Reproducible Hepatic Dysfunction Following Separate Anesthesia with Sevoflurane and Desflurane

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Both desflurane and sevoflurane have individually been reported to induce hepatic dysfunction; however hepatic dysfunction after administration of both of them separately in a single patient has not previously been reported. As their metabolites differ in nature, we considered that it would be unlikely that their combined use would cause sensitization and induce hepatic dysfunction. We report on the first patient with reproducible liver dysfunction after sevoflurane and desflurane. This 54-year-old man sequentially received 3 anesthetics over a 1-year period. The first anesthetic was isoflurane, and the course was uneventful. The second anesthetic was sevoflurane, and this resulted in fever with chills and elevated aspartate aminotransferase (543 U/l) 17 days later. The third anesthetic was desflurane which resulted in a similar clinical picture after 17 days. The symptoms improved, and the serum transaminase level returned to normal after conservative therapy. The similar time interval between the operation date and the onset of hepatic dysfunction, after excluding other possibilities, made us highly suspicious that the hepatic dysfunction was induced by sevoflurane on 1 occasion and desflurane on the other. We suggest that inhaled anesthetics should be totally replaced by intravenous anesthetics for future operations in patients with such a diagnosis. *(Chang Gung Med J 2003;26:357-62)*

Key words: isoflurane, sevoflurane, desflurane, liver function, hypersensitivity.

Desflurane and sevoflurane have each individually been reported to induce hepatic dysfunction, but not together.[1-3] As desflurane is oxidatively metabolized by liver cytochrome P-450 to form trifluoroacetylated (TFA) proteins,[4] the primary organic metabolite of sevoflurane is hexafluoroisopropanol (HFIP), and because it seldom forms liver protein adducts,[5] we considered that TFA-protein sensitization was unlikely to induce hepatic dysfunction. We hereby report on a patient who had impaired liver function after both sevoflurane and desflurane were administered on separate occasions.

CASE REPORT

A 54-year-old male, 157 cm tall, weighing 71 kg, and with an ASA physical status of II, was admitted to our surgical ward for excision of a soft tissue tumor in the posterior area of the right mandibular alveolar ridge. The operation was performed under general anesthesia, which was maintained with nitrous oxide and isoflurane and which lasted for 2 hours 15 min on August 3, 1999 (Table 1). He denied having any major systemic disease including hypertension or liver disease, had no histo-

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Table 1. Perioperative Laboratory Data of the Patient with Isoflurane, Sevoflurane, and Desflurane Anesthesia

	Date	AST U/l	ALT U/l	γ-GT U/l	ALP U/l	T. Bili mg/dl	AC sugar mg/dl	VDRL	HBsAg	HCV Ab	T3 ng/dl	T4 μg/dl	TSH μIU/dl	TG mg/dl
Sevoflurane	2 Aug. 1999	17	15				91	Neg	Neg					
anesthesia	26 Aug. 1999	14	14											
30 Aug. 1999	31 Aug. 1999													
	6 Sept. 1999	19	16											
	13 Sept. 1999	22	25											
	19 Sept. 1999	543	287				113							
	23 Sept. 1999													
Desflurane	7 July 2000										104	7.5	1.26	
anesthesia	21 Aug. 2000	23	40		73						117	6.4	2.21	
22 Aug. 2000	28 Aug. 2000										62	4.8	6.92	
	18 Sept. 2000	249	212	561	275	1.1	155		Neg	Neg		2.65	33.8	< 1
	21 Sept. 2000	91	189	440	199	1.2								
	25 Sept. 2000	72	150	373	168	1.6								
	2 Oct. 2000	40	80	211	108	1.2								
	9 Oct. 2000	41	70	155	97	1.8								
	12 Oct. 2000												> 47	< 1
	19 Oct. 2000	26	32	91	78	1.2								

Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GT: γ-glutamyltransferase; ALP: alkaline phosphatase; AC sugar: sugar before a meal; VDRL: venereal disease research laboratory; HBsAg: hepatitis B surface-antigen; T. Bili: total bilirubin; HCV-AB: hepatitis C virus antibody; T3: triiodothyronine 3; T4: triiodothyronine 4; TSH: thyroid-stimulating hormone; TG: triglyceride.

ry of drug allergies, blood transfusions, intravenous drug abuse, or exposure to hepatotoxin, and alcohol consumption was only social. Preoperative laboratory data showed mild anemia and normal liver function. The patient was discharged uneventfully 2 days after the surgery. He was readmitted about 3 weeks later because the pathologist reported a verrucose carcinoma.

Radical neck dissection and radical flap reconstruction were performed on August 30, 1999. The blood pressure on arrival in the operating theatre was 229/112 mmHg, and 35 mg labetalol was administered intravenously. Anesthesia was induced with fentanyl, 2.5% sodium thiopental, and sevoflurane and was maintained with sevoflurane in oxygen (0.5 l/min) for a duration of 14 hours without immediate morbidity. Vecuronium was used to facilitate tracheal intubation and for muscle relaxation. The heart rate and O_2 saturation remained normal, and the electrocardiogram (ECG) revealed no abnormality throughout the operation. He was discharged uneventfully on September 15. Two days after discharge, he experienced fever with chills, and visited our emergency room on September 19, where impaired liver function with elevated aspartate aminotransferase (AST) (543 U/l) was noted (Table 1). An abdominal sonogram was performed on September 23, which revealed mild hepatomegaly and mild fatty liver. No chemotherapy was administered in this period. The symptoms spontaneously subsided in 5 days.

One year later, on August 22, 2000, this patient underwent a radical thyroidectomy and left neck dissection under general anesthesia for a left thyroid papillary carcinoma with left neck lymph node metastasis. Anesthesia was induced with fentanyl, 2.5% sodium thiopental, and atracurium, and was maintained with desflurane in oxygen (1 l/min). Hypertension was also noted upon arrival in the operating theatre (238/117 mmHg), during induction of anesthesia (190/105 mmHg), and at the end of the operation (230/105 mmHg). Nicardipine at 1 mg and 10 mg labetalol were administered intravenously, and the ECG throughout the entire period showed no abnormality. The operation lasted for approximately 4 hours. However, on September 8, 2000, 18 days after the operation, he again experienced chills and fever. He returned to the hospital 8 days later, and impaired liver function was revealed by the elevated AST, alanine aminotransferase (ALT), alkaline phos-

phatase (ALK-P), and γ-glutamyltransferase (γ-GT) (Table 1). Mild jaundice developed in the following days, and an abdominal sonogram performed on September 19, 2000 revealed a moderate fatty liver of normal size; hepatitis B surface-antigen (HBsAg) and hepatitis C virus-antibody (HCV-Ab) were negative. Toxic hepatitis secondary to inhalation anesthetics was highly suspected by the GI specialists, but the patient refused a liver biopsy. The symptoms improved with conservative therapy. The concomitant medications used during and after anesthesia are presented in Table 2, and the changes in AST and ALT levels during desflurane and sevoflurane anesthesia are shown in Fig. 1.

Table 2. Perioperative Medication of the Patient with Isoflurane, Sevoflurane, and Desflurane Anesthesia

2-5 Aug. 1999	penicillin G sodium 3 MU q6h (2-3 Aug.)
	acetaminophen 500 mg q.i.d. (4-12 Aug.)
	penicillin V 800,000 U q6h (4-12 Aug.)
26 Aug.-15 Sept. 1999	metronidazole 1000 mg q.i.d. (31 Aug.-13 Sept.)
(sevoflurane on 30 Aug. 1999)	cephalothin 1g q6h (31 Aug-14 Sept.)
	meperidine 50 mg p.r.n. (31 Aug.-10 Sept.)
	gentamycin 60 mg q6h (31 Aug.-14 Sept.)
	nifedipine 10 mg q8h (2-14 Sept.)
	acetaminophen 500 mg q.i.d. (15-22 Sept.)
22 Aug.-6 Sept. 2000	penicillin G sodium 3 MU q6h (22 Aug.-5 Sept.)
(desflurane on 22 Aug. 2000)	acetaminophen 500 mg q.i.d. (22 Aug.-13 Sept.)
	meperidine 50 mg p.r.n (23-25 Aug.)
	carbetapentane 25 mg q.i.d. (22 Aug.-5 Sept.)
	cefadroxil monohydrate 500 mg q6h (6-13 Sept.)
	mefenamic acid 250 mg q.i.d. (22 Aug.-5 Sept.)
	thyroxine sodium 0.1 mg t.i.d (24-25 Aug.)
13 Sept. 2000	acetaminophen 500 mg q.i.d. (13-23 Sept.)
	diphenidol 25 mg q.i.d. (13-23 Sept.)
16-22 Sept. 2000	clindamycin 300 mg q6h (16-20 Sept.)
	felodipine 5 mg q.d. (18-27 Sept.)
	furosemide 40 mg q.d. (18-27 Sept.)
	gentamycin 80 mg q8h (16-20 Sept.)
	acetaminophen 500 mg q.i.d. (18 Sept.)
	lemobex 1# t.i.d. (20-27 Sept.)

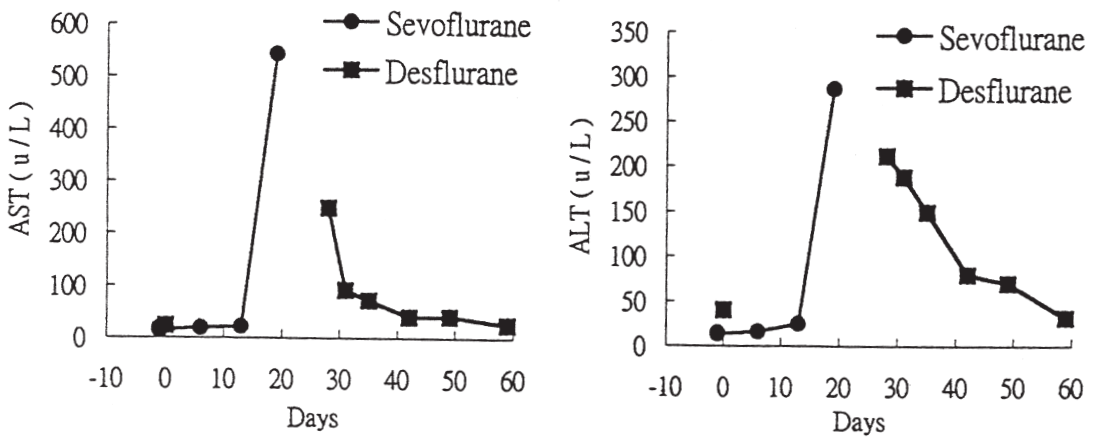

Fig. 1 Changes in serum AST and ALT levels after sevoflurane and desflurane anesthesia. Day 0 represents the first day of anesthesia.

DISCUSSION

In the first episode of hepatitis, the causative factors were difficult to identify as the course was short, and the quick spontaneous recovery did not alert anyone. However, after the second episode of hepatitis, the similar time interval of 18 days between the operation and the onset of signs of hepatitis made us curious about whether the hepatitis was related to the anesthetics.

Common causes of hepatic dysfunction include hepatic trauma, shock-induced hepatic tissue hypoxia, viral hepatitis, or drug-induced toxic hepatitis. After excluding the possibilities of hepatic trauma or intraoperative shock-induced tissue hypoxia, we considered a virus, preoperative medications, or intraoperative anesthetics to be the possible causative agents.

Acute viral hepatitis B and C can be excluded as a cause of hepatic dysfunction in this patient due to the negative findings of HBsAg and HCV-Ab. As hepatitis can cause liver damage of varying severity, we could not completely exclude viral hepatitis solely from the pattern of serum enzymes in our patient, since hepatitis A, hepatitis D, or another rarer hepatitis may still have been possible. However, the possibility of viral hepatitis infections after both operations was very low.

In searching for the possible toxic agents, we focused on the common medications administered in the second and third operations. Acetaminophen was administered preoperatively in both operations. Although it is reported to induce hepatic dysfunction,[6] it was safely administered after the last attack of hepatic dysfunction with no reported side effects. No antibiotic (second operation: metronidazole and cephalothin; third operation: penicillin G) was administered during these 2 periods, and there is no literature reporting a relationship between these antibiotics and hepatitis.

Our patient had undergone 3 operations to the head and neck region within 1 year. Low-flow anesthesia with sevoflurane in 0.5 l/min of oxygen flow was administered for 14 hours in the second operation. Sevoflurane anesthesia with low oxygen flow at 0.5-0.8 l/min had been safely used for years in our hospital, and no liver-related side effects of low-flow sevoflurane anesthesia had been reported.[7] Therefore it seemed unlikely that the impaired liver function was related to the low-flow anesthesia per se.

Although this patient denied a history of hypertension, his blood pressure on arrival in the operating theatre for the second operation was high. During the third operation when anesthesia was maintained with desflurane, hypertension was also noted upon arrival in the operating theatre (238/117 mmHg), during induction of anesthesia (190/105 mmHg), and at the end of the operation (230/105 mmHg). Anyway, his heart rate and O_2 saturation remained normal, and the ECG revealed no abnormalities throughout the operation. Furthermore, hepatic dysfunction induced by fluctuations in intraoperative blood pressure without cerebral or cardiac injury has not been reported.

Desflurane and sevoflurane are both fluorinated anesthetics, and they have been reported to induce hepatitis.[1-3] Desflurane is oxidatively metabolized by liver cytochrome P-450 to form TFA proteins, which may produce immuno-responses; thus there is the possibility of inducing acute hepatitis by a mechanism similar to that of halothane and isoflurane.[4] Desflurane-induced hepatic dysfunction has been reported with pre-exposure to halothane but not to isoflurane.[3] Although desflurane and isoflurane can only produce very low levels of TFA formation, this small amount of TFA is enough to induce massive hepatotoxicity, particularly if a patient has previously been sensitized against TFA proteins.[3] In the present case, it is believed that the TFA antibody which presented after exposure to isoflurane in the first anesthesia sensitized the liver and resulted in hepatic function impairment after exposure to desflurane at a later time. Although the presence of the anti-trifluoroacetyl antibody (anti-TFA) may provide strong support for our diagnosis,[8] we were unable to detect this antibody, since the specific laboratory kit was unavailable at that time in Taiwan.

The mechanism of sevoflurane-induced hepatitis is still not completely understood. The primary organic metabolite of sevoflurane is HFIP, which is readily and rapidly conjugated with glucuronic acid.[5] As HFIP seldom forms liver protein adducts, TFA-protein sensitization was not likely the a cause of hepatic dysfunction in this patient.

The similar time interval between the operation date and the onset of hepatic dysfunction with both the sevoflurane and desflurane anesthesia, after

excluding other possibilities, made us highly suspicious that the hepatic dysfunction was induced by the fluorinated anesthetics, sevoflurane and desflurane.

The unique aspect of this report is the nature of reproducible hepatic dysfunction following prolonged sevoflurane or desflurane anesthesia in a patient with no prior history of liver disease. While the diagnosis following both anesthetics was made by exclusion, inhalation anesthetics should be totally replaced by intravenous anesthetics for future operations.

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Sevoflurane及Desflurane引致可逆性肝功能異常

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雖然desflurane和sevoflurane曾分別被報告引致肝功能異常，但發生在同一人則未曾被報告過。由於desflurane和sevoflurane的代謝產物本質上不同，兩者間似乎並不會產生敏感，而引致肝功能異常。本文首次報告一病患在接受sevoflurane及desflurane後表現可逆性肝功能異常。此一54歲的男性病患連續接受三次麻醉，第一次以isoflurane的麻醉過程平順。第二次以sevoflurane麻醉後17天後卻產生發燒、顫抖及Aspartate aminotransferase (534 μ/L)上升。在第三次以desflurane麻醉後17天亦產生相似的臨床徵狀。症狀及血中轉胺酶在保守治療下完全恢復。由於相似的發病時間，及排除其他可能性原因下，我們高度懷疑此肝功能異常乃由sevoflurane及desflurane所引致。吾人建議於此診斷下，在後續手術中應改用完全靜脈麻醉藥，以取代吸入性麻醉藥。(長庚醫誌 2003;26:357-62)

關鍵字：isoflurane，sevoflurane，desflurane，肝功能，過敏。

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