CASE REPORT

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Fatal Accidental Enflurane Intoxication

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ABSTRACT: Among reported cases of abuse of volatile anesthetics there is only one of enflurane intoxication. We report another fatal enflurane intoxication. A 21-year-old man found dead seemed to have experimented with enflurane. Three and one-half days after death high amounts of enflurane were detected in blood, brain, and subcutaneous fat. Gas chromatographic quantification revealed the following high enflurane concentrations: blood: 130 mg/l^{-1}, brain: 350 mg/l^{-1}, and subcutaneous fat: 100 mg/l^{-1}. Histologic signs of drug-induced damage were lacking. No suicide intentions became known. It was concluded that the young man died of an accidental intoxication while abusing enflurane.

KEYWORDS: pathology and biology, toxicology, enflurane, anesthetics, fatal intoxication, volatile anesthetics misuse, enflurane tissue concentrations, gas chromatography, ^{1}H-NMR spectroscopy of DMSO standards

Drug abuse and addiction has been identified as a major problem among hospital personnel [*1–8*]. Only a limited number of cases [*9–22*] of abuse of nitrous oxide and volatile anesthetics, mainly among operating room personnel [*11–13,15,22*], have been published. Among these there is only one enflurane intoxication [*13*]. We report the postmortem and toxicologic findings in another fatal enflurane intoxication.

Enflurane is a widely used clinical anesthetic. Rapid uptake and elimination from blood and brain [*23,24*] allow an easy management of anesthesia. Compared to halothane, renal and hepatic toxicity in animals and man [*25–30*] is markedly reduced. This is due to a relatively low solubility in fat and a lower biotransformation to fluoride.

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Case History

A 21-year old student working at the department of anesthesiology was found dead in front of a couch in the basement flat of his parent's house. He was last seen alive about 6 h earlier.

Two bottles of Ethrane®, one open and empty, the other closed with only some droplets of the contents, an inflating bellows with an attached filter, and a breathing mask within reach were highly indicative of enflurane intoxication.

Autopsy Findings

A forensic autopsy was performed three and one-half days later. The corpse showed no evidence of external injury, and there were no signs indicative of suicide or earlier suicide attempts. The corpse had a striking odor of enflurane. Police officers described the odor of the flat as resembling that of disinfecting agents.

There was moderate edema of brain and lungs. All organs were markedly congested. The bronchial tree showed moderate mucous inflammation. No other pathologic features were observed.

At the autopsy, subcutaneous fat, brain, and blood were stored in disposable 20-mL glass vials. The vials were immediately sealed with Teflon®-lined, rubber septum, aluminum caps. These vials were frozen and kept at −18°C together with samples of all organs and body fluids for routine toxicologic examination. Material for histological examination was fixed in 5% formalin at room temperature and routinely stained by hematoxilin-eosin and elastica van Gieson.

Histological Findings

The lungs showed moderate to severe congestion and little mucus in all parts of the bronchial tree. In the cardiac muscle there were no signs of inflammation or fibrosis. Necrosis, fatty change, or cholestasis were lacking in liver tissue. The kidneys were normal. Brain tissue showed slight to moderate acute nerve cell damage without reactive gliosis.

Toxicologic Analysis and Findings

Routine general unknown analysis using standard thin-layer chromatography/high pressure liquid chromatography/gas liquid chromatography/mass-spectrometry screening procedures revealed negative results except a blood ethanol concentration of 0.13 g/kg^{-1}.

Enflurane was detected in blood by gas chromatography/mass spectrometry (GC/MS). A model CH-7A with a SS 100 MS data system (Varian) was used for the analysis. Quantification was performed by the internal standard method using a Multifract F 40 headspace gas chromatograph (Perkin-Elmer) equipped with a flame ionization detector [*31*]. The chromatographic column (steel, 1.8-m by 0.32-mm inside diameter [ID]) was packed with 15% Carbowax 1500 on Chromosorb W NAW (80-100 mesh). Analyses were performed at the following conditions: carrier gas pressure (N_2): 147 kPa, oven temperature: isothermal 70°C, injector and detector temperature: 160°C, and waterbath temperature: 63°C. Stock standards were prepared by pipetting approximately 0.5 mL of enflurane and isoflurane (volatile), respectively, into 10 mL of deuterium-labeled dimethyl-d_6-sulfoxide (DMSO-D_6) containing 500 mg of trioxane. The exact content of enflurane and isoflurane was measured by ^{1}H-NMR spectroscopy [*31*]. Working DMSO standards were prepared by diluting 4 mL of stock standards in 96 mL of unlabeled DMSO. The concentrations of these solutions were 3.5 g/L^{-1} for enflurane and 3.1 g/L^{-1} for isoflurane, respectively. These solutions proved to be stable for at least ten weeks.

Immediately before use, working aqueous standards were prepared by diluting 10 mL of the working DMSO standards in 90 mL of ice water.

Slightly frozen samples of brain, fat, or blood were weighed (approximately 1 g) into 20-mL disposal vials, spiked with 0.5 mL of working aqueous standards of isoflurane (internal standard 0.31 mg/L^{-1}), and 1 mL of water. Vials were immediately sealed with Teflon-lined, rubber septum, aluminum caps. For calibration, 0.2- to 1-mL aliquots of working aqueous enflurane standards and 0.8 to 0 mL of water, respectively, were pipetted into the same type of vials, followed by 0.5 mL of working aqueous isoflurane internal standards and 1 mL of water. All vials were immediately sealed and allowed to equilibrate overnight at room temperature and 2 h at 63°C. The headspace was injected automatically into the gas chromatograph. Repeated measurements over several days revealed no losses in aqueous solutions. In lipophilic biologic material, in contrast, retention of isoflurane up to 20% was noted depending on the water content of the sample [*31*]. The individual retention of isoflurane within the samples was taken into account in the estimations of the enflurane concentration in the samples, as blood/gas partition coefficients of isoflurane and enflurane are comparable. Table 1 shows the results.

Discussion

The young man's death was attributed to general muscle relaxation and respiratory paralysis [*32*] caused by high concentrations of enflurane. As no suicidal intentions in the past had been reported, it was concluded that the intoxication was accidental. Whether this was on the basis of experiments or to achieve a "high" sensation could not be evaluated.

In our case, the blood enflurane concentration was in the same range as clinically observed values after 1 h of a 2% enflurane anesthesia calculated in a five-compartment model [*23*] and comparable to peak concentrations after 30 min of anesthesia [*24*].

It has to be considered that in contrast to clinically controlled anesthesia, the enflurane concentrations in this case of intoxication might have been influenced by several circumstances.

The young man possibly was exposed to very high inspiratory enflurane concentrations while using the breathing bellows. The uptake might even have been enhanced by a rebreathing induced hypercapnia. On the other hand, interruption of enflurane supply leads to rapid decrease of blood enflurane concentration [*23,24*]. The young man might

TABLE 1:
Mean and range of enflurane concentrations of 10 measurements per tissue

Tissue	Enflurane concentrations in mg·kg^{-1}	
	Mean	Range
Subcutaneous fat	100	75 - 140
Blood	130	80 - 160
Brain	350	270 - 450

have been exposed to minimal environmental enflurane concentration as a result of evaporation from the mask and the open bottle after initial unconsciousness. Reinhold et al. [*33*] could not establish a correlation between blood enflurane concentration and elimination rate via the lungs. Deduction of the enflurane kinetics from blood concentration alone thus is not correct.

Redistribution of enflurane in the corpse as well as evaporation within the interval between death and autopsy (3½ days) have to be considered. Blood concentrations measured at the autopsy thus must not correlate with blood concentrations at the time of death.

Using aqeous dilutions of DMSO-dissolved isoflurane standards for the gas chromatographical quantification of enflurane avoids biologic influences. Furthermore quantification can be achieved by use of ordinary blood-alcohol measuring equipment [*31*], since no electron capture detector (ECD) is needed. In our case wide concentration ranges within the samples were observed possibly as a result of differences in regional perfusion or release of enflurane from tissue matrices [*31*]. Measured enflurane concentrations thus have to be regarded as minimum concentrations. The concentrations in brain tissue were more than 2.5 times higher than those in blood and subcutaneous fat indicating the relatively high solubility of enflurane in fatty tissues.

The concentration differences between brain tissue and subcutaneous fat have to be explained by different perfusion rates of these tissues. However, diffusion of enflurane between tissues cannot be excluded due to the long period between death and autopsy. Low enflurane concentration in subcutaneous fat and lack of typical tissue damage as normally found in drug abusers are suggestive of the first abuse of enflurane in our case.

Considering the danger of abuse of volatile anesthetics, the access to these compounds should be restricted, as already demanded by other groups [*15,19*].

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