METHEMOGLOBINEMIA IN CRITICALLY ILL BURNED PATIENTS

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Although rare, methemoglobinemia is a life-threatening condition and can be caused by a variety of oxidizing reagents that are commonly used in essentially all healthcare settings. Thus, it is vital for critical care nurses to be aware of the causes of methemoglobinemia, the resulting signs and symptoms, and the treatment options. We present a case of methemoglobinemia involving a patient with anemia who had mafenide acetate burn dressings and who underwent transesophageal echocardiography.

Case Report

JL, a 21-year-old man, was admitted to a regional burn center after sustaining burns on 68% of his total body surface area after an explosion. Before his episode of methemoglobinemia developed, JL had undergone numerous surgeries for burn excision and skin grafting, and he had received a bedside tracheostomy and had been weaned to pressure-support ventilation with a fraction of inspired oxygen (FIO₂) of 40%. JL’s wound care consisted of mafenide acetate dressings applied to meshed split-thickness skin grafts that had been placed 2 days previously.

Because these dressings were to remain in place for 5 days, he was treated with bed rest.

Because of chronic fevers, JL had transthoracic echocardiography to determine if he had valvular vegetations and Doppler imaging of the lower extremity to determine if he had deep venous thrombosis. However, because of his dressings, visualization with transthoracic echocardiography was poor and, therefore, transesophageal echocardiography was performed at the bedside. In preparation for this procedure, JL received intravenous boluses of midazolam and pharyngeal benzocaine spray, and he was given additional sprays of benzocaine as he continued to gag during passing of the scope. Subsequently, the transesophageal echocardiography was successfully performed, and no abnormality was detected.

Within 10 minutes of the procedure, JL’s skin color turned dusky, circumoral cyanosis developed, and he became progressively lethargic. The pulse oximeter
indicated an oxygen saturation of 88% that decreased to 20%. In response, FIO₂ was increased to 1.0, the tracheostomy was suctioned for a mucous plug, and the respiratory therapist and physician were paged. The nurse provided manual ventilation of JL's lungs, but no change was apparent in his clinical status or pulse oximeter readings. Because of his history of trauma, immobility, and indwelling central catheters, a pulmonary embolus was suspected. An initial blood sample obtained for arterial blood gas (ABG) analysis was extremely dark, almost chocolate brown (Figure 1). This sample was assumed to be venous, so a second sample was obtained. Because of the assumption that JL had a pulmonary embolism, intravenous heparin therapy was initiated. Preparations were made to transport him for spiral computed tomography of the chest while the results of ABG analysis were pending. After the results of the ABG analysis were obtained (pH 7.54, Pco₂ 24 mm Hg, PaO₂ 300 mm Hg, bicarbonate 23.6 mmol/L, and arterial oxygen saturation 98.2% at an FIO₂ of 1.0) and the chest radiograph was examined, it was still unclear what was happening, but a pulmonary embolism seemed extremely unlikely because the PaO₂ was elevated at 300 mm Hg. The blood was extremely dark, so the differential diagnosis was expanded to include methemoglobinemia, but the immediate cause seemed obscure. A quick Internet search for “burn” and “methemoglobinemia” yielded a case of methemoglobinemia thought to be caused by mafenide acetate dressings.¹

The blood samples previously sent for ABG analysis were assayed for methemoglobin levels. The values were greater than 0.40. JL's mafenide acetate dressings were immediately removed, and methylene blue, 2 mg/kg intravenously, was administered over a 5-minute period. Samples of arterial blood were periodically sent for analysis (including methemoglobin levels) until methemoglobin values were less than 0.04 (Figure 2). A repeat 1 mg/kg dose of methylene blue was required to achieve this level. The methemoglobin level in the second sample sent for ABG analysis (pH 7.42, Pco₂ 34 mm Hg, PaO₂ 199 mm Hg, bicarbonate 22.5 mmol/L, arterial oxygen saturation 99.2% at an FIO₂ of 0.6) had decreased to 0.012 from 0.40.

JL's condition stabilized, and he was rapidly weaned back to his previous ventilator settings. He recovered without any adverse outcomes. After extensive rehabilitation for his burn injuries, JL was discharged to home approximately 2 months after the episode of methemoglobinemia.

Pathology

Hemoglobin consists of 4 heme groups, each containing an iron atom. Each atom is capable of binding with oxygen only if the iron is in the reduced, or ferrous (Fe²⁺), state. When an iron atom is oxidized, an electron is removed to make the ferric (Fe³⁺) state of iron.² Methemoglobin, the form of hemoglobin that contains Fe³⁺, cannot transport oxygen because the ferric hemo-globin is shaped differently. Thus, administered oxygen remains in a free, unbound state, leading to an increased PaO₂ but decreased net oxygen delivery.³

During transesophageal echocardiography, the burned patient's arterial oxygen saturation decreased from 88% to 20% and was unresponsive to oxygen therapy.

Methemoglobin results from oxidation of iron atoms, is unable to transport oxygen, and typically accounts for less than 2% of total hemoglobin.

In the normal physiological state, small amounts of methemoglobin are formed during the reaction between oxygen and hemoglobin, but these amounts are typically limited to less than 0.02 of the total amount of hemoglobin. Any amount greater than this is quickly converted back to hemoglobin by 1 of 2 different reducing enzymes: cytochrome-₃ reductase and NADPH

Figure 2 Bright red arterial blood sample after administration of methylene blue. Results of arterial blood gas analysis were pH 7.42, Pco₂ 34 mm Hg, PaO₂ 199 mm Hg, bicarbonate 22.5 mmol/L, arterial oxygen saturation 99.2% at a fraction of inspired oxygen of 0.6, methemoglobin level 0.012.
(the reduced form of nicotinamide-adenine dinucleotide phosphate) methemoglobin reductase. Cytochrome-\(b_5\) reductase is responsible for more than 95% of the reducing capacity of erythrocytes. In contrast, NADPH methemoglobin reductase accounts for less than 5% of normal erythrocyte reducing capacity.4

Methemoglobin is typically formed as exogenous drugs or chemicals oxidize hemoglobin. As indicated in Table 1, many of these oxidizing agents are medications commonly used in healthcare settings, especially benzocaine and other local anesthetics.1,4-6 In an observational study in an echocardiographic laboratory, Novaro et al5 found that methemoglobinemia occurred in 0.115% of patients receiving benzocaine spray for transesophageal echocardiography. Furthermore, burn wound management often consists of topical silver nitrate solution or mafenide acetate, a sulfonamide. With compromised integrity of the skin barrier, increased absorption of these oxidizing agents can occur.

Nonpharmacological factors can also play a role in the development of methemoglobinemia. Anemia can make the condition apparent at lower methemoglobin concentrations, because patients with anemia have a limited reserve of oxygen-carrying capacity. Generally, signs of decreased oxygenation occur at methemoglobin levels of 0.10 to 0.25, but such signs may show up earlier in patients with anemia, possibly as soon as methemoglobin levels reach 0.025.6 With decreased reserves, the cytochrome-\(b_5\) reductase pathway is saturated much more quickly. Additionally, infants are at increased risk for methemoglobinemia because of increased gastric pH and consequent overgrowth of nitrate-producing bacteria in the stomach. These nitrates, in conjunction with nitrates in well water, often overwhelm the body’s reducing systems that normally prevent the development of methemoglobinemia.7

**Diagnosis**

Signs and symptoms of methemoglobinemia typically occur within 30 minutes of administration of the causative agent, yet are nonspecific. Clinically, patients can appear to be experiencing a pulmonary embolus7 (Table 2). Diagnosis of methemoglobinemia is based on clinical assessment when respiratory status does not explain cyanosis and the patient remains refractory to oxygen therapy.7 A defining visual characteristic of methemoglobinemia is chocolate-brown arterial blood.8 This color is in stark contrast to well-oxygenated blood, which typically is bright red.

**Methemoglobinemia produces arterial blood that is chocolate brown in color, and oxygen saturation values from arterial blood samples and pulse oximetry are inaccurate.**

Diagnosis can be difficult because of the confusing results of ABG analyses. It is important to know that the \(P_{\text{aO}_2}\) and pH in arterial blood are measured and that normally, as \(F_{\text{IO}_2}\) is increased, hemoglobin becomes saturated with oxygen.10 Once saturation occurs, an associated increase in free, unbound oxygen is manifested as an increase in \(P_{\text{aO}_2}\). Thus, with high \(P_{\text{aO}_2}\) values, a comparable increase in hemoglobin saturation occurs. However, although \(P_{\text{aO}_2}\) and pH values are measured in ABG analysis, oxygen saturation is calculated. Thus, oxygen saturation values are inaccurate in patients with methemoglobinemia because the normal relationship of \(P_{\text{aO}_2}\) to saturated hemoglobin is invalid.11

Diagnosis is further complicated by the inaccuracy of pulse oximetry readings. Pulse oximeters can measure light absorption at only 2 wavelengths: the wavelength of oxyhemoglobin and the wavelength of deoxyhemoglobin. Unfortunately for clinicians, methemoglobin absorbs equally at both of these wavelengths.

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**Table 1 Examples of oxidizing agents**

<table>
<thead>
<tr>
<th>Example</th>
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<tbody>
<tr>
<td>Amyl nitrate</td>
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<tr>
<td>Aniline dyes</td>
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<tr>
<td>Bismuth subnitrate</td>
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<tr>
<td>Dapsone</td>
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<tr>
<td>Local anesthetics (lidocaine, benzocaine, prilocaine)</td>
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<td>Naphthalene</td>
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<tr>
<td>Nitrites/nitrates (nitroglycerin, silver nitrate, nitrates in well water, trinitrotoluene)</td>
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<tr>
<td>Pyridium</td>
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<td>Sulfonamides (ie, mafenide acetate)</td>
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</tbody>
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**Table 2 Signs and symptoms of methemoglobinemia**

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<th>Example</th>
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<td>Tachycardia</td>
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<td>Tachypnea</td>
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<tr>
<td>Dyspnea</td>
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<td>Hypoxia</td>
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<td>Chest pain</td>
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<tr>
<td>Nausea/vomiting</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Metabolic acidosis</td>
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<td>Changes in mental status</td>
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Hence, pulse oximeter readings for patients with methemoglobinemia may be falsely high or falsely low. Some researchers\textsuperscript{9,11} suggest that plateau saturations of 85\% would be seen no matter what the methemoglobin concentration, but our patient and patients in other case reports\textsuperscript{4,6} had lower values. CO-oximetry should be requested because it provides measurements of 4 wavelengths, those specific for oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin.\textsuperscript{9}

**Treatment**

Treatment for methemoglobinemia requires removal of the offending oxidizing agent and in cases of severe deoxygenation, correction of the hemoglobinopathy. Rapid reduction of methemoglobin is achieved by administration of methylene blue, which is a cofactor for NADPH methemoglobin reductase and acts by increasing the activity of this system. This enzyme reacts within red blood cells to form leukomethylene blue, which converts the ferric ion back to its oxygen-carrying ferrous state.\textsuperscript{1} Methylene blue is indicated for patients with methemoglobin levels greater than 0.30. It is administered at a dose of 2 mg/kg body weight as a 1\% solution delivered intravenously over 5 minutes. The recommended maximum dosage is 7 mg/kg because of oxidizing properties that can occur at high doses and can theoretically exacerbate the methemoglobin state.\textsuperscript{9,12} Of note, methylene blue also has an absorption peak that is interpreted by pulse oximeters as deoxyhemoglobin.\textsuperscript{10} Therefore, oxygen saturation as measured by pulse oximetry will be false during administration of methylene blue.

**Methylene blue changes methemoglobin back to its oxygen-carrying state.**

Additionally, nurses should be familiar with the adverse effects commonly associated with methylene blue: anemia, vomiting, nausea, dyspnea, confusion, restlessness, and sweating.\textsuperscript{2} Rarely, adverse effects can include cardiac arrhythmias, hemolytic anemia, hypertension, and methemoglobinemia. Patients receiving methylene blue may have a blue tinge in their urine, feces, saliva, skin, and mucous membranes\textsuperscript{2} (Figure 3). Therefore, clinical judgment in monitoring patients for improvement during methylene blue administration is further impaired because cyanosis is difficult to distinguish from the skin tone caused by the methylene blue.

Patients who do not respond to methylene blue may have a genetic deficiency in the NADPH methemoglobin reductase system. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because glucose-6-phosphate dehydrogenase is required to convert methylene blue to a usable form by reducing the oxidized form of nicotinamide-adenine dinucleotide phosphate to NADPH. When treated with methylene blue, patients with this deficiency are at high risk for hemolytic anemia.\textsuperscript{11} Another contraindication to methylene blue therapy is renal failure because methylene blue is excreted by the kidneys.\textsuperscript{9} Any patient who does not respond to methylene blue or who has contraindications for its use should be transfused with packed red blood cells, thus providing hemoglobin in the ferrous state to bind and transport oxygen to the cells.\textsuperscript{6} In severe cases, an exchange transfusion may be necessary.\textsuperscript{11}

**Conclusion and Implications**

In JL, methemoglobinemia developed as a result of multiple exposures to oxidizing agents (ie, mafenide acetate and benzocaine spray) and a predisposing anemia with a hematocrit of 0.25. The purpose of this report is to increase awareness among all members of the critical care team of methemoglobinemia as a cause of hypoxia refractory to oxygen administration. Oxidizing agents such as benzocaine and other local anesthetics are used regularly, and nursing staff must increase their knowledge and understanding of the signs, symptoms, and treatment of methemoglobinemia.\textsuperscript{1,4,13}

Mafenide acetate and silver nitrate are applied in burn units without a physician present, leading to the increased need for nurses to be aware of methemoglobinemia as a life-threatening complication.

**REFERENCES**


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