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CASE REPORT

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Fatal accident caused by isoflurane abuse

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Abstract A fatal accident after isoflurane abuse is presented in this report. A hospital employee was found dead in the operating area with a plastic bag over his head. In his locker an almost empty bottle of isoflurane was found. Autopsy revealed signs of asphyxiation and toxicological examination revealed nordazepam and isoflurane in non-toxic concentrations in the blood. Quantification of the anaesthetic was also carried out in urine, gastric contents, liver, kidney and brain samples, and in addition, oxazepam, prothipendyl and metabolites of midazolam and prothipendyl were found in the urine. Although the drug problems of the deceased were known before, no efforts had been made to restrict access to these drugs.

Keywords Isoflurane · Volatile anaesthetic · Abuse · Accidental intoxication

Introduction

Isoflurane (Forane; 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether; $C_3H_2ClF_5O$) is a fluorinated inhalation anaesthetic which was patented in 1969. Due to its low blood/gas solubility coefficient of 1.4 only small volumes are needed for a rapid induction of anaesthesia [1]. It strongly depresses respiration, reduces pharyngeal reflexes and relaxes skeletal muscles. More than 99% of this agent is exhaled without being metabolised which reduces hepatic and renal toxicity compared to chemically related substances such as halothane or enflurane. The major metabolites are trifluoroacetic acid and, to a lesser extent, fluoride ions which are both excreted in the urine. Isoflurane permits a quick recovery from anaesthesia with very few side-effects and is therefore presently the most commonly used volatile anaesthetic of this group [2].

For suicidal purposes these substances seem to be more commonly ingested or even injected than inhaled [3, 4, 5]. Illicit inhalation occurs in cases of abuse to get a pleasurable sensation, similar to the "high" feeling on sniffing glue [6]. Such types of abuse have been described especially, but not exclusively among hospital personnel [7, 8, 9]. It was reported previously that members of this selected group do not hesitate to also use injection anaesthetics for abuse purposes [10, 11]. A lethal outcome due to an accidental overdose of the misused agent has been often described, but only two reports involve fatalities due to isoflurane [12, 13] and only one deals with isoflurane concentrations in different tissues. Therefore a case of a fatal abuse of isoflurane by an operating room assistant is presented here together with a discussion of the toxicological findings.

Case report

A male operating room assistant (aged 36 years) went missing during the night, and the next morning the chief nurse found a toilet door locked in the changing room area for employees. On opening this door the body of the man was found inside, still dressed in his working clothes. He was sitting cross-legged, with his back turned towards the door, and the upper part of his body was bent forward so that his head touched the floor. A plastic bag was pulled over the head and ears, but whether the bag had also covered the mouth and nose could not be reconstructed. The emergency doctor proclaimed the man dead, and no resuscitation was attempted. The face showed a dark blue colour and was stained with a blood-like liquid, but injuries could not be detected. The police physician suspected suicide by suffocation with the plastic bag.

The work colleagues said that they had noticed a change in the behaviour of the deceased over the last months, and that sometimes he had seemed to be inebriated. It was recorded in the hospital that he had had problems with substance abuse some time before.

When his locker was opened, beside some personal belongings a 100 ml bottle labelled with "Forane" was found which only contained an estimated 25–30 ml of fluid.

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Autopsy findings

Autopsy was performed 22 h after finding the corpse.

Livores with vibices were found in the front and upper part of the body including the head. The conjunctivae showed small haemorrhages. The face was swollen and had a dark blue colour. A red mucous fluid filled the mouth and nose, which had drained from there and was partly dried all over the face. From the mouth an ether-like smell was detectable.

The right side of the neck showed a scratch in the skin, nearly 4 cm in length with dried blood on it, but no other injuries were detected.

The internal organs (brain, heart, kidneys, spleen) showed signs of acute congestion. The airways and the oesophagus were filled with red, partly foamy mucus and had the same ether-like odour as the brain. Other findings were a dilatation of the right cardiac ventricle, alveolar oedema of the lungs and a fatty degeneration of the liver tissue. Scalp and meninges showed multiple haemorrhages with a maximum diameter of 1 cm.

Preparation of the soft parts of neck and extremities showed no injuries or haemorrhages. No signs of intravenous drug abuse were found.

Histological examination of the brain, heart, and kidneys gave no important additional information and confirmed the macroscopic findings. In lung tissue, no fat embolism could be detected. The liver showed fatty degeneration of some hepatocytes.

All samples taken for toxicological examinations were put into headspace vials, sealed, and stored immediately at –20°C.

A screening test for drugs in urine (Triage 8) performed during autopsy showed a positive result for benzodiazepines.

Altogether, autopsy findings were in concordance with death through functional asphyxiation.

Material and methods

Isoflurane (Forane) and sevoflurane (Sevorane) were obtained from Abbott (Vienna, Austria), acetonitrile p.a. from Scharlau (Barcelona, Spain).

Quantification of isoflurane was performed using an automated headspace sampling method combined with GC analysis with flame ionisation detection (FID). An aqueous solution of sevoflurane (50 mg/l with 2 ml of acetonitrile as solubiliser) was used as an internal standard. For preparation of samples 10 ml of tap water was pipetted into a 20 ml headspace vial. After addition of 100 µl of internal standard and 100 µl of liquid specimens (urine, cardiac blood, liquor) or approximately 50 mg of organ tissue (brain, kidney, liver) or 100 mg of gastric contents which were weighed and their exact amount noted, the vial was immediately capped with a teflon-coated silicon septum and gently vortexed. Sample preparation was performed 6 times for each specimen.

Quantification was done using peak area ratios when compared to a calibration curve. Calibrators were prepared analogous to the samples using blank blood spiked with an aqueous solution of isoflurane (100 mg/l with 2 ml of acetonitrile as solubiliser), i.e. 10 ml water, 100 µl internal standard and 100 µl of each calibrator was pipetted in the vial. A calibration range from 0 mg/l to 100 mg/l was chosen (calibration levels: 0, 5, 10, 25, 50 and 100 mg/l). Calibration was linear in this range with a limit of detection (LOD) of 0.8 mg/l and a limit of quantitation (LOQ) of 3.0 mg/l (statistical significance of 95%; calculation according to DIN 32645).

The operation conditions of the headspace autosampling system were as follows: instrumentation Perkin Elmer HS40: thermostating for 30 min at 60°C, needle and transfer line temperature 90°C, pressurisation time 0.5 min, injection time 0.1 min. The operation conditions of the GC-FID system were as follows: instrumentation Hewlett Packard GC 5890 Series II, GC: DB-Wax column (30 m×0.32 mm i.d. ×0.50 µm film thickness), column head pressure 70 kPa, injection temperature 250°C, oven 35°C, 10°C/min to 120°C, hold for 1 min, FID detector at 250°C.

For the immunological screening of the urine sample CEDIA reagents from Microgenics (Passau, Germany) on a Cobas Mira Plus System by Roche (Vienna, Austria) were used. Qualitative chemical analysis for toxic drugs was performed using a standard "general unknown analysis procedure" including acidic hydrolysis and solid phase extraction (urine) and acetone precipitation (gastric contents), combined with GC-MS analysis. The conditions of operation of the GC-MS system were as follows: instrumentation HP6890 GC and HP5973 mass selective detector, GC: DP-5 MS column (30 m×0.25 mm i.d. ×0.25 µm film thickness), carrier gas helium at 19.1 ml/min, injection temperature 270°C, injection volume 1 µl, oven 50°C, 25°C/min to 150°C, 10°C/min to 300°C, hold for 7 min, MS ionisation: electron impact (EI) at 70 eV, data collection: HP Chemstation G1701BA B01.00 including Agilent Technologies (Waldbronn, Germany) mass spectral libraries Rev. D02.00 (Pfleger-Maurer-Weber).

For quantification of benzodiazepine derivatives in blood, 0.5 ml of the sample was pipetted into 3 ml water with 40 µl of methyl-clonazepam as internal standard, centrifugated twice, and the supernatant was used for solid phase extraction (columns: Speed Scan ABN 3 ml, Inovex, Vienna, Austria). The eluate was dried, redissolved in 500 µl ethyl acetate and analysed with GC with an electron capture detector (GC-ECD). Calibration was performed by analysing spiked serum samples. The operation conditions of the GC-ECD system were as follows: instrumentation Perkin Elmer Autosystem XL, GC: HP-5 MS column (30 m× 0.25 mm i.d. ×0.25 µm film thickness), carrier gas hydrogen at 20.0 ml/min, injection temperature 250°C, injection volume 1 µl, oven 100°C, 20°C/min to 220°C, hold for 15 min, 20°C/min to 300°C, hold for 5 min, ECD detector at 350°C.

Results

Isoflurane could be detected in all of the samples tested. Quantification was subsequently done and the results are listed in Table 1. An example for typical chromatograms of blank blood and cardiac blood of the presented case are depicted in Fig. 1. No alcohol was found in the urine and blood samples. Additional toxicological findings were nordazepam in a therapeutic concentration of 0.14 mg/l in the cardiac blood. Furthermore, oxazepam, prothipendyl and its metabolic product nor-bis-prothipendyl as well as hydroxymidazolam were found in the urine. The immunological screening of the urine for drugs of abuse was negative for amphetamines, cannabinoids, cocaine, methadone, LSD, opiates, phencyclidine and propoxyphene. The gastric contents contained caffeine.

Table 1 Concentrations with standard deviation of isoflurane in body fluids and tissues (mg/l and mg/kg, respectively). Determination of standard deviation and confidence interval by analysis of six independent sample preparations (statistical significance 95%)

Specimen	Isoflurane
Urine (mg/l)	4.4± 0.14
Liquor (mg/l)	6.3± 0.27
Cardiac blood (mg/l)	47.9± 0.94
Gastric contents (mg/kg)	252.7±16.05
Kidney (mg/kg)	52.8± 4.70
Liver (mg/kg)	999.8±89.99
Brain (mg/kg)	306.9± 9.55

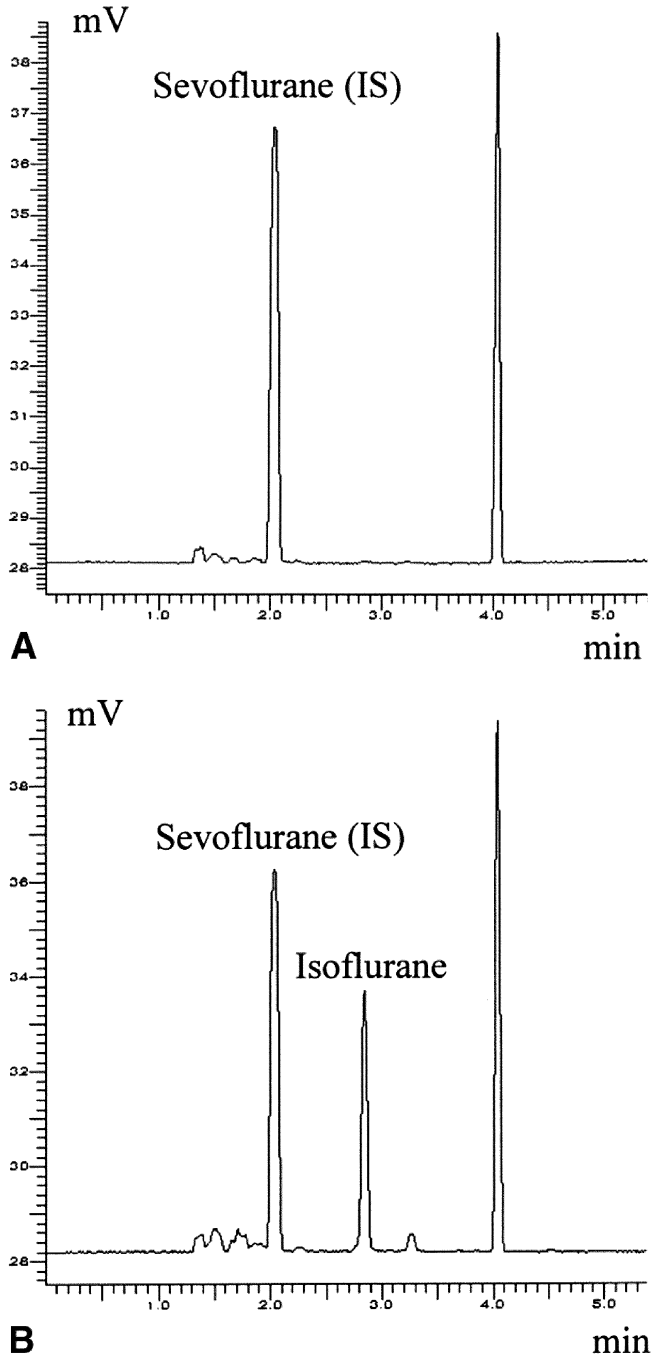

Fig. 1 GC-FID chromatograms of **A** blank blood and **B** cardiac blood of the presented case. Retention times for isoflurane and sevoflurane (internal standard, IS) were 2.84 and 2.04 min, respectively. The peak at 4.04 min represents the IS-solubiliser acetonitrile

Discussion

The deceased had never mentioned any suicidal intentions, and no suicide note was found. The death scene showed no evidence of an autoerotic background, so the manner of death in the presented case was determined as accidental in connection with isoflurane abuse. The isoflurane concentration was measured as 47.9 mg/l in cardiac blood. This value is clearly lower than the concentrations reported in venous blood achieved during general anaesthesia with 2% isoflurane, which range from 85.2 mg/l before the beginning of surgical interventions to 104.9 mg/l during the operation [14]. Isoflurane strongly depresses respiration and muscular activity, so artificial ventilation during anaesthesia is inevitable. In the presented case a lower than therapeutic isoflurane concentration apparently restricted breathing activities enough to lead to lethal asphyxiation, which is also consistent with the autopsy findings. According to the literature a similar isoflurane blood concentration (45.9 mg/l) caused death without contribution of other drugs [13]. It can be assumed that in the presented case the benzodiazepine nordazepam had additionally intensified the depressive respiratory effect of isoflurane.

Apparently, the man had used a plastic bag to volatilise and inhale the agent. Although it could not be reconstructed afterwards for certain if the bag had really covered the mouth and nose when the body was found, it is likely that breathing in the bag could have led to hypercapnia, thus facilitating suffocation. Furthermore, using a bag for volatilisation causes higher isoflurane concentrations in the inhaled air than by using special vaporisers during anaesthesia. As a consequence, rapid loss of consciousness is probable, additionally facilitated by the low blood/gas solubility coefficient of isoflurane.

Although the deceased had apparently been sniffing the agent, the isoflurane concentration in the gastric contents was very high, exceeding for example the values in cardiac blood or in kidney tissue by a factor of 5. No other data are available about isoflurane concentrations in gastric contents, but in cases with halothane intoxication the stomach concentrations in relation to other tissues were lower, even if halothane was orally ingested [5, 15].

As expected, high isoflurane concentrations were found in the brain sample, indicating the preferred distribution of the substance in lipophilic tissues. The highest levels were detected in liver tissue. Compared to the isoflurane intoxications reported in literature, both values in the presented case are extremely high, especially in liver tissue. Two facts could explain these findings: firstly, the man was not resuscitated, which did not lead to a decrease of isoflurane concentrations by resuscitation efforts and therefore movement of air in the airways. Secondly, isoflurane intoxication was suspected before autopsy and therefore the samples taken were put in headspace vials, sealed and stored immediately at –20°C to minimise substance loss. Unfortunately, no sample of lung tissue was taken. Nevertheless, it cannot be estimated to what extent the isoflurane concentrations were a consequence of post-mortem redistribution in different tissues or how much isoflurane really evaporated from the body before taking the samples. In peripheral venous blood an isoflurane concentration of 17.39 mg/l (±0.63 mg/l) was detected, but a comparison to the concentration in cardiac blood did not seem to be valid because the specimen was not stored in headspace vials.

No information could be obtained on whether the man had had experience with isoflurane sniffing before or knew about the dangers. Isoflurane does not seem to produce significant dependence with withdrawal symptoms or tolerance [16]. In the presented case, the benzodiazepine midazolam and the neuroleptic prothipendyl were additionally found in the urine. Both substances have to be medically prescribed in Austria. Moreover, a repeated administration of midazolam, which is only available as a solution for injection purposes, is forbidden. Chronic abuse of midazolam by medical staff is well known and could be proved by hair analysis in one case previously [17].

Obviously, the deceased in our case had abused more than one drug in the past and had taken advantage of his profession to get access to these substances, although the management of the hospital had known of his addiction. Not only the access to volatile anaesthetics should therefore be restricted as has already been requested on several occasions [6, 7, 8, 9, 18], but also the hospital inventory of medicaments should be controlled exactly. Lastly, especially hospital personnel should be alerted that the abuse of medicaments is not an uncommon problem among them and that a person with obvious drug problems needs professional help, even if that includes removing the person from sensitive hospital areas.

References

1. Baselt RC, Cravey RH (eds) (1995) Isoflurane. In: Disposition of toxic drugs and chemicals in man, 4th edn. Chemical Toxicology Institute, Foster City, Calif, pp 401–402
2. Pihlainen K, Ojanpera I (1998) Analytical toxicology of fluorinated inhalation anaesthetics. Forensic Sci Int 97:117–133
3. Berman P, Tattersall M (1982) Self-poisoning with intravenous halothane. Lancet 1:340
4. Curelaru I, Stanciu S, Nicolau V, Fuhrer H, Iliescu M (1968) A case of recovery from coma produced by the ingestion of 250 ml of halothane. Br J Anaesth 40:283–288
5. Spencer JA, Green NM (1968) Suicide by ingestion of halothane. JAMA 205:702–703
6. Spencer JD, Raasch FO, Trefny FA (1976) Halothane abuse in hospital personnel. JAMA 235:1034–1035
7. Yamashita M, Matsuki A, Oyama T (1984) Illicit use of modern volatile anaesthetics. Can Anaesth Soc J 31:76–79
8. Jacob B, Heller C, Daldrup T, Burrig KF, Barz J, Bonte W (1989) Fatal accidental enflurane intoxication. J Forensic Sci 34:1408–1412
9. Block S, Rosenblatt R (1980) A halothane-abuse fatality. Anesthesiology 52:524
10. Breitmeier D, Passie T, Mansouri F, Albrecht K, Kleemann WJ (2002) Autoerotic accident associated with self-applied ketamine. Int J Legal Med 116:113–116
11. Iwersen-Bergmann S, Rosner P, Kuhnau HC, Junge M, Schmoldt A (2001) Death after excessive propofol abuse. Int J Legal Med 114:248–251
12. Dooper MM, Beerens J, Brenninkmeijer VJ, Gerlag PG (1988) Fatal intoxication after ingestion of isoflurane. Neth J Med 33: 74–77
13. Kuhlman JJ, Magluilo J, Levine B, Smith ML (1993) Two deaths involving isoflurane abuse. J Forensic Sci 38:968–971
14. Yang NC, Hwang KL, Hung DZ, Wuhh HH, Ho WM (2000) Reliable gas chromatographic-mass spectrometric method combined with a headspace autosampler for isoflurane determination in blood. J Chromatogr B Biomed Sci Appl 742:277–282
15. Madea B, Musshoff F (1999) Homicidal poisoning with halothane. Int J Legal Med 113:47–49
16. Smith RA, Winter PM, Smith M, Eger EI (1979) Tolerance to and dependence on inhalational anesthetics. Anesthesiology 50:505–509
17. Cirimele V, Kintz P, Doray S, Ludes B (2002) Determination of chronic abuse of the anaesthetic agents midazolam and propofol as demonstrated by hair analysis. Int J Legal Med 116: 54–57
18. Marks WE, Wallace CT (1976) Letter: Halothane abuse. JAMA 236:139–140