CASE REPORT

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Fatal Methemoglobinemia Caused by Liniment Solutions Containing Sodium Nitrite

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ABSTRACT: We describe a case of fatal methemoglobinemia (MetHb-emia) resulting from application of liniment solution containing large quantities of sodium nitrite. As a remedial treatment of atopic dermatitis, the liniment solution was applied all over the boy's body. Autopsy findings showed no significant macroscopic or microscopic findings except blood tinted chocolate brown color and chronic atopic dermatitis over the whole surface of the body. Quantitation of the methemoglobin (MetHb) in the blood was performed using spectrophotometer; MetHb concentration of the blood was 76%. Ion chromatographic determination revealed a nitrite concentration of 1 mg/L in the serum. Such a liniment solution is not authorized by the Ministry of Public Welfare.

KEYWORDS: pathology and biology, methemoglobinemia, percutaneous absorption, sodium nitrite, atopic dermatitis

MetHb is an oxidation product of hemoglobin in which the sixth coordination position of ferric iron is bound to a water molecule or to a hydroxyl group. MetHb-emia is caused by various sources. The course of congenital MetHb-emia is benign, but patients with this disorder should be shielded from exposure to aniline derivates, nitrites, and other agents which may, even in normal persons, induce MetHb-emia. The most common cause of MetHb-emia is accidental poisoning which usually is the result of ingestion of water containing nitrates (as in well water) (1,2) or food containing nitrite (3), and inhalation or ingestion of butyl or amyl nitrite used as aphrodisiacs (4). MetHb-emia associated with sodium nitrite ingestion has been often described, although death due to percutaneous absorption is not reported. Eldadah reported a case of MetHb-emia caused by topical application of benzocaine to the skin (5). However, the case was not fatal MetHb-emia.

Here, we report a fatality associated with nitrite application and describe the method of ion chromatography (IC) for the detection and quantitation of the nitrite. This paper is the first reported case of MetHb-emia due to percutaneous absorption of sodium nitrite-containing liniment solution.

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Case History

A liniment solution (liniment solution A) had been applied all over the body of a 4-year-old boy a few days prior to his death; he had became listless and had one episode of vomiting. Another type of liniment solution (liniment solution B), which contained larger quantity of sodium nitrite, was applied all over the boy's body by his mother. Immediately after this treatment he gradually went into shock with signs of severe cyanosis. He was hospitalized immediately and was found to have severe metabolic acidosis, and survived on intensive care support for 2 hours before being declared dead.

Anatomical findings showed eczematous, lichenoid or hypertrophic exanthema spread all over his body, and blood tinted with chocolate-brown color. No significant macroscopic or microscopic lesions were found in various organs examined.

Materials and Methods

Chemicals

All chemicals and solvents were reagent grade, from Wako Chemical, Osaka, Japan. Sep Pak silica and C_{18} cartridge were purchased from Waters Co., Milford, MA.

MetHb Analysis

MetHb was measured by spectrophotometry with using the method of Rodkey et al. (6). Briefly, 20 mg of KCN was dissolved in 100 mL of the 10 mmol/L diluent and the solution was saturated the solution with CO. One blank and three sample stoppered cuvettes were prepared, each containing two mixing bars. Each cuvette was filled with the diluent used in the MetHb estimation by use of a syringe and piece of polyethylene tube, filling the cuvette from the bottom up to displace the air and retain as much CO as possible. The blank cuvette and transfer sample were stoppered with 2–3 μL, in the remaining cuvettes. The stoppered cuvettes were mixed thoroughly by shaking in such a manner that the mixing bars passed from one end of the cuvette to the other. MetHb in the sample was converted to CNMetHb and all other forms to COHb. The absorbance (A_1) at 420 nm was measured

for this two-component system. Then 10 mg of $Na_2S_2O_4$ was added to each cuvette (blank and each sample), the stoppers were replaced, and each was thoroughly mixed. The absorbance (A_2) at 420 nm was measured after 15 min of addition of hydrosulfite. The hydrosulfite treatment converted the CNMetHb to COHb, forming a one-component system.

Calculations

Absorbances A_1 and A_2 were given by the following equations:

$$X = \frac{(A_2 - A_1) \cdot \epsilon_{420}^{COHb}}{A_2 \cdot (\epsilon_{420}^{COHb} - \epsilon_{420}^{CNMetHb})}$$

The molar absorptivity (ϵ) per mole of hemoglobin ion for COHb and CNMetHb for blood have been described elsewhere (6).

IC Extraction Procedure

A Sep Pak C_{18} cartridge was pretreated by passing 10 mL of methanol and 10 mL of distilled water. Thereafter, 1 mL of the serum sample was applied to the conditioned column. The serum sample was diluted one hundred fold with distilled water and then applied to the Sep Pak C_{18} conditioned column. Thereafter, the eluent was diluted ten fold diluted with distilled water and 500 μL was applied to IC.

IC Instrumentation

The IC consisted of a Dionex (Sunnyvale, CA) Model 2012i, a Dionex AMMS-II suppressor and a Dionex conductivity detector. For the guard column, HPIC-AG4A (50 mm × 4 mm I.D., Dionex) was chosen, for the separation column, HPIC-AS4A (250 mm × 4 mm I.D., Dionex) was chosen. The ion chromatograph was operated under the following conditions: mobile phase flow-rate 1.5 mL/min and 500 μL injection volume.

Quantitative Procedure

Quantitative analysis of nitrite ion was accomplished by IC using nitrite as the external standard.

Results and Discussion

As MetHb cannot serve as an oxygen carrier, various significant organs fall into hypoxia; cases in which the MetHb concentration in blood is greater than 70% can be fatal (7,8). In this case MetHb concentration of the blood was 76%, and MetHb-emia was atributed as the cause of death.

Almost all causes of MetHb-emia are considered to be from sodium nitrate or sodium nitrite. The serum of this case was tested for these ions by IC. Nitrite ions were detected 1 mg/L in serum. Figure 1 shows the negative ion chromatogram obtained from (*B*) analysis of an extract from the decedent's postmortem serum as compared with (*C*) a similar analysis of an extract from nitrite-free serum. In Fig. 1, (*A*) and (*B*) showed negative ion chromatograms, which revealed a major peak (indicated by an *arrow*) with a retention time of 7.0 min in serum containing nitrite as control, and in decedent's postmortem serum, respectively. A similar analysis using nitrite-free serum as a negative control showed no detectable ion in this region (*C*). No other causative factors for MetHb-emia were detected. Analytical studies of the residual solutions in the bottles of the liniment which had been applied to this boy detected 30 g/L and 140 g/L of sodium nitrite in liniment solutions *A* and *B*, respectively.

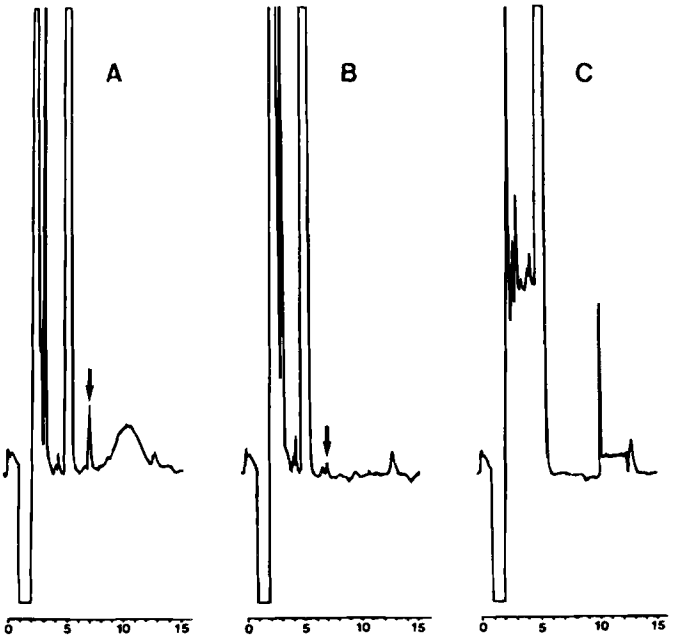

FIG. 1—*Negative ion chromatogram of* (A) *an extract of serum containing (indicated by an arrow) 5 μg/L nitrite ion;* (B) *an extract of decedent's postmortem serum; and* (C) *an extract of blank serum.*

Sodium nitrite is widely used commercially in the manufacture of azo dyes, as a food preservative and coloring agent (9). Accidental contamination in food or water is the leading cause of poisoning, formation of MetHb is the primary toxic mechanism (1–3). The serum nitrite level in an adult patient who died following intentional ingestion of sodium nitrite was reported as 0.55 mg/L (7). Thus the serum nitrite concentration in the present case is consistent with previously reported fatality.

Various chemical compounds used in the home or in industry and several therapeutic agents are capable of increasing the rate of heme oxidation from 100- to 1000-fold, thereby overwhelming the capacity of erythrocytes to maintain hemoglobin in the reduced state. Infants are especially vulnerable because the iron in hemoglobin F is oxidized more readily and infants are relatively deficient in MetHb reductase (12). Small molecules that are both water and lipid soluble are apparently the most easily absorbed. Dermal exposure by some pathological changes or chemicals, especially solvents, denaturants, and strong surfactants, is substantially more permeable than intact skin (10). In the present case, the intense scratching because of atopic dermatitis may have given the nitrite access to the systemic circulation, thereby causing MetHb-emia. Following the toxic symptoms of sodium nitrite, the initial effects are those of gastric irritation with nausea, vomiting and abdominal pain (3,11). Probably the MetHb-emia of the present case was caused by the application of liniment solution contaminated with sodium nitrite, which resulted in death.

This case may confirm the percutaneous toxicity of nitrite, especially when concomitant with dermatitis. Of interest, the manufacturer of the liniments was later prosecuted as offending the Drugs, Cosmetics and Medical Instruments Act in Japan.

Acknowledgment

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