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Hepatotoxicity after Desflurane Anesthesia

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SEVERAL fluorinated inhalation anesthetics have been associated with hepatotoxicity. Yet to date, desflurane has not been reported to cause liver damage in humans. The following is a report of a patient who experienced hepatitis after receiving a desflurane anesthetic and who may have been sensitized by prior halothane exposure.

Case Report

A 65-yr-old woman underwent a left hemithyroidectomy for a thyroid adenoma. The patient had a history of hypertension, which was treated with 50 mg atenolol per day. Her medical history was notable for pneumonia at age 9, pancreatitis at age 52, and recurrent urinary tract infections. Previous surgical and anesthetic history included a tonsillectomy in 1935 for which no records were available; a *post partum* tubal ligation in 1952, for which she received nitrous oxide, oxygen, cyclopropane, and d-tubocurare; total abdominal hysterectomy and unilateral oophorectomy in 1969, under sodium thiopental, succinylcholine, d-tubocurare, scopolamine, nitrous oxide, oxygen, and cyclopropane; an exploratory laparotomy and ovarian cystectomy in 1976, for which she received sodium thiopental, succinylcholine, pancuronium, nitrous oxide, oxygen, and halothane; and elective cholestectomy in 1982, during which she received sodium thiopental, succinylcholine, pancuronium, nitrous oxide, oxygen, and halothane. Each of these anesthetics were uneventful. The halothane anesthetics in 1976 and 1982 lasted approximately 45 min each. There was no history of jaundice, and the patient had never received a transfusion of blood or blood products. There was no history of intravenous drug abuse, tattoos, acupuncture, or occupational exposure to hepatotoxins. Alcohol consumption was less than 10 g per month. Hives had developed after she took sulfamethoxazole and trimethoprim (Bactrim) 15 yr earlier. She was also allergic to iodine-based dyes. The only other medication was 600 mg Ibuprofen once per day. She was a homemaker who had raised two children, a son who had died in his 40s from what was described as complications of myasthenia gravis, and a daughter who was alive and well. The patient had worked for 5 yr in a manufacturing facility, where she was exposed on occasion to paint products. Her last exposure was 10 yr earlier. There was no family history of liver disease.

The left hemithyroidectomy was performed on September 8, 1994. The patient was 157 cm tall and weighed 71 kg. She was afebrile with normal vital signs. The patient received 2 mg midazolam intravenously for sedation approximately 45 min before transport to the operating room. After placement of a blood pressure cuff, an electrocardiogram, and a pulse oximeter, general anesthesia was induced with 100 mg propofol, 100 μg fentanyl citrate, 40 mg atracurium, and 130 mg lidocaine, all given intravenously before tracheal intubation. Anesthesia was maintained with a mixture of 37–39% O_2 in nitrous oxide with 3–7% desflurane and intravenous fentanyl. Continuous mechanical ventilation was used without positive end expiratory pressure. Except for a brief decrease in blood pressure (systolic in the mid-80s) just before surgical incision, the patient remained hemodynamically stable. This was treated with 5 mg ephedrine and 0.3 mg glycopyrrolate intravenously. The pulse rate was 55 beats/min at the time of hypotension and increased to 90 beats/min after ephedrine administration. Blood loss was minimal. No blood or blood products were given. The total surgical time was 70 min with an anesthetic time of 90 min. The patient was discharged from the hospital in good condition the following day.

On September 20, 1994, 12 days postoperatively, the patient experienced pruritus, malaise, nausea, and polyarthralgias. There was

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Table 1. Patient's Laboratory Data before, during and after Hospitalization Following Desflurane Anesthesia

Test	Date of Assay							
	1/94*	9/24/94	10/1/94	10/2/94	10/3/94	10/4/94	10/5/94	12/14/94
AP	104	202	420	416	386		379	139
ALT	31	1886	1074	966	787		684	40
AST	36		1220	1280	1130		915	
T Bili	1.1	20.3	27.0	28.8	30.0		26.4	1.7
D Bili	0.2	13.1	17.8	19.5	16.8		18.9	0.9
PT		26.6	19.5	19.7	19.0	17.8	17.3	13.2
INR			2.0	2.0	1.9	1.8	1.7	1.1
APPT				39.6	40.8		38.3	
γ-GT	67			144	133		112	

AP = alkaline phosphatase; ALT = aminoalanine transferase; AST = aminoaspartate transferase; T Bili = total bilirubin; D Bili = direct bilirubin; PT = prothrombin time; INR = international ratio; APTT = activated thromboplastin time; γ-GT = γ-glutamyl transferase.

* These tests were obtained as part of a routine medical examination 8 months before the surgery on 9/8/94.

no fever. At the same time, a macular erythematous rash appeared over the buttocks and thighs. The patient noted that her urine was unusually dark. She received nizatidine for her nausea and 1% hydrocortisone cream for her rash the following day. By the 16th postoperative day, the patient complained of dermal jaundice and epigastric abdominal pain. She was admitted to the hospital.

Physical examination on admission revealed the patient to be afebrile with a blood pressure of 140/80 mmHg and a pulse rate of 90 beats/min. There was an irregular macular erythematous rash over the posterior thorax. Examination results of the head and face were normal with the exception of conjunctival and scleral jaundice. Cardiopulmonary findings were normal. Abdominal examination revealed a nontender liver, which was 8 cm in size by percussion. There was no splenomegaly. No ascites was present. The patient was neurologically intact, without evidence of asterixis or other evidence of encephalopathy. Admission laboratory values are listed in table 1. Albumin was 3.6 g/dl, hemoglobin was 14.8 g/dl, leukocyte count was 3.9×10^9/l, with platelets of 177×10^9/l and ferritin 554 μg/l. Anti-HAV (IgG and IgM), hepatitis B surface antibody, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody (second generation ELISA) were not detected. Although antinuclear antibody was not detected, antismooth muscle antibodies were detected to a titer of 1:40 dilutions.

On September 30, 1994 (postoperative day 22), the patient was transferred to a hepatology unit for further observation and potential liver transplantation. The physical examination was unchanged except for the presence of ascites. The patient's biochemical and hematologic data are summarized in table 1. An ultrasound of the upper abdomen revealed diffuse hepatic parenchymal heterogeneity, with normal bile ducts and normal Doppler examination of the hepatic, portal, and splenic vessels. Repeat viral serology for hepatitis A and B (including ϵ antigen and antibody) and hepatitis C were negative. Cultures for cytomegalovirus were negative. Serology for Epstein-Barr and Herpes simplex viruses indicated past infection (anti-VCA/IgG 1:2560, IgM negative, anti-HSV IgG 1:160, IgM negative). By October 5, 27 days after surgery, the patient's liver function and symptoms were improving (table 1), and she was discharged from the hospital

Table 2. ELISA Reactivity of Patient Sera with Trifluoroacetylated Liver Microsomal Proteins

Antigen	Binding Difference (Hal − Con)		
	Control Patients (mean)	Control Patients (mean + 2 SD)	Patient
Microsomes	−0.015	0.131	0.167*
DOC extracts	−0.125	0.003	0.504*

All assays were performed in triplicate in the wells of polystyrene microtiter plates (Dynatech Laboratories, Chantilly, VA) in a total reaction volume of 100 μl and plate washings were conducted with an Ultrawash II automated microplate washer (Dynatech Laboratories, Chantilly, VA). Microtiter plates were coated overnight for 16 h at 4°C with liver microsomes from control (Con) or halothane (Hal)-treated rats, or with 0.1% DOC extracts of liver microsomes from Con or Hal-treated rats, diluted to 1 mg/ml in phosphate-buffered saline, *p*H 7.4 (PBS) or with PBS alone. The plates were washed 8 times with 10 mM Tris-saline, *p*H 7.6, containing 0.5% (w/v) casein and 0.01% (w/v) Thimerosal (0.5% casein washing buffer), to remove unbound material and to block unoccupied protein binding sites. Patients' sera, diluted 1:100 in 0.5% casein washing buffer, were added to the wells, and plates were incubated for 3 h at room temperature. The plates were then washed 4 times with 0.5% casein washing buffer, followed by the addition of alkaline phosphatase conjugated goat anti-human IgG, diluted 1:1,000 in 0.5% casein washing buffer. After incubation for 1.5 h at room temperature, the plates were washed 4 times with 0.5% casein washing buffer, followed by 4 washes with PBS. Alkaline phosphatase substrate mixture, consisting of *p*-nitrophenylphosphate in diethanolamine buffer (Biorad Laboratories, Richmond, CA), was added to each well. The absorbance of the solutions in each of the wells was determined at 405 nm after 1.5 h using a Thermo Max automatic plate reader (Molecular Devices, Menlo Park, CA). The absorbance results were corrected for nonspecific reactions by subtracting from them the values obtained from the wells that contained only PBS.

* The results are expressed as the mean difference in absorbance at 405 nm between the wells containing liver proteins from halothane-treated rats and the wells containing liver proteins from control rats. A positive reaction is greater than 2 standard deviations above the mean value obtained from the sera of 20 normal patients.

the following day. By December 14 (postoperative day 97), the patient was symptom-free and had a nearly normal liver function. Her medications at this time consisted of spironolactone and furosemide for ascites.

A serum sample collected 48 days after surgery was screened by an enzyme-linked immunosorbent assay for antibodies that reacted to liver microsomes from halothane-treated rats as compared to reactivity to liver microsomes from untreated rats. This assay has been used previously for the detection of serum antibodies in patients with halothane hepatitis.[1] The assay is based on the finding that only patients with halothane hepatitis have serum antibodies that react with one or more liver microsomal proteins that have been trifluoroacetylated (TFA) by the reactive trifluoroacetyl chloride (CF_3COCI) metabolite of halothane.[1] As seen in table 2, compared to a group of 20 normal patients, the patient's antibody reactivity was significantly greater against microsomes from halothane-treated rats than microsomes from control rats. The reactivity with the TFA-proteins was markedly increased when 0.1% sodium deoxycholate (DOC) extracts of liver microsomes were used as test antigen in place of the intact liver microsomes (table 2). This is due to the preferential extraction by DOC of those proteins from the liver microsomes targeted by the CF_3COCI metabolite of halothane.[2]

Discussion

Halothane,[3] enflurane,[4] and isoflurane,[5] have been associated with jaundice, hepatitis, and death. Hepatotoxicity associated with halothane is most common and has been studied extensively. Halothane produces two types of hepatotoxicity. The first is a mild form seen in 20% of patients given halothane anesthesia[6] and is characterized by nausea, lethargy, low grade fever, and mild transient elevations in liver amino transferase enzymes (ALT, AST). In contrast, a fulminant hepatic necrosis (halothane hepatitis) occurs in approximately 1/20,000 adult patients exposed to halothane and is characterized by markedly increased serum ALT, AST, and bilirubin concentration, hepatomegaly, hepatic encephalopathy, jaundice, and, often, death.[7] The predominant histologic feature is acute hepatitis with centrilobular necrosis.[7] A variety of risk factors have been identified, which are commonly associated with halothane hepatitis. These include obesity, female sex, middle age, and having multiple anesthetics over a short period.[8–10] Compared to adults, relatively few cases of halothane hepatitis have been reported in children.[11,12]

Current evidence suggests that halothane hepatitis may have an immunologic basis.[13,14] For example, repeat halothane administrations increase the incidence of hepatitis, with fever, rash, arthralgias, and peripheral eosinophilia often observed.[15] Serum from patients with a clinical diagnosis of halothane hepatitis have been shown to contain circulating IgG antibodies directed against liver microsomal proteins that have been covalently modified by the reactive CF_3COCI metabolite of halothane (fig. 1).[16] In addition, it was found that halothane hepatitis patients' antibodies bind to epitopes consisting of the TFA hapten and structural determinants of the carrier proteins. Several of the TFA-

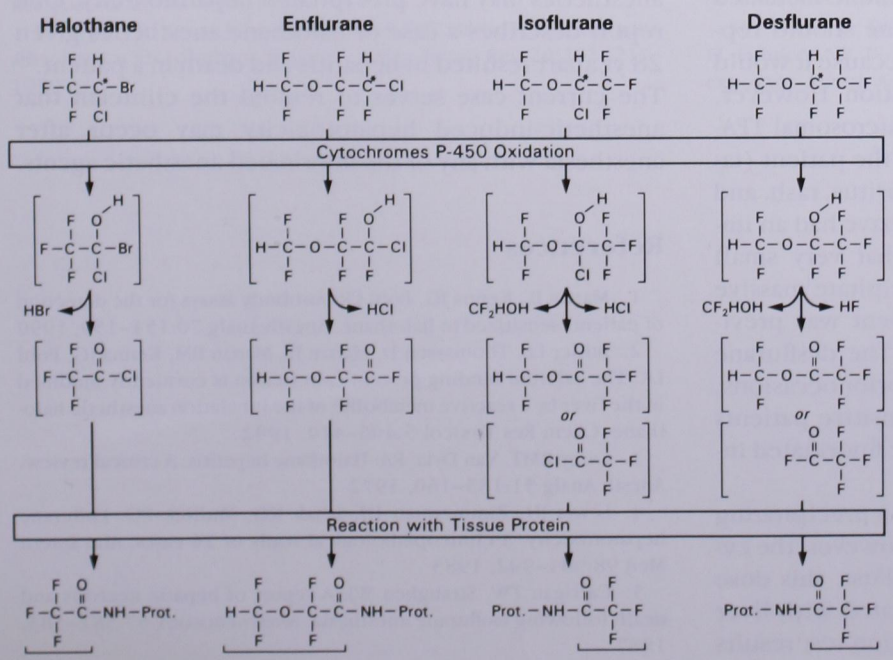

Fig. 1. Pathways for the oxidative metabolism of fluorinated inhalation anesthetics to form acylated protein adducts. Halothane is metabolized by cytochrome P-450 to trifluoroacetyl chloride, which covalently trifluoroacetylates (TFA) several liver endoplasmic reticulum proteins. In susceptible individuals, the TFA-proteins are thought to produce immune responses, which lead to halothane hepatitis. Enflurane, isoflurane, and desflurane also undergo P-450-mediated metabolism to adducts, which may generate an immune-mediated toxicity. *An asymmetric center, which is present in each of the inhalation anesthetics.

proteins recognized by the serum antibodies of patients with halothane hepatitis have been purified and identified from rat liver microsomes.[17] It also appears that similar TFA-proteins are found in the livers of patients who have been administered halothane.[18] It is thought that these proteins are immunogenic in certain patients and lead to the production of specific antibodies, or possibly specific T cells, which may be the cause of the hepatitis.

Enflurane and isoflurane are oxidatively metabolized by liver cytochrome P-450 to form acylated liver protein adducts by mechanisms similar to that of halothane (fig. 1).[19,20] The adduct formed by isoflurane is expected to be identical to that formed by halothane. Similarly, desflurane could form a TFA-adduct. This raises the possibility that enflurane, isoflurane, and desflurane might cause hepatotoxicity by a mechanism similar to that of halothane, but at a lower incidence, because the degree of anesthetic metabolism appears to be directly related to the potential for hepatic injury. For example, 20% of administered halothane undergoes metabolism,[21] and numerous cases of halothane-associated hepatotoxicity have been reported. Approximately 2.4% of enflurane is metabolized,[22] with 15–24 cases of hepatotoxicity having been well described.[4,23] Less than 0.2% of isoflurane undergoes metabolism,[24] with five cases of hepatotoxicity having been reported.[5,25–27] Desflurane strongly resists biodegradation, with only 0.01% being metabolized.[28] Therefore, from the standpoint of an immune-mediated mechanism of hepatotoxicity, desflurane should represent the safest inhalation anesthetic because it would lead to the lowest level of adduct formation. However, because antibodies reacting with liver microsomal TFA-proteins were detected in the serum of the patient (table 2), and her clinical symptoms of pruritus, rash, and polyarthralgias suggested that she may have had an immune-mediated reaction, it appears that very small amounts of adduct may be able to precipitate massive hepatotoxicity, particularly if the patient was previously sensitized against TFA-proteins. The desflurane patient had received halothane on two prior occasions. Similarly, halothane may be able to sensitize patients against protein adducts formed by other fluorinated inhalation anesthetics.[19,20,29]

It might be argued that Ibuprofen was a precipitating cause of this patient's hepatotoxicity. However, the evidence argues against this possibility. First, this dose of Ibuprofen (600 mg) is rarely associated with liver injury. Second, the patients' liver function test results were normal in January 1994, while taking Ibuprofen (table 1). Third, the patient reinstituted her Ibuprofen after surgery, and she continues to take this medication without ill effects. This is analogous to a negative rechallenge test to Ibuprofen. Fourth, her liver function tests and clinical course continue to show improvement, despite her use of Ibuprofen. Finally and most importantly, the patient's antibody response is specific to patients with anesthetic-induced hepatitis and is not seen in patients with other forms of liver disease.

To our knowledge, this represents the first report of desflurane-associated hepatotoxicity. This patient demonstrated several features commonly observed in hepatotoxicity after exposure to fluorinated anesthetics. Liver injury developed 12 days after desflurane anesthesia. This temporal relationship between exposure and injury is consistent with that of patients experiencing liver injury after halothane anesthesia. Also, she was an older female with drug allergies and a history of multiple exposures to halothane. She experienced a rash, jaundice, and marked increases in liver transaminases. The negative serologies, the otherwise negative medical history, and the presence of serum antibodies that reacted with TFA-liver microsomal proteins support the diagnosis of desflurane-induced hepatitis in this patient. It is likely that either or both of the halothane anesthetics received in 1976 and 1982 may have sensitized this patient, such that subsequent reexposure to desflurane or possibly other fluorinated anesthetics may have precipitated hepatotoxicity. One report describes a case of halothane anesthetics given 28 yr apart resulted in hepatitis and death in a patient.[30] The current case serves to remind the clinician that anesthetic-induced hepatotoxicity may occur after anesthesia with any of the fluorinated anesthetic agents.

References

1. Martin JL, Kenna JG, Pohl LR: Antibody assays for the detection of patients sensitized to halothane. Anesth Analg 70:154–159, 1990

2. Butler LE, Thomassen D, Martin JL, Martin BM, Kenna JG, Pohl LR: The calcium binding protein calreticulin is covalently modified in the liver by a reactive metabolite of the inhalation anesthetic halothane. Chem Res Toxicol 5:406–410, 1992

3. Carey RMT, Van Dyke RA: Halothane hepatitis: A critical review. Anesth Analg 51:135–160, 1972

4. Lewis JH, Zimmerman HJ, Ishak KG, Mullick FG: Enflurane hepatotoxicity: A clinicopathological study of 24 cases. Ann Intern Med 98:984–992, 1983

5. Carrigan TW, Straughen WJ: A report of hepatic necrosis and death following isoflurane anesthesia. ANESTHESIOLOGY 67:581–583, 1987

6. Wright R, Eade OE, Chilsom M, Hawksley M, Lloyd B, Moles TM, Edwards JC, Gardner JC: Controlled prospective study of the effect on liver function of multiple exposure to halothane. Lancet 1:817–820, 1975

7. Moult PJ, Sherlock S: Halothane-related hepatitis: A clinical study of twenty-six cases. QJ Med 173:99–114, 1975

8. Cousins MJ, Plummer JL, Hall PM: Risk factors for halothane hepatitis. Aust NZ J Surg 59:5–14, 1989

9. Walton B, Simpson BR, Strunin L, Doniach D, Perrin J, Appleyard AJ: Unexplained hepatitis following halothane. BMJ 1:1171–1176, 1976

10. Inman WHW, Mushin WW: Jaundice after repeated exposure to halothane: An analysis of reports to the Committee on Safety of Medicines. BMJ 1:5–10, 1984

11. Warner LO, Beach TJ, Garvin JP, Warner EJ: Halothane and children: The first quarter century. Anesth Analg 63:838–840, 1984

12. Kenna JG, Neuberger J, Mieli-Vergani G, Mowat AP, Williams R: Halothane hepatitis in children. BMJ 294:1209–1210, 1987

13. Neuberger J, Mieli-Vergani G, Tredger JM, Davis M, Williams R: Oxidative metabolism of halothane in the production of altered hepatocyte antigens in acute halothane-induced hepatic necrosis. Gut 22:669–672, 1981

14. Pohl LR, Thomassen D, Pumford NR, Butler LE, Satoh H, Ferrans VJ, Perrone A, Martin BM, Martin JL: Hapten carrier conjugates associated with halothane hepatitis. Adv Exp Med Biol 283:111–120, 1991

15. Dienstag JL: Halothane hepatitis: Allergy or idiosyncrasy? N Engl J Med 303:102–104, 1980

16. Kenna JG, Satoh H, Christ DD, Pohl LR: Metabolic basis for a drug hypersensitivity: Antibodies in sera from patients with halothane hepatitis recognize liver neoantigens that contain the trifluoroacetyl group derived from halothane. J Pharmacol Exp Ther 245:1103–1109, 1988

17. Pohl LR: An immunochemical approach of identifying and characterizing protein targets of toxic reactive metabolites. Chem Res Toxicol 6:786–793, 1993

18. Pohl LR, Kenna JG, Satoh H, Christ DD, Martin JL: Neoantigens associated with halothane hepatitis. Drug Metab Rev 20:203–217, 1989

19. Christ DD, Satoh H, Kenna JG, Pohl LR: Potential metabolic basis for enflurane hepatitis and the apparent cross-sensitization between enflurane and halothane. Drug Metab Dispos 16:135–140, 1988

20. Christ DD, Kenna JG, Kammerer W, Satoh H, Pohl LR: Enflurane metabolism produces covalently-bound liver adducts recognized by antibodies from patients with halothane hepatitis. ANESTHESIOLOGY 69:833–838, 1988

21. Cohen EN, Trudell JR, Edwards HD, Watson D: Urinary metabolites of halothane in man. ANESTHESIOLOGY 43:392–401, 1975

22. Chase RE, Holaday DA, Fiserova-Bergerova V, Saidman LJ, Mack FE: The biotransformation of ethrane in man. ANESTHESIOLOGY 35:262–267, 1971

23. Eger EI, Smuckler EA, Ferrell LD, Goldsmith CH, Johnson BH: Is enflurane hepatotoxic? Anesth Analg 65:21–30, 1986

24. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA: Resistance of isoflurane to biotransformation in man. ANESTHESIOLOGY 43:325–332, 1975

25. Brunt EM, White H, Marsh JW, Holtman B, Peters MG: Fulminant hepatic failure after repeated exposure to isoflurane anesthesia: A case report. Hepatology 6:1017–1021, 1991

26. Gunza JT, Pashayan AG: Postoperative elevation of serum transaminases following isoflurane anesthesia. J Clin Anesth 4:336–341, 1992

27. Scheider DM, Klygis LM, Tsang TK, Caughron MC: Hepatic dysfunction after repeated isoflurane administration. J Clin Gastroenterol 17:168–170, 1993

28. Sutton TS, Koblin DD, Gruenke LD, Weiskopf RB, Rampil IJ, Waskell L, Eger EI: Fluoride metabolites after prolonged exposure of volunteers and patients to desflurane. Anesth Analg 73:180–185, 1991

29. Sigurdsson J, Hreidarson AB, Thjodleifsson B: Enflurane hepatitis: A report of a case with a previous history of halothane hepatitis. Acta Anaesthesiol Scand 29:495–496, 1985

30. Martin JL, Dubbink DA, Plevak DJ, Peronne A, Taswell HF, Hay EJ, Pumford NR, Pohl LR: Halothane hepatitis 28 years after primary exposure. Anesth Analg 74:605–608, 1992