TAB # 9

Case Report

A Motor Vehicle Accident Fatality Involving the Inhalation of 1,1-Difluoroethane

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Abstract

A 24-year-old female driver with a history of substance abuse was pronounced dead following a single car motor vehicle accident. A surviving front seat passenger witnessed the decedent inhaling "Dust Off" cleaner just prior to losing control of the vehicle. The propellant compound used in this product is the halogenated hydrocarbon 1,1-difluoroethane (DFE). Sealed autopsy specimens were examined for the presence and subsequent quantitation of DFE utilizing an Agilent 6850 gas chromatograph (GC)–flame-ionization detector. The levels of DFE obtained were as follows: 29.8 mg/L in femoral blood, 40.3 mg/L in pulmonary arterial blood, 85.6 mg/L in aortic blood, 79.9 mg/L in chest cavity blood, 21.2 mg/L in vitreous, 11.7 mg/kg in brain, 27.9 mg/kg in liver, 71.0 mg/L in urine, and 51.8 mg/total gastric contents. The presence of DFE was confirmed in the decedent's urine by injection on an Agilent 6890/5973 GC–mass spectrometer in full scan mode. This case presents a uniquely witnessed observation of the apparent impairing effects and consequences of the acute inhalation of halogenated hydrocarbons such as DFE and the operation of a motor vehicle. The proximity of time of death to inhalant use may also provide insight to postmortem distribution patterns of DFE in relation to normal physiologic blood flow. With further investigations, estimating the time of final use of an inhalant prior to death may be deciphered from such patterns, although a degree of caution should be applied in deaths resulting from severe trauma in which normal tissue structure is compromised because postmortem redistribution may result.

Introduction

The study of inhalant compounds of abuse poses a challenge to postmortem analysis because of their inherent high volatility, short half-life, and rapid elimination from the blood. Proper specimen collection in sealed containers within a timely manner after death is crucial to the validity of obtained results and any inferences proposed from such data. As we have previously reported, a comparison of calculated levels of inhalant compounds in various specimens may be used to infer chronic or acute inhalant abuse (1). Despite the problems and variability associated with inhalant analysis, these compounds remain an active part of testing in many clinical settings as shown by the number of cases reported each year to the American Association of Poison Control Centers (2). One such commonly abused inhalant is 1,1-difluoroethane (DFE). This halogenated hydrocarbon, known as Freon 152a, is used as a propellant in many commonly available aerosolized products such as keyboard cleaners. Fluorocarbon compounds containing DFE produce a sudden onset of intoxication. This intoxication has been associated with sudden death involving cardiac arrhythmias termed "sudden sniffing death syndrome" (3–7).

Although inhalant use is still quite prevalent, as shown in a recent drug use survey of high school students by the Center for Disease Control (8), the incidence of inhalant abuse involvement in motor vehicle operation is low when compared to more common drugs of abuse such as marijuana, as demonstrated by DUI drug stop statistics (9). This low prevalence among drivers may be related to a lack of detection of volatile compounds within an optimal time frame for measuring such short-lived compounds. As shown in a case report by Broussard et al. (10), the psychomotor impairment delivered by inhalant compounds can produce consequences just as grave as the more commonly abused and detected drugs. The sudden death associated with traumatic injuries of traffic accidents may provide a snapshot of the pharmacokinetic characteristics of acute inhalant use. In the following text, we describe a uniquely witnessed fatal motor vehicle accident involving the inhalation of DFE that may provide insight into postmortem levels of DFE.

Case History

A 24-year-old female driver with a history of substance abuse and depression was pronounced dead following a single car motor vehicle accident. A surviving front seat passenger provided crucial information on the events leading up to the subject's death. Following an argument with the passenger the

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female driver was described to be huffing Dust Off Duster (Dupont, Wilmington, DE) while operating the motor vehicle. This common computer keyboard cleaner contains DFE as the propellant. Subsequently, she became irate and began to drive erratically at a very high rate of speed. Ignoring the passenger's plea to slow down, the driver lost control of the car and struck a telephone pole, shearing the car in half. The driver was pronounced dead at the scene, and the passenger was treated and released from a local hospital with minimal injuries. The decedent's body was transferred to cold storage (4°C) within 1 h of the time of death and autopsied within 24 h.

Findings at autopsy showed multiple organ lacerations involving the liver, spleen, and kidneys with internal hemorrhaging. An examination of the head and cervical region revealed alanto-occipital disarticulation with incomplete ponto-medullary avulsion and basilar arterial transection. No systemic disease processes or pathologic abnormalities were noted. The manner and cause of death were determined to be accidental blunt force trauma.

At the autopsy, biological specimens were collected and submitted for a comprehensive toxicological analysis. These specimens included blood, urine, vitreous fluid, brain, liver, and gastric contents. The submitted samples were stored at 4°C for 24 h. Based on the investigative report of the accident a 2.0 g or 2.0 mL sampling of each specimen was then stored at –20°C in 10-mL glass headspace vials sealed with Teflon caps. Additionally, a chest cavity blood sample was immediately sealed at autopsy in a 10-mL glass vial and stored at –20°C.

Experimental

Samples

A toxicological analysis of the submitted samples was performed under the guidelines of our general unknown drug screening protocol. This includes a urine screen for drugs of abuse utilizing the enzyme multiplied immunoassay technique, EMIT® II Plus assay from Dade Behring (Cupertino, CA) with analysis on an Olympus AU400e. A basic drug screen of the liver homogenate was performed involving liquid–liquid extraction with gas chromatography–mass spectrometry (GC–MS) analysis on an Agilent 6890N/5973 in full scan mode over the atomic mass range of 43–550 amu. An additional screen was carried out for weak acids and neutrals in blood with liquid/liquid extraction followed by GC–MS analysis. A volatile compound screen was performed on blood utilizing a Hewlett-Packard 6850 capillary GC with a flame-ionization detector (FID) coupled with a 7694 vial autosampler. A blood sample was additionally screened for carbon monoxide involving a visible spectrophotometric analysis on a Varian Cary 100 Scan Spectrophotometer. Any non-volatile drugs detected were submitted for quantitation by blood extraction with single ion monitoring analysis on GC–MS or liquid chromatography–MS instrumentation.

The liver drug screen indicated the presence of sertraline and norsertraline. The urine drug screen was positive for the carboxylic acid metabolite of tetrahydrocannabinol (THC-COOH). The basic, weak acidic/neutral, carbon monoxide, and EMIT analyses were negative for all other drugs. The volatile screen of aortic blood was negative for ethanol but did reveal an unknown peak.

Methods

Materials and reagents. A standard of 98+% DFE was purchased from Aldrich Chemical (Milwaukee, WI) to prepare a working stock solution of DFE. Omni Solv high purity solvent methanol used during the analysis was obtained from EMD Chemicals (Gibbstown, NJ). The working stock solution was prepared by the addition of the DFE (Aldrich Chemical) standard to a sealed and weighed glass vial containing 10 mL of methanol. The DFE was added to the vial until a final concentration of 0.98 mg/mL was prepared. A negative whole blood matrix used in calibrator and control samples was obtained from Long Island Blood Services and screened prior to use in the laboratory.

Headspace GC–FID analysis. The 0.98 mg/mL working methanolic solution of DFE was used to establish a set of calibrator solutions. This was accomplished by the addition of varying amounts of the prepared solution to 10-mL headspace vials containing 2 mL of negative whole blood. This was performed to create a seven-point calibration curve from the level of 0.0 µg/mL to 245.0 µg/mL. A separate 10-mL headspace vial containing 2 mL negative blood, designated as a positive control, was created with the addition of the 0.98 mg/mL methanolic DFE solution to establish a control level of 171.5 µg/mL. In addition, a negative control was prepared with the addition of 2 mL of negative blood to a 10-mL vial devoid of DFE. All calibrator and control samples prepared were sealed immediately upon preparation. Specimens obtained at autopsy and subsequently sealed and frozen were weighed on an analytical balance tared with an empty sealed 10-mL headspace vial. The following specimens and corresponding weights were submitted for DFE analysis: femoral blood (2.3 mL), aortic blood (2.0 mL), pulmonary arterial blood (1.8 mL), chest cavity blood (2.1 mL), vitreous fluid (1.7 mL), brain (2.0 g), liver (1.9 g), gastric contents (1.8 mL), and urine (1.9 mL).

Analysis was carried out on an HP 5890 GC–FID with a 7694 autosampler utilizing a Restek RTX-BAC1 30-m × 0.53-mm i.d. column with helium as the carrier gas. As we described in previous work (1,4), instrumentation parameters were the following: equilibration at 40°C for 15 min, 1-mL sample loop, pressurization 0.15 min, loop fill 0.15 min, and sample inject 0.25 min. An isothermal oven temperature of 40°C was maintained along with an injector temperature of 200°C and a detector temperature of 225°C. An instrument calibration curve was established by the correlation of the measured area under the generated DFE peak to each corresponding calibrator level. The control and unknown DFE concentrations were calculated by comparison of their generated peak area to the calibration curve. The levels of DFE in the decedent's samples were corrected for sample weight and volume prior to reporting.

GC–MS confirmation. To confirm the presence of DFE in the decedent's specimens, a 50-µL aliquot of the decedent's urine was added to 2 mL methanol solution and mixed, and a small sample was transferred to an autosampler vial for GC–MS anal-

ysis. A positive control containing the DFE methanolic working solution and a solution of DFE-free methanol were analyzed along with the urine sample. The samples were injected on an HP 6890/5973 GC–MS utilizing an RTX-5MS 30-m × 0.25-mm i.d. column in scan mode from 34.0 to 70.0 amu. Analysis was carried out under the following instrument parameters: injector temperature of 225°C, initial oven temperature of 40°C, column flow of 0.8 mL/min, run time of 5.0 min, and a detector temperature of 280°C.

Results and Discussion

Along with the postmortem levels of DFE generated, all other drugs of toxicological interest were quantitated. The levels of sertraline and norsertraline in femoral blood were determined to be 0.28 and 0.25 mg/L, respectively. Subsequent quantitation of THC-COOH and the parent Δ^9-tetrahydrocannabinol in the femoral blood produced levels of 24.0 and 5.5 µg/L, respectively.

The results of DFE quantitation by headspace GC–FID in the decedent's tissues are listed in Table I. The calibration curve constructed had a linear correlation coefficient of 0.998. Control specimens analyzed were acceptable with a calculated positive level of 174.3 mg/L (target: 171.5 mg/L) along with a negative control devoid of DFE. The resultant chromatogram of the urine specimen analyzed by GC–MS scan confirmed the presence of DFE as compared to the DFE standard's chromatographic spectrum. The urine specimen chromatographic peak, at a retention time of 1.67 min, was similar to the retention time of 1.61 min for the DFE standard and produced a mass spectrum with the major mass ions of 65, 51, and 47; which matches the ion spectrum obtained for the DFE standard.

Most deaths associated with volatile substance abuse (VSA) are attributed to the direct toxic effects delivered by the inhalant on sensitive tissues, with deaths caused by trauma related inhalant abuse representing only a small fraction (11). Sudden deaths caused by sniffing are usually unwitnessed, with a substantial delay between estimated time of death and discovery of the decedent. As previous investigators have noted (10), the unknown final time of use of the inhalant substance leads to great difficulty in developing an accurate pharmacokinetic and postmortem distribution model for toxic inhalant exposure in humans. Examining the postmortem inhalant levels of individuals where the cause of death was trauma related to VSA might diminish the uncertainty associated with final time of use. In situations involving VSA and a traumatic death, such as a motor vehicle accident, the event is usually witnessed so as the establishment of an exact time of death in such cases is not difficult. The sudden cessation of normal physiologic activity following a traumatic death will "freeze" (11) conditions within the body to provide a snapshot in time of drug levels at that moment. This proposition will remain valid only if the death is instantaneous, the event is witnessed, and the body is not subjected to extreme environmental conditions (e.g., heat, dismemberment, chemical contamination). These stipulations should also include a thorough examination of autopsy findings to note any compromise in the structural integrity of tissues and blood vessels in which compartmentalization is diminished. This should ensure the valid interpretation of volatile results in regards to possible postmortem redistribution following severe trauma to the body. In the case we present in this article, these conditions were satisfied. The decedent suffered no major trauma or disruption of the thoracic and femoral blood vessels in which DFE was measured. In addition, information was provided by the surviving passenger so as to confirm the acute inhalation of DFE immediately prior to death. It is tempting to speculate that the levels of DFE we calculated may be used to construct a mechanism in which the extent of VSA, in relation to time of final product use and degree of exposure, may be determined from postmortem blood and tissue levels.

As shown in Table I, the levels of DFE in sampled tissue sites displayed a significant variability. Blood obtained from the aorta, which contains recently oxygenated or ventilated blood, contained the highest DFE level of 85.6 mg/L. This is consistent with a very recent inhalation of the DFE inhalant compound into the lungs as described by Wegner and Grow (12). Lower blood levels were calculated in sites further from the lungs and heart; the femoral blood contained 29.8 mg/L, whereas blood in the pulmonary artery, just prior to being ventilated, contained 40.3 mg/L. This demonstrates the absorption of DFE through the body tissues while traveling from the site of introduction (lungs) to more peripheral arterial blood sites with transportation of mixed blood back to the heart through the venous system and finally back to the lungs. This variability in DFE levels throughout the circulatory system indicates a dynamic process of DFE distribution related directly to the acute inhalation. In a study of fluorocarbon propellant arterial-venous distribution in dogs (13), blood equilibrium following inhalation cessation was achieved 100 min after introduction. The lack of equilibrium of blood levels in our case further indicates an acute inhalation of DFE. Tissue distribution of inhalants, such as DFE, follows a dose-dependent pathway directed by the degree of blood perfusion of the specific tissue site (14,15). The more blood delivered to the tissue the higher the concentration of inhalant found in that

Table I. Postmortem 1,1-Difluoroethane Levels

Tissue	Concentration
Aortic blood	85.6 mg/L
Chest cavity blood*	79.9 mg/L
Pulmonary arterial blood	40.3 mg/L
Femoral blood	29.8 mg/L
Vitreous fluid	21.2 mg/L
Brain	11.7 mg/kg
Liver	27.9 mg/kg
Urine	71.0 mg/L
Gastric contents	51.8 mg/total

* Sealed at autopsy.

tissue. It has also been shown that tissues high in lipid content retain volatile compounds longer and will attain comparatively higher volatile compound levels (1,15). The levels we obtained in the brain and liver reflected these postulates. The lack of similarity of our highest obtained levels in aortic blood (85.6 mg/L) and chest cavity blood (79.9 mg/L) to these well-perfused organs reflects the timing of the last dose of DFE inhalation prior to the cessation of blood circulation. The levels determined in the brain and liver, 11.7 and 27.9 mg/kg, respectively, show the early distribution of DFE through the body and are more comparable to the peripheral blood site levels away from the heart and lungs. Although the brain is very high in lipid content, the acute use of DFE in this case has not allowed for the build up of levels in lipid-containing tissues typically seen in extended use or chronic abusers, as we noted in previous work (1). In this previous report on DFE abuse (1), we were able to detect DFE in blood from non-sealed specimens six months after autopsy. Such stability may allow for more conclusive estimates of pharmacokinetic parameters of DFE than would be suggested, given the low boiling point of such compounds. Therefore, we propose that this comparison of DFE levels between recently perfused tissue sites and the levels in more lipid-rich and peripheral blood sites may be used in determining acute or chronic use and establishing a time frame from last exposure to death, when the criteria discussed are satisfied.

Conclusions

With its unique record of the events preceding death, this case represents clearly the detrimental effect of combining the operation of a motor vehicle and the acute inhalation of a volatile substance such as "Dust Off". It is reasonable for one to assume that the indication of recent marijuana use, via the presence of the parent THC in the blood, was also a factor in this unfortunate event. Although a review of available literature produces no controlled studies on the effect of marijuana use with volatile abuse, for this individual, the combination of the sedative effects of marijuana use with the sudden intoxicating high of volatile inhalation produced severe and tragic results. However, from this tragedy, we may gain a valuable insight into the abuse of volatile substances.

The relationship between blood and tissue levels to timing of last inhalant use that we propose here should be considered with a degree of caution. Such conclusions are difficult to make given the high volatility of the compound and the elapsed time interval to sample collection along with an unknown postmortem distribution of DFE. Any correlation derived from such patterns should be based on volatile levels obtained from specimens in which adequate compartmentalization of the tissue site has been maintained following death. In the case presented, the failure to seal specimens other than the chest cavity blood immediately at autopsy led to a degree of uncertainty in the calculated values. However, the short time from death to body storage at 4°C (1 h) and a timely autopsy (< 24 h) supported the maintaining of accurate levels of DFE in the body at time of death. This premise is corroborated by previous reports suggesting that volatile substances exhibit an increased retention in an intact body in comparison to improperly stored tissue specimens (16). It is of paramount importance in suspected VSA cases to properly collect multiple tissue specimens in sealed containers within a short postmortem time period (17). This time period would ideally be less than 12 h after death, as a study showed that 87% of suspected inhalant abuse cases were detected in a hospital emergency room within an optimal 10-h window (18). A difficulty in investigating possible inhalant abuse in postmortem cases is the lack of any physiologic signs at autopsy (19). In cases of unexplained death involving adolescents or fatal motor vehicle accidents with no explained cause, it may be beneficial to obtain a sealed blood/tissue specimen to screen for volatile inhalants. With increased awareness of VSA involvement in fatal traumatic events and further investigation of suspected postmortem cases involving inhalant abuse, an accurate method for deciphering the intensity of inhalant exposure may be determined from a comparison of calculated blood and tissue levels.

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Cardiotoxic (Arrhythmogenic) Effects of 1,1-Difluoroethane Due to Electrolyte Imbalance and Cardiomyocyte Damage.

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Author information

Abstract

Inhalant abuse is the intentional inhalation of chemical vapors to attain euphoric effects. Many common household products are abused by inhalation and one is 1,1-difluoroethane (DFE), which is a halogenated hydrocarbon used in refrigeration, dust-off spray, and airbrush painting. Although many human DFE abuse cases have been studied, the etiology and mechanism of sudden death is still unknown. In this study, an animal model was used to simulate the human conditions of DFE inhalation abuse that results in sudden death.Current research targets mechanistic studies involving electrolyte changes and cardiomyocyte damage after DFE administration in vivo. To investigate these changes, Sprague Dawley rats (N = 6) were exposed to 30 seconds of 20 L/min of DFE in multiple doses. Isoflurane acted as a control. Two additional groups, epinephrine and epinephrine + DFE, were included to simulate the clinical condition of DFE abuse. Plasma sodium, potassium, calcium, and magnesium levels were measured, followed by lactate dehydrogenase, creatine kinase, and cardiac troponin I levels. In addition, oxidative stress markers were also evaluated in all animal groups. Electrolyte levels showed a significant rise in plasma potassium and magnesium levels for the treated groups. In addition, lactate dehydrogenase, creatine kinase, and cardiac troponin I levels in DFE and epinephrine + DFE administered rats were significantly elevated as compared with control. Some oxidative stress makers were also elevated significantly in treatment groups. Furthermore, histopathological analysis showed hyperemia/congestion in treated rats.These results support cardiotoxic effects indicating that DFE results in fatal arrhythmias, and the study can be important during clinical cases involving inhalant abuse.

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[Indexed for MEDLINE]

Desquamative interstitial pneumonia

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Research output: Contribution to journal › Article

Abstract

Desquamative interstitial pneumonia (DIP) is one of the rarest of the idiopathic interstitial pneumonias. It is characterized by the accumulation of macrophages in large numbers in the alveolar spaces associated with interstitial inflammation and/or fibrosis. The macrophages frequently contain light brown pigment, and because of their association with smoking have been called 'smoker's macrophages'. Lymphoid nodules are common, as is a sparse but distinct eosinophil infiltrate. Most cases of DIP are caused by cigarette smoking, but drugs and other inhaled agents, including marijuana smoke, can also produce the same disease. Although respiratory bronchiolitis-interstitial lung disease (RB-ILD) is a closely related process, there are prognostic reasons for continuing to separate it from DIP when possible. The proposed relationship of DIP to fibrotic non-specific interstitial pneumonia (NSIP) remains uncertain. The prognosis of DIP appears to be significantly better than that of fibrotic NSIP, so while there can be morphological overlap between the two, merging them into one disease may hide important prognostic information. Although the majority of DIP patients improve on treatment, some patients develop progressive irreversible fibrosis.