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A Report of Hepatic Necrosis and Death Following Isoflurane Anesthesia

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Several halogenated anesthetics have been associated with hepatotoxicity. Yet, isoflurane has not been reported to cause liver damage in humans. The following is a report of a patient who had hepatic failure and death after receiving an anesthetic that included isoflurane.

CASE REPORT

On March 7, 1986, a 44-yr-old white woman was admitted for lysis of abdominal adhesions. She had no medical problems except chronic hypogastric pain presumed to be secondary to adhesions from previous surgeries. Her surgical history included four abdominal procedures, each with exposure to halogenated anesthetics: 3/74 hysterectomy—halothane, 4/84 cholecystectomy—enflurane, 5/85 hernia repair—enflurane, and 11/85 lysis of adhesions—isoflurane. She denied a history of hepatitis or blood transfusions. She had no allergies, but reported nausea after taking oral codeine. Prior to admission, she had a minor dental procedure, and was taking oral phenoxymethyl penicillin. There was no history of smoking or alcoholic intake.

The admission physical examination revealed a healthy-appearing female, of medium build, with normal vital signs. She was not icteric, and showed no skin manifestation of liver disease. No adenopathy was noted. Cardiopulmonary findings were normal. The abdomen was not distended. There were several well-healed laparatomy scars. The liver and spleen were not palpable. The extremities were well-developed and without edema. The preoperative aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, and coagulation profile were normal. The white blood cell count was slightly elevated at 14,500/mm^3, with no immature forms.

She was taken to surgery the following morning. Preoperatively, the patient received midazolam 4 mg iv. Anesthesia was induced with sufentanil 25 μg and metocurine 2 mg, followed by thiopental 250 mg and succinylcholine 100 mg. Anesthesia was maintained with a mixture of 50% oxygen and nitrogen with isoflurane 0.5–0.8%. Twenty-five micrograms of sufentanil were added. Atacurium 20 mg was administered for relaxation. Intraoperative monitoring included electrocardiogram, esophageal stethescope and temperature probe, nerve stimulator, and oxygen analyzer. Continuous mechanical ventilation was used without PEEP. The Dräger-Narkomed 2A machine was used.

The laparatomy was performed and multiple dense adhesions were observed between the liver, stomach, small intestine, and anterior abdominal wall. These were removed by sharp dissection. No retractors or packs were used in the area of the hepatic artery or portal vein. A solution of Solu-Cortef 100 mg, Hyskon 100 ml, and 100 ml saline was instilled into the abdominal cavity. Forty milliliters bupivacaine 0.25% was injected into the abdominal fascia. There was no period of intraoperative hypotension. Total blood loss was 200 milliliters. Fluid replacement was made with 600 milliliters dextrose 5% Ringer's Lactate. Anesthesia was reversed using edrophonium 40 mg, atropine 0.4 mg, and naloxone 0.1 mg. The duration of anesthesia was 90 min.

The patient tolerated the surgery and anesthesia well, and was taken to the recovery room and extubated while awake. She remained on electrocardiographic monitoring, and her vital signs were taken every 15 min. The patient did well, and was transferred back to her room that same afternoon. That evening she complained of nausea, but was otherwise asymptomatic.

The following morning she became lethargic, progressed to total unresponsiveness, and required mechanical ventilation. Her temperature was 99°. Serum bilirubin was 9.6 mg/dl, aspartate aminotransferase greater than 2,000 units/l, lactate dehydrogenase greater than 4,000 units/l, and prothrombin time greater than 180 s (control less than 12 s). Her serum ammonia level was 182 mmol/l (nl 11–35). Blood cultures showed no growth. The patient subsequently developed disseminated intravascular coagulation with fibrin split products at 1:160 dilution, fibrinogen 51 mg/dl, and platelets 70,000/mm. She continued to deteriorate, and expired on the fourth postoperative day.

A post-mortem examination was performed. The gross findings of the liver were consistent with acute fulminant necrosis. On light microscopy, there was evidence of canalicular cholestasis, which is often seen with drug reactions. No viral particles were demonstrated. Electron microscopy revealed no spherical or tubular structures or filaments in the nucleus or cytoplasm as seen with hepatitis B.

Serum for viral studies revealed negative assays for Hepatitis B surface antigen and B core antibody. Hepatitis A antibody was present; however, an IgM fraction was not detected, suggesting prior exposure to hepatitis A without current infection. Herpes virus I and II index (by ELISA) was negative. Cytomegalovirus (CMV) IgG (ELISA) was weakly positive. In light of the historical and clinical presentation, it is unlikely that the patient had active CMV hepatitis.

DISCUSSION

Halogenated anesthetics have been associated with hepatic dysfunction. Halothane hepatotoxicity has been the most commonly studied,[1–4] and is the subject of a review by Stock and Strunin.[5] Halothane can produce a syndrome of clinical features[4] and laboratory findings[6,7] that are similar to viral hepatitis or drug-induced liver damage.[4,8,9] Following halothane exposure, susceptible patients may develop fever, mental changes, and elevated transaminase and bilirubin levels, as well as coagulation abnormalities. The histopathology spectrum is wide, ranging from panlobular to multifocal necrosis to fulminant necrosis.[10]

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The mechanism of hepatic injury is unknown. Studies have been directed toward hypersensitivity reactions,[11] toxicity of intermediary metabolites,[12] multiplicity and duration of exposure,[9,13] hypoxia,[14] obesity,[15,16] and nutritional status[17] as factors potentially involved in halothane hepatotoxicity.

There is evidence to suggest cross reactivity between halothane and other halogenated anesthetics.[18] Other anesthetics, methoxyflurane,[18,19] and enflurane[20] have been associated with hepatic injury. Isoflurane, an isomer of enflurane, has not been shown to be hepatotoxic in humans, but can produce centrilobular necrosis in experimental animals.[21] In a study of 12 surgical patients, slight but insignificant ($P < .05$) elevations in transaminases were noted following isoflurane anesthesia.[22] Fisher *et al.*[23] reported hepatic necrosis after isoflurane exposure, but concluded the cause to be herpes virus hepatitis.

McLaughlin and Eger[24] discussed a case of hepatic dysfunction following repeated exposure to isoflurane anesthesia, but dismissed isoflurane as the cause. Recently, Grégoire and Smiley[25] reported "the first case" of hepatitis attributable to isoflurane anesthesia. Their results do not show definitive causal relationship between isoflurane and liver dysfunction, and have received criticism from others.[26]

The cause of massive liver necrosis in this patient, which resulted in her death, is not clear. However, there is a temporal relationship of liver failure and exposure to isoflurane. It is of interest to us that features of this patient's history and clinical course have been observed in cases of anesthetic-associated hepatotoxicity. While liver damage after halogenated anesthesia is rare, and this rarity makes prospective randomized studies impractical, it may be useful to analyze case studies as reported here.

This patient had no history of preexisting liver disease, but she had been exposed to halogenated anesthetics several times—a feature thought by some to increase the likelihood of hepatotoxicity on reexposure.

She had been taking oral phenoxymethyl penicillin prior to hospitalization. Liver dysfunction has been reported in association with penicillin therapy. Asymptomatic reversible trans-aminasemia has been noted after parenteral ampicillin[27,28] and carbenicillin.[28–30] Liver tenderness, nausea and vomiting, and transaminase elevations have followed administration of parenteral oxacillin.[31,32] Liver necrosis associated with anaphylactic shock has been reported after intramuscular penicillin.[33] This patient had taken oral penicillin several days prior to her preoperative chemistry profile. The liver enzymes were all within normal limits at that time.

Preoperatively, the patient received thiopental and narcotics. Albeit rare, these drugs have been associated with liver dysfunction.[34,35]

Disturbances in hepatic blood flow can account for liver necrosis in surgical patients. There were no retractors or packs used in the area of hepatic artery or portal vein during this operation. However, hepatic blood flow is diminished during many surgical procedures; the decrease is directly related to the degree of surgical trauma.[36] It is unlikely that a short, uncomplicated laparotomy with lysis of abdominal adhesions, and no periods of intraoperative hypotension, could account for the massive necrosis observed in this woman.

Hyskon (Dextran 70) was instilled into the abdomen for prevention of adhesions. Anaphalactoid reactions have been reported with intravenous glucose polymers,[37,38] but his patient did not receive intravenous Dextran 70. One might speculate that the Dextran 70 was absorbed from the peritoneum, precipitated vascular spasm of the hepatic artery, and caused hepatic ischemia and subsequent injury. This would probably be accompanied also by spasm of the mesenteric arteries, and ischemic necrosis of the large and small intestines. Necropsy findings of the intestines, pancreas, and spleen do not support occlusive vascular events in the branches of the celiac or mesenteric arteries. However, the liver is at a disadvantage when considering ischemia, because the majority of blood perfusing the liver is from the portal circulation, and is highly deoxygenated.

Common features said to be related to halogenated anesthetic hepatitis have been reported.[4,11] Eger and Smuckler,[39] in a study of enflurane, devised a "syndrome score," and examined 12 variables. Although our patient did not receive enflurane, she demonstrated eight positive features: 1) prior anesthesia with halogenated anesthetics; 2) nausea; 3) anorexia; 4) jaundice; 5) total bilirubin exceeding 2.5 mg/dl; 6) serum glutamic-oxaloacetic transaminase (now referred to as aspartate aminotransferase or AST) above 370 IU; 7) hepatic necrosis; and 8) death of the patient. Features of "the syndrome score" not demonstrated in this patient were: 1) fever; 2) chills; 3) rash; and 4) eosinophilia. In addition, the patient was not obese and did not have a history of atopy.

We have evidence to exclude viral hepatitis due to hepatitis A, hepatitis B, Herpes I or II, Epstein-Barr, or cytomegalovirus. It is possible this patient had subclinical non-A, non-B hepatitis, but unlikely, as she had no history of blood transfusions or known contact with carriers.

In summary, we cannot conclude that isoflurane was the cause of the fulminant hepatic failure which resulted in the death of this patient. However, many (but

not all) factors thought to be associated with anesthetic-induced hepatitis were present. Further, we attempted to exclude other possibilities which could account for the rapid development of hepatic necrosis. If isoflurane does cause hepatic injury in rare patients, reports such as this one will be needed to aid in the identification of patients at risk.

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