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CASE REPORT

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Death Associated with Nitrite Ingestion: Report of a Case

Sodium nitrite reacts with the ferrous iron of hemoglobin and oxidizes it to ferric (Fe^{3+}) iron. This converts hemoglobin to methemoglobin, which does not react with oxygen, and thus the oxygen-carrying capacity of blood is reduced. Poisoning from accidental ingestion of sodium nitrite has been reported [*1–5*], and although it has been suggested that a dose of 2 mg/kg body weight will cause toxic symptons [*1*], recovery was reported when up to 30 mg/kg body weight (2 to 30 mg/kg body weight) was ingested and medical treatment was available within minutes. Death was reported following an accidental ingestion by a four-month-old infant of a "small amount" of 4% ethyl nitrite in liquid formula. The concentration of methemoglobin in blood from this infant was 80% of the total hemoglobin, while that of the surviving twin who had consumed less of the formula was 38% [*2*]. Generally, survivors have had methemoglobin levels of less than 60%, and prompt treatment with methylene blue has limited the morbidity. We present a case of suicidal sodium nitrite poisoning that caused death within 1 h and resulted in detectable concentrations of both nitrite and nitrate in certain tissues.

Case Summary

The deceased was a 34-year-old male white night watchman who had been denied a better paying job. His roommate stated that the deceased seemed only mildly upset and had his usual glass of iced tea before going to bed. A few minutes after the deceased retired, the roommate heard him coughing and saw him clutching his chest and "foaming at the mouth." A rescue team responded and resuscitation was attempted. However, he was dead on arrival at a local emergency room and the cause of death was not apparent to the emergency room physician. The time interval between ingestion and death was less than 1 h.

An undated suicide note and a bottle containing whitish crystalline material were found at the scene. The suicide note was articulate and expressed dissatisfaction with general economic conditions. Also at the scene was a drinking glass that contained a small amount of medium brown "tea-like" liquid and a crystalline material on the upper portion of the glass.

An autopsy was performed 5 h after death. External examination revealed a well-developed, 34-year-old white male weighing 78 kg with defibrillator paddle marks on the chest, a puncture in the left antecubital fossa, and a puncture corresponding to the distribution of the left external jugular vein. These puncture wounds had been produced during resuscitation attempts. No external injuries were present.

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Internal examination revealed dark brown ("chocolate" or "soy sauce") blood with all organs and muscles demonstrating a similar discoloration. The gastric rugal folds were accentuated and hyperemic, and 60 ml of frothy white-yellow gastric contents were present. Lungs, liver, spleen, and kidneys demonstrated marked congestion. All other organs were unremarkable except for being discolored. Heart blood, bile, vitreous humor, gastric contents, and samples of liver were submitted to the toxicology laboratory. The urinary bladder was empty.

Microscopically, the gastric mucosa revealed congestion of vessels and extravasation of erythrocytes, but an acute inflammatory infiltrate was not present. The lungs, liver, spleen, and kidneys demonstrated congestion of blood vessels on microscopic examination.

Toxicological Methods

Sample Preparation

Tissues were homogenized in one volume of deionized water and filtered through cellulose filter cones (Amicon Corp., Lexington, Mass.). Blood, bile, vitreous fluid, and stomach contents were filtered directly after dilution. Aliquots of the tissue filtrates were diluted 1000-fold before being analyzed for nitrite and nitrate.

Nitrite Assay

The method described by Saltzman [*6*] was modified as follows.

One-millilitre aliquots of the filtrates from the sample preparations were added to 20-ml reaction flasks that were then sealed with rubber stoppers. Nitrogen gas was bubbled through the filtrate in each flask for 3 min to evacuate oxygen that might convert nitrite to nitrate during the subsequent color reaction. After nitrogen flushing, 9 ml of a solution containing 5 g of sulfanilic acid, 140 ml glacial acetic acid, and 20 ml of 0.1% *N*-(1-naphthyl)-ethylenediamine dihydrochloride in one litre was added to each flask. After 15 min, the absorbance of the solution was measured at 550 nm. The nitrite concentration was calculated by comparing the absorbance of the unknown with the absorbance of a series of nitrite standards prepared by dissolving 0.750 g of sodium nitrite in 1000 ml of water and diluting to obtain the appropriate assay standards.

Nitrate Assay

The method described by Hyde et al [*7*] was applied to analysis of nitrate in 0.2 ml of the filtrate from the sample preparation by reducing the nitrate to nitrite with hydrazine in the presence of copper at pH 10.2. This nitrite is used to diazotize sulfanilamide, which is then coupled with *N*-(1-naphthyl)-ethylenediamine to form a red complex measured at 520 nm. The nitrate concentration was determined by comparing the absorbance of the sample with the absorbances of processed nitrate standards and then subtracting the "endogenous" nitrite concentration.

Methemoglobin Assay

Methemoglobin was determined on a blood sample that had been stored at −20 °C for two weeks after collection. The assay was performed by a spectrophotometic technique using a Co-oximeter, Model 282 (Instrumentation Laboratory Inc., Lexington, Mass.), as described generally by Fairbanks [*8*].

Results

No common tranquilizers, narcotics, stimulants, or hypnotics were detected in the tissues submitted for toxicological studies. The whitish crystalline material found in the bottle, the brown tea-like liquid found in the drinking glass, and the crystalline material from the top of the glass were found to contain high concentrations of sodium nitrite and no detectable sodium nitrate. Examination of the tissues taken at autopsy yielded concentrations of nitrite and nitrate as shown in Table 1. It is interesting to note that while a nitrite/nitrate ratio of 18.6 was present in the stomach contents, this same ratio in tissue and blood was much lower, about 0.03.

Analysis of the blood for methemoglobin revealed that 90% of the hemoglobin had been converted to methemoglobin, which is higher than the percentage reported for survivors of severe methemoglobinemia [*4,8*].

Discussion

The toxic effects of acute nitrite ingestion are likely related to its oxidation of heme iron, which results in a diminished oxygen-carrying capacity of hemoglobin and subsequent cardiovascular collapse leading to death. Oxygen saturation of hemoglobin in persons who survived nitrite ingestion has been as low as 50%, with as much as 60% of the hemoglobin converted to methemoglobin [*3,9*]. In one lethal case of acute nitrite poisoning in an infant [*2*], the methemoglobin concentration rose to 80%; however, only 49% methemoglobinemia was reported in suicidal poisoning by nitrite in an adult [*10*].

The reaction mechanism by which nitrite converts oxyhemoglobin to methemoglobin has been described by Rodkey [*11*]. According to this report, nitrite reacts with oxyhemoglobin to form a hemoglobin-nitrite complex. Within this complex, oxygen from oxyhemoglobin reacts with nitrite to form nitrate with concomitant oxidation of ferrous heme iron to the ferric (Fe^{3+}) form. Thus, methemoglobin is formed with no release of molecular oxygen. Apparently this nitrite-induced conversion of oxyhemoglobin to methemoglobin proceeds rapidly until about 65% of the oxyhemoglobin is converted [*11*]. At this point the oxyhemoglobin concentration becomes rate-limiting and the reaction rate diminishes. This is consistent with the rapid development of toxic symptoms associated with methemoglobinemia that has been observed in acute nitrite poisoning.

The production of nitrate from nitrite is consistent with our finding significant quantities of nitrate in those tissues that contain relatively high concentrations of hemoglobin. In this regard, the ratio of nitrate to nitrite was tenfold higher in blood, muscle, and kidney than in the gastric contents. It is interesting to note that neither we nor DeBeer et al [*10*] detected any nitrite in liver tissue following acute nitrite poisoning.

TABLE 1—*Concentrations of nitrite and nitrate salts in tissue following an overdose of sodium nitrite.*

Sample	Salt Concentration	
	Nitrite	Nitrate
Blood, mg/litre	0.55	30.0
Bile	ND[a]	ND[a]
Vitreous humor	ND[a]	ND[a]
Liver	ND[a]	ND[a]
Muscle, mg/kg wet weight	0.70	26.0
Kidney, mg/kg wet weight	0.50	19.5
Stomach tissue, g/kg wet weight	96	48
Gastric contents, g/kg wet weight	31.6	1.7

[a]ND = none detected. The detection limit of this procedure is 0.20 mg/litre.

While the exact amount of nitrite ingested in this case is not known, we estimated the dose from a calculated total body burden of about 50 g by assuming that the measured nitrate had been converted from nitrite. This calculated dose is considerably higher than that found in survivors of nitrite ingestions and likely is higher than that previously reported to cause death [*2,10*], although no exact doses were given.

In this case, the nitrite concentration in blood (0.5 mg/litre) equals that reported for a survivor [*5*] and is also similar to that reported to cause death by ingestion [*8*]. This suggests that the blood and tissue nitrite concentrations found in this study are consistent with toxicity and lethality. However, because of the extensive, and perhaps variable, conversion of nitrite to nitrate by hemoglobin, it is difficult to assign any particular significance to a nitrite concentration in blood for determining cause of death. In this regard, an assay of gastric contents and stomach tissue should prove helpful.

Summary

The tissue concentrations of nitrite and nitrate found at autopsy of a case of intentional ingestion of nitrite salts have been reported. The percentage of methemoglobin and the serum nitrite concentrations are consistent with those reported for acute overdoses. We conclude that both nitrite and nitrate salts may be identified in tissues from persons ingesting only nitrite salts and that a significant conversion to nitrate may result from oxidation of nitrite during the conversion of heme iron to Fe^{3+}.

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