General Anesthesia

Severe desflurane hepatotoxicity after colon surgery in an elderly patient

[Sévère hépatotoxicité au desflurane après une opération du colon chez une patiente âgée]

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Purpose: To report a case of desflurane hepatotoxicity.

Clinical features: An 81-yr-old woman with a remote history of abdominal surgery developed severe acute liver injury after general anesthesia with desflurane for resection of colonic cancer. Serum alanine aminotransferase and aspartate aminotransferase peaked at postoperative day six (2188 and 425 $U \cdot L^{-1}$ respectively), with the development of coagulopathy with an international normalized ratio of 2.29 on postoperative day eight, progressive jaundice with a peak serum total bilirubin of 214 $\mu mol \cdot L^{-1}$ on postoperative day 12 and hepatic encephalopathy on postoperative day ten. Other causes for liver disease were excluded. Treatment with corticosteroids was started. The liver biochemistry normalized completely by postoperative day 30 and the patient was discharged from hospital on postoperative day 21.

Conclusions: To our knowledge, this represents only the third report of desflurane hepatotoxicity and the first with reversible fulminant liver failure. Our experience suggests that all fluorinated anesthetics may cause acute hepatic damage.

Objectif : *Présenter un cas d'hépatotoxicité au desflurane.*

Éléments cliniques : *Une lésion hépatique aiguë sévère s'est développée chez une femme de 81 ans, déjà opérée à l'abdomen longtemps auparavant, à la suite d'une anesthésie générale avec du desflurane pour la résection d'un cancer du colon. L'alanine aminotransférase et l'aspartate aminotransférase sériques ont présenté des valeurs maximales au jour six après l'opération (2188 et 425 $U \cdot L^{-1}$ respectivement). Une coagulopathie selon un ratio international normalisé de 2,29 s'est développée au jour huit, un ictère progressif avec un taux maximal de bilirubine totale de 214 $\mu mol \cdot L^{-1}$ au jour 12 et une encéphalopathie hépatique au jour dix. D'autres causes de lésion hépatique ont été exclues. Un traitement aux corticostéroïdes a été amorcé. La biochimie hépatique s'est complètement normalisée au jour 30 et la patiente a quitté l'hôpital au jour 21.*

Conclusion : *Nous croyons que c'est seulement le troisième cas documenté sur l'hépatotoxicité au desflurane et le premier à présenter une insuffisance hépatique fulminante réversible. Notre expérience laisse penser que tous les anesthésiques fluorés pourraient causer des atteintes hépatiques aiguës.*

HEPATOTOXICITY has been associated with volatile fluorinated anesthetics since their introduction and halothane hepatotoxicity[1,2] is the classic example. Modification of liver proteins through trifluoroacylation by metabolites of volatile anesthetics is thought to produce immunogenic adducts eliciting a specific immune response resulting in hepatic damage[3,4] and possible sensitization to future exposure. Desflurane is a newer anesthetic agent that is not generally considered to be associated with liver injury. We report a patient who developed acute hepatotoxicity after desflurane anesthesia.

Case report

A slightly overweight 81-yr old Caucasian female patient was admitted for right hemicolectomy for adenocarcinoma. There was no evidence of metastasis and a preoperative computed tomography scan did not reveal lesions in the liver. She was otherwise in good

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Accepted for publication February 24, 2004.

Revision accepted November 5, 2004.

TABLE Serial serum liver biochemistry postoperatively. Total bilirubin is reported in μmol·L^{-1}, all other values are reported in U·L^{-1}

	Postoperative day									
Test	6	8	10	12	14	16	18	20	30	34
ALP	149	231	296	277	252	278	335	316		
GGT	130	381	438		409	535	737	637		
T B	118	166		214		109	98	116	54	41
D B	80	128		167		81	70	73		
ALT	2188	905	567		250	200	189	153	52	45
AST	425	108	103	97	85	89	95	89	34	46
INR		2.29	1.63	1.50	1.50	1.46	1.37	1.21		
PTT		38.4	32.1	32.0	33.0	30.4	39.9	32.3		

ALP = alkaline phosphatase (normal 50–200 U·L^{-1}); GGT = gamma-glutamyl transferase (10–55 U·L^{-1}); T B = total bilirubin [0–18 μmol·L^{-1}); D B = direct bilirubin (0–5 μmol·L^{-1}); AST = aspartate aminotransferase (10–40 U·L^{-1}); ALT = aspartate aminotransferase (20–65); INR = international normalized ratio (0.9–1.2); PTT = partial thromboplastin time (25–38 sec).

health with no history of liver problems. She had never received blood transfusions, had no tattoos, did not use *iv* drugs, did not consume significant amounts of alcohol and there was no recent travel history. Medications prior to surgery consisted of atenolol for hypertension and she had no known allergies. The family history was negative for liver disease. Her surgical history consisted of an appendectomy 36 years previously and cystocele repair approximately 20 years previously. Records of these procedures were not available.

Seven weeks prior to surgery her liver biochemistry was unremarkable. The serum alkaline phosphatase (ALP) and aspartate aminotransferase (AST) levels were 72 U·L^{-1} (normal range: 40–120 U·L^{-1}) and 15 U·L^{-1} (10-40 U·L^{-1}) respectively. On the day of the surgery her hemoglobin was 94 g·L^{-1} (120–150 g·L^{-1}) and the international normalized ratio (INR) was 1.0 (0.9–1.2). An epidural catheter was placed and hydromorphone and bupivacaine were employed before intubation of the trachea under anesthesia with fentanyl (100 μg) and propofol (80 mg). This was followed by rocuronium (40 mg) for muscle relaxation and 6% desflurane in an air-oxygen mixture. Operative findings revealed a mass extending to the serosa with no gross extra-serosal involvement. The procedure continued without complications such as hypotension or hypoxemia. Total anesthesia time was 90 min and surgery was 70 min. In the immediate postoperative period the patient received two units of packed red blood cells. There were no new electrocardiogram findings at that time and serial troponin I levels were normal.

On the sixth day after surgery the patient was noted to be jaundiced and complained of malaise and anorexia. The vital signs were stable and she was afebrile She appeared to have no cognitive deficit and had no rash or pruritus. There was no evidence of eosinophilia on hematologic profile. The liver biochemistry was markedly abnormal: serum gamma-glutamyl transferase 130 U·L^{-1} (10–55 U·L^{-1}), ALP 149 U·L^{-1} (50–200 U·L^{-1}); alanine aminotranferase (ALT) 2188 U·L^{-1} (20–65 U·L^{-1}), AST 425 U·L^{-1} (10–38 U·L^{-1}), total bilirubin 118 μmol·L^{-1} (0–18 μmol·L^{-1}). Although the ALT and AST began to decrease (Table), the patient's coagulation tests and jaundice worsened with an INR of 2.29 on postoperative day (POD) eight and total bilirubin 214 μmol·L^{-1} on POD 12. Clinically the patient developed confusion consistent with stage I/IV hepatic encephalopathy on POD ten. Because of the apparent severity of the liver dysfunction, she was started on methylprednisone 60 mg *iv* daily for five days. The liver biochemistry and hepatic encephalopathy improved such that she was discharged from hospital on POD 21.

Investigations failed to reveal a cause of acute liver failure other than desflurane hepatotoxicity. Abdominal ultrasonography revealed gallbladder sludge with no biliary dilatation and an unremarkable liver. Viral serologies for anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core antibody and anti-hepatitis C antibodies were negative. The patient was seropositive for herpes simplex IgG and Epstein-Barr virus IgG, indicating previous infection, but negative for cytomegalovirus IgG. Serum iron was 5 μmol·L^{-1} (9–30 μmol·L^{-1}) and percent saturation was 24% (20–55%). Ceruloplasmin, serum copper, anti-mitochondrial, anti-smooth muscle and antinuclear antibodies were all negative or normal.

Discussion

Halothane-induced hepatotoxicity is well-recognized.[1] It presents in either a self-limited form with modest elevation of serum transaminases or a more severe form

with large increases in serum aminotransferases and jaundice. The latter is known as "halothane hepatitis" and can progress to severe hepatic necrosis and death.[2] The mechanism responsible for the hepatic damage is thought to be immunologic. Oxidation of halothane by the cytochrome P-450 (CYP) system results in the formation of several reactive intermediates, principally trifluoroacetyl chloride[3,4] that can bind covalently to amino groups of proteins. This leads to the formation of trifluoroacetylated (TFA) liver microsomal proteins that are thought to be immunogenic, and elicit specific antibody and/or T-cell responses. The incidence of severe hepatic damage is related to the degree of oxidative biotransformation of halogenated anesthetic gases. The extent of CYP metabolism of halothane, enflurane, isoflurane and desflurane is reported to be 20%, 2.4%, 0.2% and 0.01%, respectively.[5–8] Accordingly the risk of hepatic damage by these agents follows a similar pattern.[9] This model also explains the sensitization of patients to TFA-adducts by past exposure and the cross-reactivity between these agents. Formation of the TFA-adducts may also induce autoantibodies against the unmodified precursor protein such as CYP2E1.[10] In this patient, the remote surgical history of an appendectomy 36 years previously, may assume importance as halothane was probably the agent used in that era and could have resulted in sensitization to desflurane.

The presentation of hepatic failure in this patient is typical for anesthetic-induced hepatitis. These features include delayed onset of jaundice and severe hepatic damage after anesthesia. She was likely sensitized to TFA-adducts by prior exposure to volatile anesthetics during her previous two surgeries. Investigations ruled out viral and metabolic causes of hepatic failure. We note that reduction in hepatic blood flow during surgical procedures has been reported in the older surgical literature[11] dating back to the 1970's, however, this patient did not have any of the pathogenic conditions associated with ischemic hepatitis (also known as "shock liver" or "hypoxic hepatitis") such as severe cardiac or respiratory compromise or septic shock.[12–14] Moreover, the biochemical features of this patient's acute liver dysfunction, a prolonged period of hyperbilirubinemia (which itself is rare in ischemic hepatitis)[14] and a slow normalization of serum transaminases, were inconsistent with ischemic hepatitis. Therefore, despite the unavailability of a commercial TFA assay in Canada, a diagnosis of anesthetic-induced hepatotoxicity is secure with the noteworthy aspect of this case being that desflurane was the agent that resulted in acute drug hepatotoxicity.

Although probably under-reported, the present case is only the third reported case of desflurane induced hepatitis in the medical literature. This case is similar to the two other cases,[9,15] in that the patient eventually recovered from desflurane hepatotoxicity. Where this case differs significantly from the two previously reported cases, is in the fact that the patient developed hepatic encephalopathy. This indicates severe hepatic dysfunction and fulfills the definition of "fulminant" liver failure. Whether the corticosteroid treatment played a role in the patient's recovery remains speculative. Despite the fact that all three cases, including this one, of desflurane hepatotoxicity have recovered, it is important to keep in mind that acute liver failure secondary to halothane hepatotoxicity is a negative prognostic factor for recovery.[16] Furthermore, in a recent study, transplant-free survival for non-acetaminophen drug hepatotoxicity in general, was poor at 25%.[17] Although this patient, for reasons of advanced age, and extra-hepatic malignancy, would not have been a feasible candidate for transplantation had her liver failure not recovered, it is important to keep this possibility in mind when investigating other patients with progressive anesthetic-induced acute liver failure.

In conclusion, our experience supports the suggestion that all fluorinated anesthetics, including desflurane, can cause severe hepatic damage and, when investigating postoperative liver failure, anesthetic hepatotoxicity should be on the list of differential diagnoses even if halothane is not used.

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