CASE REPORTS


Suspected Isoflurane Hepatitis in an Obese Patient with a History of Halothane Hepatitis

Naresh T. Gunaratnam, M.D.,† Jay Benson, M.D.,‡ A. Jay Gandolfi, Ph.D.,§ Mingli Chen, B.S.

VOLATILE halogenated anesthetics are known to produce a sporadic low incidence of hepatotoxicity. Halothane is the principal agent associated with hepatotoxicity, as documented by numerous case reports and laboratory investigations. The hepatotoxicity varies from a mild, acute, self-limited injury, which is seen in 20% of patients, to an often fatal, idiosyncratic fulminant hepatic cellular necrosis, which occurs in 1 of 30,000 patients.1,2 Isoflurane has also been associated with hepatitis in a few case reports.3–6 We describe the case of a patient with a history of halothane hepatitis, who showed similar hypersensitivity toward isoflurane.

† Fellow in Gastroenterology, University of Michigan Medical Center.
‡ Clinical Associate Professor of Medicine, University of Connecticut School of Medicine and St. Francis Hospital Medical Center.
§ Professor of Anesthesiology, Pharmacology, and Toxicology, University of Arizona.

Received from the University of Michigan Medical Center, Department of Medicine, Division of Gastroenterology,Ann Arbor, Michigan; the University of Connecticut School of Medicine and St. Francis Hospital Medical Center, Hartford, Connecticut; and the Department of Anesthesiology, College of Medicine, University of Arizona, Tucson, Arizona. Submitted for publication February 17, 1995. Accepted for publication August 3, 1995.

Address reprint requests to Dr. Gunaratnam: University of Michigan Medical Center, Department of Medicine, Division of Gastroenterology, Ann Arbor, Michigan 48109-0362.


Anesthesiology, V 83, No 6, Dec 1995

Case Report

The patient, a 47-yr-old man, was exposed to halothane in 1970. At that time, he was 23 yr of age, obese (weight, 122 kg; height, 1.65 m) and healthy, while anesthetized with halothane, he underwent elective reduction of gynecomastia induced by obesity. Two days after surgery, the patient developed fever, arthralgias, and frank hepatitis. Detailed records were unavailable, but the patient’s hepatitis required hospitalization for 3 weeks. On discharge, the patient was told by the treating physicians that the hepatitis was probably halothane induced; and he was instructed to avoid future halothane exposure. The initial episode of hepatitis resolved completely in that the patient became asymptomatic and results of his liver function tests were normal. In October, 1980, the patient was evaluated for irritable bowel syndrome and was noted to have slightly increased hepatic transaminases, with AST 46 U/l (normal, 0–35 U/l), ALT 108 U/l (normal, 0–35 U/l), and a total bilirubin of 1.4 mg/dl (normal 0.3–1.0 mg/dl). The patient worked as a school teacher and did not have a history of any blood transfusion, alcohol abuse, intravenous drug use, or exposure to other hepatotoxic chemicals or medications, and had no serologic evidence of hepatitis A or B. The patient did not manifest stigmata of chronic liver disease, and hepatocellular enzymes remained increased, but stable, over the next 2 yr. In May, 1982, liver biopsy revealed moderate diffuse fatty metamorphosis, slight focal chronic inflammation, and rare degenerated liver cells. The patient’s physicians believed that the hepatic pathology was either a sequela of his episode of halothane hepatitis or secondary to his morbid obesity (weight, 122 kg). Liver function studies remained minimally abnormal on close follow up over the next 11 yr.

In August, 1993, the patient underwent endoscopic sinus surgery for removal of nasal polyps. He was in good health otherwise, and physical examination was only remarkable for obesity (weight, 134 kg). Laboratory examinations 1 day before surgery documented that results of his liver function tests were normal (AST 32, ALT 35). The patient was premedicated with 3 mg midazolam and anesthesia was induced with 3 ml (50 µg/ml) fentanyl and 20 ml propofol. General anesthesia was maintained with 1% isoflurane, N₂O/O₂ 60:40 for 1 h. During anesthesia, the patient received succinylcholine, as well as ephedrine, topically for local hemostasis. There were no episodes.
of intraoperative hypotension (minimum blood pressure, 100 mmHg). One day after the surgery, the patient developed low-grade fevers to 38°C, and was treated with oral cephalixin for presumed sinus infection. The patient was discharged, but continued to have fevers and chills over the next 4 days. On day 10 after the procedure, he presented with darkening of his urine, icterus, and low-grade fever. On physical examination, he was jaundiced and appeared to be ill; abdominal examination revealed a smooth but tender liver edge palpable two finger breadths below the right costal margin. Laboratory examination was consistent with acute hepatitis (AST 1698 U/l, ALT 1576 U/l, total bilirubin 2.6 mg/dl, direct bilirubin 1.4 mg/dl; erythrocyte sedimentation rate, 20 mm/h; and total white count, 7,500 with 4% eosinophils). Laboratory evaluation for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, herpes virus; antinuclear antibodies; antimitochondrial antibodies; and rheumatoid factor were all negative. Ultrasound examination of the abdomen revealed hepatomegaly (liver span, 17 cm) mild splenomegaly, without evidence of bile duct pathology, cholelithiasis, or ascites. Hepatic transaminases peaked 20 days after isoflurane exposure (AST 2650 U/l, ALT 2491 U/l) and, thereafter, decreased to near normal by 40 days postexposure; total bilirubin peaked at 5.5 on day 29. Hepatic synthetic function became progressively impaired (peak PT, 16.9 s; INR 2.5 [range 1.2 -- 1.5 normal] on day 29), and then returned to normal. Eosinophilia peaked at 9%, with a corresponding total white count of 12,500 on postexposure day 14. Serum samples from postexposure days 25--97 were evaluated for antitrifluoroacetylated (anti-TFA) antibodies. These antibodies are indicators of a halothane-induced hepatic hypersensitivity response. Synthetic trifluoroacetylated rabbit serum albumin is used as the antigen in an enzyme-linked immunosorbent assay (ELISA). Serum was diluted 1/100 and the titer was recorded as the absorbance at a 410- versus a 490-nm reference wavelength. The titers were highest at the first time point tested (25 days) and slowly decreased over the next 20 days. By day 97, the titers were only slightly increased over typical control levels (fig. 1). Specificity of the antibodies for the TFA moiety, measured by inhibition with 25 mM trifluoroacetylated lysine, maintained its fidelity (>75% specific). The patient had gradual symptomatic improvement and was discharged on postexposure day 35.

Discussion

The pathophysiology of halogenated anesthetic-related hepatotoxicity remains unclear. Possible mechanisms include direct toxicity, hypoxic injury, or an immune response-mediated injury. Isoflurane is the most commonly used general anesthetic in the United States, and its hepatotoxicity has not been established. Expert panel review of cases of liver dysfunction associated with isoflurane use did not find an association between the use of isoflurane and postoperative hepatic dysfunction.2

Halothane can be biotransformed by both oxidative and reductive mechanisms leading to reactive intermediates that are associated with liver injury.5 Even under optimal conditions, the quantity of reductive metabolites produced is less than 1% of that produced by oxidation.9 In humans, the predominant mechanism of halothane biotransformation is oxidative and results in a highly reactive acylating intermediate metabolite of trifluoroacetylated chloride.10 This intermediate can cause direct chemotoxic injury to hepatocytes and may also trifluoroacetylate (TFA) liver proteins, rendering those proteins antigenic for immune-mediated injury.7 Isoflurane and enflurane are oxidatively metabolized by hepatic cytochrome P-450 to produce protein ad-
CASE REPORTS

Products that are structurally similar (enflurane) or identical (isoflurane) to those produced by halothane metabolism. However, the extent of metabolism varies dramatically (30% for halothane, 2.5% for enflurane, and less than 0.2% for isoflurane). The rate of metabolism correlates directly with the number of reported cases of anesthetic-associated hepatitis. This correlation strongly indicates that the products of oxidative metabolism cause liver injury. Such injury may result from chemo-toxic injury by the trifluoroacetylated proteins or by immune-mediated destruction targeted toward those modified proteins.

Clinically, patients with halothane hepatitis tend to be obese and present with fever, rash, arthralgias, and eosinophilia a few days after halothane exposure. These patients also have a history of previous exposure to halothane in more than 90% of cases, with severity of hepatitis correlating inversely with the latency between exposures. These historical findings indicate that a hypersensitivity reaction is the major cause of the fatal hepatitis in humans. This patient's history and presentation is classic for halothane hepatitis, except that he did not have a rash.

Antibodies toward trifluoroacetylated proteins (anti-TFA antibodies) can be measured in patients with halothane hepatitis. Using the ELISA method and trifluoro-acetylated rabbit serum albumin (TFA-RSA) as the antigen, anti-TFA antibodies can be detected in up to 67% of patients with halothane hepatitis. The sensitivity of the assay can be increased to 92% by combining the TFA-RSA with a trifluoroacetyl-l-lysine (TFA-lysine) blocking antibody. False-positive reactions have been reported in patients with chronic autoimmune liver diseases, including chronic active hepatitis and primary biliary cirrhosis. An evaluation for coexistent autoimmune disease and the measurement of multiple antibody titers correlating with this activity will enhance the specificity of the assay.

Recent guinea pig studies have demonstrated that the products of enflurane and isoflurane metabolism are capable of modifying liver proteins such that they can be bound by antibodies induced by halothane exposure. Histologic evaluation of the guinea pig livers revealed that the modified liver proteins were located in the centrlobular zone, where, classically, the lesions of halothane hepatitis occur. The centrlobular location of the modified liver proteins and the reactivity of halothane-induced antibodies toward these proteins indicate that the use of enflurane or isoflurane in a patient with known hypersensitivity to halothane may result in pathologic and immune-mediated insults similar to those initially induced by halothane.

This is the first case recorded in which serial titers of halothane-related antibodies have been documented in a patient with suspected isoflurane hepatitis. The patient had studies that ruled out viral hepatitis (including hepatitis A, B, and C; Epstein-Barr virus; herpes virus; and cytomegalovirus), autoimmune hepatitis (normal ESR and negative antinuclear and antimitochondrial antibodies), and cholangitis (abdominal ultrasound showed no evidence of biliary tract pathology), and the patient was not exposed to any other potentially hepatotoxic drugs. The patient had normal liver function tests before the surgery, did not have any episodes of intraoperative hemodynamic instability, and developed fulminant hepatitis approximately 1 week after his anesthesia. It is, therefore, extremely unlikely that his hepatitis was the result of surgical anesthetic-induced stress superimposed on his preexisting fatty liver. The antibody titer correlated well with the degree of hepatocellular damage, as manifested by the hepatic transaminases. The titers observed were comparable with those seen in halothane hepatitis cases with substantial liver injury (antibody titers of 0.85–1.87 in halothane hepatitis patients). The antibody titer reached background levels when the transaminases became normal, indicating resolution of the immune-mediated insult.

These findings indicate that a patient who was previously sensitized to halothane may show a similar hypersensitivity response when challenged with isoflurane. The probable mechanism implicated is an autoimmune reaction toward the trifluoroacetylated liver proteins that result from the oxidative metabolism of both halothane and isoflurane. The significantly lower rates of oxidative metabolism of isoflurane (0.2%) compared with halothane (30%) probably results in fewer isoflurane-induced antigens, which, in nearly every case, are inadequate to produce a clinically significant immune-mediated hepatitis. However, immune recognition as a result of a previous halothane hypersensitivity appears to be capable of attacking antigens induced by isoflurane to produce clinically significant episodes of immune-mediated hepatitis.

References


Anesthesiology. V 83, No 6, Dec 1995
Spinal Anesthesia in an Infant with Epidermolysis Bullosa

Neil E. Farber, M.D., Ph.D.,* Todd J. Troshynski, M.D.,† Glenn Turco, D.O.‡

EPIDERMOLYSIS bullosa is a rare group of genetic disorders of the skin with dominant and recessive modes of transmission. The dominant simplex form of epidermolysis bullosa is characterized by vesicles at sites of friction or trauma. The anesthetic concerns and difficulties have been described previously.1-5 A variety of general, regional, and local anesthetic techniques have been used successfully in adults with epidermolysis bullosa.6-9 In infants and children with this disorder, although anesthetic management usually consists of general anesthesia delivered by mask or endotracheal tube, or intravenous or intramuscular anesthesia, these techniques may pose formidable problems. Regional brachial plexus anesthesia in children5,10 and the use of caudal anesthesia in an infant with epidermolysis bullosa11 have been reported. We describe the successful use of spinal anesthesia in a pediatric patient with epidermolysis bullosa that obviated the need for either face-mask or endotracheal intubation.

Case Report

A 3.1-kg, 12-week-old male infant with a history of failure to thrive presented for placement of a gastrostomy tube. He was the 2.1-kg

* Assistant Professor of Anesthesiology, Pharmacology, and Toxicology, Medical College of Wisconsin and Children's Hospital of Wisconsin.  
† Assistant Professor of Anesthesiology, Medical College of Wisconsin, Director, Pain Clinic, Children's Hospital of Wisconsin.  
‡ Assistant Professor of Anesthesiology.

Received from the Department of Anesthesiology, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, Wisconsin. Submitted for publication May 10, 1995. Accepted for publication August 3, 1995.  
Address reprint requests to Dr. Farber: Department of Anesthesiology, MEB 462C, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226.

Key words: Anesthetic techniques: spinal anesthesia. Epidermolysis bullosa. Pediatric. infant.