

A Case of Dapsone-Induced Cyanosis in the Emergency Department

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Abstract

The authors present the case of a patient with a dapsone overdose. This is accompanied by a review of the essential features of this drug. The pathophysiology, and the emergency department diagnosis and treatment of methemoglobinemia are discussed.

MeSH Words: Dapsone, Methemoglobin, Poisoning, Cyanosis

Introduction

Dapsone (4,4'-diaminophenylsulfone) is a drug that has traditionally been employed in the treatment of leprosy and acne vulgaris. However, the indications for dapsone are varied and include the management of *Pneumocystis carinii* pneumonia (PCP) in immunosuppressed patients, dermatitis herpetiformis, psoriasis, pemphigus, lupus erythematosus profundus, brown recluse spider bites, as well as prophylaxis and treatment of falciparum malaria [1-5].

In light of this wide spread use, the emergency physician (EP), may encounter patients who present to the Emergency Department (ED) with symptoms and signs that are caused by the toxic effects of this drug. Timely and accurate diagnosis and management are essential.

Case Presentation

A 34-year old HIV positive Caucasian woman who was taking 100mg dapsone daily for PCP prophylaxis presented to the ED via ambulance

14 hours after an intentional overdose on 30 of her dapsone tablets. On presentation, she felt lightheaded, nauseous, and mildly dyspneic. She was noticeably cyanosed peripherally and centrally.

Her medical history was significant for HIV, previous PCP pneumonia, mild asthma, and severe depression. She was allergic to codeine and ASA and was currently taking only dapsone. She recently decided to discontinue both her antidepressant and antiretroviral medications. She smoked ½ packs per day and did not drink.

On arrival in the ED, she had a blood pressure of 124/88 mm Hg, heart rate of 116/min, respiratory rate of 18/min. Oxygen saturation on 15L O₂ by non-rebreather mask was 82%. Temperature, blood glucose and level of consciousness were normal. Examination revealed that she was in no respiratory distress, but remained extremely cyanosed both centrally in the lips, gums, face, and peripherally in the digits and nail beds. Complete examination of the patient was otherwise normal.

Initial investigations included a blood gas on 15L/min O₂: pH 7.44, PCO₂ 31, PO₂ 307, saturation 98%, HCO₃ 20.7, lactate 1.0 mmol/L, methemoglobin (metHb) level 41%. Complete blood count showed a hemoglobin level of 149 g/L, leucocyte count of 7.7 with a normal differential count, and platelets of 285. Blood glucose, electrolytes, troponin, creatinine, alkaline phosphatase, transaminases, bilirubin, lipase, INR and PTT were normal. Her cardiogram showed a sinus tachycardia.

Initially, decontamination was not undertaken, given the prolonged time since ingestion. Treatment with methylene blue was initiated at a dose of 1mg/kg intravenously over 5 minutes. Within the next hour, her metHb level dropped to 9%. Three hours later, the patient became cyanotic again and her metHb level rose to 21%. She received repeated doses of methylene blue during her ED stay to a total of 4mg/kg. She was then admitted to the internal medicine ward for six days, where she received supplemental oxygen, methylene blue, and multidose activated charcoal. She developed a hemolytic anemia and her hemoglobin fell to 108 g/L, but she did not

require transfusion. Psychiatric consultation was also undertaken while in hospital. She was

discharged home in good condition after the sixth day.

Discussion

The exact incidence of dapsone-related intoxication is not known, even though information on this drug is available since about 1950. Search of PubMed using the major MeSH word “dapsone” and subheading “poisoning,” and then expanding the search to “related links” found 44 articles that had the word “dapsone” in the title. In a search for “methemoglobin,” a publication was found that reviewed all the cases of acquired methemoglobinemia from one institution, over a 28 month period. A total of 138 cases were found, and dapsone was the most common offender, accounting for 42% of the cases [6]. Data on the incidence of mortality related to intoxications with this drug was not found. An older publication reported 3 cases of mortality in India; however in all of these cases the antidote, methylene blue, was not available. [7].

Dapsone is a powerful oxidant which has two primary toxicities: methemoglobinemia and hemolytic anemia.

Dapsone is absorbed from the gastrointestinal tract and undergoes enterohepatic circulation. Peak plasma concentrations are reached within 2 to 8 hours after ingestion. Mean half-life of plasma elimination varies from 10 to up to 80 hours in overdose situations.

In healthy erythrocytes, small quantities (up to 2%) of metHb are formed constantly by the process of oxidizing iron in the hemoglobin from its ferrous (Fe²⁺) form which can bind oxygen, to its ferric (Fe³⁺) state which cannot bind oxygen. Cellular enzymes rapidly reduce any naturally occurring metHb. These endogenous metHb reducing systems can be easily overwhelmed with exposure to oxidative medications, such as dapsone. Because metHb is unable to bind with oxygen, arterial oxygen saturation is reduced by the same amount that metHb is increased. Methemoglobinemia therefore reduces total oxygen-carrying capacity. In addition, the presence of metHb in the erythrocyte increases the oxygen affinity of normal hemoglobin molecules, thereby shifting the oxygen dissociation curve to the left and further impairing oxygen delivery to the tissues [9].

The key to clinical diagnosis is cyanosis unresponsive to oxygen, with a normal arterial oxygen concentration (PaO_2). At levels above 10%, metHb gives the skin a blueish colour. Cyanosis is evident with only 1.5g/dL of metHb, in contrast to the 5g/dL of deoxygenated hemoglobin required to see hypoxia-related cyanosis. Organ systems with high oxygen demands (i.e., central nervous system (CNS), cardiovascular system (CVS)) usually are the first to show toxicity, and clinical features correlate to the degree of methemoglobinemia. Levels between 20–45% are associated with dyspnea, lethargy, dizziness, lightheadedness, weakness and headaches. MetHb levels above 45% are usually associated with impaired consciousness, and levels above 55% can cause seizures, coma and cardiac arrhythmias. Although the lethal concentration for adults is considered to be >70%, survival has been reported with levels as high as 83%. [8,9,11]

While the cyanosis is a key to diagnosis, confusion often occurs because of the low oxygen saturation seen with pulse oximetry. Standard colorimetric pulse oximeters provide a constant reading in the low 80s in the presence of metHb, thus giving falsely low readings in mild toxicities, and falsely high readings in severe toxicities. On the other hand, most arterial blood gas analyzers calculate the oxygen saturation based on the PaO_2 and therefore give false high values. Consequently, the EP may find a “saturation gap” between the recorded saturation from the pulse oximeter and the reported saturation in the arterial blood gas. A saturation gap of greater than 5% suggests the presence of dysfunctional hemoglobin: carboxyhemoglobin, sulfhemoglobin, or methemoglobin. These abnormal hemoglobins can be measured in a co-oximeter, a companion to the blood gas machine that is available in most hospital blood gas labs. [8,10,12]

A simple bedside test that may help the EP to distinguish between deoxyhemoglobin and metHb is to place 1 or 2 drops of the patient's blood on a white filter paper; deoxyhemoglobin brightens after exposure to atmospheric oxygen, but metHb does not change color. Blowing oxygen on the filter paper speeds the reaction.

Where available, a potassium cyanide test can also be tried. This test can distinguish between metHb and sulfhemoglobin, as the former reacts

with cyanide to form cyanomethemoglobin, which has a bright red colour. Sulfhemoglobin does not react with cyanide and therefore does not change colour. [13]

In addition to confirming the presence of metHb with co-oximetry, the diagnostic workup should look to exclude cardiovascular and respiratory causes of hypoxia and any other abnormal hemoglobins. Tests to rule out hemolysis, a complication of dapsone poisoning, (e.g., CBC, reticulocyte counts, lactate dehydrogenase [LDH], indirect bilirubin, haptoglobin) and tests for organ failure or dysfunction (e.g., ECG, liver function tests, electrolytes, BUN, creatinine, lactate) should be performed. [9,13]

In the ED, the antidote for methemoglobinemia is intravenous methylene blue (methylthioninium chloride): 1 to 2 mg/kg (0.1-0.2mL/kg of a 1% solution). Reduction of metHb to hemoglobin takes place within 60 minutes. Repeat doses are often required and the total dose should not exceed 7mg/kg. If the patient does not respond, it may be due to a glucose-6-phosphate dehydrogenase (G6PD) deficiency, continued presence of the toxin, the presence of sulfhemoglobin, or an overdose of methylene blue. This antidote can cause a factitious cyanosis or add to the oxidative stress and paradoxically worsen the methemoglobinemia.

All patients should receive supplemental oxygen, and hyperbaric oxygen therapy has also been recommended for patients who are not candidates for methylene blue (e.g. those with G6PD deficiency).

In light of the prolonged half life of dapsone, patients can have initial treatment success but their symptoms may reoccur and prolonged treatment may be required. Because of its enterohepatic circulation, dapsone is one of the few poisonings for which multidose activated charcoal is recommended [1,4]. Intravenous cimetidine (300mg bolus or 50mg/hour infusion) can also be started in the ED. The dapsone-mediated metHb formation can be reduced by cimetidine through the activation of liver enzymes [2,9,15]. Ascorbic acid, 300 to 1000 mg/day intravenously in three to four doses, provides nonenzymatic metHb reduction but is slow and has little role in acute management[12].

Conclusion

In summary, the prolonged oxidative action of dapsone sustains the production of methHb making it imperative to diagnose toxicity quickly and to monitor treatment over time. Cyanosis not responsive to oxygen and a gap between recorded and measured oxygen saturations are two features that assist the EP in diagnosing methemoglobinemia. The mainstay of therapy is methylene blue.

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