Dapsone-Induced Methemoglobinemia: Case Report and Literature Review

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Dapsone is a potent cause for intragenic methemoglobinemia that is frequently unrecognized. We describe such a case with successful antidotal therapy.

Keywords: dapsone, methemoglobinemia, cyanosis

INTRODUCTION

Methemoglobin is a form of hemoglobin in which the iron molecule is in the ferric state rather than the normal ferrous state. The abnormal hemoglobin is incapable of carrying oxygen, leading to a functional anemia and cellular hypoxia. The mainstay of treatment is supportive care and use of methylene blue. We present a case of a patient with drug-induced methemoglobinemia from use of dapsone.

CASE REPORT

A 37-year-old black woman with a history of ANA-negative lupus presented because of fevers for 1 month. She also reported a cough and shortness of breath for the last 3 days. In the review of symptoms, she also noted a bluish hue to her fingertips and lips the day before admission. For her lupus, she was being treated with 200 mg dapsone daily (started 8 months before admission with a dose increase 2 months before admission), 200 mg hydroxychloroquine daily (for several years), and 2.5 mg prednisone every other day (for several years). On admission, the blood pressure was 135/61 mm Hg, pulse 99 beats/min, respiratory rate 22 breaths/min, temperature 98.2°F orally, and oxygen saturation 94% while on 2 L oxygen per nasal cannula. The remainder of her physical examination was normal. Her white blood count was within normal limits, whereas her hemoglobin was 11.4 g/dL. She had pulmonary infiltrates on computed tomography of the chest and subsequently was started on antibiotics. However, she felt her shortness of breath was getting worse and she began requiring bilevel positive airway pressure at night. On hospital day 10, an arterial blood gas on 5 L oxygen per nasal cannula showed a pH of 7.48, pCO2 31, pO2 161, and HCO3 24.5. Her oxygen saturation was 94% to 97% on 5 L oxygen per nasal cannula. Her blood was noted to be a dark purplish color. Given her history of peripheral cyanosis before admission and the color of her blood, methemoglobinemia was suspected. Therefore, a methemoglobin level was checked, which was 25%.

Dapsone was subsequently stopped. She was treated with methylene blue at a dose of 1 mg/kg or 100 mg intravenously once. Her methemoglobin level after initial treatment was 7%. The methemoglobin level was then rechecked in 6 hours and it was 13.6%. Given it was rising again, a second treatment of 100 mg intravenous methylene blue was administered. Her methemoglobin levels continued to fall until reaching normal limits. Her shortness of breath resolved and there was no evidence of hemolysis. She was discharged home on hospital day 15 (5 days after the dapsone was stopped).

DISCUSSION

Methemoglobin is an abnormal form of hemoglobin that is formed when unoxygeanated hemoglobin is transformed by oxidation from the normal ferrous (Fe +2) to the ferric form (Fe +3). The ferric form is unable to carry oxygen and carbon dioxide.
Methemoglobinemia occurs when the concentration of methemoglobin in erythrocytes is greater than 1%.1,2

In normally healthy patients, symptoms of cyanosis appear at levels around 15%. Headache, fatigue, tachycardia, weakness, and dizziness appear at levels of 30% to 40%. Hypoxia leading to acidosis, paralysis, arrhythmias, coma, and convulsions is present at concentrations of approximately 60% and death at concentrations of 70% to 80%.2

The erythrocyte has two main mechanisms for keeping methemoglobin levels low. One is by reducing oxidant compounds before they are able to react with hemoglobin to form methemoglobin. Another is to reduce methemoglobin back to normal hemoglobin as soon as it is formed. Methemoglobinemia may be hereditary or acquired. Acquired methemoglobinemia is induced by exposure to chemicals or drugs when the rate of formation of methemoglobin exceeds the rate of reduction. Common offenders include nitrate, dapsone, benzocaine, and aniline dyes.3 In one retrospective study that described 138 cases of acquired methemoglobinemia at two tertiary care hospitals over 28 months, dapsone was the most common etiology, accounting for 42% of all cases (with a mean peak methemoglobin level of 7.6%) followed by benzocaine spray at 20%.3

Dapsone is a sulfone antibiotic and antiinflammatory that inhibits folate synthesis. Dapsone is metabolized by cytochrome P-450 to hydroxylamines, which can cause methemoglobinemia and Heinz body hemolytic anemia resulting from oxidant stress.4 It is used in the treatment of a variety of diseases. Several case reports have been published of patients developing methemoglobinemia from dapsone therapy, often after overdose.5–9 However, it often occurs at therapeutic dosing for Pneumocystis carinii prophylaxis in immunosuppressed patients3,4 or for treatment of leprosy.10–13

Although seemingly rare, the incidence of dapsone-induced methemoglobinemia has been examined in a handful of studies. In a pediatric study, 20% (three of 15) of children with acute lymphoblastic leukemia on prophylaxis developed methemoglobinemia.3,4 The mean duration of prophylaxis to diagnosis was 6.6 weeks. The mean metHb level in symptomatic patients was 11.67% and 1.3% in asymptomatic patients.14 In one series, 16 solid organ transplant recipients fit case definitions for dapsone-related adverse events, including hemolytic anemia (n = 11) or methemoglobinemia (n = 5). Median time from event to dapsone discontinuation was 15 days, indicating a lag time in the removal of the offending agent. All patients improved after drug discontinuation.15

“Chocolate cyanosis” is a hallmark of methemoglobinemia, causing lips and mucus membranes to appear brownish. Despite this, arterial oxygen tensions will read as normal or high. Pulse oximetry can be deceiving. With increasing levels of metHb, the pulse oximeter is less sensitive to hypoxemia. The degree of oxygen saturation is overestimated. In fact, when methemoglobinemia is 30% or greater, the SpO2 plateaus at 85% and is unaffected by oxygenation status.16 Patients with elevated levels of methemoglobin improve little when given high concentrations of oxygen. Venous blood normally will become red when oxygen is bubbled through it. Blood with elevated methemoglobin concentration will not change color when oxygen is bubbled through it. Ultimately, an elevated methemoglobin concentration from a blood gas is diagnostic.2

General supportive care of the patient with methemoglobinemia should be initiated. In an acute overdose, activated charcoal may be used to decrease gastrointestinal absorption. The mainstay drug of treatment is methylene blue, which acts by enhancing the erythrocyte’s ability to reduce methemoglobin. It should be given to patients with methemoglobin levels greater than 30% or to those with signs of hypoxia. When given in appropriate doses (1–2 mg/kg of 1% solution given over 5 minutes), it is generally very effective. If symptoms do not improve, a second dose can be given in an hour. In high concentrations, it can actually worsen methemoglobinemia. Other side effects include precordial pain, restlessness, aggression, tremor, apprehension, and a mild hemolysis. In severe or refractory cases, blood transfusions and even exchange transfusions can be given.2

REFERENCES