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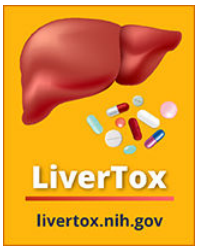

Sevoflurane

Updated: January 1, 2018.

OVERVIEW

Introduction

Sevofurane is one of the most commonly used volatile anesthetic agents, particularly for outpatient anesthesia and has an excellent safety record. Sevoflurane has been implicated in rare single case reports of severe acute liver injury similar to halothane hepatitis.

Background

Sevoflurane (see' voe flur' ane) is a widely used major anesthetic agent with rapid onset of action and rapid dispersal. Because of its rapid onset of action and lack of irritability to the airways, sevoflurane can be used to both induce and maintain anesthesia. Sevoflurane became available for use in the United States in 1995. Sevoflurane must be administered in a controlled situation by a properly trained and credentialed anesthesiologist or nurse anesthetist and is typically given in concentrations of 2% to 4% with oxygen.

Hepatotoxicity

Prospective, serial blood testing often demonstrates minor transient elevations in serum aminotransferase levels in the 1 to 2 weeks after major surgery. Appearance of ALT levels above 10 times the upper limit of normal, however, is distinctly unusual and points to significant hepatotoxicity. Clinically apparent, severe hepatic injury from sevoflurane is very rare, only isolated case reports having been published. The injury is marked by acute elevations in serum aminotransferase levels (5- to 50-fold) and appearance of jaundice within 2 to 21 days of surgery. There are usually minimal increases in alkaline phosphatase and gammaglutamyl transpeptidase levels. Jaundice is usually preceded by a day or two of fever and may be accompanied by rash and eosinophilia. The acute liver injury may be self-limited and resolve within 4 to 8 weeks, but can be severe and associated with acute liver failure. A strong risk factor is previous exposure to any of the halogenated anesthetics and particularly a history of halothane hepatitis or unexplained fever and rash after anesthesia with one of these agents. The differential diagnosis of acute liver injury after surgery and anesthesia is sometimes difficult, and a clinical picture similar to sevoflurane induced hepatitis can be caused by shock or ischemia, sepsis, other idiosyncratic forms of drug induced liver injury and acute viral or herpes hepatitis.

Likelihood score: B (highly likely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of sevoflurane hepatotoxicity is suspected to be similar to that of halothane and associated with creation of reactive intermediates. Sevoflurane is metabolized to a small extent by the microsomal drug

metabolizing enzyme CYP 2E1 to a trifluoroacetylated reactive intermediate (TFA) that is capable of binding to multiple intracytoplasmic proteins forming potentially immunogenic adducts. The TFA adducts induce antibodies that can be detected in patients with sevoflurane- as well as halothane hepatotoxicity and are also found in a proportion of health care workers exposed to the volatile anesthetics.

Outcome and Management

Severity ranges from mild and transient aminotransferase elevations without symptoms or other evidence of liver injury, to a self limited symptomatic acute hepatitis-like reaction to a severe, acute hepatic failure. The severity and prognosis may relate in part of patient age, being more severe in the elderly and both milder and less common in children. Obesity may also be both a predisposing factor and predictor of outcome. Chronic liver injury from sevoflurane exposure has not been described. Patients with sevoflurane induced hepatitis should be cautioned against future exposure to a fluorinated hydrocarbon anesthetic such as halothane, enflurane, isoflurane or desflurane.

Drug Class: Halogenated Anesthetics

Other Drugs in the Class: Desflurane, Enflurane, Halothane, Isoflurane

CASE REPORTS

Case 1. Suspected sevoflurane induced acute liver injury.

[Modified from a case in the database of the Drug-Induced Liver Injury Network]

A 49 year woman underwent arthroscopic surgery on her knee using midazolam, fentanyl, propofol and sevoflurane. She received a single IV infusion of cefazolin at the time of surgery. Eighteen days after surgery, she developed nausea, heartburn, and pruritus followed by dark urine. She had undergone general anesthesia three times in the past, but not in the previous year and the anesthetics used were not known. On admission, she was afebrile and physical examination revealed jaundice and mild hepatic tenderness. Laboratory tests showed elevations in serum enzymes and a total bilirubin of 4.0 mg/dL. There was no eosinophilia. Tests for hepatitis A, B and C and autoantibodies were normal. A liver ultrasound showed a gall bladder polyp, but no evidence of biliary obstruction. A liver biopsy showed cholestatic hepatitis with mild bile duct injury. She recovered rapidly and was asymptomatic and had normal liver tests a few weeks later.

Key Points

Medication:	Sevoflurane, 60 minutes anesthesia time
Pattern:	Hepatocellular (R=5.4)
Severity:	3+ (hospitalization for jaundice)
Latency:	18 days to symptoms
Recovery:	3 weeks
Other medications:	Anesthesia included fentanyl, propofol and versed. One dose of cefazolin given at the time of surgery. Postoperatively given ibuprofen, naproxen, hydrocodone, and occasional acetaminophen. Chronic therapy of allergies with Allegra and Nasonex.

Laboratory Values

Postoperative Days	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0	Arthroscopic surgery under sevoflurane anesthesia			

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Postoperative Days	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
24	618	328	4.0	
25	630	373	5.1	Liver biopsy
28	543	406	5.0	
34	267	285	1.3	
39	119	181	0.7	
Normal Values	**<45**	**<130**		

Comment

This patient developed jaundice and hepatic injury within 3 weeks of surgery under sevoflurane anesthesia. While the liver injury was attributed to the anesthetic by the reviewing physicians, the pattern of onset (latency of 3 weeks), clinical features (absence of fever, early appearance of pruritus) and liver histology (cholestasis) were atypical of anesthetic induced hepatotoxicity and more characteristic of penicillin or cephalosporin induced liver disease. The liver biopsy suggested a cholestatic hepatitis, even though the initial liver enzyme elevations were "hepatocellular". Indeed, this case was later re-adjudicated as being very likely due to cefazolin rather than sevoflurane.

Case 2. Sevoflurane induced acute liver injury.

[Modified from: Singhal S, Gray T, Guzman G, Verma A, Anand K. Sevoflurane hepatotoxicity: a case report of sevoflurane hepatic necrosis and review of the literature. Am J Ther 2010; 17: 219-22. PubMed Citation]

A 37 year man underwent resection of an abdominal wall mass under midazolam, nitrous oxide, propofol and sevoflurane anesthesia and was discharged the same day. Three days after surgery, he developed nausea, vomiting, abdominal pain and jaundice. He had no history of liver disease, drug reactions, alcohol abuse or risk factors for viral hepatitis. He had undergone an appendectomy under general anesthesia four years previously, but the anesthetics used were not known. Other medications included postoperative pain management with codeine and acetaminophen (<1 gram daily). On admission, laboratory tests showed mild jaundice (total bilirubin 4.2 mg/dL, direct 1.8 mg/dL), but marked elevations in serum aminotransferase levels (ALT 3364 U/L, AST 3013 U/L) and minimal increase in alkaline phosphatase (336 U/L) and mild eosinophilia. These values had been mildly elevated one week previously at the time of a preoperative evaluation (Table). Tests for hepatitis A and B and autoantibodies were normal. Tests for Ebstein Barr virus suggested recent infection. A liver ultrasound showed no gallstones or evidence of biliary obstruction. During the first few days after admission he worsened with deepening jaundice and coagulopathy, the INR rising to 4.8. A liver biopsy showed centrolobular necrosis and inflammation and cholestasis with minimal or no fibrosis, suggestive of acute drug induced liver injury. Liver transplantation was considered, but he then began to improve spontaneously and over the next 4 months his symptoms resolved and liver test results returned to normal.

Key Points

Medication:	Sevoflurane anesthesia
Pattern:	Hepatocellular (R=20)
Severity:	4+ (hospitalization, jaundice and coagulopathy)
Latency:	3 days to symptoms
Recovery:	4 months

Table continued from previous page.

Other medications:	Anesthesia included nitrous oxide, propofol and midazolam. Postoperatively given acetaminophen (<1 gram daily) and codeine for pain

Laboratory Values

Postoperative Days	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	199	188	0.8	
3	3064	336	4.2	Admission
6	4861	308	9.3	
8	4137	292	12.7	
10	1456	212	16.5	
13	619	200	25.6	Liver biopsy
18	130	208	30.4	
21	120	214	31.2	
60	43	364	16.1	
105	39	140	1.3	
Normal Values	**<60**	**<121**	**<1.2**	

Comment

This patient developed jaundice and severe hepatic injury within 3 days of surgery under sevoflurane anesthesia. The clinical course was typical of halogenated anesthetic liver injury with a rapid onset, mild eosinophilia, a hepatocellular pattern of injury and severe course. Risk factors included previous anesthesia (although the agent used was not known). Unexplained were the abnormal liver tests obtained before surgery and the equivocal serology of EBV infection. Results of tests for hepatitis C and E were not provided.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sevoflurane – Generic, Sevorane®, Ultane®

DRUG CLASS

Anesthetics, Halogenated

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Sevoflurane	28523-86-6	C4-H3-F7-O	

ANNOTATED BIBLIOGRAPHY

References updated: 01 January 2018

Zimmerman HJ. Anesthetic agents. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 457-82.

(Expert review of hepatotoxicity of anesthetic agents published in 1999; mentions that the newer halogenated anesthetics appear to be safer than halothane, but that hints of liver injury from desflurane and sevoflurane have appeared).

Kenna JG. Mechanism, pathology, and clinical presentation of hepatoxicity of anesthetic agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp 403-22.

(Review of liver injury from anesthetic agents mentions that several cases of sevoflurane hepatotoxicity were reported from Japan, where it was used widely at least 10 years before introduction into the United States, and several cases have subsequently been reported from other countries).

Patel PM, Patel HH, Roth DM. General anesthetics and therapeutic gases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 527-64.

(Textbook of pharmacology and therapeutics).

Ogawa M, Doi K, Mitsufuji T, Satoh K, Takatori T. [Drug induced hepatitis following sevoflurane anesthesia in a child] Masui 1991; 40: 1542-5. Japanese. PubMed PMID: 1766104.

(11 year old boy with first exposure to sevoflurane developed 15-20 fold elevations in ALT and AST without jaundice 11-22 days after anesthesia).

Shichinohe Y, Masuda Y, Takahashi H, Kotaki M, Omote T, Shichinohe M, Namiki A. [A case of postoperative hepatic injury after sevoflurane anesthesia] Masui 1992; 41: 1802-5. Japanese. PubMed PMID: 1460759.

(63 year old man underwent surgery under sevoflurane anesthesia and had ALT elevations starting on postoperative day 3 and jaundice on day 7 [peak bilirubin 14.5 mg/dL, ALT 700 U/L], resolving within 2 months).

Watanabe K, Hatakenaka S, Ikemune K, Chigyo Y, Kubozono T, Arai T. [A case of suspected liver dysfunction induced by sevoflurane anesthesia] Masui 1993; 42: 902-5. Japanese. PubMed PMID: 8320810.

(One month old male infant developed fever followed by 5-8 fold elevations in ALT [326 KU/L], AST [242 KU/L] and LDH [901 WU/L], without jaundice after sevoflurane anesthesia).

Ohmori H, Seki S, Kanaya N, et al. A case report of postoperative liver dysfunction following sevoflurane anesthesia after isoflurane anesthesia. J Jpn Soc Clin Anesth 1994; 14: 68-71.

Not in PubMed.

Fee JP, Thompson GH. Comparative tolerability profiles of the inhaled anaesthetics. Drug Saf 1997; 16: 157-70. PubMed PMID: 9098654.

(Review of metabolism and literature on hepatotoxicity of halogenatic anesthetics: halothane is extensively metabolized [oxidized] by the liver and major metabolite is TFA which may be a toxic intermediary metabolite).

Nishiyama T, Yokoyama T, Hanaoka K. Liver function after sevoflurane or isoflurane anaesthesia in neurosurgical patients. Can J Anaesth 1998; 45: 753-6. PubMed PMID: 9793665.

(Prospective analysis of ALT, AST, Alk P and bilirubin levels after sevoflurane or isoflurane [n=45 each] showed minimal increases in ALT and AST peaking at 7 days; elevated in ~20% of patients, but none were symptomatic or jaundiced).

Bruun LS, Elkjaer S, Bitsch-Larsen D, Andersen O. Hepatic failure in a child after acetaminophen and sevoflurane exposure. Anesth Analg 2001; 92: 1446-8. PubMed PMID: 11375824.

(3 year old girl developed marked ALT [>10,000 U/L], AST [>7000 U/L] and LDH [37,923 U/L] elevations by day 4 after appendectomy under sevoflurane anesthesia, with jaundice [3.5 mg/dL], coma and coagulopathy, ultimately resolving; exposed to many other drugs including rectal acetaminophen).

Siddiqui MS, Vollers JM, Mayhew JF. Did sevoflurane contribute to hepatic failure in a child given large doses of acetaminophen? Anesth Analg 2002; 95: 253; PubMed PMID: 12088983.

(Letter arguing that case described by Bruun [2001] was due to acetaminophen).

Reich A, Everding AS, Bulla M, Brinkmann OA, Van Aken H. Hepatitis after sevoflurane exposure in an infant suffering from primary hyperoxaluria type 1. Anesth Analg 2004; 99: 370-2, table of contents. PubMed PMID: 15271707.

(11 month of infant developed marked ALT [543 U/L], AST [683 U/L] and LDH [960 U/L] elevations 2 days after sevoflurane anesthesia, which returned to baseline within days without jaundice, fever, or eosinophilia, possibly due to ischemic hepatitis).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the United States between 1990 and 2002, 137 [0.2%] were done for idiosyncratic drug induced acute liver failure, of which 3 were attributed to halothane and 1 to isoflurane, but none to other halogenated anesthetics).

Jang Y, Kim I. Severe hepatotoxicity after sevoflurane anesthesia in a child with mild renal dysfunction. Paediatr Anaesth 2005; 15: 1140-4. PubMed PMID: 16324041.

(6 year old girl had rise of ALT [peak 744 U/L] and AST [peak 2125 U/L] levels 2-7 days after renal biopsy and sevoflurane anesthesia, with fever and malaise but no jaundice; no previous exposures).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101. PubMed PMID: 16165719.

(36 years of reporting to Swedish registry identified 103 cases of acute liver failure due to drugs, of which 16 were attributed to halothane [ranking #1], but none to other halogenated anesthetics).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis 2006; 38: 33-8. PubMed PMID: 16054882.

(In WHO database of fatal adverse drug reactions from 1968-2003, there were 4690 reports of drug induced liver fatalities; halothane ranked fifth in frequency but most cases were reported before 1991).

Lehmann A, Neher M, Kiessling AH, Isgro F, Koloska A, Boldt J. Case report: fatal hepatic failure after aortic valve replacement and sevoflurane exposure. Can J Anaesth 2007; 54: 917-21. PubMed PMID: 17975238.

(76 year old woman developed acute liver failure within days of sevoflurane anesthesia for cardiac surgery [bilirubin 1.0 rising to 2.7 mg/dL, ALT 10504 U/L, Alk P 125 U/L, LDH 12,944 U/L]; course more typical of ischemic than anesthetic hepatitis).

Turillazzi E, D'Errico S, Neri M, Riezzo I, Fineschi V. A fatal case of fulminant hepatic necrosis following sevoflurane anesthesia. Toxicol Pathol 2007; 35: 840-5. PubMed PMID: 17943651.

(69 year old man developed marked rises in ALT [641 U/L], AST [2196 U/L] and LDH 20 hours after initial surgery under sevoflurane anesthesia, with further rises >1000 U/L after emergency surgery and reexposure to sevoflurane, with death 8 days later).

Alotaibi WM. Severe hepatic dysfunction after sevoflurane exposure. Saudi Med J 2008; 29: 1344-6. PubMed PMID: 18813426.

(6 year old underwent craniotomy under sevoflurane anesthesia developed high ALT levels [2891 U/L] immediately postoperatively, which fell to normal by day 7 at which time she developed thrombocytopenia, intracerebral bleeding and coma resulting in death by day 9).

Fernández-Meré LA, Muñoz González F, Sopena Zubiria LA, Alvarez Blanco M. [Sevoflurane and liver dysfunction]. Rev Esp Anestesiol Reanim 2008; 55 :184-5. Spanish. PubMed PMID: 18401994.

(61 year old woman developed fatigue, fever and elevations in ALT [334 and 109 U/L and GGT 121 and 194 U/L] 2 to 4 weeks after sevoflurane anesthesia on two occasions without jaundice and with full resolution in 2 weeks).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease collected in the US between 2003 and 2008, 2 cases were attributed to desflurane and 1 to sevoflurane [see Case 1], none to other halogenated anesthetics).

Zizek D, Ribnikar M, Zizek B, Ferlan-Marolt V. Fatal subacute liver failure after repeated administration of sevoflurane anaesthesia. Eur J Gastroenterol Hepatol 2010; 22: 112-5. (PubMed PMID: 19657276.

66 year old woman exposed to sevoflurane anesthesia twice in 25 days developed jaundice and subacute liver failure arising 2 weeks later [bilirubin 31.5 mg/dL, ALT 2400 U/L, Alk P 282 U/L, INR 2.0], progressing to hepatic failure and death 66 days after second anesthesia; autopsy showed massive necrosis).

Singhal S, Gray T, Guzman G, Verma A, Anand K. Sevoflurane hepatotoxicity: a case report of sevoflurane hepatic necrosis and review of the literature. Am J Ther 2010; 17: 219-22. PubMed PMID: 19455019.

(37 year old man developed nausea and jaundice 3 days after sevoflurane anesthesia [bilirubin 4.2 rising to 30.4 mg/dL; ALT 3364 U/L, Alk P 336 U/L], resolving within 3 months).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed Citation (313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; none were attributed to anesthetic agents).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. Multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury inlcuding one due to halothane and one to isoflurane, but none to other anesthetic agents).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed Citation (Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, no anesthetic agent ranked in the top 41 causes).

Nicoll A, Moore D, Njoku D, Hockey B. Repeated exposure to modern volatile anaesthetics may cause chronic hepatitis as well as acute liver injury. BMJ Case Rep 2012; 2012. (Description of 4 cases of chronic hepatitis in patients who had repeated surgical exposures to sevoflurane and were found to have antibodies to CYP 2E1 and TFA). PubMed PMID: 23131606.

Masin-Spasovska J, Dimitrovski K, Stavridis S, Stankov O, Dohcev S, Saidi S, Jakovski K, et al. Acute fulminant hepatatis in kidney transplant recipient after repeated sevoflurane anesthesia--a case report and literature review. Curr Drug Saf 2013; 8: 141-4. PubMed PMID: 23845191.

(47 year old woman developed renal failure and hypotension after renal transplantation and required reoperation 2 days later, which was followed by ALT [3,300 U/L] and LDH [8,900 U/L] elevations which the authors attributed to sevoflurane anesthesia, but may have been due to shock and ischemia).

Nishiyama T. Effects of repeat exposure to inhalation anesthetics on liver and renal function. J Anaesthesiol Clin Pharmacol 2013; 29: 83-7. PubMed PMID: 23493664.

(Retrospective analysis of 206 patients who underwent anaesthesia twice within a 1 year period found higher rates of ALT elevations within 16 days after isoflurane [60-83%] than sevoflurane [24-30%] or propofol-fentanyl [12-17%], most elevations being less than twice ULN and no differences between first and second exposures).

Safari S, Motavaf M, Seyed Siamdoust SA, Alavian SM. Hepatotoxicity of halogenated inhalational anesthetics. Iran Red Crescent Med J 2014; 16: e20153. PubMed PMID: 25593732.

(Review of hepatotoxicity of the volatile halogenated anesthetics).

Lin J, Moore D, Hockey B, Di Lernia R, Gorelik A, Liew D, Nicoll A. Drug-induced hepatotoxicity: incidence of abnormal liver function tests consistent with volatile anaesthetic hepatitis in trauma patients. Liver Int 2014; 34: 576-82. PubMed PMID: 23944929.

(Retrospective analysis of records from 1556 patients admitted to a trauma unit during 2008 identified 47 cases of possible volatile anesthetic related liver injury, including 12 who developed ALT levels above 200 U/L of whom 11 had fever and 6 eosinophilia, but none were jaundiced or developed acute liver failure).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. (Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases of which 5 [3%] were attributed to halothane and caused acute liver failure, while PubMed PMID: 24552865.

no other volatile anesthetic was listed).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 2 were attributed to isoflurane, 1 to sevoflurane, but none to halothane, enflurane or desflurane).