

Benzocaine-Induced Methemoglobinemia During Transesophageal Echocardiography

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Acquired or toxic methemoglobinemia is an uncommon complication of topically administered anesthetic agents in patients of all ages—but particularly in pediatric and elderly patients. This report describes a case of acquired methemoglobinemia that occurred after benzocaine spray was applied orally to a 69-year-old white woman weighing 175 lb who was undergoing transesophageal echocardiography. Patient care was successfully managed. Fundamental concepts regarding methemoglobinemia are also reviewed to heighten physician awareness of this potentially life-threatening complication associated with the application of common topical anesthetic agents.

Benzocaine spray is commonly used for local, topical anesthesia of mucous membranes before a variety of procedures performed at physicians' and dentists' offices or in hospitals on an outpatient basis. This medication is also widely available to the public in several over-the-counter formulations.

This article describes a case in which benzocaine was applied to a patient's throat using Hurracaine topical anesthetic aerosol spray (20% benzocaine) (Beutlich LP Pharmaceuticals, Waukegan, Ill) in preparation for transesophageal echocardiography.

Benzocaine-induced methemoglobinemia is an uncommon occurrence in clinical practice, and though few reports of benzocaine-induced methemoglobinemia are available in the English-language cardiology literature, knowledge of this potentially life-threatening condition is essential for clinicians performing routine procedures in which topically administered anesthetic agents are used.

When untreated, methemoglobinemia can lead to major cardiopulmonary compromise, neurologic sequela, and even death. Physicians who perform procedures involving the application of topical anesthesia must be aware of these potential adverse effects.

Report of Case

On July 1, 2003, a 69-year-old white female patient weighing 175 lb presented at Mercy Medical Center in Mason City, Iowa, for a transesophageal echocardiogram to assist in the evaluation of intracardiac thrombus in preparation for synchronized cardioversion.

The patient had a history of ischemic heart disease, post-coronary artery bypass surgery, hypertension, postmenopausal hyperlipidemia, type 2 diabetes mellitus, obesity, and symptomatic atrial fibrillation that was believed to be recent though the specific time of onset was unclear. She was a nonsmoker and reported an unconfirmed allergy to diazepam. The patient was currently taking the following medications: amiodarone, aspirin, enoxaparin, glyburide, levothyroxine sodium, metoprolol succinate, niacin as a dietary supplement, rabeprazole sodium, simvastatin, and warfarin sodium. Her physical examination preprocedure was notable only for atrial fibrillation, and her oxygen saturation level was 99% by room-air pulse oximetry. Previous laboratory studies were within normal ranges, and an electrocardiogram performed the previous day demonstrated atrial fibrillation with a controlled heart rate and nonspecific changes.

During transesophageal echocardiogram, the patient's oxygen saturation level was measured at 90% by room-air pulse oximetry, so the oxygen level (as delivered by nasal cannula) was adjusted to a saturation level of 92%. Results from the procedure were within normal limits; therefore, synchronized cardioversion was completed and was successful.

At 15 minutes postprocedure, however, the patient developed central cyanosis, and her oxygen saturation level suddenly decreased to 70%. Her lung fields were clear and she did not exhibit chest pain or arrhythmia. Vital signs were stable. An arterial blood sample was taken and appeared chocolate in color (Figure 1).

Methemoglobinemia was suspected and then confirmed by arterial blood gases that were obtained using co-oximetry. Oxygen was administered at 100% by mask. Arterial blood gases were taken with pH, 7.47; P_{CO₂}, 33.1; P_{O₂}, 293; oxygen saturation, 56.7%; and methemoglobin at 41.1% of total hemoglobin. Methylene blue, 2 mg, was delivered intravenously, and, as a result, one hour later, methemoglobin levels had decreased to 18.4% with an improvement in the symptoms of cyanosis. Two hours later, methemoglobin levels were at 4% of total hemoglobin.

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Figure 1. An arterial blood sample was taken and appeared chocolate in color.

The patient was admitted to inpatient care and was observed overnight. The next morning, her methemoglobin level had decreased to 0.9%. The rest of her hospitalization (2 days total) was uneventful, and she was discharged that day with no further complications.

Review of Literature

Methods

A search of published literature was performed using the National Library of Medicine's MEDLINE database. The following search terms were used: *methemoglobinemia*, *benzocaine*, *oxygen delivery*, and *methylene blue*.

Discussion

Acquired methemoglobinemia is thought to be a complication of benzocaine, a topical anesthetic commonly used for a variety of procedures, including dental procedures, endoscopy, and endotracheal intubation. Since the condition was first documented in a 1950 case report by Bernstein,¹ fewer than 100 cases were reported as of 1994.

In addition to benzocaine products, various other chemicals and medications can accelerate the formation of methemoglobin, such as acetanilide, aniline dyes, antimalarial agents, flutamide, metoclopramide hydrochloride, nitrate and nitrite compounds, nitric oxide (inhaled), phenacetin, phenazopyridine hydrochloride, phenytoin, probenecid, sodium nitroprusside, and sulfonamides. It is thought that some of these agents may cause methemoglobinemia indirectly, by the for-

Amyl nitrite
Benzocaine
Dapsone (diaminodiphenylsulfone)
Fentanyl citrate
Lidocaine
Nitroglycerin
Phenazopyridine hydrochloride
Prilocaine hydrochloride
Procaine
Sulfamethoxazole
Sulfisoxazole (sulfafurazole)

Figure 2. Methemoglobinemic agents: A partial list of medications associated with methemoglobinemia.

mation of oxygen-free radicals during their breakdown, rather than directly from the chemical or medication itself.²

None of the other medications the patient was then taking—except the benzocaine—has been associated with methemoglobinemia. The underlying mechanism of benzocaine-induced methemoglobinemia is not clear, but it appears to involve direct oxidation of the heme iron.

■ Etiologic Process and Pathophysiology

Methemoglobinemia refers to the presence of an elevated, circulating fraction of methemoglobin within the erythrocytes. Normal hemoglobin contains an iron molecule that exists in the divalent ferrous state (Fe^{2+}). Methemoglobin results from the conversion of the iron ferrous ion (Fe^{2+}) into a trivalent ferric (Fe^{3+}) state, making it unable to bind oxygen (ie, unable to carry oxygen and carbon dioxide).³ Methemoglobinemia increases the affinity of normal hemoglobin for oxygen, thereby hindering oxygen release in the tissue. This condition results in severe cyanosis out of proportion to the degree of respiratory distress and a dark pigment that causes blood to appear chocolate in color. Methemoglobin is continuously formed in red blood cells and is reduced to deoxyhemoglobin by nicotinamide adenine dinucleotide phosphate (NADPH)-dependent methemoglobinemia. In a normal physiologic state, the methemoglobin level is less than 2% of normal hemoglobin.⁴

Methemoglobinemia can be either hereditary or acquired (toxic). Hereditary methemoglobinemia is caused by a deficiency of NADPH methemoglobin reductase, an erythrocyte enzyme that usually maintains methemoglobin levels within the normal range. This autosomal recessive disease is most common in the Inuit population and in Alaskan Native Americans. Hemoglobin M is another form of congenital methe-

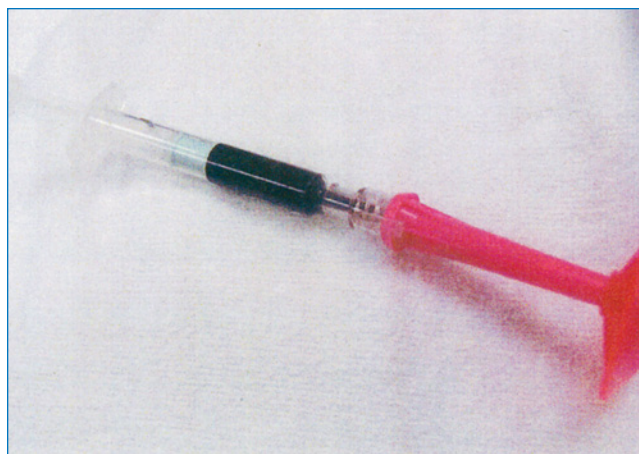


Figure 3. A blood sample taken from a patient with methemoglobinemia has a distinct chocolate color.

methemoglobinemia characterized by an abnormal hemoglobin molecule.

Acquired methemoglobinemia results from exposure to noxious substances that cause the rate of methemoglobin formation to exceed its rate of reduction. This cause is particularly relevant when clinicians are treating pediatric and elderly patients.⁵ In clinical practice, the most common medications associated with methemoglobinemia are linked to an alanine ring that is found in many over-the-counter medications and in all anesthetics (Figure 2).⁶

Although nearly all topical anesthetic preparations have been associated with methemoglobinemia, benzocaine is the most common and is the largest component of Cetacaine topical anesthetic (benzocaine/butamben/tetracaine hydrochloride) (Cetylite Industries, Pennsauken, NJ) formulations.⁶

■ Diagnosis

Methemoglobinemia should be immediately suspected in any patient who has central cyanosis and a decrease in oxygen saturation level that develops after the administration of benzocaine for topical anesthesia.

Administration of high concentrations of oxygen via nasal cannula in these patients typically does not correct the decrease in oxygen saturation levels. In patients to whom topical benzocaine has been administered, if a decrease in oxygen saturation cannot be attributed to cardiac or pulmonary problems—as determined by physical examination—arterial blood gases should be checked, including the methemoglobin level. A blood sample taken from a patient with methemoglobinemia has a distinct chocolate color (Figure 3).

Other signs and symptoms associated with methemoglobinemia are described in Table. Even in severe cases of methemoglobinemia, the directly measured P_{O2} level is usually normal, because it is the arterial P_{O2} measures that will show dissolved oxygen in the blood. As a result, laboratory

studies that calculate oxygen saturation from the dissolved oxygen values have been known to report normal oxygen saturation even in the presence of a markedly impaired oxygen-carrying capacity.^{7,8} Therefore, co-oximetry is the diagnostic test of choice for methemoglobinemia, because this testing method measures both the concentration of methemoglobin and oxyhemoglobin.

■ Treatment

When a patient is diagnosed with methemoglobinemia, initial attention should be directed to improving oxygen delivery. Treatment for symptomatic methemoglobinemia (typically with methemoglobin levels of >30%) includes administration of methylene blue, delivered intravenously, 1 mg to 2 mg per kg of body weight, over five minutes. This treatment may be repeated if the methemoglobinemia does not resolve within 30 minutes.

Methylene blue (methylthionine chloride) itself is an oxidant. The metabolic product of methylene blue, called leukomethylene blue, is the reducing agent and provides an artificial electron acceptor via the NADPH-dependent pathway.^{9,10}

Patients with methemoglobinemia who are asymptomatic should be admitted to inpatient care and observed to ensure

Table Methemoglobinemia Common Signs and Symptoms by Methemoglobin Level*	
Signs and Symptomst	Methemoglobin Level (%)*‡
Coma	>55
Cyanosis, acquired methemoglobinemic	10 to 20
Death	>70
Dizziness	>55
Heart failure	>55
Lethargy	>55
Muscle weakness	>30
Nausea	>30
None	<10
Respiratory arrest	>55
Seizure	>55
Stupor	>55
Tachycardia	>30
Vomiting	>55

* **Source:** Pasternack AS. A puzzling case of methemoglobinemia in the intensive care unit. *Hosp Physician*. 2004;30–32,38.
 † Other signs and symptoms include: ataxia, drowsiness, dyspnea, fatigue, and headache. Patients with methemoglobinemia may have signs and symptoms that appear sooner or grow more intense with lower methemoglobin levels if the condition is concomitant with anemia or if myocardial damage or abnormal hemoglobins are present.
 ‡ Proportion of methemoglobin to total hemoglobin.

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that levels of methemoglobin have decreased. Most cases of methemoglobinemia resolve within 24 to 72 hours. If levels of methemoglobin persistently increase—as may be the case if continued absorption of the responsible agent occurs—repeated dosing of methylene blue may be necessary. Dosing should not exceed 7 mg per kg, however, because higher doses of methylene blue may result in dyspnea, tremors, or hemolytic anemia.

If patients respond poorly to methylene blue, as seen in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency, or in severe cases of methemoglobinemia (methemoglobin levels of >70%), exchange transfusions or hemodialysis may be necessary.³ Patients with a G6PD deficiency who show a decreased production of NADPH will not respond to treatment with methylene blue.^{3,7} In these cases, exchange transfusions or hemodialysis should be begun immediately.

Comment

This report of case and literature review highlight the potentially life-threatening adverse effects of commonly used topical anesthetics, which may result in benzocaine-induced methemoglobinemia in some patients. Cyanosis in the absence of cardiopulmonary symptoms should alert the physician to the possibility of an intraerythrocytic hemoglobin abnormality, in particular methemoglobinemia.

The diagnosis is mainly clinical—based the presence of chocolate-colored blood and cyanosis that remains unresponsive to oxygen therapy—with high index of suspicion.

Diagnosis should be confirmed by co-oximetry. The treatment of choice is low-dose, intravenous methylene blue, which should be made readily available at medical and dental facilities where topical anesthetics are frequently used.

References

1. Bernstein BM. Cyanosis following use of anesthetic; case report. *Rev Gastroenterol*. 1950;17:123.
2. Ferraro-Borgida MJ, Mulhern SA, DeMeo MO, Bayer MJ. Methemoglobinemia from perineal application of an anesthetic cream. *Ann Emerg Med*. 1996;27:785–788.
3. Novaro GM, Aronow HD, Militello MA, Garcia MJ, Sabik EM. Benzocaine-induced methemoglobinemia: experience from a high-volume transesophageal echocardiography laboratory. *J Am Soc Echocardiogr*. 2003;16:170–175.
4. Ellenhorn MJ. Respiratory toxicology. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2nd ed. Baltimore, Md: Lippincott Williams & Wilkins; 1996:1496–1499.
5. Bunn HF. Disorders of hemoglobin. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, et al, eds. *Harrison's Principles of Internal Medicine*. 12th ed. New York, NY: McGraw-Hill Health Profession Division; 1991:1543–1552.
6. Khan NA, Kruse JA. Methemoglobinemia induced by topical anesthesia: a case report and review. *Am J Med Sci*. 1999;318:415–418.
7. Rodriguez LF, Smolik LM, Zbehlik AJ. Benzocaine-induced methemoglobinemia: report of a severe reaction and review of the literature. *Ann Pharmacother*. 1994;28:643–649.
8. Barker SJ, Tremper KK, Hyatt J. Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. *Anesthesiology*. 1989;70:112–117.
9. Sass MD, Caruso CJ, Axelrod DR. Mechanism of the TPNH-linked reduction of methemoglobin by methylene blue. *Clin Chim Acta*. 1969;24:77–85.
10. DiSanto AR, Wagner JG. Pharmacokinetics of highly ionized drugs. II. Methylene blue—absorption, metabolism, and excretion in man and dog after oral administration. *J Pharm Sci*. 1972;61:1086–1090.