

FATAL METHEMOGLOBINEMIA DUE TO INHALATION OF ISOBUTYL NITRITE

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ABSTRACT

Isobutyl nitrite is a popular recreational drug among both homosexuals and heterosexuals as it is alleged to enhance sexual pleasure and prolong orgasm. In contrast to the ingestion of this volatile nitrite, inhalation is associated only rarely with serious sequelae, though symptomatic methemoglobinemia may occur. The case reported is the first documented fatality from inhalation of isobutyl nitrite. The widespread use of isobutyl nitrite is a cause for concern and physicians should be aware of the potentially fatal consequence of abuse, particularly in those with ischemic heart disease, and its management. (*Key Words: isobutyl nitrite; poisoning; methemoglobinemia; inhalation*).

INTRODUCTION

Isobutyl nitrite is well recognized as a recreational drug of abuse (1). Initially exploited in homosexual circles as a smooth muscle relaxant, it is now

popular among both the older heterosexual population and teenagers to promote a sense of abandon and to enhance and prolong orgasm (2-4). Products containing isobutyl nitrite are marketed as "room odorizers". Inhalation of isobutyl nitrite is associated generally with few serious sequelae. The case reported is therefore unusual in that severe methemoglobinemia developed and a fatal outcome ensued; this is the first such reported incident after inhalation.

Case Report

A 69-year-old man with a past history of a myocardial infarction and stable angina died following approximately 20 min inhalation of isobutyl nitrite used to augment the electrical stimulation and enhance the excitement of sexual bondage engineered by his usual female therapist. He had undertaken this practice for seven years and regularly developed cough, dyspnea, "bright red skin" and body shaking during continuous inhalation for some 30-40 min. However, on the occasion of his death he was noted, during the period of maximal stimulation, to suddenly have difficulty in breathing, to slump back on the couch, change color from red to purple/blue and to die within a few minutes. Postmortem toxicological analysis was consistent with the inhalation but not ingestion of isobutyl nitrite.

Although the deceased was found to have severe triple vessel coronary artery disease and an old cerebral infarction, there was no evidence of a recent myocardial event, a stroke or other cause of death. The skin color observed by his attendant is consistent with the development of methemoglobinemia. Unfortunately, the methemoglobin concentration was not measured until several weeks after death so the value of 23% probably does not reflect that found premortem. We believe that this patient died from hypoxia secondary to isobutyl nitrite-induced methemoglobinemia.

DISCUSSION

Isobutyl nitrite is a volatile, inflammable liquid with an unpleasant ("locker room") smell. It became popular as a recreational drug during the 1970s (5). It is now sold under various names (e.g. 'Bolt', 'Bullet', 'Climax', 'Liquid Gold', 'Rush', 'Thrust') usually as a solution containing up to 96% isobutyl nitrite with small amounts of isobutyl alcohol and vegetable oil (3,5) to render the formulation less volatile. These solutions are marketed as "room odorizers" and carry the instruction that they are not to be inhaled, precisely the intended use by the purchasers.

Isobutyl nitrite is inhaled more often than ingested and induces profound, though transient, vasodilatation with blurred vision, headache, flushing, a "warm

feeling", a widespread throbbing sensation and postural hypotension (1-7). Reflex vasoconstriction follows with tachycardia and it is likely that transient ECG changes, including T wave inversion and ST segment depression, observed after amyl nitrite inhalation (4) may occur. Other reported features include nausea (7), burning in the nose (7), syncope (7), facial dermatitis (8), eye irritation (9), cough (7,9), dyspnea (7,9), tracheobronchitis (9), hemoptysis (9), coma (6,10) and respiratory distress (6).

Isobutyl nitrite is used to augment sexual pleasure by enhancing and prolonging orgasm and, in homosexuals, by relaxing the anal sphincter (1-3). Other pleasant effects reported include light-headedness (secondary to hypotension), altered perception of reality, momentary loss of identity and feelings of warmth, happiness and calmness (1). This potential for temporary detachment from reality has led to an increased popularity of isobutyl nitrite among adolescents. In a survey undertaken in 1985, 74 of 173 chemically dependent adolescents were found to be abusing isobutyl nitrite by inhalation (7) and it has been estimated that the average inhaled 'dose' is 0.2 mL (1). Less commonly, isobutyl nitrite is ingested (5,6,10-12) usually in relatively substantial amount (e.g., 15 mL) so that the features of intoxication are more marked and prolonged and fatalities have been recorded (6,11). Our patient had experienced cough, dyspnea, body shaking and skin color change regularly after inhaling isobutyl nitrite for some 30-40 min; all of these features are in keeping with the known effects of this volatile nitrite.

At a molecular level, isobutyl nitrite is a potent oxidizing agent and may cause oxidative stress to the red blood cell which manifests as methemoglobinemia. Methemoglobin cannot serve as an oxygen carrier and high methemoglobin concentrations are associated therefore with significant tissue hypoxia; without antidotal treatment concentrations greater than 70% may be fatal (6,11). The likelihood of a fatal outcome will be influenced not only by the rate but also by the duration and frequency of exposure, the subject's genetic complement of reducing enzyme and the presence of ischemic heart disease or anemia which may limit the body's ability to withstand a hypoxic insult (6). It has also been suggested that as frequent users of volatile nitrites tend also to be heavy cigarette smokers, the presence of carboxyhemoglobin may compound the isobutyl nitrite-induced tissue hypoxia (13). Most reports of isobutyl nitrite-induced methemoglobinemia relate to ingestion (5,6,10-12,14) and the general view has been that inhalation produces clinically serious sequelae only rarely (15), though symptomatic methemoglobinemia has occurred in two reported cases (15,16). In the only death involving isobutyl nitrite inhalation reported previously, the subject had also self administered cocaine and the postmortem blood cocaine concentration (23 mg/L) was similar to that recorded

in other fatal cases of cocaine intoxication. Moreover, this patient did not develop methemoglobinemia (17).

Normal blood contains approximately 1% methemoglobin and concentrations averaging 5% have been recorded without adverse clinical effect in workers employed in isobutyl nitrite bottling plants (18). Horne *et al.* (16) investigated the production of methemoglobin in a man with a partial deficiency of NADPH-dependent methemoglobin reductase and demonstrated a methemoglobin concentration of 14% after 12 min inhalation of isobutyl nitrite; a value of 7.5% was found in normal subjects. This supports the view that brief exposure to inhaled isobutyl nitrite is unlikely to be clinically significant in healthy subjects. It has been suggested that the half-life of methemoglobin in non-NADPH dependent methemoglobin reductase deficient individuals is of the order of 55 min (16), but this estimate is far shorter than expected from our clinical experience and the literature. For example, the patient described by Guss *et al.* (15) had a methemoglobin concentration of 37% 14 h after his last exposure to isobutyl nitrite, which is incompatible with a half-life of approximately one hour. Methemoglobinemia can be reversed successfully by the intravenous administration of methylene blue in a dose of 1-2 mg/kg.

Even in the absence of a genetic predisposition to hemolysis, such as glucose 6-phosphate dehydrogenase deficiency, isobutyl nitrite can produce hemolysis secondary to Heinz Body formation, particularly after the inhalation of substantial amounts (19,20).

Our patient was known to have inhaled isobutyl nitrite for no more than 20 min immediately prior to his death, but the presence of severe ischemic heart disease may have rendered him more susceptible to a hypoxic insult or the development of a clinically significant arrhythmia. Unfortunately, the methemoglobin concentration of 23% was measured three weeks after death and, therefore, we cannot relate this concentration to that found premortem as it is known that the postmortem estimation of methemoglobin is unreliable (21); we have confirmed this observation in a small series. We do know, however, that the terminal event in his case was not a myocardial infarction or cerebral incident and that the clinical features observed by the therapist were compatible with significant methemoglobinemia.

The widespread abuse of isobutyl nitrite by homosexuals and heterosexuals is a cause for concern as inhalation and particularly ingestion of this volatile nitrite can lead to significant methemoglobinemia. Unless the diagnosis is suspected and treatment with methylene blue instituted promptly death may ensue, particularly in the presence of ischemic heart disease, anemia or methemoglobin reductase deficiency.

ACKNOWLEDGEMENT

Presented at the Scientific Meeting of the European Association of Poisons Centres and Clinical Toxicologists, Birmingham, England, May 26-28, 1993.

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