Halothane Hepatitis/Post-operative Jaundice

Halothane hepatitis is a rare, idiosyncratic reaction likely immune-mediated. It is a diagnosis of exclusion. The single most important risk factor is previous exposure to halothane. Post-operative jaundice has a wide-differential diagnosis and is best approached from a pre-hepatic, hepatic or post-hepatic diagnostic format.

ANESTHETIC CONSIDERATIONS:

- Avoid halothane and other fluorinated inhalationals if prior history of hepatotoxicity secondary to these agents
  - Sevoflurane likely safe, though
- Halothane still safe in pediatrics

ANESTHETIC GOALS:

- Maintain hemodynamic stability avoiding decreases in hepatic blood flow and oxygen delivery

HISTORY

- Classic presentation
  - Fever, anorexia, nausea, chills, myalgias and rash followed by jaundice 3-6 days later
  - Procedures are usually of short duration (<30min)
- Risk factors
  - Prior history of exposure (#1!)
  - Adult
  - Women
  - Obesity

PHYSICAL

- Vitals
- Full physical exam with attention paid to abdominal exam
- May be encephalopathic if severe liver dysfunction

INVESTIGATIONS

- Bloodwork – CBCD, lytes, urea, Cr, AST, ALT, bilirubin (total and direct), lipase, Alk phos, GGT, ammonia, cultures, hepatidites serology and other tests (i.e. hemolysis workup) as guided by history
- U/S abdomen
- +/- CT abdo
- +/- Liver biopsy
- +/- ERCP if calculus

OPTIMIZATION

- Involve appropriate service for underlying cause (GI/hepatobiliary, Gen Surg, etc.)
- Supportive care and symptomatic management (treat pruritis; encephalopathy – lactulose, etc.; sepsis – antibx, etc.; N-acetylcysteine – acetaminophen and some other causes of fulminant hepatic failure; etc….)
- Treat underlying cause

ANESTHETIC OPTIONS

- Avoid halothane and other fluorinated inhalational agents is previous history of hepatotoxicity secondary to these agents

ANESTHETIC SETUP – N/A

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MANAGEMENT OF ANESTHESIA – N/A

- **Induction**
- **Maintenance**
- **Emergence**

DISPOSITION & MONITORING – N/A

- **ANALGESIA**:
- **OXYGENATION**:
- **POSITIONING**:
- **MONITORING**:

COMPLICATIONS

- Hepatotoxicity/fulminant liver failure

PATHOPHYSIOLOGY

- Halothane introduced ~ 1956
  - High incidence of hepatotoxicity noted post-op
  - "The National Halothane Study" undertaken (retrospective)
- Incidence of fatal hepatic necrosis was ~ 1 in 10,000
- Drug-induced liver injury caused by intrinsic or idiosyncratic mechanisms
  - Intrinsic – predictable and independent of host influences
  - Idiosyncratic – rare, host-dependent and difficult to produce in animals
- Two distinct types of hepatic injury seen with halothane
  - Mild injury – mild elevations of AST and ALT
    - Incidence 1 in 5!
  - Fulminant (aka **halothane hepatitis**)

- Elevated AST, ALT, bili, alk phos
- Massive hepatic necrosis
- Fatality 50-75%
- Halothane oxidized by CYP2E1 to reactive trifluoroacetyl-chloride metabolite
  - TFA then can covalently bind hepatocyte proteins producing trifluoroacetylated-protein adducts
  - These become neoantigens
  - Most pt have antibodies to TFA-modified proteins (i.e. immune-response)
    - A serum test is available for this
  - Histologic appearance indistinguishable from viral hepatitis
- Risk factors
  - Prior history of exposure (#1!)
  - Adult
  - Women
  - Obesity
- Classic presentation
  - Fever, anorexia, nausea, chills, myalgias and rash followed by jaundice 3-6 days later
  - Procedures are usually of short duration (<30min)
- Very rare in pediatrics
- Sevoflurane is not metabolized to TFA-adducts
  - Only ever 1 case-report of fulminant hepatitis
  - Other volatiles worse than sevo but not nearly as bad as halothane

Box 24-1

Clinical Considerations

Halothane should not be used in adult patients without a specific, well-documented indication.

In patients experiencing postoperative hepatotoxicity after fluorinated inhaled anesthetics, these anesthetics should be avoided in the future.

Despite reports of **halothane hepatitis** in children, halothane remains an acceptable anesthetic choice for use in children.

Enflurane, isoflurane, and desflurane remain safer inhaled anesthetics.

Anesthetic-induced hepatitis remains a diagnosis of exclusion.

Post-Operative Jaundice

This is an urgent situation that demands immediate attention

DIFFERENTIAL DIAGNOSIS (if non-hepatic surgery)

1. Hemolysis
2. Drugs / Anesthesia
3. Hypotension / hypovolemia

EXPANDED DIFFERENTIAL DIAGNOSIS

1. Unconjugated Hyperbilirubinemia (Pre-Hepatic)
   a. Excessive bilirubin production
      i. **Hemolysis (intravascular or extravascular)**
   b. Immaturity of enzyme systems
      i. Physiologic jaundice of newborn
      ii. Jaundice of prematurity
   c. Inherited defects
      i. Crigler-Najjar (children die without exchange transfusions & phototherapy)
      ii. Gilbert (most common 5%, lack of glucuronyl transferase)
   d. Drug effects

2. Conjugated Hyperbilirubinemia (Hepatic and Post Hepatic)
   a. Hepatocellular disease
      i. Hepatitis – viral, autoimmune, etc.
      ii. Cirrhosis
      iii. Ischemic liver/shock liver
      iv. Drugs
         1. **Drug induced hepatitis**: all inhalationals except sevoflurane
            - Transient liver dysfunction: non-immune mediated (reductive metabolism) – only halothane
            - Immune mediated (desflurane has 1 case report): halothane > enflurane > isoflurane > desflurane
   b. Intra-hepatic cholestasis (hepatic)
      i. Drugs
      ii. Pregnancy
      iii. Sepsis
      iv. TPN
      v. Post-operative
   c. Benign postoperative jaundice
   d. Congenital conjugated hyperbilirubinemia
      i. Dubin-Johnson syndrome
      ii. Rotor syndrome
   e. Obstructive jaundice (Post-hepatic)
      i. Extrahepatic
         1. Choledocholithiasis
         2. Pancreatitis
         3. Stricture
         4. Neoplasm
         5. Post-ERCP
         6. Parasites (ascaris, liver flukes, etc.)
      ii. Intrahepatic
         1. PSC
         2. Neoplasm
         3. PBC

REFERENCES

- UpToDate, 2010
- Barash 6th, Miller, Coexisting