Methemoglobinemia: An unusual cause of postoperative cyanosis

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Methemoglobinemia, although rare, must be considered in surgical patients presenting with acute respiratory distress and cyanosis. We report two cases of methemoglobinemia in patients undergoing aortic reconstruction. The first patient developed methemoglobinemia while on a nitroglycerin infusion, and the second after receiving benzocaine spray before intubation. Both patients were treated with methylene blue and ascorbic acid, with resolution of their hypoxia and cyanosis. The pathophysiology, etiology, diagnosis, and treatment of methemoglobinemia are reviewed. (J Vasc Surg 2004;39:686-90.)

Methemoglobin (MHb) is formed when the ferrous (Fe^{2+}) iron moiety of hemoglobin is oxidized to the ferric (Fe^{3+}) state. Excess MHb leads to cyanosis, impaired aerobic respiration, metabolic acidosis, and in severe cases, death. The most common etiology of methemoglobinemia is ingestion or skin exposure to oxidizing agents.[1] Other etiologies include genetic deficiencies of cytochrome-b_5 and cytochrome-b_5 reductase, dietary ingestion of nitrates in well water, and idiopathic causes.[2,3] As a life-threatening condition, methemoglobinemia must be recognized early and treatment initiated promptly. Unfortunately, pulse oximetry and arterial blood gases can be misleading in patients with methemoglobinemia.[4-7] Co-oximetry is the most accurate way of measuring the MHb level and of diagnosing the disorder.[8] We have recently managed two patients who developed acute respiratory distress and cyanosis following aortobifemoral bypass grafting procedures. In this report, we review the pathophysiology, etiology, diagnosis, and treatment of methemoglobinemia in these two critically ill patients.

CASE REPORT

Case 1. The patient was a 57-year-old Caucasian female with a history of hypertension, coronary artery disease, myocardial infarction, paroxysmal atrial fibrillation, and chronic obstructive pulmonary disease. After preoperative evaluation, she was admitted for an aortobifemoral bypass for bilateral lower-extremity rest pain. Her outpatient medications included clonidine, verapamil, coumadin, nitroglycerin, amlodipine, digoxin, hydrochlorothiazide, and diazepam.

Aortobifemoral bypass grafting was performed without major complications. The patient remained intubated and was transferred to the surgical intensive care unit. Postoperatively, she received fenoldopam, nitroglycerin (0.25 mcg/kg per min), metoprolol, and two units of packed red blood cells. The next morning, she was extubated uneventfully.

On the second postoperative day, the patient's pulse oximetry value fell to 90% despite being on 50% oxygen by aerosol face mask. On physical examination, she had labored breathing, with a respiratory rate of >20 breaths per minute and diminished air entry bilaterally. After two albuterol and ipratropium nebulizer treatments, her dyspnea resolved and her oxygen (O_2) saturation improved to >95%, with improvement in breath sounds in both lungs.

Four hours later, the patient was noted to be lethargic, with confused speech. Her pulse rate was 119 beats per minute and her blood pressure 118/65 mm Hg. Her respirations were labored, with accessory muscle recruitment. Coarse rales with rhonchi were noted on auscultation. Pulse oximetry showed O_2 saturation of 88%. The patient was placed on a nonrebreather face mask at 100% O_2. Initially, the O_2 saturation increased to 98%, then decreased to 94% with the development of cyanosis. Because of her labored breathing and decreased O_2 saturation, the patient was intubated. Despite an O_2 saturation of 95%, her cyanosis continued to increase. When arterial blood gas samples were obtained, it was noted that the blood was chocolate brown in color (Fig 1). Methemoglobin levels were ordered and co-oximetry revealed MHb level of 31.0%.

The nitroglycerin infusion (0.25 mcg/kg per min) was discontinued after a total dose of 50 mg. A single dose of methylene blue (2 mg/kg) was infused intravenously over 5 minutes, and 2 gm of ascorbic acid was given intravenously piggyback. Arterial blood gases and MHb levels were redrawn 30 minutes after administration of the methylene blue (Table I). Over the next 24 hours, the patient's cyanosis, tachypnea, and tachycardia resolved as her MHb level returned to within the normal range (0.4%-1.5%). She was later extubated uneventfully.

Case 2. The patient, a 73-year-old Caucasian female with a history of hypertension, diabetes mellitus, osteoarthritis, and congestive heart failure, underwent an aortobifemoral bypass with bilateral common femoral artery endarterectomies for infrarenal aortic occlusion. The patient's postoperative course was complicated by a hemothorax after central line placement, requiring thoracotomy 18 days after the bypass procedure. Four days after the thoracotomy, the patient was extubated.

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Fig 1. An arterial blood sample from our first patient at 12.7% MHb (*left*) and 31.0% MHb (*right*). Notice the dark brown hue of the sample with the higher MHb level.

One hour later, the patient became tachypneic and dyspneic, with an oxygen saturation of 95% on 100% O_2 nonrebreather face mask. She was given a nebulizer treatment of albuterol and ipratropium and placed on bilevel positive airway pressure, with improvement in her dyspnea and anxiety. Later that morning, the patient was again tachypneic and tachycardic, but now with cyanosis and a pulse oximetry value of 65%. A blood gas was drawn and processed on a co-oximeter, showing a PaO_2 of 30 mm Hg and MHb level of 0.5%. Immediately before reintubation, the patient was given two oropharyngeal sprays of benzocaine. She was placed on synchronized intermittent mandatory ventilation at a rate of 10 breaths per minute, and FiO_2 of 1.0. O_2 saturation was increased to 98%.

An hour later, the patient developed peripheral and central cyanosis associated with tachypnea and tachycardia. Another arterial blood gas was drawn and processed on a co-oximeter, revealing

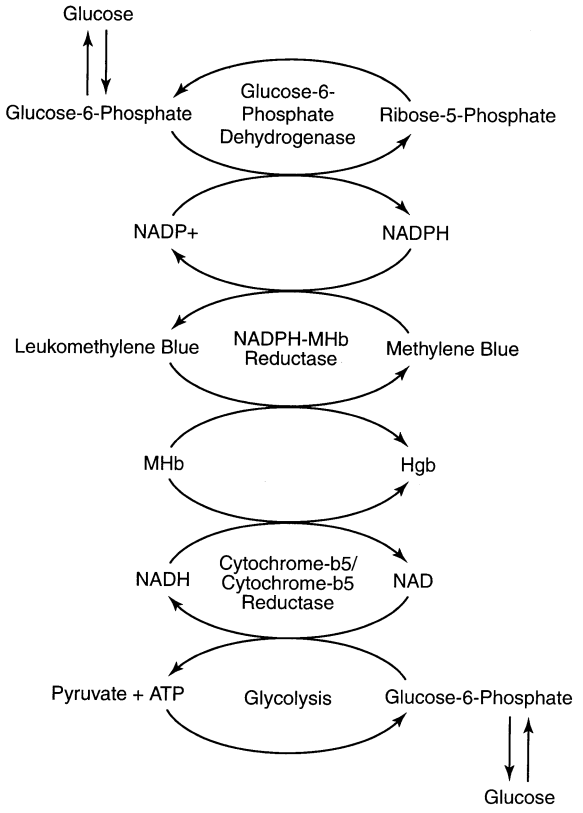

Fig 2. Reduction of methemoglobin to hemoglobin. (From Wright OR, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med 1999;34:646-56. By permission).

a PaO_2 of 322 mm Hg and an MHb level of 43.7%. The patient was somnolent, but able to follow commands. She was given single doses of methylene blue (2 mg/kg, infused over 5 min) and ascorbic acid (2 gm, intravenously piggyback) intravenously. Within 30 minutes, her MHb level had decreased to 27.1%. She was given a repeat intravenous dose of methylene blue and ascorbic acid. O_2 saturation was 94% at that time, and the patient's respirations and heart rate had appropriately decreased. Within 2 hours of the first dose of methylene blue, the MHb level fell to 5.1%. The patient's cyanosis resolved and she was later extubated uneventfully.

DISCUSSION

When the ferrous (Fe^{2+}) iron moiety of hemoglobin is oxidized to the ferric (Fe^{3+}) state to form MHb, hemoglobin loses its ability to transport molecular oxygen and carbon dioxide. Excess MHb leads to cyanosis, impaired aerobic respiration, metabolic acidosis, and in severe cases, death. Cytochrome-b_5-MHb reductase, reduced NADPH-MHb reductase, and reduced glutathione within erythrocytes function as antioxidants to convert MHb back to hemoglobin (Fig 2).[1] Methemoglobinemia becomes life threatening when these enzyme systems become overwhelmed.

Table I. Arterial blood gases for patient 1

	Reference Range	*Pretreatment*	*30 minutes after MB*	*3 hours after MB*	*6.5 hours after MB*	*17 hours after MB*
pH	7.35-7.45	7.18	7.31	7.36	7.30	7.30
PCO_2 (mm Hg)	35-45	52	36	34	40	42
PO_2 (mm Hg)	80-100	236	284	280	160	64
HCO_3 (meq/L)	22-26	19	18	19	19	20
%MHb	0.4-1.5	31.0	23.6	12.7	5.5	2.0

MB, Methylene blue.

Table II. Correlation of clinical signs and symptoms associated with %MHb blood levels

%MHb	*Clinical signs and symptoms**
<10	None
10-20	Cyanosis
20-30	Anxiety, headache, lightheadedness, tachycardia
30-50	Fatigue, dizziness, confusion, tachypnea, increased tachycardia
50-70	Arrhythmias, acidosis, coma, seizures
>70	Death

*Symptoms may be more severe for a given %MHb in patients with anemia or underlying cardiac and pulmonary disease.

As the MHb concentration increases, patients become cyanotic, as evidenced in our two patients. Anxiety, lightheadedness, headache, and tachycardia, followed by confusion and tachypnea, are the usual symptoms. As the MHb level rises, patients may develop acidosis, seizures, arrhythmias, and eventually coma and death (Table II). Patients with underlying cardiac, pulmonary, or hematologic disease may experience more severe symptoms for a given MHb concentration.[1] In our patients, it is likely that anxiety, agitation, tachycardia, lethargy, confusion, hypoxia, and cyanosis were symptoms of worsening methemoglobinemia. Both patients had underlying cardiac and pulmonary disease that could have worsened their symptoms in response to high MHb levels.

The most common etiology of methemoglobinemia in adults is ingestion or skin exposure to oxidizing agents. There is a growing list of medications that have been found to produce methemoglobinemia (Table III). Common agents include aniline dyes, benzocaine, dapsone, nitrates, nitrites, and naphthalene. It appears likely that our first patient formed MHb in response to intravenous nitroglycerin, which was possibly exacerbated by using benzocaine spray before her intubation. The total dose of nitroglycerin that the patient received was 50 mg, which is a reasonable dose to treat hypertension. Although it is possible that there was a pharmacy error or a variation in infusion rate, this could not be substantiated from the medical record. Kaplan et al[2] have shown that the dose and rate of infusion of nitroglycerin are significant factors in the development of methemoglobinemia. Patient age, weight, renal and hepatic function, and arterial oxygen saturation are additional confounding variables. Because multiple factors contribute to the risk of developing methemoglobinemia (ie, anemia, pulmonary and cardiac disease, peripheral vascular disease, shock, sepsis, acidosis, and genetics), the exact dose and rate of nitroglycerin necessary to cause methemoglobinemia remain poorly defined.[3]

In our second patient, the methemoglobinemia seemed temporally related to the benzocaine spray used before intubation and may have been exacerbated by her concurrent respiratory distress, as was the case in our first patient. It is difficult to determine the critical dose of benzocaine spray necessary to cause methemoglobinemia because the administered dose is usually so variable. The dose of drug delivered depends on the number of sprays and on the length of each spray. Complicating the issue is the practice of concomitantly administering varying doses of 2% viscous lidocaine. Lidocaine was not used in either of our patients and, therefore, could not be implicated in the development of methemoglobinemia. Novaro et al,[4] in a review of the incidence of benzocaine-induced methemoglobinemia in an echocardiography laboratory, found that the degree of mucosal damage plays a role in the systemic absorption of benzocaine and, as a consequence, the development of methemoglobinemia. Breakdown of oropharyngeal, esophageal, or gastric mucosa can contribute to increased absorption, as does exposure of the drug to the tracheobronchial tree. Mucosal damage secondary to her prior intubation may have contributed to the development of methemoglobinemia in the second patient.

Other etiologies of methemoglobinemia include genetic predisposition, dietary ingestion of nitrates, and idiopathic sources (most often seen in infants with severe metabolic acidosis). Genetic deficiencies in cytochrome-b_5 reductase and cytochrome-b_5 result in moderately elevated MHb levels that are generally well tolerated.[5] Neither of our patients had a known deficiency of either cytochrome-b_5 or cytochrome-b_5 reductase. Dietary ingestion of nitrates in well water may also cause methemoglobinemia.[3] This presentation is most common in young infants who live in rural areas where the water source may be contaminated by fertilizer runoff. Intestinal bacteria convert the nitrates to nitrites, which are potent MHb-forming agents. Neither of our patients had drunk well water, and they were not exposed to fertilizers before their hospitalizations. Finally, MHb formation may be idiopathic, especially in young infants (<6 months of age) who have severe

Table III. Common drugs or toxins that can cause methemoglobinemia

Acetanilid	Dinitrophenol	Paraquat
Alloxan	Exhaust fumes	Phenacetin
Aniline (dyes, ink)	Ferricyanide	Phenazopyridine HCl
Arsine	Flutamide	Phenol
Benzene derivatives	Hydroxylamine	Phenytoin
Benzocaine	Lidocaine hydrochloride	Prilocaine
Bivalent copper	Metoclopramide	Primaquine
Bismuth subnitrate	Methylene blue	Rifampin
Bupivacaine hydrochloride	Naphthalene	Silver nitrate
Chlorates	Nitrates	Sodium valproate
Chloroquine	Nitric oxide	Smoke inhalation
Chromates	Nitrites	Sulfasalazine
Clofazimine	Nitrofuran	Sulfonamides
Dapsone	Nitroglycerin	Trinitrotoluene
Dimethyl sulfoxide	Sodium nitroprusside	

Modified from Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: Etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999;34: 646-56; and from Rehman HU. Methemoglobinemia. *West J Med* 2001;175:193-6.

metabolic acidosis from diarrhea and dehydration. Iatrogenic causes (ie, same unit, same shift, pharmacy error) for the development of methemoglobinemia in these patients are unlikely as they occurred over a year apart.

Evaluation of cyanosis in Intensive Care Unit patients. When assessing a cyanotic patient in the intensive care unit, two of the first diagnostic measures usually taken include pulse oximetry and arterial blood gases. Unfortunately, in the case of methemoglobinemia, the results of these tests can be misleading. Pulse oximetry can give the clinician a false sense of security despite the presence of increasing methemoglobin levels. The reason for this dilemma stems from the technique used to determine O_2 saturation in pulse oximetry. A pulse oximeter gauges light absorbance at two wavelengths: 660 and 940 nm.[9,10] O_2 saturation is determined by the ratio of absorbance at these two wavelengths (660 and 940 nm). MHb absorbs light almost equally at both 660 and 940 nm. Therefore, at 100% MHb in the blood, the absorbance ratio is approximately 1.0, which corresponds to an 85% O_2 saturation reading by pulse oximetry. In reality, when MHb levels reach 30% to 35%, the light absorbance reaches a plateau and the pulse oximeter reading becomes stable in the 82% to 86% range, regardless of rising MHb levels.[9,10] As a consequence, pulse oximetry is a poor indicator of the actual percentage of MHb in the blood and of tissue oxygenation in patients with methemoglobinemia.

Arterial blood gas values can also be misleading. The arterial Po_2 is a measure of dissolved oxygen and does not directly correlate with oxygen molecules bound to hemoglobin. This explains why patients with life-threatening methemoglobinemia may have normal Po_2 values. The hemoglobin O_2 saturation level may be unreliable, as an arterial blood gas analyzer calculates this level from the pH and Pco_2 values, using the Henderson-Hasselbach equation for serum bicarbonate and standardized oxygen-hemoglobin dissociation curves.[7,8] This calculation assumes the presence of normal hemoglobin. The presence of MHb shifts the oxygen-hemoglobin dissociation curve to the left, resulting in false elevations of the O_2 saturation levels calculated by the arterial blood gas analyzer. Co-oximetry, which measures light absorbance at four different wavelengths, using spectrophotometry, is the most accurate way of measuring MHb levels. Each of the four wavelengths corresponds to absorbance characteristics of deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and hemoglobin.[11] A peak absorbance of light at 630 nm characterizes MHb. Combined co-oximetry and blood gas analysis machines measure oxygen saturation values based on all four types of hemoglobin and, therefore, are more accurate. It is important to specifically request a MHb level so that the blood may be processed in a co-oximeter, as MHb levels are not routinely performed on arterial blood gas analyzers.

Two bedside tests can be used to diagnose methemoglobinemia. The first test distinguishes between MHb and deoxyhemoglobin. Blood that is saturated with MHb appears chocolate brown, whereas deoxyhemoglobin appears dark red to violet. The test involves placing one to two drops of the patient's blood on a piece of white filter paper. When exposed to oxygen, deoxyhemoglobin will brighten in color whereas MHb will remain chocolate brown. Blowing 100% oxygen over the sample will speed up the reaction. The second bedside test distinguishes between sulfhemoglobin and MHb. MHb reacts with cyanide to form cyanomethemoglobin, a bright-red compound. Sulfhemoglobin, which has a similar chocolate-brown appearance, does not react with cyanide. The addition of potassium cyanide (Drabkin's reagent) turns MHb bright red but does not alter sulfhemoglobin.[12]

Management When the diagnosis of symptomatic methemoglobinemia is made, an infusion of methylene blue should be initiated immediately. Methylene blue is usually provided as a 1% solution (10 mg/mL), and 1 to 2 mg/kg (0.2 mL/kg of a 1% solution) should be infused intravenously over a 3- to 5-minute interval. An additional dose of 1 mg/kg may be repeated after 30 minutes if the methemoglobinemia does not resolve.[1] Methylene blue should reduce the MHb levels significantly within an hour.

Our patients were also given 2 gm of ascorbic acid as an additional antioxidant.[13,14]

An infusion of dextrose may be used in conjunction with methylene blue, as it up-regulates the glycolytic cycle—a major source of NADH in erythrocytes (Fig 2). Dextrose is also necessary to form NADPH via the pentose phosphate pathway. Methylene blue interacts with NADPH to form leukomethylene blue, which converts MHb back to hemoglobin.[1,15] Wright et al[1] suggest that maintenance amounts of dextrose should be provided for normoglycemic patients and that standard dextrose therapy should be administered to hypoglycemic patients. Olson and McEvoy[16] gave methylene blue, 80 mg as a 1% solution in 5% dextrose in water, infused over 20 minutes, after their patient developed methemoglobinemia in response to topical local anesthetic. We did not administer dextrose to either of our patients, as the benefits of its routine use have not been established.

The patient should be monitored for complications of methylene blue therapy. Paradoxically, excessive doses of methylene blue may cause methemoglobinemia if it is not converted to leukomethylene blue at an adequate rate. Patients with glucose-6-phosphate dehydrogenase deficiency are at particular risk for both a suboptimal response to methylene blue and an overdose, as they cannot produce sufficient NADPH. Finally, patients with methemoglobinemia caused by drugs such as dapsone, benzocaine, and aniline dyes may initially respond to methylene blue therapy and then experience rebound methemoglobinemia 4 to 12 hours later.[14,17] We did not observe this rebound effect in our second patient, in whom the methemoglobinemia was temporally related to benzocaine administration.

Methemoglobinemia, although rare, should be included in the differential diagnosis of cyanosis with respiratory distress, especially in critically ill patients with known exposure to oxidizing agents such as nitroglycerin and benzocaine. It is a potentially life-threatening condition that can be diagnosed by using bedside tests and co-oximetry. Treatment with methylene blue and adjuvants such as dextrose and ascorbic acid should be initiated promptly.

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