A Puzzling Case of Methemoglobinemia in the Intensive Care Unit

Adam S. Pasternack, DO

Physicians use anesthetic drugs during hospital and office-based procedures, and these drugs are widely available to the public in multiple over-the-counter preparations. Along with various other classes of medications, anesthetic drugs may cause life-threatening methemoglobinemia. This article describes a case in which a patient developed methemoglobinemia after the topical anesthetic Cetacaine (Cetylite Industries, Inc., Pennsauken, NJ) was applied to her throat. The effects of methemoglobin on the accuracy of arterial blood gas (ABG) analysis and pulse oximetry may confound a diagnosis of methemoglobinemia. Its occurrence also may be vastly underdiagnosed.

CASE PRESENTATION

History

A 47-year-old unemployed white woman presented to the emergency department after developing fever, shortness of breath, cough productive of white sputum, and right lateral chest pain exacerbated by coughing and deep inspiration.

The patient's past medical history was significant only for an unspecified psychiatric illness. Her current medications included quetiapine 100 mg twice daily and benztropine mesylate 1 mg daily. She had no known drug allergies. She admitted to a 35 pack-year smoking history but denied any alcohol or illicit drug use. Family history was noncontributory.

Physical Examination

On review of systems, the patient denied nausea, vomiting, diarrhea, abdominal pain, constipation, dizziness, syncope, or the presence of any new skin rashes. On physical examination, the patient's vital signs revealed a temperature of 101.6° F (38.7°C), a pulse rate of 128 bpm, a blood pressure of 125/73 mm Hg bilaterally, respirations of 30 breaths/min, and an oxygen saturation of 92% by pulse oximetry on room air. The patient was alert; oriented to person, place, and time; and appeared to be in only mild respiratory distress. Head and neck examination was significant for dry mucous membranes, poor dentition, and left anterior cervical adenopathy. Her heart was tachycardic but regular without murmur or ectopy. Lung auscultation revealed right middle and lower lobe egophony, whispered pectoriloquy, dullness to percussion, and inspiratory/expiratory rales and rhonchi. Accessory muscle use was noted as well as tenderness on palpation of the right middle and lower lung fields. Abdominal and extremity examinations were unremarkable. A rectal examination was refused.

Laboratory Studies

Laboratory studies were obtained in the emergency department. A complete blood count showed a leukocyte count of $26.4 \times 10^3/\text{mm}^3$ (normal range, 4.5–$11.0 \times 10^3/\text{mm}^3$), hemoglobin of 10.8 g/dL, hematocrit of 33.1%, platelet count of $482 \times 10^3/\text{mm}^3$ (normal range, 150–$450 \times 10^3/\text{mm}^3$), and 16% absolute bands. A chemistry panel revealed a sodium level of 135 mEq/L, potassium level 3.9 mEq/L, chloride level 92 mEq/L, carbon dioxide level of 26 mEq/L, blood urea nitrogen level of 7.0 mg/dL, serum creatinine of 0.6 mg/dL, and a glucose level of 95 mg/dL. Urinalysis, a coagulation panel, and electrocardiogram were all within normal limits. Blood and sputum cultures were obtained and subsequently were found to have no growth. An ABG revealed a pH of 7.46, $P\text{CO}_2$ of 39 mm Hg, $P\text{O}_2$ of 105 mm Hg, HCO_3^- of 28 mEq/L, and an oxygen saturation ($S\text{aO}_2$) of 98% on 6 L of oxygen via nasal cannula. A chest radiograph revealed a right lower lobe infiltrate with a moderate pleural effusion. A right lateral decubitus film further revealed loculations within the effusion. The left lung was well aerated and free of active inflammatory disease.

Hospital Course

The patient was admitted to the general medical floor with a diagnosis of right lower lobe pneumonia with a

At the time of submission, Dr. Pasternak was a senior family practice resident, Mercy Suburban Hospital, Norristown, PA. He currently is an associate family physician, Oxford Circle Family Medicine, Philadelphia, PA.

loculated pleural effusion. Intravenous saline, oxygen via nasal cannula, and intravenous antibiotics (ceftriaxone sodium and azithromycin) were initiated. The patient's outpatient medications also were continued.

On hospital day 2, a chest computed tomogram revealed a large, loculated effusion on the right with compression atelectasis and increased density of the anterior trachea and subcarinal region consistent with adenopathy. Several days later, a right thoracoscopy with decortication and placement of a 32-F chest tube was performed under general anesthesia in the operating room. Cultures of the pleural fluid (including acid-fast bacilli), fungal assays, cytology, and pathology specimens were significant only for inflammation consistent with an empyema.

The patient was transferred to the recovery room while still intubated because the anesthesiologist observed laryngeal edema when the endotracheal tube was switched to a single-lumen tube. She remained intubated for several days in the intensive care unit, where she continued to be weaned gradually from mechanical ventilation.

On postoperative day 4, the in-house resident was called to evaluate the patient at the request of the intern on call. The patient's pulse oximetry had dipped suddenly into the low 70s, and the patient appeared cyanotic. The resident rechecked the pulse oximetry lead and it appeared to be working properly. The patient's other vital signs remained stable. Lung auscultation revealed occasional right lower lobe rhonchi. An immediate ABG sampling appeared chocolate brown and revealed a pH of 7.59, P_{CO_2} of 36 mm Hg, P_{O_2} of 378 mm Hg, HCO_3^- of 31 mEq/L, and an Sa_{O_2} of 100% on an assist control setting of 12, fractional concentration of oxygen in inspired gas (Fi_{O_2}) of 100%, and tidal volume of 520 mL. An immediate chest radiograph showed the endotracheal tube to be in the proper position, without pneumothorax, and there was little change from the previous film. A repeat arterial blood sample obtained under the supervision of the resident again appeared dark brown but clearly had been obtained from a pulsatile radial artery. Analysis of the new arterial blood sample revealed a pH of 7.61, P_{CO_2} of 29 mm Hg, P_{O_2} of 301 mm Hg, HCO_3^- of 30 mEq/L, and Sa_{O_2} of 100%.

A presumptive diagnosis of methemoglobinemia from an unknown source was made and the patient's benztropine mesylate, haloperidol, and metoclopramide orders were immediately discontinued. Co-oximetry revealed a methemoglobin concentration of 28% (normal, 0.4%–1.5%). Because methylene blue was not available, the tidal volume on the ventilator was decreased to 400 mL and a transfusion of 1 unit of packed erythrocytes was given to correct the patient's anemia and improve oxygenation. The patient's oxygen saturation and coloring returned to normal on the following day, and the patient continued to improve to the point where she successfully self-extubated 3 days later. She subsequently was discharged on oral antibiotics and was scheduled for follow-up at the hospital's family practice center 5 days later.

Approximately 1 week after the event in the intensive care unit, glucose-6-phosphate dehydrogenase (G6PD) and reduced nicotinamide dinucleotide (NADH)-methemoglobin reductase levels that had been ordered at the time of the event were discovered to be normal. No personal or family history of cyanosis or adverse reactions to medicines could be ascertained. No abnormal hemoglobin types were detected by electrophoresis. It was later discovered that a nurse had administered 2 "quick" sprays of topical Cetacaine to the patient's posterior pharynx to relieve the discomfort of the endotracheal tube. The crisis began within 1 hour of administration.

DISCUSSION

Cetacaine (a proprietary formulation consisting of butamben, tetracaine, benzocaine, benzalkonium chloride, and cetyldimethylethylammonium bromide) is a topical anesthetic commonly used for a variety of procedures, including endoscopy, endotracheal intubations, and dental procedures. Although Cetacaine often is used without regard for systemic adverse reactions, it has been known to cause life-threatening methemoglobinemia and, for these reasons, could easily be overlooked as the cause of a patient's clinical deterioration.[1]

Although methemoglobinemia has complicated topical anesthesia for many years, it has not been considered a common event. Since the condition was first documented by Bernstein in 1950, local anesthetics had been implicated as its cause in fewer than 100 cases as of 1994.[2] It is likely that methemoglobinemia is more common than originally thought and is probably underdiagnosed.

Etiology and Pathophysiology of Methemoglobinemia

Methemoglobinemia is a condition that occurs when the ferrous ion (Fe^{2+}) in the porphyrin ring of hemoglobin is oxidized to the ferric state (Fe^{3+}) and is unable to bind oxygen. The causes of methemoglobinemia may be categorized as either hereditary or acquired. Hereditary methemoglobinemia usually is due to a deficiency of NADH-methemoglobin reductase, an erythrocyte enzyme that normally maintains

Table 1. A Partial List of Medications Associated with Methemoglobinemia

Amyl nitrate

Benzocaine

Dapsone

Fentanyl

Lidocaine

Nitroglycerin

Prilocaine

Procaine

Pyridium

Sulfamethoxazole

Sulfisoxazole

Table 2. Manifestations of Methemoglobinemia

Methemoglobin Level*	Symptoms/Signs
< 10%	None
10%–20%	Cyanosis
> 30%	Weakness, tachycardia, nausea
> 55%	Vomiting
	Lethargy, dizziness, stupor
	Heart failure, respiratory arrest, seizure, coma
> 70%	Death

Note: Symptoms/signs may appear sooner or more intense with lower methemoglobin levels if concomitant anemia, myocardial damage, or abnormal hemoglobins are present.

*Proportion of methemoglobin to total hemoglobin.

methemoglobin levels within the normal range. This autosomal recessive disease is more common in Alaskan or Inuit Native Americans and causes an increased susceptibility to oxidative stress from drugs or toxins.[3] Hemoglobin M is another form of congenital methemoglobinemia characterized by an abnormal hemoglobin molecule. Patients with either hereditary form may be cyanotic but nonetheless symptom free.[4]

Acquired methemoglobinemia results from exposure to substances, which cause the rate of methemoglobin formation to exceed its rate of reduction. This mechanism is particularly relevant in pediatric and elderly populations. Neonates express low levels of functional NADH-methemoglobin reductase, whereas the elderly have a less efficient form of NADH-methemoglobin reductase.[5] In fact, more than half of the methemoglobinemia cases reported in the literature involved infants and the elderly.[2]

In clinical practice, the most common medications associated with methemoglobinemia are nitrite (after conversion from nitrates to nitrites in the gut by bacteria) and aniline derivatives.[6] The aniline ring is found in many commonly available drugs, such as acetaminophen, all the sulfones and sulfonamides, and virtually all the local anesthetics (**Table 1**). Nearly all topical anesthetic preparations have been associated with methemoglobinemia; however, benzocaine is the most commonly implicated and is the largest component of Cetacaine formulations.[7]

Initially, the most serious aspect of methemoglobinemia is not that a certain portion of the hemoglobin molecule cannot bind oxygen but rather its effect on the remaining oxidized heme moieties. A left shift in the hemoglobin dissociation curve is produced and the total oxygen available for delivery to tissues is greatly decreased.[8] The manifestations of methemoglobinemia appear to correlate with increases in the proportion of methemoglobin to total hemoglobin (reflecting tissue hypoxia) (**Table 2**).[9]

Diagnosis of Methemoglobinemia

Methemoglobinemia should be suspected immediately in any person exposed to certain offending agents who has central cyanosis and a low pulse oximetry unresponsive to increased oxygen administration. ABG sampling often will show a characteristic chocolate brown color that does not turn red on exposure to air, a high Po_2, and Sao_2 nearing 100%. The presence of elevated methemoglobin levels assures the diagnosis.

When trying to diagnose methemoglobinemia and assess the patient's clinical status, pulse oximetry readings will often relay confusing information. Pulse oximeters overestimate oxygen saturation of blood by an amount proportional to the amount of methemoglobin present. As methemoglobin levels increase, oxygen saturation readings decrease to 85%.[10] Pulse oximeters measure tissue absorbance at 660 nm and 940 nm, and information is yielded on the differential light absorption of the 2 wavelengths. Methemoglobin has a similar absorbance pattern to that of hemoglobin and exceeds that of oxyhemoglobin at 660 nm. Interestingly, methemoglobin also has a greater absorbency of light than both hemoglobin and oxyhemoglobin at 940 nm. Thus, when there is increased methemoglobin in the blood, light absorbance is increased at both wavelengths and the differential is altered. Co-oximetry, which detects concentration of both methemoglobin and oxyhemoglobin, determines

the true percentage of hemoglobin saturation and is considered the test of choice.

Treatment of Methemoglobinemia

The goal in the treatment of methemoglobinemia is to restore the original oxygen-carrying and unloading capability of the hemoglobin molecule. Management should include supportive therapy (eg, supplemental oxygen administration) and close monitoring of neurologic and cardiopulmonary status. Foxworth et al feel that only close observation is necessary in asymptomatic patients with methemoglobin levels less than 30%.[11] As the half-life of methemoglobin is approximately 55 minutes, most cases resolve in 72 hours following clearance of the offending agent.

When methemoglobin levels rise above 30%, the patient is symptomatic, or there is coexisting anemia and decreased cardiac output, other treatment usually is warranted. The treatment of choice in more serious cases is methylene blue. Typical doses of 1 to 2 mg/kg body weight are given intravenously over 5- to 10-minute period and may be repeated 20 minutes later if necessary. Methylene blue acts as a cofactor for reduced nicotinamide adenine dinucleotide phosphate (NADPH)-methemoglobin reductase, greatly increasing the reduction of methemoglobin. Administration of methylene blue at levels greater than 7 mg/kg may be associated with dyspnea, tremors, and hemolytic anemia. Patients with G6PD deficiency who have decreased production of NADPH will not respond to treatment with methylene blue. In the case patient, methemoglobin levels were low, the patient was essentially asymptomatic, and methylene blue was not readily available. We decided to transfuse one unit of packed erythrocytes, believing that the offending agent would be flushed from her system, and that the blood would essentially improve the anemia (and therefore, the oxygen-carrying capacity of her blood).

CONCLUSION

This case report highlights many lessons to keep in mind about the dangers of commonly used topical anesthetics and their association with methemoglobinemia. First, a drug applied topically has the ability to create serious adverse reactions. It must further be kept in mind that associated factors, such as excessive absorption due to breaks in the mucosal barrier (as occurs in gastritis and eczema) or one too many sprays, may influence these adverse reactions.[5] Secondly, when topical anesthetics are applied to the mouth, nose, or throat, the patient should be asked to spit out excess solution to avoid increased absorption because there

seems to be no standard on how long and hard a syringe plunger is to be depressed. Varying amounts of medication may increase the likelihood of adverse reactions such as methemoglobinemia. Studies by the manufacturers of topical anesthetics to create a more uniform standard may be warranted. Third, physicians need to explain to patients that methemoglobinemia is a possibility with procedures involving topical anesthesia.

Finally, it is an important lesson for physicians to follow their clinical suspicions even when increasingly advanced laboratory and diagnostic tools contradict each other. As was seen in the patient described above, increased methemoglobin levels compromised oxygen delivery, although she essentially was asymptomatic. Also, her pulse oximetry values were drastically incorrect even though the machine was functioning the way it was designed to. The usefulness of pulse oximetry and ABG analysis is greatly decreased in the diagnosis of methemoglobinemia without the aid of co-oximetry or placing a drop of a patient's blood on a piece of blotter paper to check for the presence or absence of a color change. **HP**

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