A Case of Methemoglobinemia after Ingestion of an Aphrodisiac, Later Proven as Dapsone

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Abstract

Methemoglobin (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. The most common cause of acquired MetHb-emia is accidental poisoning which usually is the result of ingestion of water containing nitrates or food containing nitrite, and sometimes the inhalation or ingestion of butyl or amyl nitrite used as an aphrodisiac. We herein report a case of MetHb-emia after ingestion of an aphrodisiac, later identified as dapsone by gas chromatograph/mass selective detector (GC/MSD). A 24-year-old male was admitted due to cyanosis after ingestion of a drug purchased as an aphrodisiac. On arterial blood gas analysis, pH was 7.32, PaCO2 26.8 mmHg, PaO2 75.6 mmHg, and bicarbonate 13.9 mmol/L. Initial pulse oxymetry was 89%. With 3 liter of nasal oxygen supplement, oxygen saturation was increased to 90–92%, but cyanosis did not disappear. Despite continuous supplement of oxygen, cyanosis was not improved. On the fifth hospital day, MetHb was 24.9%. Methylene blue was administered (2 mg/kg intravenously) and the patient rapidly improved. We proved the composition of aphrodisiac as dapsone by the method of GC/MSD.

Key Words: Methemoglobinemia, dapsone, poisoning

INTRODUCTION

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 derivatives, nitrates, 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 nitrates1,2 or food containing nitrite,3 and sometimes the inhalation or ingestion of butyl or amyl nitrite used as aphrodisiacs.3

Here, we report a case of MetHb-emia after ingestion of an aphrodisiac, later identified as dapsone by gas chromatograph/mass selective detector (GC/MSD).

CASE REPORT

A 24-year-old male was admitted to Inha General Hospital due to cyanosis and dysarthria 8 hours after ingestion of alcohol and an undetermined amount of drug purchased as an aphrodisiac on July 28, 1998. On past history, he had frequently inhaled butane gas or adhesives (toluene) since high school. He had been admitted to our hospital due to pesticide ingestion in 1991. There was no history of other illnesses. One day before admission, he had purchased drugs known as aphrodisiacs and 5 hours after ingestion with alcohol, cyanosis and dysarthria developed. On admission, his mental state was alert to slightly drowsy. Blood pressure was 120/70 mmHg, pulse rate 128 beat/minute, body temperature 36.8°C, respiratory rate 24/minute. He acknowledged the ingestion of drugs but did not exactly know the amount. He denied inhalation of butane or toluene gas. No other focal neurologic deficits were found. His skin color was dark and his face, lips, fingers and toes were cyanotic. Lung, heart, and abdomen were normal.
Arterial blood gas analysis showed that pH was 7.32, PaCO₂ 26.8 mmHg, PaO₂ 75.6 mmHg, and bicarbonate 13.9 mmol/L on room air. After administration of 5 L oxygen, pH was 7.39, PaCO₂ 26.1 mmHg, PaO₂ 94.1 mmHg, and bicarbonate 16.1 mmol/L. Initial pulse oximetry was 89%. After oxygen inhalation, O₂ saturation was 92%. Other laboratory data showed that hemoglobin was 15.1 g/dl, hematocrit 44.8%, white blood cell 16200 cells/µl, platelet 363000 cells/µl, blood urea nitrogen 16.9 mg/dl, serum creatinine 1.5 mg/dl, aspartate aminotransferase 23 IU/L, total bilirubin 0.6 mg/dl, and alanine aminotransferase 22 IU/L. On urinalysis, pH was 5.0, specific gravity >1.030, protein 100 mg/dl, blood (2+), glucose (-), ketone (+), bilirubin (1+), red blood cell 10−29/high power field, and some uric acid crystal. Chest X-ray was normal. Electrocardiography showed sinus tachycardia. Gastric decontamination was done. After admission, cyanosis did not disappear despite improved O₂ saturation (96.7−97.5%) by continuous administration of 5 L oxygen via nasal prong. On the second hospital day, heart was normal on echocardiography. On the fifth hospital day, the MetHb level was found to be 24.9% by co-oximetry. Methylene blue was administered (2 mg/kg intravenously) and cyanosis rapidly disappeared after 8 hours of infusion. MetHb level was 2.6%, 1.4%, and 0.2% on the sixth, seventh, and eighth hospital day, respectively. The patient was discharged on the 10th hospital day. Drug was analyzed with total ion chromatogram by GC/MSD (Model HP 5890 series II GC/HP 5970 MSD, Hewlett-Packard).

![Graph A](image1)

**Fig. 1.** (A) Total ion chromatogram by GC/MSD using HP ultra-2 column showed major peak at 17.1 minutes. (B) Molecular weight of drug was 248 on peak wave spectrum scan.

![Graph B](image2)

**Fig. 2.** (A) Spectrum scan after subtraction of background wave. (B) On library spectrum, 248 molecular weight of substance was compatible with dapsone (4,4'-sulfonyldi-benzanamine).

![Graph C](image3)

**Fig. 3.** Mass spectrum by the direct insertion probe with Finnigan MAT 95 showed that the drug was composed of dapsone only.
Packard, Palo Alto, California, USA) with HP ultra-2 (23 m x 0.2 mm i.d., 0.53 μm). The major column peak was shown at 17.1 minutes (Fig. 1A) and molecular weight of the drug was 248 on peak spectrum scan (Fig. 1B). Spectrum after subtraction of background wave (Fig. 2A) was identified as dapsone (4,4'-sulfonylbiis-benzenamine) on library spectrum (Fig. 2B). Mass spectrum by the direct insertion probe with Finnigan MAT 95 S analyzer showed that the drug was composed only of dapsone (Fig. 3).

DISCUSSION

MetHb-emia is the oxidative product of hemoglobin in which the ferrous (Fe²⁺) form has been converted to the ferric (Fe³⁺) form and then bound to either a water molecule or a hydroxyl group. This additional positive charge renders the ferric molecule unable to bind oxygen. Methemoglobin shifts the oxygen-hemoglobin dissociation curve to the left, thereby reducing the oxygen-carrying capacity of the blood and impairing tissue oxygen delivery. The normal MetHb level is less than 1%; MetHb-emia occurs when the concentration rises above this level.

Four mechanisms maintain the equilibrium between hemoglobin and methemoglobin. NADH-MetHb reductase accounts for approximately 95% of MetHb reduction. An auxiliary enzyme, NADPH-MetHb reductase, is dependent on NADPH provided by the hexose monophosphate shunt and is responsible for approximately 5% of MetHb reduction in vivo. Thus, the auxiliary system assumes greater clinical significance when the primary system is overwhelmed during poisoning with an oxidative toxin. Methylene blue can act as a cofactor and greatly accelerate the enzymatic reduction of MetHb along the NADPH dependent pathway. Two nonenzymatic mechanisms of MetHb reduction using ascorbic acid and glutathione play only a very minor role in maintaining the normal physiologic equilibrium.

MetHb-emia may be either congenital or acquired. Acquired MetHb-emia is encountered more frequently and is caused by a wide variety of xenobiotics, either those that may directly oxidize hemoglobin or those that require metabolic activation to an oxidizing species. The most clinically relevant direct producers of MetHb include local anesthetics (such as benzocaine and prilocaine), as well as amyl nitrite and isobutyl nitrite, which have become abused drugs (aphrodisiac). MetHb is indirectly formed by metabolic activation of dapsone.

In this case, the cause of MetHb-emia was dapsone. We initially assumed the cause of MetHb-emia in this case by nitrates or nitrites because the patient said he purchased the drug as an aphrodisiac on the black market and nitrates or nitrites are currently abused as aphrodisiacs. However, the analysis of ingested drugs by GC/MSD showed it was dapsone. Therefore, clinicians should aware of the possibility of dapsone in cases of MetHb-emia known be caused by ingestion of an aphrodisiac.

Dapsone-induced MetHb-emia usually occurs as a result of acute poisoning by accidental or suicidal purpose or during treatment. However, we could not find any report of dapsone ingestion as an aphrodisiac. Thus, to our knowledge, this is the first report of dapsone being ingested as an aphrodisiac.

MetHb levels of up to 20% are usually well tolerated by otherwise healthy adults and children without underlying disease. As levels reach 30–40%, symptoms such as headache, fatigue, tachycardia, weakness, and dizziness are experienced. Levels of 60% produce lethargy, convulsions, and coma. MetHb levels greater than 70% are usually lethal, although survival has been reported with a MetHb level of 81.5%.

The definitive diagnosis is made by arterial blood gas analysis with co-oximetry. MetHb-emia should be considered in patients with a normal arterial PO₂ and a low measure of oxyhemoglobin saturation.

Initial treatment is supportive and includes removing the inciting agent from clothes, skin and the gastrointestinal tract (i.e., emesis, gastric lavage, activated charcoal). Use of activated charcoal may reduce the dose of methylene blue. Patients who are symptomatic or have a MetHb level greater than 30% should receive 1–2 mg/kg of methylene blue intravenously over 5 minutes. If the patient remains severely symptomatic following methylene blue administration, alternative forms of therapy, including exchange transfusion or hyperbaric oxygen, should be used.

There has been only limited experience with exchange transfusion in the treatment of MetHb-emia. Hyperbaric oxygen therapy may be a useful adjunct to standard therapy.

Although ascorbic acid can also reduce MetHb and has been used to treat hereditary MetHb-emia, it has...
no place in the management of acquired MetHb-emia because the rate at which it reduces MetHb is too slow to be of any benefit for severe poisoning and may produce a large number of Heinz bodies.\textsuperscript{24}

MetHb reduction using glutathione has also been attempted. In vitro study, N-acetylcysteine, the predecessor of glutathione, reduced MetHb formation.\textsuperscript{25} In an in vivo study using rats, however, N-acetylcysteine did not reduce the MetHb concentration.\textsuperscript{26}

Dapsone is a potent anti-inflammatory and anti-parasitic compound which is metabolized by cytochrome P-450 to hydroxylamines, which in turn cause MetHb-emia and hemolysis.\textsuperscript{27} Thus, recent efforts have been made to reduce the formation of active metabolite hydroxylamines using a metabolic inhibitor. In animal study,\textsuperscript{28} cimetidine, a known inhibitor of several hepatic P450 isozymes administered 1 hour before dapsone, prevented MetHb-emia. Thus, the use of cimetidine may provide an immediate route to increasing patient tolerance and reducing adverse reaction during dapsone therapy, especially in patients with chronic dapsone treatment.

REFERENCES