CASE REPORT

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Fatal Methemoglobinemia Resulting from Ingestion of Isobutyl Nitrite, a "Room Odorizer" Widely Used for Recreational Purposes

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ABSTRACT: The alkyl nitrites, specifically isobutyl nitrite, have taken a prominent place among those substances enjoying widespread recreational use, primarily in discotheques and during sexual activity. Though the usual route of administration by inhalation has not resulted in any toxicologically verified deaths, the chemical may cause fatal toxic methemoglobinemia if ingested. A case with a fatal outcome is presented, and the chemistry and toxicology of the substance are discussed.

KEYWORDS: toxicology, isobutyl nitrite, death, drug abuse

A 30-year-old black male collapsed and lost consciousness outside a discotheque after having been observed to be agitated and confused. He had been inside the disco where he had had one drink; an employee had seen him in the men's room with a small brown bottle that was not recovered despite a search by the police.

The patient was taken at 2:30 a.m. to an emergency room where he was combative, incoherent, intermittently lethargic, and in respiratory distress. Physical examination revealed a blood pressure of 78/50 mm Hg, a pulse of 126/min, respirations 26/min and labored, a temperature of 36.2°C, dilated and sluggishly reactive pupils, chest clear to auscultation, tachycardia, and cyanotic but warm extremities. Laboratory data included these values: sodium, 136 meq/L; potassium, 3.5 meq/L; chlorine, 98 meq/L; bicarbonate, 13.5 meq/L; blood urea nitrogen, 8 mg/dL; creatinine, 1.9 mg/dL; calcium, 9.1 meq/L; glucose, 178 mg/dL; blood pH, 7.25; pressure of oxygen, 250 mm Hg; and pressure of carbon dioxide, 27 mm Hg (on 100% oxygen). A toxicology screen gave negative results for many drugs, including barbiturates and methaqualone. Testing for opiates was not included in the hospital toxicology screen.

Resuscitation attempts consisted of intravenously administering normal saline, Narcan®, and one ampule of a 50% solution of dextrose in water, but there was no response; diaphoresis increased, and the patient became hypotensive. Pressor agents, sodium bicar-

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bonate, and 100% oxygen were given, but sinus bradycardia ensued, followed by an idioventricular rhythm unresponsive to atropine, calcium, and isoproterenol. Because the arterial blood appeared brown, methemoglobinemia was suspected with a visually estimated level of greater than 70% oxidized hemoglobin. (Blood drawn 1 h prior to death failed to turn red despite infusion with 100% oxygen.) At 4:10 a.m., the patient was given 20 mg of methylene blue intravenously. He died at 4:20 a.m. No attempt was made to document in this patient an undue susceptibility to oxidant drugs secondary to an unrecognized enzyme deficiency; the significance of that fact will be discussed below.

Autopsy Findings

The autopsy began 5 h after the patient's death. There were the following serosanguinous effusions: pericardial, 25 mL; peritoneal, 400 mL; and pleural, 150 mL, each side. Organ weights included: heart, 335 g; lungs, 1110 g; spleen, 155 g; liver, 1550 g; kidneys, 380 g; and brain, 1230 g. The lungs were hyperemic and edematous. There was marked edema of the epiglottis and aryepiglottic folds, but the airway was patent. The laryngeal mucosa demonstrated scattered petechial hemorrhages. The gastric contents had a distinctive aromatic odor; the mucosa of the stomach was intensely hyperemic with multiple 0.2- to 0.4-cm superficial ulcerations.

There was a progressive dark blue color change in certain organs after exposure to air: the fibroadipose tissue paralleling the coronary arteries beneath the epicardium; the endothelial linings of the heart, aorta, and pulmonary arteries; the fluid beneath the arachnoid at the base of the brain and over the cerebellum; and urine. This finding was judged to be secondary to therapy with methylene blue for methemoglobinemia. Since commercially available and widely abused nitrites sold in brown bottles like that allegedly in the possession of the decedent at the disco may cause methemoglobinemia, tissues and fluids were submitted for toxicology studies to confirm acute nitrite poisoning.

Microscopic sections of lung showed edema with many alveolar macrophages. The stomach demonstrated acute hemorrhagic gastritis with focal loss of mucosa, a submucosal round cell inflammatory infiltrate, submucosal vascular dilatation and engorgement, and interstitial hemorrhage. There was fatty metamorphosis of the liver.

Postmortem Studies

The results of postmortem toxicology and chemistry studies are summarized in Table 1.

Blood, lung, bile, and urine were screened for other drugs by a modification of the method of Goldbaum and Dominguez [*1*]. No other drugs were detected.

The level of ethanol is consistent with the history of the decedant's having had one drink at the discotheque.

Methemoglobin levels were determined by the spectrophotometric method [*2*]. The level of methemoglobin in postmortem blood in this case represents the therapeutic effect of 20 mg of methylene blue administered intravenously on a clinically estimated methemoglobinemia of greater than 70%.

Nitrite/nitrate assays were performed by the imipramine test of Irudayasami and Natarajan [*3*]. Quantitation was made from a standard curve prepared from pooled sera from cases known not to be associated with nitrite/nitrate poisoning, to which were added known amounts of nitrate. The standards were analyzed simultaneously with the autopsy specimens. The distribution of nitrite/nitrate radicals suggests that the route of administration in this case was oral ingestion, with a high concentration in the gastric contents.

Isobutanol was determined by gas chromatography using a 1.8-m (6-ft) glass column packed with Porapak-Q®. Samples were diluted and injected on-column, along with aqueous isobutanol standards. The limit of detection for isobutanol by this procedure was 2

TABLE 1—*Results of postmortem toxicology and chemistry studies.*

Examination and Specimen	Value
Ethanol, blood, %	0.02
Methemoglobin, blood, %	38
Nitrite/nitrate, mg/dL or mg/100 g	
Serum taken in hospital	1.8
Blood at autopsy	2.2
Gastric contents	90
Liver	0.9
Lung	1.4
Kidney	1.1
Brain	0.3
Isobutanol, mg/dL or mg/100 g	
Blood	<2
Lung	<2
Gastric contents	80
Methylene blue, mg/dL or mg/100 g	
Blood	0.06
Liver	0.5
Lung	0.6
Kidney	0.06
Brain	0.07

mg/dL. Isobutanol, produced when isobutyl nitrite is hydrolyzed in the acid-aqueous contents of the stomach, was demonstrated only in the gastric contents. The instability of aliphatic nitrites in aqueous solution was demonstrated to us when an aqueous dilution of isobutyl nitrite was chromatographed shortly after dilution and found not to match the retention time of the undiluted ester; however, it did match that of the corresponding aliphatic alcohol.

Methylene blue was demonstrated by extraction using the method of Goldbaum and Dominguez [*1*].

Chemistry and Pharmacology of Nitrites

The industrial uses of nitrites are varied, ranging from food preservation to perfume fragrance, and, medicinally, amyl nitrite's uses range from a vasodilator in the treatment of angina pectoris to a component of therapy for cyanide poisoning.[2]

The volatile alkyl nitrites, predominantly amyl, butyl, and isobutyl nitrite, are formed by combining the corresponding alcohol with sodium nitrite and sulfuric acid. They are powerful oxidizing agents and are flammable. In the body, the nitrites are hydrolyzed to nitrite ion and the corresponding alcohol [*4*].

Alkyl nitrites produce relaxation of smooth muscle in vessels such as the coronary arteries, thereby producing tachycardia; the meningeal vessels, thereby producing throbbing headache, and the subcutaneous vasculature, thereby producing a cutaneous blush in the upper torso and head. Concomitant with this pooling of blood may be transient hypotension. There is also relaxation of smooth muscle in the uterus, gastrointestinal tract, bronchi, biliary system, and ureters.

[2]Amyl nitrite forms methemoglobin, which combines with cyanide to form nontoxic cyanmethemoglobin. Administration of sodium thiosulfate releases the dissociated cyanide as thiocyanate.

Toxicology of Alkyl Nitrites

The transient acute toxicological effects of alkyl nitrite inhalation are treated by removal from exposure; these effects include dizziness, syncope, headache, hypotension, and tachycardia. The authors are aware of several patients hospitalized in the District of Columbia for treatment of these side effects, and it is possible that hypotension might prove contributory to a fatal accident in the proper situation. No chronic damage to brain, lungs, liver, or kidneys has been documented.

The major physiological danger from the alkyl nitrites is methemoglobinemia secondary to the oxidation of hemoglobin by the nitrite ion; the mechanism of this reaction is discussed below. There is considerable debate about inhalation as a cause of significant methemoglobinemia. Studies of workers in plants producing isobutyl nitrite show minimal methemoglobinemia, in the range of 5%, and no cumulative effect [*4*]. In a recent case report, however, Horne et al [*5*] indicate that intense nitrite inhalation "could lead to significant methemoglobin accumulation even in normal subjects." This effect is further enhanced in those individuals who, knowingly or unknowingly, have certain enzyme deficiencies in the red cell, as discussed below.

Methemoglobinemia

The list of materials that may cause toxic methemoglobinemia is extensive [*6-10*] and will not be reproduced here; alkyl nitrites are included among these substances.

Methemoglobin, a form of hemoglobin in which the ferrous ion (Fe^{++}) has been oxidized to the ferric form (Fe^{+++}), is "incapable of binding molecular oxygen reversibly because the sixth coordination position of iron, normally available to oxygen, has lost its unpaired electron and is occupied by water" [*11*]. Normally, approximately 1% of hemoglobin is in the oxidized form.

The normal red cell has several mechanisms to convert oxidized hemoglobin to usable reduced hemoglobin: the glutathione reductase reaction, the nicotinamide adenine dinucleotide (reduced form) ($NADH_2$)-methemoglobin reductase reaction, and the nicotinamide adenine dinucleotide phosphate (reduced form) ($NADPH_2$)-methemoglobin reductase reaction [*11*]. Each of these reactions may be compromised by hereditary inability to synthesize glutathione and by congenital deficiencies of $NADH_2$-methemoglobin reductase.

Abnormal hemoglobin molecules (hemoglobin M) that have an increased sensitivity to oxidation as well as a decreased rate of self-reduction have been documented.

The relationship between methemoglobin levels and symptoms has been studied. Cartwright [*12*] indicates that as little as 1.5 g/dL of oxidized hemoglobin is needed to produce cyanosis; he also states that methemoglobin levels of less than 20% of total hemoglobin are asymptomatic and that 20 to 50% levels produce fatigue, weakness, dyspnea, tachycardia, headaches, and dizziness. Jaffe and Heller [*11*] state that concentrations of 20 to 45% produce prominent cyanosis and that 70% methemoglobinemia is fatal. Leavell and Thorup [*13*] also indicate that levels of 70% are fatal. Several studies referenced by Nickerson et al [*4*] indicate that, in dogs given sodium nitrite, a level of 60% methemoglobinemia produces ataxia, 75% produces salivation and prostration, 85% produces unconsciousness, and 95% leads to death.

Susceptible Individuals and Methemoglobinemia

Infants and fetuses are particularly sensitive to nitrite-induced toxic methemoglobinemia since the rate at which nitrite oxidizes fetal oxyhemoglobin is twice as rapid as the rate for adult hemoglobin [*11*]. The capacity of red blood cells of newborn infants to reduce methemoglobin appears to be less than that of adult red blood cells [*11*]; this finding is

especially significant in the context of a study that demonstrated that sodium nitrite given to pregnant rats will not only cause methemoglobinemia in the mother but will also cross the placenta and induce methemoglobinemia in fetuses with levels of methemoglobin up to 27.2% for the dosages of nitrite given (30 mg/kg body weight) [*14*].

There is one reported fatality [*15*] in an infant resulting from an alkyl nitrite, specifically ethyl nitrite, which was orally administered to twins in the form of "Sweet Spirits of Nitre" (4% ethyl nitrite and 70% ethyl alcohol). One child developed methemoglobinemia of 80% and died despite therapy with methylene blue. The other twin survived despite a methemoglobin level of 38%.

Several cases of nonfatal toxic methemoglobinemia resulting from enzyme deficiency have been reported. One involved a suicide attempt with carburetor cleaning fluid consisting of 18% aniline and 5% toluene, which caused a methemoglobin level of 70 to 80% [*16*]. Methylene blue therapy was unsuccessful, and a glucose-6-phosphate dehydrogenase deficiency was found; oxygen and intravenously administered ascorbic acid reversed the methemoglobinemia. A second case involved a patient who was sniffing isobutyl nitrite in the form of a "room odorizer" and who twice presented with cyanosis and methemoglobin levels of 18% and 7.7%; he was found to have a deficiency of NADH-methemoglobin reductase [*5*].

Combination of isobutyl nitrite with drugs that induce methemoglobinemia, such as acetanilide, phenacetin, primaquine, and the anti-leprosy sulfones, could potentiate their oxidative effect.

Further study is needed on the possibility of initiating a sickling crisis by a drug-induced hypoxia of significant degree in hemoglobin S disease (both heterozygous and homozygous), though it is known that the life span of red blood cells in sickle cell disease is prolonged by levels of methemoglobin greater than 20% and that methemoglobin S is not susceptible to sickling [*11*].

Therapy of Toxic Methemoglobinemia

The agent of choice for treatment of toxic methemoglobinemia is methylene blue, which acts with NADP-methemoglobin reductase and uses $NADPH_2$. It therefore requires active cell metabolism and an intact hexose monophosphate shunt; the therapeutic failure of methylene blue in the patient with glucose-6-phosphate deficiency demonstrates this fact [*16*].

Ascorbic acid, also a reducing agent, may be used but is most effective against genetic methemoglobinemia rather than the drug-induced variety [*17*].

Hyperbaric oxygen was experimentally administered with inconclusive results to treat methemoglobinemia in rats given sodium nitrite [*18,19*].

One case of accidental ingestion of nitrobenzene and aniline resulting in methemoglobinemia of greater than 65% has been reported; the patient was aggressively treated with methylene blue and ascorbic acid and by exchange transfusion. The methemoglobin level was lowered to 25%, and the patient survived [*20*].

Abused Alkyl Nitrite Inhalants

Because of the cerebral "rush" associated with use of amyl nitrite and the alleged enhancement of male orgasm [*21*], the drug enjoyed widespread recreational use after the prescription requirement was abandoned in 1960 [*4*].

The Food and Drug Administration reestablished prescription controls in 1969. Butyl nitrite, however, is not included under those controls and has become widely available as a "room odorizer," "liquid aroma," or "liquid incense," sold under such brand names as Rush®, Locker Room®, Bolt®, Climax®, Satan's Scent®, Oz®, Hardware®, Bang®, Mama

Poppers®, Hi Ball®, and Discoroma®.[3] It is available either in bottles (often brown glass) containing approximately 10 to 15 mL of liquid or in crushable ampules. The price of isobutyl nitrite ranges from $4.00 to $6.00. Also available are inhalers, including models with neck chains as well as double-barrel designs, one barrel for each nostril.

Labels, sometimes bilingual, on the bottles warn of the hazards of flammability, syncope, eye irritation, ingestion, inhalation, and use by children. The labeling for some brands, however, consists of a plastic coating that is often removed when the bottle is opened.

The widespread use of butyl nitrite is suggested by advertising and marketing data. One brand, Rush, marketed by Pacific Western Distributing Corp. of San Francisco, Calif., is alleged to have sold 12 600 000 bottles from 1973 through the first half of 1978, with a projected yearly sales for 1978 of 5 000 000 bottles [*4*] in more than 40 000 stores around the world, according to product advertising; it is available in so-called head shops, adult book stores, some discotheques, and by mail order. Advertisements appear in both male- and female-oriented magazines.

Chemical analysis of six brands of volatile nitrite, specifically Hardware, Locker Room, Rush, Discoroma, Climax, and Satan's Scent, was performed as part of this study. All brands except Satan's Scent contained isobutyl nitrite (also known as l-nitrosoxy-2-methylpropane); the material found in Satan's Scent was butyl nitrite.

The subject of the present case report represents the first toxicologically verified fatality related to use of abused nitrite inhalants. It should be emphasized that the nitrite poisoning resulted from ingestion of the chemical, as demonstrated by autopsy findings and by the distribution of nitrite and isobutanol in tissue. A second fatality secondary to ingestion has been reported to the authors:[4] a 15-month-old child drank isobutyl nitrite from a bottle of "room odorizer" that had been found in the home by the child.

Another case possibly related to nitrite inhalation has been reported to the authors[5] involving a man found in bed with a bottle of one of the available inhalants next to his body. Toxicology tests demonstrated no nitrite but a blood alcohol concentration of 0.18%.

Summary

Though acute and chronic damage from abuse of commercially available isobutyl nitrite is unusual in the normal individual who inhales this substance, the possibility exists that ingestion will result in death from methemoglobinemia secondary to acute nitrite poisoning. Furthermore, the case from New Orleans[5] raises the question of whether death can occur through inhalation, presumably on a cardiogenic basis or perhaps from a combined drug effect; the inhalants are frequently combined with alcohol, marijuana, or methaqualone [*21*].

Because of the transplacental effects of nitrites in experimental animals [*14*], it is possible that use of the substance during pregnancy may induce methemoglobinemia in the unborn fetus. Infants are also more sensitive to poisoning because of the relative ease with which fetal hemoglobin is oxidized and the decreased capability of red blood cells for self-reduction.

Individuals with red cell abnormalities, including enzyme deficiencies and abnormal hemoglobin molecules, have also been shown to be particularly susceptible to intoxication.

The flammability of the material and the possibility that nitrite-induced syncope might precipitate an accident under proper circumstances of risk are additional hazards.

[3]There is no intent to implicate any particular brand in this or any other death; the listing is included simply to show the available sources of this material.

[4]Case courtesy of Dr. Page Hudson, chief medical examiner, State of North Carolina, Chapel Hill, N.C.

[5]Case courtesy of Dr. Frank Minyard, coroner, Parish of Orleans, New Orleans, La.

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