

# Desflurane-Induced Hepatitis

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## Abstract

Inflammatory hepatitis following desflurane anesthesia was once thought to be a rare occurrence. However, case reports documenting complications related to the use of this anesthetic continue to accumulate <sup>(1-5)</sup>

Risk factors for desflurane-induced hepatitis likely exist. Female gender, prior anesthetic experience with halothane, occupational exposure to halogenated anesthetics, atopy, and autoimmune disease may predispose an individual to immune-mediated hepatitis following desflurane anesthesia <sup>(6,7)</sup>

## CASE REPORT

A healthy, thin (body mass index = 22.4), 37-year-old, female, operating room nurse presented to our community hospital for a scheduled laparoscopic total hysterectomy. Drug allergies included ciprofloxacin, meperidine, morphine, and tetracycline. Her only previous surgery was a bilateral tonsillectomy and adenoidectomy, 20 years earlier. Social history was negative for tobacco use and alcohol consumption. Vital signs on the day of surgery were within normal limits.

General anesthesia was induced with propofol and maintained with desflurane mixed in oxygen. Droperidol, ondansetron, and dexamethasone were administered for post-operative nausea and vomiting prophylaxis. The total intraoperative anesthetic time was 90 minutes. At the conclusion of the surgery she was extubated and transported to the post-anesthesia care unit in stable condition. Estimated blood loss was 50 ml, urine output was 350 ml, and 1.1 l of intravenous (IV) fluid was given. A complete blood count (CBC) performed on postoperative day 1 was unremarkable.

On postoperative day 19 she presented to an emergency department complaining of diffuse itching, jaundice, and nausea. Blood work revealed several elevated liver function tests (LFTs): a total bilirubin of 1.9 mg/dl (0.2-1.0), an alanine transaminase (ALT) of 272 IU/L (7-40), an aspartate aminotransferase (AST) of 81 IU/L (12-45), and an alkaline phosphatase of 371 IU/L (37-107). A lipase level was normal. Her CBC was notable for eosinophilia. Infectious etiologies of hepatitis were all non-reactive. Immunological studies, including anti-nuclear, anti-centromere, and anti-mitochondrial antibodies, were negative. A computed

tomography scan of the abdomen and pelvis revealed a non-obstructive renal stone. An ultrasound of the upper abdomen demonstrated a normal-appearing liver and gallbladder. Treatment rendered in the emergency department consisted of IV fluids, ondansetron, famotidine, promethazine, and lorazepam.

Elevated total bilirubin, ALT, AST, and alkaline phosphatase levels persisted on succeeding LFTs. Hepatic synthetic function remained undisturbed, as evidenced by normal albumin, protein, and international normalized ratio levels. One month after her original presentation, all LFTs had returned to normal, beginning with her AST and ALT, and subsequently followed by her alkaline phosphatase. The eosinophilia resolved without any medical intervention.

Serum testing demonstrated the presence of IgG<sub>4</sub> antibodies against trifluoroacetyl chloride and CYP2E1, which is the most common autoantibody seen in anesthetic induced hepatitis<sup>(1)</sup>. In the context of this case, these serum results are highly suggestive of, if not pathognomonic for, desflurane-induced hepatitis<sup>(1)</sup>.

## DISCUSSION

Desflurane is poorly soluble in blood, has a quick recovery profile, and is the least metabolized volatile anesthetic<sup>(8)</sup>. This makes it an attractive anesthetic agent. Despite being minimally metabolized, desflurane has been implicated in inducing hepatitis in several case reports<sup>(1-5)</sup>. With desflurane-induced hepatitis it appears that the hepatic protein CYP2E1 is covalently altered by a trifluoroacetyl chloride hapten during CYP2E1-mediated desflurane oxidative metabolism<sup>(9)</sup>. The altered CYP2E1 generates an

immune response with production of IgG<sub>4</sub> autoantibodies in susceptible individuals.

Occupational exposure to halogenated anesthetics increases an individual's likelihood of generating autoantibodies to hepatic proteins, including CYP2E1<sup>(6)</sup>. Elevated serum levels of autoantibodies to CYP2E1 have been documented in pediatric anesthesia providers, and were most pronounced in female pediatric anesthesiologists<sup>(6)</sup>. It follows that non-anesthesia intraoperative personnel are also at increased risk for developing autoantibodies to CYP2E1. The subject of this case report worked and was asymptomatic in the operating room setting for several years prior to her post-operative hepatitis. She has since resumed working in the operating room without evidence of symptomatic hepatitis and her liver function tests have returned to and remain within normal limits. The impact of chronic exposure to trace amounts of volatile anesthetic agents in this case remains speculative and undetermined.

The details of this patient's only prior anesthetic administration are unknown. However, given the nature of her surgery, a bilateral tonsillectomy and adenoidectomy, and the date at which it occurred, before the release of sevoflurane and desflurane, it is likely that halothane was administered. Prior halothane exposure can produce cross sensitization to desflurane<sup>(7)</sup>.

The diagnostic differential for postoperative hepatitis is broad and compounded by the paucity of commercial laboratories that test for autoantibodies to the volatile anesthetic metabolite, trifluoroacetyl chloride, and to CYP2E1. The difficulty in diagnosis is further exacerbated by the temporal disconnect between anesthetic exposure and the manifestation of physical symptoms and laboratory abnormalities. This delayed presentation, typically 1-3 weeks following exposure, impairs accurate diagnosis and hampers efforts to detail the incidence of desflurane-induced hepatitis<sup>(1,3)</sup>. As such, symptomatic patients who do seek medical attention are likely to be improperly evaluated and misdiagnosed leading to underreporting. It is also plausible

that a subpopulation of mildly-symptomatic patients do not even seek medical attention.

The clinical implications of this case are not insignificant to the future anesthetic care of this patient. With a strongly-suspected adverse reaction to a volatile anesthetic agent it is imperative to avoid re-exposure, since fulminant liver failure can occur<sup>(3)</sup>. Future anesthetic considerations are not unlike those for malignant hyperthermia. Total intravenous anesthesia should be administered, vaporizers removed from the anesthesia machine, and high flow oxygen run through the anesthetic circuit for 10-20 minutes before anesthetic induction<sup>(10)</sup>. Elective surgery should be scheduled for the first case of the day, and this patient should wear a medical bracelet listing volatile anesthetic agents as an allergy.

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