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CASE REPORT

Acute liver injury following re-exposure to sevoflurane after a 12-year interval

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Abstract

Background: Sevoflurane is a commonly used halogenated inhalational anesthetic with a relatively low risk of hepatic toxicity compared to other agents. Unlike other halogenated anesthetics, sevoflurane undergoes minimal metabolism into reactive intermediates that could induce hepatotoxicity. However, rare cases of acute liver injury following re-exposure have been reported. **Case**: We present a case of a 70-year-old woman who underwent elective clipping of a left middle cerebral artery aneurysm under general anesthesia with sevoflurane. She had previously received sevoflurane, 12 years earlier, without complications. Liver function tests performed two hours after surgery showed a significant elevation in liver enzymes. A thorough evaluation, including virological, autoimmune and drug-induced liver injury assessments, yielded no alternative cause. An urgent multidisciplinary consultation was conducted, and a diagnosis of sevoflurane-induced liver injury was considered after excluding other potential causes. The patient was then promptly treated with hepatoprotective agents and had, rapid enzyme normalization. After full recovery without further complications, she was discharged. **Conclusions**: Although sevoflurane is considered to have minimal hepatic toxicity, this case highlights the potential risk of liver injury upon re-exposure. Vigilant liver function monitoring in patients with prior exposure to halogenated anesthetics is essential, particularly when re-administering sevoflurane. Early recognition and timely intervention may prevent severe complications.

Keywords

Sevoflurane; Hepatotoxicity; Liver injury; Anesthesia; Halogenated anesthetics; Acute liver dysfunction

1. Introduction

Sevoflurane is a widely used halogenated inhalational anesthetic with a favorable safety profile, particularly in terms of hepatic toxicity, when compared to other halogenated agents such as halothane, enflurane, isoflurane and desflurane [1]. Unlike these agents, sevoflurane undergoes minimal metabolism into reactive intermediates capable of forming hepatotoxic proteins, contributing to its reputation as the halogenated anesthetic with the lowest risk of liver injury [2–9]. However, since its introduction into clinical practice, rare cases of sevoflurane-associated hepatotoxicity have been reported, some of which have resulted in fatal outcomes (a summary of related reported cases is presented in Table 1 (Ref. [10–16]). Due to the rare occurrence and often insidious onset of symptoms, the pathophysiological mechanisms underlying sevoflurane-induced liver injury remain unclear. Furthermore, no prior reports have described acute hepatic dysfunction manifesting within hours of exposure in the immediate postoperative period. This present case report presents the case of a middle-aged woman who developed acute liver injury within hours of undergoing middle cerebral artery aneurysm clipping surgery under sevoflurane anesthesia, 12 years after her last exposure to the drug. Additionally, a summary of related cases is provided to enhance the understanding of this rare but potentially serious adverse event.

2. Case report

A 70-year-old woman underwent elective clipping of a left middle cerebral artery aneurysm, which was incidentally detected during a Magnetic Resonance Imaging (MRI) performed for dizziness. Her medical history included hypertension, which was well controlled with amlodipine, and a documented penicillin allergy characterized by a rash. She had previously undergone three surgical procedures, with only the first *involving* the use of sevoflurane. Twelve years earlier, she had undergone radical rectal cancer resection under general anesthesia with sevoflurane inhalation in combination with intravenous propofol and sufentanil. The perioperative course was uneventful, and liver function tests (LFTs) were within normal limits preoperatively and on the first postoperative

TABLE 1. Summary of related published literature on sevoflurane-induced liver injury in adults.

Author	Year	Age, sex	Type of surgery	Repeated exposure	Pre-op liver enzyme	Symptoms	Post-op liver enzymes	Time to peak	Death	Pathological examination
Reeker W [10]	1997	36 F	Vaginal hysterectomy	Yes 1 Year	Normal	Nausea, vomiting and fever	AST: 5080 ALT: 2070	D5	Yes D12	Yes
Lehmann A [11]	2007	76 F	Aortic valve replacement	Not mentioned	Normal	Fever	AST: 10,50⁴ ALT: 15,51⁶	D3	Yes D8	Yes
Turillazzi E [12]	2007	69 M	Surgical vascular repair	Yes 2 Days	Normal	Jaundice	AST: 6169 ALT: 1690	D3	Yes D8	Yes
Zizek D [13]	2010	66 F	Mastectomy for breast cancer	Yes 3 Weeks	Normal	Jaundice and nausea	AST: 1860 ALT: 1690	W2	Yes D66	Yes
Singhal S [14]	2010	37 M	Resection of the abdominal wall mass	Not mentioned	Normal	Nausea, vomiting and jaundice	AST: 1860 ALT: 1690	D36	No	Yes
Masin-Spasovska J [15]	2013	47 F	Kidney transplantation	Yes 3 Days	Not mentioned	Not mentioned	AST: 5100 ALT: 3300	D1	Yes D4	No
Rajan S [16]	2019	58 M	L5–S1 laminectomy	Yes	Normal	Not mentioned	AST: 1373 ALT: 1309	D3	No	No

F: female; M: male; BMI: Body Mass Index; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; Y: Year; D: day; W: week; Post-op: Post-operative; Pre-op: Pre-operative.

day, with no abnormalities detected during subsequent routine follow-up (Table 2). Her later surgical interventions were minor ophthalmic procedures performed under local anesthesia, without exposure to sevoflurane.

For the current procedure, the patient, weighing 61 kg, underwent anesthesia induction with 15 mg of propofol, 17.5 μg of sufentanil citrate, and 6 mg of vecuronium bromide, achieving successful tracheal intubation. Anesthesia was maintained with 0.5% sevoflurane inhalation, continuous infusion of propofol at 5 mg/kg/h for sedation, remifentanil hydrochloride at 0.05–0.11 μg/kg/min, and sufentanil citrate at 0.1 μg/kg/h, with additional 5 μg doses administered as needed for analgesia. The intraoperative course was uneventful, with the patient remaining deeply sedated and hemodynamically stable throughout. The procedure lasted 2 hours and 43 minutes, with an estimated blood loss of 100 mL and a urine output of 650 mL. Her mean arterial pressure (MAP) remained approximately 100 mmHg (systolic 130–140 mmHg, diastolic 70–80 mmHg), and oxygen saturation was consistently maintained between 99% and 100%. After the surgery, she was transferred to the intensive care unit (ICU), where she remained intubated and sedated.

Two hours after surgery, liver function tests (LFTs) revealed a significant increase in liver enzymes, with aspartate aminotransferase (AST) at 1641 U/L, alanine aminotransferase (ALT) at 477 U/L, total bilirubin at 25.9 μmol/L, bile acids at 91.4 μmol/L, gamma-glutamyl transferase (GGT) at 146 U/L and alkaline phosphatase (ALP) at 132 U/L. By six hours postoperatively, these values had further increased, peaking at AST 2911 U/L, ALT 868 U/L, total bilirubin 25.5 μmol/L, lactate dehydrogenase (LDH) 1588 U/L, GGT 185 U/L and ALP 145 U/L (Table 1). Given the rapid and clinically atypical progression of enzyme elevation, an urgent workup was initiated to identify potential hepatotoxic factors.

Comprehensive blood tests were performed, including hepatitis B virus DNA (HBV-DNA), hepatitis A virus (HAV), hepatitis E virus (HEV), the Toxoplasmosis, Other (Syphilis, HIV, *etc.*), Rubella, Cytomegalovirus, Herpes simplex virus (TORCH) panel, Epstein-Barr virus DNA (EBV-DNA), cytomegalovirus DNA (CMV-DNA), autoimmune antibodies, antinuclear antibody (ANA), immunoglobulin G4 (IgG4), immunoglobulin levels, ceruloplasmin and thyroid function, all of which returned negative results. Then, a thorough review of all administered medications was conducted to rule out drug-induced liver injury. Furthermore, bedside ultrasound showed no abnormalities in hepatic vasculature or the biliary system and no signs of inferior vena cava congestion (IVC diameter: 1.6 cm, distance maximum (dmax) 1.838 cm, distance mini-

TABLE 2. Liver function changes before and after the patient's first and current exposures to sevoflurane anesthesia.

Surgery	First surgery		Current surgery						
Variables	Pre-op	Post-op	Pre-op	2 h	6 h	18 h	36 h	D3	D5
AST	22	22	28	1641	2911	539	91	30	19
ALT	20	26	34	477	868	598	321	127	65
Total bilirubin	7.7	12.9	9.0	25.9	25.5	16.3	16.9	5.1	8.0
Direct bilirubin	1.7	4.5	2.5	11.6	14.4	7.1	5.9	1.8	2.1
TBA	5.4	5.5	6.4	91.4	46.9	4.2	5.2	1.8	4.4
Albumin	41.6	36	46.9	43.4	41.3	37.9	38.0	36.8	38.6
PT	9.9	10.7	10.9	10.9	11.2	11.6	11.1	11.1	10.7
INR	0.89	0.98	0.95	0.93	0.96	0.97	0.97	0.95	0.94
LDH	144	157	170	819	1588	481	214	234	156
CK	51	74	63	100	110	185	118	45	32
GGT	12	23	21	146	185	150	111	95	77
HBDH	119	120	123	404	648	245	145	181	119
ALP	79	67	73	132	145	125	115	122	105

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; TBA: Total Bile Acids; PT: Prothrombin Time; INR: International Normalized Ratio; LDH: Lactate Dehydrogenase; CK: Creatine Kinase; GGT: Gamma-Glutamyl Transferase; HBDH: Hydroxybutyrate Dehydrogenase; ALP: Alkaline Phosphatase; Pre-op: Pre-operative; Post-op: Post-operative; h: hours; D: day.

mum (dmin) 1.649 cm) or right ventricular dysfunction (Tricuspid Annular Plane Systolic Excursion TAPSE: 2.0 cm). The patient's cardiovascular status remained stable, with no evidence of venous stasis or impaired hepatic perfusion.

An urgent multidisciplinary team (MDT) consultation, with specialists from anesthesiology, pharmacy and gastroenterology, was conducted. After systematically excluding other potential causes, a diagnosis of sevoflurane-induced liver injury was established. Given the severity of liver enzyme elevation, preparations were made for a liver biopsy in case of further deterioration.

The patient was immediately treated with hepatoprotective agents, including magnesium isoglycyrrhizinate hydrate and polyene phosphatidylcholine. At 18 hours postoperatively, liver enzyme levels began to decline, with AST decreasing to 539 U/L, ALT to 598 U/L, total bilirubin to 16.3 μmol/L, and bile acids to 4.2 μmol/L. Given this improvement, and after discussion with the patient's family, the planned liver biopsy was deferred, considering the risk-benefit balance. Over the following week, liver function normalized, the patient was successfully extubated, regained full consciousness, and was eventually discharged without further complications.

3. Discussion

Postoperative liver dysfunction associated with inhalational anesthetics is diagnosed after a systematic exclusion of other potential causes [17]. In the present case, intraoperative factors such as hypoxia, inadequate hepatic perfusion, ischemia-reperfusion injury or direct hepatic compression were ruled out, as the patient remained hemodynamically stable throughout surgery, and the procedure itself, a neurosurgical intervention with minimal blood loss, did not predispose her to hepatic injury.

Unlike other halogenated anesthetics, which undergo metabolism into trifluoroacetyl compounds capable of triggering immune-mediated liver injury, sevoflurane is primarily metabolized into hexafluoroisopropanol. This metabolite constitutes approximately 85% of its organic derivatives and is rapidly conjugated with glucuronic acid for urinary excretion, resulting in a relatively low hepatotoxic potential [18, 19]. However, despite this favorable profile, reports of severe hepatotoxicity following sevoflurane exposure have been documented, particularly in individuals with impaired renal function. One such case *involved* a child with mild renal insufficiency who developed significant liver injury after exposure to sevoflurane, suggesting that impaired renal clearance of its metabolites may contribute to hepatic dysfunction [20].

Despite concerns regarding potential hepatotoxicity, multicenter randomized controlled trials have demonstrated the safety of sevoflurane in liver transplantation, a procedure in which avoiding hepatotoxic agents is essential. These studies have found no significant differences in biochemical markers or clinical outcomes when comparing sevoflurane anesthesia with propofol [21]. However, in adults, cases of sevoflurane-induced liver injury remain limited to isolated reports, primarily following re-exposure (Table 1) [10–16]. These cases are often characterized by a rapid rise in liver enzymes, peaking within three days post-exposure, and are associated with symptoms of acute liver injury, including nausea, vomiting and fever [10–13]. Even in patients without preexisting hepatic dysfunction, the progression of liver injury can be rapid, with some cases requiring liver transplantation or resulting in fatal outcomes [10–13]. Histopathological findings in sevoflurane-induced liver injury typically reveal cholestatic damage, which

is consistent with laboratory findings of elevated direct bilirubin, bile acids, alkaline phosphatase and gamma-glutamyl transferase. Liver biopsy specimens often show hepatocellular vacuolation, necrosis, and zone 3 cholestasis, further supporting the diagnosis [16, 22].

Animal studies suggest that sevoflurane-induced liver injury may result from disruptions in calcium homeostasis, leading to hepatocellular damage through mechanisms such as increased intracellular free calcium and membrane destabilization [12]. Further investigations have indicated that the sevoflurane metabolite, fluoromethyl-2, 2-difluoro-1-(trifluoromethyl) vinyl (Compound A), may contribute to cellular injury by activating free radical enzymes. Moreover, re-exposure has been associated with more severe hepatic reactions, with hepatocellular necrosis occurring due to excessive cytoplasmic free calcium accumulation [12]. In this present case, early recognition of hepatic injury in the ICU, along with timely supportive care, effectively mitigated the disease progression and prevented a more severe outcome. Thus, it could be recommended that clinicians remain vigilant for early signs of liver dysfunction in patients with prior exposure to halogenated anesthetics, particularly during re-exposure and consider early intervention, including liver biopsy or liver transplantation, in severe cases.

This case highlights the potential risk of acute liver injury following re-exposure to sevoflurane, even after an interval of 12 years. While sevoflurane is generally regarded as having minimal hepatotoxicity, the findings emphasize the need for careful liver function monitoring in patients with prior exposure to halogenated anesthetics, particularly when re-exposure occurs. Thus, recognizing the early signs of liver dysfunction and initiating timely intervention may be critical in preventing severe complications.

This case report has several limitations. First, although liver injury occurred following sevoflurane anesthesia, the possibility of other contributing factors, such as drug interactions, undiagnosed liver disease or unidentified variables, cannot be completely excluded. Second, the absence of a control group limits the ability to compare the risk of liver injury following repeated sevoflurane exposure with that associated with other anesthetics or the absence of exposure. Third, this report does not investigate the specific mechanisms underlying sevoflurane-induced liver injury, which limits its ability to provide a theoretical basis for targeted prevention or treatment strategies. Finally, the 12-year interval between the patient's initial and subsequent sevoflurane exposure introduces uncertainty, as potential health changes or environmental exposures during this period cannot be fully accounted for.

In conclusion, while this case highlights the potential risk of liver injury following sevoflurane re-exposure, the findings cannot be generalized due to the inherent limitations of a single-case report. Larger prospective studies are necessary to validate this association, further elucidate the mechanisms underlying sevoflurane-induced hepatotoxicity, and identify patients who may be at increased risk.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

AUTHOR CONTRIBUTIONS

ZPW—designed the present study; supervised the study; ensured correctness and revised the manuscript. SJM—wrote the manuscript and collected data. Manuscript revision and final approval of the version to be published.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, with approval granted by the Human Research Review Committee at West China Hospital, Sichuan University (Chengdu, China) (Number: 2024WCH-10277). The patient provided written informed consent. Consent was signed by the patient's gave consent for her data, including images, to be published in the journal.

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CONFLICT OF INTEREST

There were no interest conflict and legal liability in our report.

All the authors had completed disclosure of relationships and activities on the manuscript.

REFERENCES

[1] Sanchez LV, Pichardo P, Adames V, Zovi A, Pradegan N. Fatal hepatotoxicity due to sevoflurane use in a paediatric patient after aortic repair: reality or fiction? A case of pharmacovigilance. European Journal of Hospital Pharmacy. 2023; 30: 57–59.

[2] Yu X, Ma X, Lyu J, Jiang N, Lu Y, Liao Y, *et al*. Ferroptosis *involved* in sevoflurane-aggravated young rats brain injury induced by liver transplantation. NeuroReport. 2022; 33: 705–713.

[3] Ryu DK, Park M, Woo S, Cho HS, Min JJ. Postoperative liver injury after sevoflurane or propofol anesthesia in patients undergoing noncardiac surgery: a retrospective cohort study. Scientific Reports. 2024; 14: 11178.

[4] Gobut H, Erel S, Ozdemir C, Mortas T, Arslan M, Kucuk A, *et al*. Effects of cerium oxide on liver tissue in liver ischemia reperfusion injury in rats undergoing sevoflurane anesthesia. Experimental and Therapeutic Medicine. 2023; 25: 164.

[5] Yavuz A, Tuna AT, Ozdemir C, Mortas T, Küçük A, Kasapbaşı E, *et al*. Effects of fullerene C60 on liver tissue in liver ischemia reperfusion injury in rats undergoing sevoflurane anesthesia. Libyan Journal of Medicine. 2023; 18: 2281116.

[6] Şengel N, Küçük A, Özdemir Ç, Sezen ŞC, Kip G, Er F, *et al*. The effect of

sevoflurane and fullerenol C 60 on the liver and kidney in lower extremity ischemia-reperfusion injury in mice with streptozocin-induced diabetes. International Journal of Nanomedicine. 2023; 18: 7543–7557.

[7] Lee MO, Cho S, Kim C, Koh H. Does drug-induced liver injury still occur after sevoflurane anesthesia?—A case report. Anesthesia and Pain Medicine. 2024; 19: 227–232.

[8] Njoku D, Laster MJ, Gong DH, Eger EI 2II, Reed GF, Martin JL. Biotransformation of halothane, enflurane, isoflurane, and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. Anesthesia & Analgesia. 1997; 84: 173–178.

[9] Teschke R, Danan G. Advances in idiosyncratic drug-induced liver injury issues: new clinical and mechanistic analysis due to Roussel Uclaf causality assessment method use. International Journal of Molecular Sciences. 2023; 24: 10855.

[10] Reeker W, Kochs E. Sevoflurane in elderly patients. Anaesthesist. 1998; 47: S58–S62. (In German)

[11] Lehmann A, Neher M, Kiessling AH, Isgro F, Koloska A, Boldt J. Case report: fatal hepatic failure after aortic valve replacement and sevoflurane exposure. Canadian Journal of Anesthesia. 2007; 54: 917–921.

[12] Turillazzi E, D'Errico S, Neri M, Riezzo I, Fineschi V. A fatal case of fulminant hepatic necrosis following sevoflurane anesthesia. Toxicologic Pathology. 2007; 35: 840–845.

[13] Zizek D, Ribnikar M, Zizek B, Ferlan-Marolt V. Fatal subacute liver failure after repeated administration of sevoflurane anaesthesia. European Journal of Gastroenterology & Hepatology. 2010; 22: 112–115.

[14] Singhal S, Gray T, Guzman G, Verma A, Anand K. Sevoflurane hepatotoxicity: a case report of sevoflurane hepatic necrosis and review of the literature. American Journal of Therapeutics. 2010; 17: 219–222.

[15] Masin-Spasovska J, Dimitrovski K, Stavridis S, Stankov O, Dohcev S, Saidi S, *et al*. Acute fulminant hepatatis in kidney transplant recipient after repeated sevoflurane anesthesia—a case report and literature review. Current Drug Safety. 2013; 8: 141–144.

[16] Rajan S, Garg D, Cummings KC 3III, Krishnaney AA. Hepatotoxicity after sevoflurane anaesthesia: a new twist to an old story. British Journal of Anaesthesia. 2019; 122: e63–e64.

[17] European Association for the Study of the Liver. EASL clinical practice guidelines: drug-induced liver injury. Journal of Hepatology. 2019; 70: 1222–1261.

[18] Kharasch ED, Karol MD, Lanni C, Sawchuk R. Clinical sevoflurane metabolism and disposition. I. Sevoflurane and metabolite pharmacokinetics. Anesthesiology. 1995; 82: 1369–1378.

[19] Ji H, Li H, Zhang H, Cheng Z. Role of microRNA 218 5p in sevoflurane induced protective effects in hepatic ischemia/reperfusion injury mice by regulating GAB2/PI3K/AKT pathway. Molecular Medicine Reports. 2022; 25: 1.

[20] Park I, Min EK, Koo BN, Park JH, Kim DG, Joo DJ, *et al*. Effects of desflurane versus sevoflurane on graft outcome of patients with cirrhosis receiving steatotic liver graft in deceased donor liver transplantation. Journal of Clinical Anesthesia. 2024; 99: 111674.

[21] Koker A, Arslan G, Özden Ö, Karaarslan U, Köroğlu T. Acute fulminant hepatic failure caused by sevoflurane linked to influenza A. Experimental and Clinical Transplantation. 2023; 21: 540–542.

[22] Ma H, Yang B, Yu L, Gao Y, Ye X, Liu Y, *et al*. Sevoflurane protects the liver from ischemia-reperfusion injury by regulating Nrf2/HO-1 pathway. European Journal of Pharmacology. 2021; 898: 173932.

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