CASE REPORT

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Two Deaths Involving Isoflurane Abuse

REFERENCE: Kuhlman, J. J., Jr., Magluilo, J., Jr., Levine, B., and Smith, M. L., **"Two Deaths Involving Isoflurane Abuse,"** *Journal of Forensic Sciences*, Vol. 38, No. 4, July 1993, pp. 968–971.

ABSTRACT: Two deaths due to isoflurane abuse are reported. One case was a suicide and the other a multiple drug death including isoflurane. A simple headspace gas chromatographic method was used for isoflurane quantitation. A review of the literature did not reveal blood and tissue concentrations of isoflurane. Drug tissue distributions and a discussion of the toxicological findings are presented.

KEYWORDS: toxicology, isoflurane, death, drugs of abuse

Isoflurane (Forane), 1-chloro-2,2,2,-trifluoroethyl difluoroethyl difluoromethyl ether, is an anesthetic used for the induction and maintenance of general anesthesia. Isoflurane has a low blood:gas solubility coefficient that enables a smaller volume of anesthetic vapor to be used and allows for a rapid induction and recovery from anesthesia. Safe and effective use of isoflurane requires the use of a precision vaporizer.

Metabolism of isoflurane is minimal. Greater than 99% of it is excreted unchanged. This accounts for its lack of renal and hepatic toxicity caused by related halogenated anesthetics such as halothane and enflurane. Isoflurane also does not possess the convulsant activity of its isomer, enflurane [*1*].

Abuse of halogenated anesthetics has most often been by medical personnel using halothane and enflurane [*2*]. Within the past two years, this laboratory has had two cases where isoflurane was involved in deaths due to multiple drug ingestion. This report presents the toxicological findings of these two cases.

Received for publication 20 July 1992; revised manuscript received 28 Oct. 1992; accepted for publication 29 Oct. 1992.

The opinions herein are those of the authors and not those of the Department of the Air Force, the Department of the Army or the Department of Defense.

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Case Histories

Case #1

A 21-year-old hospital employee was found dead at 6:15 A.M. with a bottle of Forane in his hand. Extensive resuscitation was performed with no success. An investigation of his work section found several bottles of Forane missing. A search of his personal effects and residence found Indocin, Norgesic, Tylenol 3, codeine, Motrin, terpin hydrate with codeine and numerous empty over-the-counter medications. The investigation also revealed that he had been stealing large amounts of cough medicine from the hospital pharmacy. There was no suggestion of suicidal intent and his friends were unaware of any financial, emotional, or marital problems. The deceased had played cards during the previous night and was last seen alive at 2 A.M. The cause of death was combined drug overdose and the manner of death was undetermined.

Case #2

A 33-year-old research laboratory employee was found dead on the floor next to a laboratory table. He had a towel wrapped around his face and two plastic bags covering his head. A three-quarters empty 100 mL bottle of Forane was found on the table nearby. A suicide note was later found.

Materials and Methods

Reagents

Isoflurane (Forane) and Enflurane (Ethrane) were obtained from Anaquest, Madison, Wisconsin.

Analytical Procedures

Isoflurane was quantitated in blood and tissue specimens using headspace gas chromatography with enflurane as the internal standard. One mL blood or approximately 1 g tissue was added to 20 mL Tekmar headspace gas chromatography vials. Fifty μL of 0.94 mg/mL enflurane in methanol was added to each vial as the internal standard. Five mL of water was added to each vial, then capped and gently vortexed. Headspace analysis was performed using the Tekmar 7000 Headspace Analyzer equipped with a 7050 Autosampler and a Hewlett Packard 5880 gas chromatograph equipped with a flame ionization detector. Conditions for the Tekmar headspace autosampler were as follows: platen 75°C, valve 75°C, transfer line 75°C, platen equilibration 0.10 min, sample equilibration 30 min, vial size 20 mL, pressurize 0.3 min, pressure equilibration 0.3 min, loop 0.3 min, loop equilibration 0.2 min. and injection time 0.5 min. The gas chromatograph was operated isothermally at an oven temperature of 100°C, injector temperature 150°C and detector temperature 150°C. The column was a Supelco 6 ft 80/100 Carbopack C 0.2% Carbowax 1500. The run time was 8 min. Isoflurane quantitation was performed using isoflurane to internal standard peak area ratios compared to a standard curve prepared using spiked whole blood calibrators.

Diphenhydramine, orphenadrine and lidocaine were identified by gas chromatography using a modified procedure of Watts and Simonick [*3*] and confirmed by gas chromatography/mass spectrometry. Quantitations were performed using nitrogen phosphorus detection gas chromatography or gas chromatography/mass spectrometry (GC/MS). Salicylate was identified by color test [*4*] and quantitated by fluorescence polarization

immunoassay (FPIA) using the Abbott TDx analyzer. Cocaine was identified by FPIA and confirmed and quantitated by GC/MS using a modification of the procedure published by von Minden and D'Amato [5].

Results

Isoflurane is easily detected using this procedure. Its relative retention time to the enflurane internal standard is 1.11. Isoflurane and other drugs found in these two cases are listed in Table 1.

In Case #1, 33 mg/L of salicylate was also found in the blood. The lidocaine found was given in the resuscitative procedure. Case #2 had cocaine and benzoylecgonine identified and confirmed in the urine. There was no cocaine found in the blood at a limit of quantitation of 0.05 mg/L and no benzoylecgonine found in the blood at a limit of quantitation of 0.2 mg/L by GC/MS.

Discussion

In case #1, isoflurane was a contributing factor in the death. The diphenhydramine concentrations found were much higher than therapeutic concentrations but less than an average of six fatalities due to acute diphenydramine ingestion reported in the literature [6]. The blood/liver and blood/brain ratios of diphenhydramine in this case were considerably higher than the ratios found in the literature cases.

	Case #1	*Literature*	*% Difference*
Blood/liver	0.73	0.47	+55%
Blood/brain	1.52	0.89	+71%

The orphenadrine concentrations fall in the lower end of the range found in eight reported orphenadrine fatalities [7]. The blood/liver ratio of orphenadrine in case #1 is 0.28, a two fold increase over the 0.14 blood/liver ratio of the eight reported orphenadrine fatalities. Given the degree of CNS depression induced by the high concentrations of diphenhydramine and orphenadrine, the additional insult by isoflurane may have caused death to occur sooner than would be expected.

A review of the literature did not produce any references to blood or tissue isoflurane levels. The blood isoflurane level in case #2 was over four times greater than was found in case #1. This difference was not unexpected since case #2 was a suicide and case #1 probably was not a suicide. Therapeutic blood levels for halogenated anesthetics are inversely related to their blood/gas partition coefficients (see Table 2). Enflurane's blood/

TABLE 1—*Drug concentrations in two isoflurane deaths (mg/L or mg/kg).*

Case #1	Isoflurane	Diphenhydramine	Orphenadrine	Lidocaine
Blood	9.9	3.2	4.1	4.1
Liver	31.0	4.4	14.7	6.9
Lung	17.0	3.7	10.8	3.4
Kidney	22.3	1.2	5.0	2.3
Brain	107.0	2.1	9.6	6.3
Case #2	Isoflurane			
Blood	45.9			
Liver	97.2			
Lung	34.5			
Kidney	27.3			

TABLE 2—*Halogenated anesthetic blood gas coefficients and therapeutic blood levels.*

Drug	Blood/Gas partition coefficient [1]	Blood Level [8]
Methoxyflurane	12.0	125–200 mg/L
Halothane	2.3	80–260 mg/L
Enflurane	1.9	50–100 mg/L
Isoflurane	1.4	?

gas partition coefficient is not very different from isoflurane's, thus, you might expect their therapeutic blood levels to be similar. Unfortunately, the isoflurane level found in case #2 is not consistent with this pattern. Possibly isoflurane's low blood/gas partition coefficient may also contribute to its postmortem loss.

Acknowledgment

This work was funded in part by the American Registry of Pathology.

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