The Recognition, Physiology, and Treatment of Medication-Induced Methemoglobinemia: A Case Report

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Dapsone is a leprostatic agent commonly prescribed for the management of leprosy, malaria, and the immunosuppression-induced infections of *Pneumocystis carinii* and *Toxoplasma gondii*. In susceptible patients, methemoglobinemia, a potentially life-threatening event, can occur. We report a case of dapsone-induced methemoglobinemia which was observed during general anesthesia for the management of a fractured mandible. The pathophysiology, diagnosis, and management of dapsone-induced methemoglobinemia will be discussed.

Key Words: Dapsone; Methemoglobinemia; Methemoglobin; Cyanosis; Glucose-6-phosphate dehydrogenase deficiency; Cytochrome b5 reductase; Acquired methemoglobinemia; Congenital methemoglobinemia.

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CASE REPORT

A 56-year-old Asian woman presented for the treatment of a fracture of the body of the mandible. The proposed treatment was closed reduction in the operating room under general anesthesia. Her past medical history was significant for liver transplantation performed 6 months earlier, secondary to fulminant hepatitis caused by hepatitis C. Current medications were prednisone and tac-

rolimus for immunosuppression and dapsone for *P. carinii* pneumonia (PCP) prophylaxis.

The patient was taken to the operating room and standard monitors were placed by the anesthesiologist. Presurgical vital signs revealed a normal sinus rhythm, blood pressure of 134/86 mm Hg, pulse rate of 92/min, respiratory rate of 18/min, core temperature of 98.7°F, and oxygen saturation of 94% via pulse oximetry. Preoxygenation prior to induction was administered via full face mask. The patient was induced using midazolam, fentanyl, and propofol. The patient was intubated without complications and vital signs remained stable throughout the induction. An injection of 6 mL of 1% lidocaine with 1 : 100,000 epinephrine was then given. After approximately 30 minutes, during fixation of the mandible, oxygen saturation decreased to 79%. Immediately, 100% oxygen was administered, circuit integrity was checked, and end tidal CO₂ was verified at 44 mm Hg with a tidal volume of 550 mL. Arterial blood gas analysis was obtained with the following results:

pH	7.37
SAO ₂	99.4%
PaO ₂	485 mm Hg

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PaCO ₂	26 mm Hg
Oxyhemoglobin	81%
Methemoglobin	18%

Methylene blue (1 mg/kg) was injected intravenously over 3 minutes. Pulse oximetry revealed an increase in saturation to 96%. Blood for arterial blood gas analysis was redrawn 10 minutes later. The results showed:

pH	7.41
SaO ₂	96%
PaO ₂	324 mm Hg
PaCO ₂	25 mm Hg
Oxyhemoglobin	93.9%
Methemoglobin	4.7%

The operation was completed with no further decrease in oxygen saturation and no other complications.

DISCUSSION

The most frequent reaction to occur with dapsone toxicity is hemolytic anemia and methemoglobinemia. Hemoglobin levels can decrease by 1–2 g/dL with an increase of 2–12% in the reticulocyte count.¹ Most patients are asymptomatic until approximately 30% of hemoglobin is present as methemoglobin, although lower levels may be associated with cyanosis. Discontinuation of therapy is only indicated when the methemoglobinemia causes symptomatic, hemodynamic instability.

Dapsone is an antimicrobial in the sulfone family that was originally used to treat leprosy. Currently, dapsone has become a component of second-line regimens for the prophylaxis of *P. carinii* pneumonia and malaria, and for primary prophylaxis against *T. gondii* in HIV-infected patients with CD4 T-lymphocyte counts lower than 100 cells/mm.² It is also used in organ transplant recipients for PCP prophylaxis secondary to long-term immunosuppression. In addition, it also has significant anti-inflammatory effects that have led to its use in a range of autoimmune disorders. The antimicrobial action of dapsone occurs through the inhibition of folate synthesis. The anti-inflammatory effects of dapsone are not clearly understood, but it does inhibit neutrophil function by interfering with chemoattractant-induced signal transduction.³

Methemoglobinemia can occur either in congenital or acquired forms and is the most common cause of hemoglobin-specific cyanosis. The congenital form is present at birth and manifests in two distinct forms. Type I is an erythrocyte form with a deficiency of NADH-cytochrome b5 reductase gene (b5R). It normally is observed only in the erythrocytes of mildly cyanotic patients.⁴ Type II is a generalized form that is characterized

by a b5R deficiency in all tissues. Cyanosis and severe neurologic deficiency are hallmarks of the type II form.⁵

Acquired forms are usually pharmacokinetically induced responses that result in an increase in the rate of oxidation of hemoglobin to methemoglobin. Amyl nitrite, aniline dyes, benzocaine, bismuth subnitrate, cetacaine, dapsone, lidocaine, nitroglycerin, p-aminosalicylic acid, phenytoin, prilocaine, artacaine, primaquine, pyridine, silver nitrate, and sulfonamides have all been implicated.⁶ Aniline derivatives, ie, lidocaine, prilocaine, and nitrites are the most common methemoglobinemic inducing drugs.⁶ It is possible that the 60 mg of lidocaine given to this patient may have contributed to the patient's preoperative level of methemoglobinemia, causing this acute exacerbation.

The clinical signs of methemoglobinemia are a result of the inability of methemoglobin to bind oxygen, causing a state of functional anemia, and increasing the binding affinity of the nonreduced ferrous heme for oxygen.⁷ Clinical severity of the presenting symptoms and signs depends on the blood level of methemoglobin.⁷ Levels greater than 15% are associated with cyanosis. Levels between 20 and 45% present with signs and symptoms of headache, lethargy, tachycardia, weakness, and dizziness. Dyspnea, acidosis, cardiac dysrhythmias, heart failure, seizures, and coma may occur at levels exceeding 45%. A high mortality rate is associated with methemoglobin levels above 70%.⁸

Oxyhemoglobin saturation detected by pulse oximetry is analyzed as low in methemoglobinemia. Pulse oximetry is based on the light absorption of oxyhemoglobin and reduced hemoglobin at the wavelengths of 660 nm and 940 nm. Methemoglobin has 2 absorption peaks at approximately 630 nm and 960 nm. At 660 nm and 940 nm, red and infrared light are absorbed at a 1:1 ratio. This ratio corresponds to an arterial saturation of 85% by the pulse oximetry conversion algorithm, which includes only oxyhemoglobin (O₂Hb) and deoxyhemoglobin (deO₂Hb) waveforms. With increasing levels of methemoglobin, the pulse oximeter will be insensitive to hypoxemia and will overestimate the degree of oxygen saturation. More specifically, when methemoglobinemia is 30% or greater, the oxygen saturation (SpO₂) plateaus at 85% and is unaffected by oxygenation status.⁹ Clinically, the presence of dark brown blood that does not turn red on exposure to air is also suggestive of methemoglobinemia.¹⁰

Intravenous administration of methylene blue is the treatment for methemoglobinemia. Methylene blue works as a cofactor for the enzyme NADPH-methemoglobin reductase. Methylene blue is oxidized into leukomethylene blue by accepting an electron from NADPH in the presence of NADPH-methemoglobin reductase. Leukomethylene blue then donates this elec-

tron to methemoglobin resulting in its conversion back to hemoglobin.⁷

The therapeutic dose of methylene blue is 1 to 2 mg/kg administered intravenously. An additional dose may be repeated if there is an insufficient response after 1 hour. Reported side effects are nausea, diarrhea, oral dysesthesia, dyspnea, and excessive perspiration. In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a delay in hemolysis can occur because of a decreased production of NADPH. Administering doses above 15 mg/kg can initiate methemoglobinemia by oxidation of hemoglobin to methemoglobin. No current therapy is available for the treatment of life-threatening, methylene blue refractory methemoglobinemia. Alternative therapies like exchange transfusions and hyperbaric oxygen therapy may be the remaining options for such patients, but the efficacy of these modalities has not been proven.³

In patients with a known history of methemoglobinemia, cimetidine may be used prophylactically to inhibit the formation of the toxic hydroxylamine metabolite of dapsone. This has been shown to reduce the degree of methemoglobinemia and to improve tolerability in patients on high levels of dapsone.^{3,11}

CONCLUSION

All patients on dapsone are predisposed to developing methemoglobinemia. The appearance of cyanosis and/or a decrease the saturation levels on pulse oximetry in patients using dapsone should alert the practitioner to the possibility of methemoglobinemia. It is imperative that the practitioner understand that the oxyhemoglobin saturation reported by the pulse oximeter should be considered inaccurate in this condition, and that arterial

blood gas analysis must be performed, including methemoglobin for appropriate assessment and monitoring of the therapeutic intervention.

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