

Benzocaine-Induced Methemoglobinemia

A Potentially Fatal Complication of Transesophageal Echocardiography

Rajesh Sachdeva, MD
Jaime G. Pugada, MD
Linda R. Casale, MD
Jay L. Meizlish, MD
Stuart W. Zarich, MD

We describe the cases of 2 patients who developed benzocaine-induced methemoglobinemia after the administration of benzocaine as premedication for transesophageal echocardiography. The use of intravenous methylene blue resolved the cyanosis in both patients. Physicians who perform procedures involving the application of topical anesthesia need to be aware of this side effect to prevent morbidity and mortality. (*Tex Heart Inst J* 2003;30:308-10)

Benzocaine spray is a local anesthetic commonly used for topical anesthesia of mucous membranes before endoscopic procedures. Benzocaine-induced methemoglobinemia is a rare complication associated with topical anesthesia and can be life-threatening.¹⁻⁷ We present 2 cases of methemoglobinemia caused by topical benzocaine spray used as premedication for transesophageal echocardiography. Few such reports of benzocaine-induced methemoglobinemia are available in the English-language cardiology literature. Physicians who perform procedures involving the application of topical anesthesia need to be aware of this side effect to prevent morbidity and mortality.

Case Reports

Patient 1

April 2001, a 72-year-old man presented at our institution for transesophageal echocardiography for evaluation of endocarditis. He had a history of hypertension, coronary artery disease, and recent repair of a mycotic thoracoabdominal aortic pseudoaneurysm complicated by *Streptococcus viridans* bacteremia. Before transesophageal echocardiography, the patient's oxygen saturation by pulse oximetry was 97% on room air. Topical 20% benzocaine spray was administered to achieve oropharyngeal anesthesia. During the procedure, the patient's oxygen saturation fell to 86% on pulse oximetry, for which the supplemental oxygen was increased to 6 L/min by nasal cannula without improvement.

Within a few minutes, the patient's saturation decreased to 80% on 10 L/min nasal cannula and he became cyanotic. He was placed on 60% oxygen supplementation by face mask but his oxygen saturation continued to fall without associated symptoms. Initially, the blood pressure was 150/80 mmHg, and the heart rate was 91 beats/min. Methemoglobinemia was suspected, and arterial blood gas performed by CO-oximetry on 6 L nasal cannula showed pH, 7.42; PO₂, 248; PCO₂, 34; oxygen saturation, 99%; and methemoglobin, 41.8% of total hemoglobin. The patient was treated with methylene blue, 2 mg/kg intravenously. The result of a repeat methemoglobin test 2 hours later was 2.8%, with resolution of the cyanosis.

Patient 2

In June 2001, a 65-year-old man presented at our institution with several days' history of shortness of breath and dyspnea on exertion. He had previously undergone aortic valve replacement: the 1st prosthesis was a St. Jude valve in 1991, which was subsequently replaced with a porcine heterograft in 1997. He had atrial flutter. He had undergone left shoulder surgery in 2000, with discontinuation of oral anticoagulation.

Key words: Anesthetics, local/adverse effects; benzocaine/adverse effects; cyanosis/chemically induced; echocardiography, transesophageal; methemoglobinemia/chemically induced/diagnosis/etiology/therapy; methylene blue/therapeutic use

From: Division of Cardiology, Department of Medicine, Bridgeport Hospital, Yale School of Medicine, Bridgeport, Connecticut 06610

Address for reprints: Stuart W. Zarich, MD, Chief, Section of Cardiology, Bridgeport Hospital, Yale School of Medicine, 267 Grant Street, P.O. Box 5000, Bridgeport, CT 06610

E-mail: pszari@bpthosp.org

© 2003 by the Texas Heart® Institute, Houston

At the current presentation, the patient's chest radiograph showed bilateral congestion, and he was also found to be in atrial fibrillation with rapid ventricular response. He was admitted to the hospital and treated with furosemide for diuresis and diltiazem to control heart rate, and his condition stabilized. Cardioversion was planned to revert his arrhythmia to sinus rhythm. Transesophageal echocardiography was performed to rule out atrial thrombus. The initial oxygen saturation by pulse oximetry was 99% on a non-rebreather mask that had been placed for congestive heart failure. A 20% topical benzocaine spray was administered to the oropharynx before the procedure. The absence of an atrial thrombus was confirmed, and the sinus rhythm was restored by cardioversion at 200 joules.

Approximately 40 minutes after cardioversion, the patient became cyanotic, and his saturation decreased from 99% to 80% on the same non-rebreather mask. The blood pressure was 110/80 mmHg, with a heart rate of 80 beats/min and a respiratory rate of 22/min. He had neither chest pain nor worsening shortness of breath. At that point, congestive heart failure, pulmonary embolism, and aspiration were considered to be the most likely causes of desaturation. A new chest radiograph revealed no change from the previous study. Arterial blood gas by CO-oximetry revealed a pH of 7.44; PCO₂, 44%; PO₂, 394; and oxygen saturation, 99%. The methemoglobin level was 37%. After the diagnosis of methemoglobinemia was made, the patient received 1 mg/kg of intravenous methylene blue. Fifteen minutes later, his oxygen saturation had increased to 90% with resolution of the cyanosis.

Discussion

Methemoglobinemia refers to the presence of an elevated circulating fraction of methemoglobin within the erythrocytes. Methemoglobin is a dark pigment that causes blood to appear chocolate in color. Severe cyanosis out of proportion to the degree of respiratory distress and dark arterial blood suggest methemoglobinemia.⁸

Normal hemoglobin contains an iron molecule that exists in the divalent ferrous state. Methemoglobin results from the conversion of the iron to a trivalent ferric state. Methemoglobin is continuously formed in red blood cells and is reduced to deoxyhemoglobin by nicotinamide adenine dinucleotide-dependent (NADPH) methemoglobin reductase enzyme. Under normal physiologic circumstances, the methemoglobin level is below 2%.⁹ Methemoglobin is unable to bind and carry oxygen; therefore, high levels of methemoglobin result in functional anemia and disrupt oxygenation by 2 mechanisms. First, methemoglobin reduces the oxygen-carrying capacity of blood; second, the presence of oxidized iron changes the heme

tetramer in a way that reduces oxygen release in the tissues, thus shifting the oxyhemoglobin dissociation curve to the left, as in alkalosis.

Various chemicals and drugs can accelerate the formation of methemoglobin—for example, antimalarials (chloroquine, primaquine), nitrites or nitrates, inhaled nitric oxide, nitroprusside, sulfonamides, acetanilide, flutamide, metoclopramide, phenacetin, phenytoin, probenecid, chlorates, and phenazopyridine hydrochloride^{8,10}—by direct oxidation or indirect inhibition of NADPH. Neither of our patients was taking any of the above medications at that time. Possible predisposing factors for the development of methemoglobinemia include an excessive dose of one of the aforementioned agents, concomitant therapy with other agents known to cause this disorder, a break in the mucosal barrier, and partial or severe deficiency of the methemoglobin reductase enzyme.

The signs and symptoms of methemoglobinemia correlate with the amount of methemoglobin and the presence of underlying medical disease (predominantly anemia, coronary artery disease, and pulmonary disease). The symptoms are similar to those of hypoxemia. The half-life of methemoglobin is 55 minutes.¹¹ The onset of methemoglobinemia is usually within 20 to 60 minutes of drug administration. Normally, 5 g/dL of deoxyhemoglobin (compared with 1.5 g/dL [10%–15%] of methemoglobin) produces noticeable cyanosis.¹² Methemoglobin levels below 30% in a healthy person produce minimal symptoms (fatigue, lightheadedness, and headache) or none, whereas levels from 30% to 50% produce moderate depression of the cardiovascular and central nervous systems (weakness, headache, tachycardia, tachypnea, and mild dyspnea). Levels between 50% and 70% cause severe symptoms (stupor, bradycardia, respiratory depression, convulsions, dysrhythmias, and acidosis). Levels above 60% can be lethal, and levels above 70% usually are not compatible with life.⁹

Diagnostic suspicion of methemoglobinemia arises from the clinical findings. Even in severe cases of methemoglobinemia, the directly measured PO₂ level is usually normal, because the arterial PO₂ measures dissolved oxygen in blood. The dissolved oxygen in the blood is presumed to be in equilibrium with oxygen carried by hemoglobin in the red blood cells, which is not the case with methemoglobinemia. Laboratories that calculate oxygen saturation from the dissolved oxygen values will therefore report normal oxygen saturation in the setting of markedly impaired oxygen-carrying capacity. CO-oximetry is the diagnostic test of choice, because it measures the concentration of methemoglobin and oxyhemoglobin.

When a patient is diagnosed with methemoglobinemia, initial attention should be directed toward improving oxygen delivery—if necessary, with assisted

ventilation and 100% oxygen. Methylene blue is indicated as the best agent for treatment of drug-induced methemoglobinemia.¹³ Methylene blue acts as a reducing agent via the NADPH methemoglobin reductase pathway. The drug is thiazine dye with antiseptic and dose-dependent oxidative or reductive properties. Methylene blue, in low concentrations (recommended doses), is reduced in red blood cells and presumably in tissues, to leucomethylene blue.^{14,15} Leucomethylene blue reacts spontaneously with high concentrations of methemoglobin in blood, rapidly reducing methemoglobin to hemoglobin, even in the presence of oxygen.¹⁴ Leucomethylene blue also converts ferric iron back to the ferrous state and restores the oxygen-carrying capacity of hemoglobin. Cyanosis usually resolves within 15 to 30 minutes. Marked reduction in methemoglobinemia, usually by 50%, is seen within 30 to 60 minutes.^{7,10} However, when given in high doses, methylene blue oxidizes the ferrous iron of hemoglobin to ferric iron, resulting in methemoglobin production, thus intensifying the toxic methemoglobinemia. The usual dose of methylene blue is 1 to 2 mg/kg of 1% solution intravenously over 5 min. The same dose may be repeated within 1 hour if symptoms of hypoxia fail to subside.

In conclusion, cyanosis in the absence of cardiopulmonary symptoms should alert the physician to the possibility of an intraerythrocytic hemoglobin abnormality, especially methemoglobinemia. The diagnosis is mainly clinical, with chocolate-colored blood and cyanosis unresponsive to oxygen therapy. The diagnosis should be confirmed by CO-oximetry. The treatment of choice is low-dose intravenous methylene blue, which should be readily available in areas where topical anesthetics are frequently used.

References

1. Olson ML, McEvoy GK. Methemoglobinemia induced by local anesthetics. *Am J Hosp Pharm* 1981;38:89-93.
2. Spielman FJ, Anderson JA, Terry WC. Benzocaine-induced methemoglobinemia during general anesthesia. *J Oral Maxillofac Surg* 1984;42:740-3.
3. Marcovitz PA, Williamson BD, Armstrong WF. Toxic methemoglobinemia caused by topical anesthetic given before transesophageal echocardiography. *J Am Soc Echocardiogr* 1991;4:615-8.
4. Ho RT, Nanevich T, Yee R, Figueredo VM. Benzocaine-induced methemoglobinemia—two case reports related to transesophageal echocardiography premedication. *Cardiovasc Drugs Ther* 1998;12:311-2.
5. Fisher MA, Henry D, Gillam L, Chen C. Toxic methemoglobinemia: a rare but serious complication of transesophageal echocardiography. *Can J Cardiol* 1998;14(9): 1157-60.
6. Grauer SE, Giraud GD. Toxic methemoglobinemia after topical anesthesia for transesophageal echocardiography. *J Am Soc Echocardiogr* 1996;9(6):874-6.
7. Guerriero SE. Methemoglobinemia caused by topical benzocaine. *Pharmacotherapy* 1997;17:1038-40.

8. Ferraro-Borgida MJ, Mulhern SA, DeMeo MO, Bayer MJ. Methemoglobinemia from perineal application of an anesthetic cream. *Ann Emerg Med* 1996;27:785-8.
9. Ellenhorn MJ. *Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning*. 2nd ed. Baltimore: Williams & Wilkins; 1997. p. 1496-9.
10. Posthumus MD, van Berkel W. Cytochrome b5 reductase deficiency, an uncommon cause of cyanosis. *Neth J Med* 1994;44:136-40.
11. Coleman MD, Coleman NA. Drug induced methemoglobinemia. Treatment issues. *Drug Saf* 1996;14:394-405.
12. Curry SC, Carlton MW. Hematologic consequences of poisoning: methemoglobinemia. In: Haddad LM, Shannon MW, Winchester JF, editors. *Clinical management of poisoning and drug overdose*. 3rd ed. Philadelphia: WB Saunders; 1998. p. 226-30.
13. Ellenhorn MJ. *Ellenhorn's Medical toxicology: diagnosis and treatment of human poisoning*. 2nd ed. Baltimore: Williams & Wilkins; 1997. p. 844-52.
14. Sass MD, Caruso CJ, Axelrod DR. Mechanism of the TPNH-linked reduction of methemoglobin by methylene blue. *Clin Chim Acta* 1969;24:77-85.
15. 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;61:1086-90.