients with FHF can develop severe coagulopathy and bleed due to the diminished capacity of the failing liver to synthesize coagulation factors. Prophylactic administration of fresh frozen plasma is usually not recommended since it has not been proven to influence mortality.\(^{(42)}\) It can interfere with assessments of liver function, and it may worsen cerebral edema. Fresh frozen plasma (FFP) is indicated only in the setting of active hemorrhage or prior to invasive procedures, such as placement of intracranial pressure monitors. In extreme settings, correction of the coagulopathy is necessary but cannot be achieved adequately with FFP, particularly in patients who are severely volume overloaded.

Pulmonary edema and pulmonary infections are encountered in approximately 30 percent of patients with FHF.\(^{(39)}\) Mechanical ventilation may be required to ensure adequate oxygenation. However, extreme caution must be used with positive end-expiratory pressure in patients with FHF since PEEP can worsen cerebral edema.\(^{(39)}\)

Liver transplantation remains the backbone of treatment of FHF. However, depending upon the etiology of FHF, specific therapies may be applicable. Auxiliary liver transplantation involves placement of a graft adjacent to the patient’s native liver (auxiliary heterotopic liver transplantation) or in the hepatic bed after a portion of the native liver (auxiliary orthotopic liver transplantation) has been removed. A potential advantage is that this procedure may support the patient while the native liver regenerates, obviating the need for chronic immunosuppression.\(^{(37)}\) Consult with a hepatologist, a critical care specialist, and with organ transplant team, if liver failure is imminent.

**Conclusion:**

Pre- and post-operative hepatic evaluation helps in selecting the appropriate anesthetic drug and adjusting the dosage with regard to patient’s medical condition, body weight, drug interactions, inhaled amount of oxygen and other parameters.

**Pre-operative hepatic evaluation**

1. Interviewing and examining the patient
2. Discuss previous anesthesia, number of anesthesia, list of anesthetic drugs that have used, any drug reaction and/or post-operative fever or jaundice in patient and/or her family.
3. Regard history of hepatitis, stigmata of chronic liver disease, prolonged or unusual bleeding, hematemesis, drug history and dosage, habits, alcohol intake, obesity, other associated background disease
4. Risk assessment and liver function tests performed and conducted in the patient’s record if necessary, obtaining or reviewing tests and consultations.
5. Informed consent should be obtained that includes the indications for use and the possible risks of hepatotoxicity.

**Post-operative hepatic evaluation**
1- Interviewing and examining the patients again in the first week and first month post-surgery; order liver function tests.

2- Remind the patient call whenever they experience the following symptoms: flu-like symptoms, high fever day 3-14 (onset more rapid if recent exposure to halothane), joint pain, fatigue, nausea and vomiting, decreased appetite, rash, dark urine, arthralgia, or headache. It seems reasonable to re-estimate halothane hepatotoxicity, other side effects of halogenated anesthetics, relation of halothane hepatotoxicity with any special genetic predisposition, CYP polymorphism and genetic variation. The hepatotoxic potential of halothane depends on the susceptibility of the patient and the factors that promote the production of hepatotoxic or immunogenic metabolites. The routine use of halothane for general anesthesia in adults is difficult to justify. General anesthesia is not contraindicated for future surgery because it can be provided without the use of volatile agents.

Post-test

1- Which one is not a risk factor for Halothane hepatitis:
   a- Obesity
   b- Two or more exposures
   c- Induction of CYP2E1 by Phenobarbital, alcohol, isoniazid
   d- Older age (>40 years)
   e- Phenytoin
2- A 28 year-old pregnant (first-trimester) woman after therapeutic abortion that was her first operation, consulted for nausea and jaundice, ALT of 1400 U/L, serum bilirubin of 9 mg/dL. IgG level, hemoglobin, platelet count, and albumin are normal as is prothrombin time and alkaline phosphatase. An ANA is negative. Serologic studies fail to reveal markers of active HBV or HCV infection, but positive IgM anti-HAV. She has a history of returning from visit to Syria six weeks ago. She reports two weeks ago had mild symptoms similar to these with bilirubin of 7 mg/dL; serum ALT is 420 U/L that subsided gradually. The most likely diagnosis at this point is:
   a- Fatty liver of pregnancy
   b- Autoimmune hepatitis
   c- HELLP syndrome
   d- Anesthetic-induced hepatitis
   e- Relapsing hepatitis A
3- Which one is not an adverse reverse prognostic finding in Halothane hepatitis:
   a- Bilirubin >20 mg/dL
   b- Coagulopathy
   c- Obesity
   d- Childhood
4- A running athlete admitted in emergency room for foot sprain during a competition.
   His lab data show: mild metabolic asodosis, serum creatin 1.6 mg/dl, total bilirubin 1.4 mg/dl, direct 0.3 mg/dl, serum alkaline phosphatase 84 U/L, AST 1570 U/L, ALT 128 U/L, serum creatine kinase:10,000 IU/L, serum potassium 5.1, serum calcium 7.5. What is the most likely diagnosis?
   a- Anesthetic-induced hepatitis
   b- Rhabdomyolysis
   c- Ischemic hepatitis
   d- Acetaminophen overdose
5- A 46-year old woman with elevated indirect bilirubin level and ALT 1.5 times the upper limit of normal with normal complete blood count and differential,
and no rash two days after hysterec-
tomy. The diagnosis is most likely:
a- Analgesic-induced hepatotoxicity
b- Anesthetic-induced hepatotoxicity
c- Hemolytic anemia
d- Postoperative cholestasis

6- In which one emergent referral to a
liver transplant center is not part of
management for a case of acute liver
failure and encephalopathy:
a- Newly diagnosed decompensated
autoimmune hepatitis
b- Acute liver failure and encephalopathy
due to acetaminophen overdose
c- Acute alcoholic hepatitis in current al-
cohol abuser
d- Halothane hepatitis

7- An addicted subject 2 months after
hernia surgery admitted for liver function
test abnormality. Acute intoxication with
which one is accompanied by hepatotox-
icity:
a- Cocaine
b- Ecstasy (3,4-
methylenedioxyamphetamine)
c- Phencyclidine and/or methamphet-
aire

d- Either of a,b,c
e- All inhalational anesthetic drugs

8- A patient with shock and abdominal
pain referred to surgery for repair of im-
pending aortic dissection. Following sur-
gery consulted for abnormal liver func-
tion tests: Aminotranferases level greater
than 1500 U/L. Which one is the most
likely cause of abnormal LFT:
a- Blood transfusion reaction
b- Autoimmune hepatitis
c- Ischemic hepatitis
d- Pylephlebitis due to bowel ischemia
during surgery

9- A 40-year factory worker admitted
with nausea, vomiting, diarrhea, direct
bilirubinemia, and transaminases 20
times the normal range, and renal fail-
ure. Which question help to detect the
most possible cause:
a- Amanita phylloides
b- Carbon tetrachloride
c- Phosphores
d- Exposure to vinyl chloride monomer of
plastics manufacture
e- History of recent surgery

10- Which one of these haloalkaline an-
esthetics is most likely to produce hepa-
totoxicity:
a- Desflurane
b- Enflurane
c- Methoxyflurane
d- Isoflurane

d- Either of a,b,c
e- All inhalational anesthetic drugs
f- A patient with shock and abdominal
pain referred to surgery for repair of im-
pending aortic dissection. Following sur-
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during surgery

Correct Answers:
1 E 5 D 9 C
2 E 6 C 10 C
3 D 7 D 11 A
4 B 8 C
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