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**CASE REPORT**

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# Sevoflurane Concentrations in Blood, Brain, and Lung After Sevoflurane-Induced Death

**ABSTRACT:** Sevoflurane concentrations in blood, brain, and lung were measured in an individual apparently dying from sevoflurane inhalation. Sevoflurane is a volatile nonflammable fluorinated methyl isopropyl ether inhaled anesthetic, chemically related to desflurane and isoflurane. The incidence of abuse of sevoflurane is lower than that of other drugs of abuse possibly due to its inaccessibility to the general public and less pleasurable and addicting effects. The dead subject was an anesthetist found prone in bed holding an empty bottle of sevoflurane (Ultane®). Serum, urine, and liver were screened for numerous drugs and metabolites using enzyme immunoassays and gas chromatography-mass spectrometry. Analysis did not reveal presence of any drug, including ethanol, other than sevoflurane. Sevoflurane was determined by headspace gas chromatography and revealed concentrations of 15 μg/mL in blood and 130 mg/kg in brain and lung. Autopsy revealed pulmonary edema and frothing in the lung, pathological findings associated with death by sevoflurane or hypoxia. The cause of death was ruled as sevoflurane toxicity and the manner of death as accident.

**KEYWORDS:** forensic sciences, sevoflurane, Ultane, fatality

Sevoflurane (Ultane®) is colorless, nonflammable, nonirritant, fluorinated methyl isopropyl ether chemically related to desflurane and isoflurane. It has been used as an inhaled anesthetic since 1985. Its poor solubility in blood and minimal pungency promote a rapid increase in alveolar concentration and a rapid induction of anesthesia. Its major distribution is initially to areas of high blood flow (brain, heart, liver and kidney) and later to less perfused organs. Most of the sevoflurane absorbed is eliminated unchanged by the lungs. The terminal half-life of sevoflurane is approximately a day (1). Hepatic cytochrome P450 isoenzyme CYP2E1 metabolizes *c.* 5% of the absorbed sevoflurane to its major metabolite hexafluoroisopropanol, which is rapidly conjugated with glucuronic acid and eliminated in the urine with half-life of *c.* 20 h (2,3).

Sevoflurane can cause cardiorespiratory depression, hypotension, and malignant hyperthermia. Seizures (convulsions) can occur during anesthesia with sevoflurane (4). Sevoflurane related deaths are rare. Only one report describes intentional self-induced overdose and death by sevoflurane (5). In this report amphetamine, caffeine, pseudoephedrine, nicotine, nicotine metabolite, and valproate were found in the deceased, possibly contributing to the death. To our knowledge, the present report is the first in which sevoflurane appears to be the sole cause of death.

## Case Report

A 31-year-old white male anesthetist was found dead in the break room of the surgery area. He was lying prone in bed holding an uncapped empty bottle labeled Ultane®. The body had lividity in the face, neck and chest, consistent with the subject's position. The decedent had a history of gastritis/heartburn treated with antacids. The family medical history included heart disease.

## Material and Methods

Femoral venous blood and various tissues were collected for toxicological and/or pathological analyses. For sevoflurane assay, samples of blood, brain and, lung were collected in headspace vials and shipped to the University of California in San Francisco. Toxicological drug screen for more than 300 acidic, basic, and neutral drugs was performed by gas chromatography-mass spectrometry. Drugs of abuse screening by enzyme immuoassays were performed for amphetamines, barbiturates, cannabinoids, cocaine, methadone, opiates, phencyclidine, and propoxyphene. Volatile screening for ethanol, methanol, isopropanol, and acetone was performed by gas chromatography with flame ionization detector.

For the sevoflurane assay, three tissue samples were analyzed: 2.14 g of blood, 8.12 g of brain, and 4.10 g of lung. Assuming an average tissue density of 1.07 g/mL, these weights equaled volumes of 2.0, 7.6, and 3.8 mL. The tissues arrived in 21.2 mL (total volume) glass vials. From these vials 2 mL of gas space was sampled and diluted to 10 mL and analyzed by gas chromatography using sampling loop to deliver samples into the carrier stream of the gas chromatograph. Gow-Mac gas chromatograph (Gow-Mac Instrument Corp., Bridgewater, NJ) equipped with a flame ionization detector was used to measure concentrations of carbon-containing compounds. The 4.6-m-long, 0.22 cm (ID) column was packed with SF-96. The column temperature was 100°C. The detector was maintained at 150°C. The carrier gas flow was nitrogen at a flow of 15–20 mL/min. The detector received 35 mL/min hydrogen and 240 mL/min air. Secondary standards referenced to a primary standard were used for the estimation of sevoflurane in the samples. A primary standard was prepared by the introduction of an aliquot of liquid sevoflurane into a closed flask of known volume.

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Volume of vapor produced by sevoflurane was calculated from the volume injected and density of sevoflurane. When corrected for flask volume, temperature and pressure, the concentration of primary standard used in the study was 1.51%. A secondary standard was made by evacuating an H cylinder. The resulting vacuum within the cylinder was used to pull (i.e., inject) a known volume of liquid sevoflurane into the cylinder. The cylinder was then pressurized with oxygen or nitrogen to a pressure that produced approximately the desired concentration of sevoflurane. The gases within the cylinder were mixed by rolling and heating the cylinder. The heating was continued for 24–48 h. A sample from the cylinder was then taken and injected into the gas sampling loop of the gas chromatograph and the resulting peak compared with the peak produced by the primary standard. The concentration of secondary standard used in the study was 1.76%. Linearity was checked by two-, four-, eight-, and 16-fold dilutions of secondary standard. The response was linear throughout the tested range. Physical properties of sevoflurane such as density and its behavior as an ideal gas which are used in the calculation of concentrations have been published (6,7). The identification of sevoflurane was based on the retention time match with the standard and absence of any artifact peak in the area of interest. Furthermore, the circumstances of this case, that is, the finding of the deceased with an opened bottle of sevoflurane points to sevoflurane as the likely compound found in this case. Tissue concentrations of sevoflurane were calculated from the peak heights referenced to standard peak heights. Intra- and interassay variations of the assay used is <5%.

## Results

No drug was detected by enzyme immunoassays or gas chromatography-mass spectrometry or flame ionization detection. At room temperature, the sevoflurane concentration in the gas phase was 0.0155%, 0.404%, and 0.223% for the blood, brain, and lung specimens, respectively. Tissue/gas partition coefficients ($\lambda_{t37}$) for these tissues at 37°C are 0.65, 1.1, and (assumed) 1.1 (8). Assuming a 4% increase in solubility per degree decrease to the temperature of determination (23°C) (9), these values for solubility become 1.13, 1.9, and 1.9 at 23°C ($\lambda_{t23}$). By definition, $\lambda_t$ is the concentration in tissue/concentration in gas when the two phases are in equilibrium. If $A_o$ is the volume of sevoflurane originally in the tissue, then $A_o = C_g V_g + \lambda_{t23} C_g V_t$, where $C_g$ is the concentration in the gas phase, $V_g$ is the volume of the gas phase, and $V_t$ is the volume of the tissue phase. Correcting $A_o$ for the temperature difference, at 37°C, $A_{o37} = A_o \times 310/296$. Finally, the concentration of sevoflurane in the gas phase at 37°C, $C_{g37}$ may be calculated as follows: $C_{g37} = A_{o37}/(V_t \lambda_{t37})$. Using these calculations, the gas phase concentrations at 37°C are 0.3% (blood) and 1.5% (brain and lung) or by weight 15 μg/mL in blood and 130 mg/kg in brain and lung.

The autopsy revealed pulmonary edema and frothing in the lung. Autopsy also revealed atherosclerotic coronary artery disease with 50% occlusion of the left main coronary artery. The remainder of the external and internal examination revealed a healthy individual. The cause of death was ruled as sevoflurane toxicity and the manner of death as accidental.

## Discussion

In the present case, although the exact mechanism of death is not known, one might postulate two possible causes of death. First, a sufficiently great concentration of sevoflurane could produce irreversible circulatory depression (10). This is a less likely cause than that given next because depression of ventilation by sevoflurane would limit the concentration that would be reached in the lungs (i.e., the depression produces an element of negative feedback). Second, hypoxia might result from obstruction to or depression of breathing (11), including depression of the response to hypoxia (12). That is, the subject probably died because his breathing became obstructed and he asphyxiated or (less likely), his cardiorespiratory system became depressed to the point of apnea, and/or cardiovascular collapse. Negative pressure pulmonary edema can result from obstruction to breathing, and high-pressure pulmonary edema can result from acute hypoxia.

The tissue concentrations found in the present case do not indicate excessive concentrations, another reason to believe that the subject died from hypoxia. However, some sevoflurane surely was lost in transferring tissue to the vial, and the plastic components of the vial may have absorbed some of the sevoflurane (13). The gas phase anesthetizing concentration of sevoflurane is *c*. 1.8% (14), and thus the gas phase concentration of 1.5% in equilibrium with the brain indicates that the deceased probably was anesthetized at the time of death.

The low blood concentration of sevoflurane (0.3% gas phase equivalent) probably resulted from the source of the blood (the femoral vein). As indicated earlier, the initial tissues to equilibrate with anesthetic are those that are highly perfused (heart, liver, kidney, brain), while tissues with far smaller perfusions (muscle and fat) may require hours to days for equilibration (1). Sevoflurane concentrations in femoral venous blood would reflect sevoflurane partial pressures in muscle and fat.

The death described in the present report is not the first death reported from administration of sevoflurane in a nonsurgical milieu (5). In a previously reported case of death after apparent abuse of sevoflurane by inhalation, the decadent had postmortem concentrations of 26.2 μg/mL in blood, 30.8 mg/kg in liver, and 12.8 mg/kg in kidney (5). In addition to sevoflurane, amphetamine, caffeine, pseudoephedrine, nicotine, nicotine metabolite, and valproate were found. Whether these drugs contributed to the death is not clear. In the present case, no other drug was detected and we attribute the death solely to sevoflurane. Sevoflurane concentrations in the present case were 15 μg/mL in blood and 130 mg/kg in brain and lung. The previous report did not indicate brain and lung concentrations of sevoflurane.

In conclusion, we report a case of self-inflicted death from sevoflurane inhalation. The autopsy findings revealed pulmonary edema and frothing, in an otherwise normal individual probably due to respiratory obstruction and depression with consequent hypoxia. The novel findings in the present report include sevoflurane as the sole cause of death and a description of the resulting sevoflurane concentrations in brain and lung tissues. The case also suggests the danger of sevoflurane abuse.

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## References

1. Yasuda N, Lockhart SH, Eger EI II, Weiskopf RB, Liu J, Laster M, et al. Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 1991;72:316–24.
2. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 1981;54:100–6.
3. Kharasch ED, Karol MD, Lanni C, Sawchuk R. Clinical sevoflurane metabolism and disposition. I. Sevoflurane and metabolite pharmacokinetics. Anesthesiology 1995;82:1369–78.

4. Adachi M, Ikemoto Y, Kubo K, Takuma C. Seizure-like movements during induction of anaesthesia with sevoflurane. Br J Anaesth 1992;68:214–5.
5. Burrows DL, Nicolaides A, Stephens GC, Ferslew KE. The distribution of sevoflurane in a sevoflurane induced death. J Forensic Sci 2004;49:394–7.
6. Laster MJ, Fang Z, Eger EI II. Specific gravities of desflurane, enflurane, halothane, isoflurane, and sevoflurane. Anesth Analg 1994;78:1152–3.
7. Eger EI II, Johnson BH. Do volatile anesthetics act as ideal gases? Anesth Analg 1979;58:322–3.
8. Yasuda N, Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 1989;69:370–3.
9. Allott PR, Steward A, Flook V, Mapleson WW. Variation with temperature of the solubilities of inhaled anaesthetics in water, oil and biological media. Br J Anaesth 1973;45:294–300.
10. Malan TP Jr, DiNardo JA, Isner RJ, Frink EJ Jr, Goldberg M, Fenster PE, et al. Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. Anesthesiology 1995;83:918–28.
11. Doi M, Takahashi T, Ikeda K. Respiratory effects of sevoflurane used in combination with nitrous oxide and surgical stimulation. J Clin Anesth 1994;6:1–4.
12. Tamura C, Doi M, Ikeda K. Hypoxic ventilatory response in cats lightly anesthetized with ketamine: effects of halothane and sevoflurane in low concentrations. J Anesth 1991;5:233–8.
13. Targ AG, Yasuda N, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in plastics and rubber composing a conventional anesthetic circuit. Anesth Analg 1989;69:218–25.
14. Eger EI II. Age, minimum alveolar anesthetic concentration, and minimum alveolar anesthetic concentration-awake. Anesth Analg 2001;93:947–53.

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