Hepatitis, Halothane

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Risk

- Multiple exposures to halothane is the most important risk factor.
- Prior Hx of jaundice or fever after anesthesia.
- Females more susceptible.
- Obesity an important factor.
- Age:
  - Halothane hepatitis is rare in pts <10 y old (3% of all cases).
  - Pts <30 y of age make up about 10% of all cases.
  - Most cases occur in pts >40 y.
  - In older pts, the disease is more devastating.
- Genetics: There is a strong family linkage associated with halothane hepatitis.

Perioperative Risks

- Type or duration or extent of surgery is not a risk factor.
- Hx of non-halothane-related liver disease is also not a risk factor.

Worry About

- Concerns arise with the induction of cytochrome P450 2E1 enzyme by alcohol, barbiturates, or isoniazid. Hepatitis is more severe if CYP450 2E1 was previously induced by other medications/substances.

Overview

- Estimated incidence:
  - First exposure: 0.3 -1.5:10,000
  - With multiple exposures: 10-15:10,000
  - F:M ratio: 2:1
  - Latency period before clinical symptoms
  - After first exposure: ~6 d, with overt jaundice in ~11 d
  - After multiple exposures: ~3 d, with overt jaundice in ~6 d
- Presenting symptoms:
  - Fever: 75%
  - Leukocytosis, eosinophilia: 20–60%
  - Myalgias: 20%
  - Rash: 10%
  - Jaundice: 25%
  - Ascites, coagulopathy, GI hemorrhage: 20–30%
- Liver enzyme markers:
  - Alanine aminotransferase: 25–250× upper limit of normal
  - Aspartate aminotransferase: 25–250× upper limit of normal
  - Alkaline phosphatase: 1–3× upper limit of normal
- Histologic liver findings:
  - Zone 3 necrosis (massive in 30% of cases, submissive in 70% of cases)
  - Inflammation, granulomas, eosinophilic infiltrates
- Clinical course:
  - Mortality rate in preliver transplant era is as high as 80% if encephalopathy is present.
  - Recovery becomes evident as symptoms resolve over 5–14 d, with full recovery taking weeks to months.

Etiology

- Two distinct types of hepatitis are associated with halothane exposure:
  - Halothane hepatotoxicity (type I):
    - Subclinical disease with mild elevation of liver enzymes, no jaundice
    - Mild pattern of injury characterized by nausea, lethargy, and fever
    - Caused by the anaerobic, reductive metabolism of halothane
    - May occur in up to 20–30% of pts receiving halothane
    - Transaminases remain elevated for 1–2 wk postexposure, then resolve spontaneously.
    - Nonimmune reaction
    - Hepatic hypoxia may play a role.
  - Halothane hepatitis (type II):
    - Fulminant liver failure with massive zone 3 liver necrosis
    - Caused by oxidative metabolism of halothane
    - TFA intermediates conjugate liver proteins.
    - Strong evidence for immune reaction:
    - In susceptible individuals, antibodies to the metabolite-liver protein complex are formed causing an immune response.
    - Incidence is 10 times higher in second exposure cases, and severity of illness greater if second exposure follows soon after first exposure.

Drug Class/Metabolism

- Halothane: A nonvolatile anesthetic; a halogenated hydrocarbon
  - Molecular formula C2HBrClF3
  - Systematic (IUPAC) name: 1-bromo-1-chloro-1,1,1-trifluoroethane
  - Metabolized in the liver through both oxidative and reductive pathways
- Comparison of oxidative metabolism of volatile anesthetics:
  - Halothane: 20%
  - Enflurane: 2%
  - Isoflurane: 0.2%
  - Desflurane: 0.02%
- There are a few case reports of type II hepatitis associated with isoflurane and desflurane in the world literature.

Assessment Points

System	Assessment by Hx	PE	Test
GI	N/V, malaise	Jaundice (about 6 d after second exposure, longer if first exposure)	Eosinophilia, leukocytosis Elevated liver enzymes: 1. AST 2. ALT (25–250× upper limit of normal) 3. Alk phos (1–3× upper limit of normal)Liver biopsy: Zone 3 centrilobular necrosis

Key References: Habibollahi P, Mahboobi N, Esmaeili S, et al.: Halothane-induced hepatitis: a forgotten issue in developing countries, *Hepat Mon* 11(1):3–6, 2011; Lewis JH: Liver disease caused by anesthetics, toxins, and herbal preparations. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger & Fordtran's gastrointestinal and liver disease,* ed 9, Philadelphia, PA, 2010, Elsevier, pp 1447–1460.

Perioperative Implications

Preoperative Preparation

- Prior records should be reviewed and prior exposure documented.
- Avoid volatile anesthetics in a pt with a confirmed Hx of postop liver dysfunction from halogenated agents.
- Total IV anesthesia is one approach if general anesthesia is planned.
- RA not contraindicated.

Anticipated Problems/Concerns

- How to evaluate postop liver dysfunction:
  - Incidence: 25–75% of surgical pts may have some form of hepatic dysfunction, from mild elevation in liver enzymes to global liver failure.
  - Up to 50% of pts with cirrhosis may have postop jaundice.

Categories of Postoperative Liver Dysfunction

- Hepatocellular injury (elevated alanine amino-transferase, +/– hyperbilirubinemia)
  - Etiologies: Inhalational anesthetics and other drugs, hypotensive shock, transfusion reactions, unrecognized preop liver dysfunction
- Cholestatic jaundice (elevated alkaline phosphatase, +/– elevated ALT; direct hyperbilirubinemia)
  - Etiologies: Benign postop cholestasis, prolonged cardiac bypass, sepsis, prolonged administration of total parenteral nutrition, cholecystitis, cholangitis, microlithiasis, drugs (especially antibiotics)
- Indirect hyperbilirubinemia (other liver enzyme markers often normal)
  - Etiologies: Multiple transfusions, hemolysis, glucose-6-phosphate dehydrogenase deficiency, Gilbert's syndrome
- Diagnosis: Liver biopsy usually not necessary; histologic appearance often identical to viral hepatitis.

Differential Diagnosis for Inhalational Anesthetic Induced Hepatitis

- First rule: AIH is a diagnosis of exclusion
- Preexisting liver disease:
  - Viral hepatitis
  - Steatohepatitis: Alcoholic or nonalcoholic (NASH)
  - Autoimmune hepatitis
  - Wilson disease
- Periop disorders:
  - Drug reactions
  - Hypotensive shock and other causes of liver ischemia
- Second rule: In pts with drug-induced liver injury, jaundice may herald impending global liver failure and should be considered life threatening.
- Third rule: Treatment is supportive in nature, and orthotopic liver transplant may be life saving.
- Fourth rule: In a pt with documented or suspected AIH, avoiding all volatile anesthetics is the safest course for future anesthetics, due to immune cross reactivity, the possibility of trace amounts of volatile anesthetics in the anesthesia circuit, as well as the many unanswered issues regarding this disorder.