Methemoglobinemia secondary to over-the-counter Anbesol

Timothy M. Orr, DMD,a and Daniel L. Orr II, DDS, PhD, JD, MD,b Stony Brook, New York; and Las Vegas, Nevada
STONY BROOK MEDICAL CENTER AND UNIVERSITY OF NEVADA

Background. Methemoglobinemia is a potentially lethal condition which may result from exposure to benzocaine. It must be treated promptly, because it may cause a significant decrease in oxygen delivery to tissues and organs.

Case description. A 39-year-old caucasian man presented to the emergency department (ED) with dental pain. After a review of systems and a dental exam, an oxygen saturation of 90% was noted. The patient reported no previous cardiac or pulmonary pathology, but did report using a large amount of over-the-counter Anbesol. A second oxygen saturation measurement had fallen to 87%. An arterial blood gas sample was taken, and the patient was found to have high levels of methemoglobin. He was transferred to the critical care ED and treated with 2 mg/kg intravenous methylene blue.

Clinical implications. Dentists must be aware of the possible lethal effects of benzocaine toxicity, including methemoglobinemia. It is important to recognize the signs and symptoms and act in a judicious manner. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e7-e11)

Methemoglobinemia is an anemic disease caused by the oxidation of normal oxygen-carrying hemoglobin (Hb) from ferrous (Fe2+/Hb) to ferric (Fe3+/Hb). The inability of oxidized hemoglobin, methemoglobin, to bind or carry oxygen results in systemic functional anemia and tissue hypoxia. The net result is a shift to the left of the oxygen dissociation curve, indicating greater oxygen affinity by the remaining normal Hb and thus less tissue distribution throughout the body.

The oxidation and reduction of hemoglobin is a process that occurs constantly in the human body. Pathologic methemoglobinemia results from the body’s incapacity to reduce oxidized hemoglobin. This can be caused by impaired reduction pathways in the body or by an overproduction of methemoglobin, often due to a toxic substance.1 Such substances are either direct oxidizers or indirect oxidizers. Agents capable of oxidizing erythrocytes directly, such as nitrates, are direct oxidizers. Indirect oxidizers, such as local anesthetics, form methemoglobin in vivo only after metabolic modification.1

Clinically, methemoglobinemia can present in 2 types: acquired and hereditary. Treatment may differ based on severity of disease and its type, ranging from observation only to invasive procedures during inpatient hospitalization. In a literature review by Guay,1 242 episodes of methemoglobinemia in response to local anesthetic use were recently identified. Of these, 159 resulted from benzocaine, and over 80% of cases occurred in a hospital, medical, or dental setting. In 9 cases reported by Wilburn-Goo and Lloyd,2 methemoglobinemia occurred in patients undergoing a dental procedure, all of which resolved without serious complications. However, documented adverse outcomes include the death of a 51-year-old patient, death of a 4-month-old patient, and neurologic impairment of an 83-year-old patient.1 In addition, the occurrence of methemoglobinemia as a result of over-the-counter (OTC) use of benzocaine is infrequent and is important to be recognized by the dental team when the situation arises.

CASE PRESENTATION

A 39-year-old caucasian man presented to the Stony Brook University Hospital Emergency Department (ED) with a chief complaint of severe pain in the left mandibular posterior region, radiating from his jaw to his ear. The pain began 1 week earlier, becoming gradually worse, leading to the hospital visit.

The patient denied any past medical history of congenital heart defects, heart disease, or pulmonary pathology. He reported that he had smoked from the age of 15 years, ~2 packs a day, but quit at the age of 24. He also claimed to use "a lot" of chewing tobacco on a daily basis. He reported taking 2,400 mg of ibuprofen during the previous 8-hour period and approximately 1.5 tubes of Anbesol (containing about 7.0 mL 20% benzocaine) within the preceding 2 hours. He denied any alcohol use and reported no drug allergies.
Vital signs reported from triage were as follows, with normal value references in parentheses:

- **O₂ saturation:** 90% (98%-100%)
- **Respiratory rate:** 16 (12-18)
- **Heart rate:** 84 (60-80)
- **Temperature:** 35.9°C (37.0°C)
- **Blood Pressure:** 155/95 (120/80)
- **Height:** 195 cm
- **Weight:** 128 kg

The extraoral examination revealed light blue cyanotic lips. The patient’s overall color was dusky and pale. When asked about this, he replied that his wife thought he looked more pale than normal. There were no other significant findings.

The intraoral exam revealed multiple carious teeth and moderate generalized periodontal disease. Tooth #17 was sensitive to percussion, palpation, and cold with lingering effect. Radiographic analysis showed a radiolucent lesion from the mesial of #17 approaching the pulp. There was no evidence of periapical pathology or impaction on the x-ray (Fig. 1).

Stony Brook University Hospital protocol prohibits extractions and root canal therapy from being performed in the ED; however, the patient was offered a local anesthetic block to relieve the pain, and he enthusiastically accepted. He was given a left inferior alveolar and lingual nerve block with 1.8 mL 0.5% bupivacaine containing 1:200,000 epinephrine. He was happy with the rapid effect of the anesthetic and was then given an appointment to the Stony Brook Dental Care Center the following week. Sixteen tablets of Vicodin 5/500 were prescribed to help with pain control until the appointment date.

Before discharge, the oxygen saturation was again measured from the patient’s index finger and was now 87%. The patient was awake, alert, and oriented and did not complain of shortness of breath or lightheadedness. Calloused fingertips from frequent guitar playing were thought to possibly be affecting the oximeter measurement. The pulse oximeter sensor was then moved to his ear lobe, and another reading of 87% was recorded. The attending physician was informed of the situation and then asked the patient about his smoking history, pulmonary status, and cardiac situation. The patient was transferred to critical care ED, where a chest x-ray was taken to rule out any possible pulmonary pathology (Fig. 2) and was in fact read as within normal limits by radiology.

Complete blood count (CBC) and Chemistry-7 panels were performed, as well as arterial blood gas (ABG) analysis. Subsequently it was revealed that the patient had moderately high levels of methemoglobin, at 33.2%, along with a visually appreciated rusty red-brown hue to his arterial blood. Normal methemoglobin levels range from 0.5% to 3%.

The CBC and Chemistry-7 analyses returned with the following values, with normal value references in parentheses:

- **Na:** 139 (136-144 mEq/L)
- **K:** 4.3 (3.7-5.2 mEq/L)
- **Cl:** 106 (101-111 mmol/L)
- **CO₃:** 23 (22-30 mmol/L)
- **Blood urea nitrogen:** 21 (8-25 mg/dL)
- **Creatinine:** 1.2 (0.8-1.4 mg/dL)
- **Glucose:** 81 (64-128 mg/dL)
- **White blood cells:** 8.8 (4.5-10 × 10⁹/mL)
- **Hb:** 13.8 (13.5-16.5 g/dL)
- **Hematocrit:** 42.3 (45%-52%)
- **Platelets:** 356 (150-400 × 10⁹)

The patient was placed on oxygen via nasal canulae, and peripheral intravenous (IV) access was established. After the diagnosis of methemoglobinemia was confirmed, treatment was initiated with 250 mg IV methylene blue (1-2 mg/kg) administered slowly over 5-10 minutes. The patient was monitored for 5-6 hours with serial ABG analyses being performed. The patient was discharged with methemoglobin levels of 2.2% and an oxygen saturation of 98%.

![Fig. 1. Panoramic radiograph illustrating symptomatic tooth #17.](image1)

![Fig. 2. Chest x-ray taken to rule out pulmonary pathology, read as within normal limits.](image2)
DISCUSSION

A review of the literature revealed that patient-induced methemoglobinemia from a benzocaine-containing OTC pharmacologic agent is rare. A few sparsely documented cases were reported in the *Journal of the American Dental Association* in 1999.2 Nearly all well-documented instances of topical benzocaine–induced methemoglobinemia resulted from intubations and endoscopic procedures done in a hospital setting.3,4 However, it is now evident that this potentially lethal condition can be auto-induced secondary to OTC treatment with topical anesthetics, such as benzocaine for toothache (*Table I*).5

As stated above, the body’s ability to bond, transport, and release oxygen for use is dependent upon the level of hemoglobin in the blood. Hereditary disease and exposure to various exogenous agents can occasionally cause oxidation of ferrous Hb to ferric Hb, or methemoglobin, and render the associated red blood cells relatively incapable of oxygen transport. Resultant effects of decreased hemoglobin concentrations in the body cause a left shift of the oxygen dissociation curve (Fig. 3)6 that is indicative of increased binding affinity of the remaining healthy oxygen-hemoglobin compound.

In normal healthy individuals, hemoglobin is oxidized to methemoglobin and reduced back to hemoglobin on a continual basis, with normal levels of methemoglobin ranging from 0.5% to 3.0% of the available hemoglobin.7,8 Diagnosis of the hereditary form of methemoglobinemia is performed using biochemical and genetic analysis, including differentiation between autosomal dominant Hb M disease, an autosomal recessive deficiency of cytochrome b5R or b5, and glucose-6-phosphate dehydrogenase deficiency.9 Because these pathways are essential in the reduction of methemoglobin, it is evident why a deficiency or genetic mutation could cause dangerous levels of oxidized Hb. Reduction of methemoglobin can be accomplished through any of 3 different pathways, although 95% of reductions occur via the nicotinimide adenine dinucleotide phosphate (NADPH) enzyme system1 (Fig. 4). Acquired cases can result from exposure to a number of agents, including the local anesthetics prilocaine, benzocaine, articaine, and lidocaine. When prilocaine is administered (generally in doses of >600 mg to an adult), the oxidizing agent toluene transforms Hb to methemoglobin and prevents the reduction pathway.10 Dapsone, aniline dyes, and ingestion of nitrates are also tagged as key oxidative agents (*Table I*).5

The common OTC topical local anesthetic benzocaine gels or sprays can also cause methemoglobinemia. OTC benzocaine formulations can contain up to 20% benzocaine, and sprays containing benzocaine can deliver 45-60 mg benzocaine in 1 second.11 The present

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*Table I.* Various exogenous agents with known risk to induce methemoglobinemia

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
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<tbody>
<tr>
<td>Benzocaine</td>
<td>Lidocaine</td>
<td>Phenothiazines</td>
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<td>Sulfonamides</td>
<td>Nitrous oxide</td>
<td>Meperidine</td>
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<td>Bupivacaine</td>
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<td>Naphthalene</td>
<td>Aspirin</td>
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<td>Acetaminophen</td>
<td>Propofol</td>
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<td>Mepivacaine</td>
<td>Succinylcholine</td>
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<td>Acetanilid</td>
<td>Articaine</td>
<td>Benzodiazepines</td>
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<td>Etidocaine</td>
<td>Ibuprofen</td>
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<td>Nitric oxide</td>
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<tr>
<td>Phenacetin</td>
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<td>Dapsone</td>
<td>Quinine sulfate</td>
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<td>Phenobarbital</td>
<td>Nitroprusside</td>
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<td>Isosorbide dinitrate</td>
<td>Aniline (dyes, ink)</td>
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<tr>
<td>Nitrofurantion</td>
<td>Chloroquine</td>
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<td>Benzene derivatives</td>
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<td>Trimethoprim</td>
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<tr>
<td>Nitrates</td>
<td>Phenelzine</td>
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<td>Amyl nitrate</td>
<td>Flutamide</td>
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<tr>
<td>Nitroprusside</td>
<td>Ciprofloxacin</td>
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![Fig. 3. Oxygen dissociation curve showing a left shift with methemoglobinemia. Other factors causing a left shift include a decrease in temperature, decrease in diphosphoglycerate (DPG), and an increase in pH. (Reproduced with permission from Stoelting and Miller, Basics of Anesthesia, 5th Ed.; Elsevier, 2007; p. 55.)](image-url)
patient also ingested approximately 2,400 mg of ibuprofen and used a substantial amount of tobacco chew. Chewing tobacco has not been implicated as a cause of methemoglobinemia; however, ibuprofen has been identified as a possible cause of methemoglobinemia in a pediatric patient. That case, reported in a letter to the editor, is the only report known to the authors linking ibuprofen to methemoglobinemia. Although several agents could possibly act synergistically to produce methemoglobinemia, considering all of the clinical factors and the patient history in the present case, the authors think that the most likely agent responsible for the methemoglobinemia is the recognized triggering agent benzocaine contained in Anbesol.

Clinicians should look for key signs and symptoms when suspicion of methemoglobinemia occurs, including cyanosis of the perioral region and nail beds, loss of color, a dusky gray appearance, and a rusty or red-brown hue to blood. Patients may also express symptoms of classical anemic disease, such as lightheadedness, dizziness, nausea, lethargy, and syncope.

Dentists who use pulse oximetry should include methemoglobinemia in their differential diagnosis with these clinical findings. Furthermore, although PO₂ readings will likely be depressed, such depressed readings may still be artificially high. This is because oxygenated Hb absorbs more infrared light, whereas deoxygenated blood absorbs more red light. The ratio of these 2 values is converted to a percentage, which is easily read and understood by the health practitioner. Studies have shown that patients with methemoglobin levels of as little as 10% will have erroneously high pulse oximetry readings. Higher levels of methemoglobin (>30%) will cause the readings to trend to ~85%.

If methemoglobinemia is suspected, the clinician should cease all treatment and immediately administer oxygen, although this may not always improve the clinical situation. Intravenous access can be established and 1-2 mg/kg methylene blue administered slowly over 5-10 minutes. Methylene blue acts as an available artificial electron acceptor in the NADPH methemoglobin reductase pathway, allowing reduction of the ferric Hb to normal healthy ferrous Hb. It must be noted, however, that excessive amounts of methylene blue have been known to cause rebound methemoglobinemia by the very same pathway for up to 18 hours after administration. It would not be unusual for a clinician to obtain several ABG samples, depending on the period of observation of the patient, before the final ABG sample confirming that methemoglobin levels have returned and stabilized to normal values. When the patient is discharged, he or she should also be instructed to return for further treatment should symptoms indicative of methemoglobinemia arise.

Precise documentation and vigilance is necessary to convey accurate information to emergency medical services before transportation of the patient for more advanced care.

**CONCLUSION**

Dental professionals should be aware of these complications and be able to treat or arrange for expeditious treatment of the symptoms. Some practitioners, such as oral and maxillofacial surgeons and dentist anesthesiologists, may routinely have access to methylene blue and be prepared to treat methemoglobinemia. It is clear that this life-threatening disease can occur from an overdose of local anesthesia, and/or from inadvertent mucosal absorption of OTC benzocaine-containing compounds. Some treatment options, such as those requiring the establishment of an IV line, may not be realistic options for dentists not so trained. However, all clinical dentists should be familiar with the side effects and complications of agents they use and be prepared to differentially diagnose any untoward effects. Early recognition and treatment can save the life of someone who unexpectedly develops methemoglobinemia.

The case reported herein happened to occur in a hospital ED. ED physicians, the laboratory, the radiology clinic, and the entire hospital infrastructure were immediately available to facilitate a rapid diagnosis and treatment. If methemoglobinemia were to occur in a private dental office, such resources would not be available. However, dentists can greatly increase the chances...
of survival of such patients if the following steps are implemented:

1. Suspend all dental treatment after controlling hemorhage and securing the airway.
2. Administer oxygen.
3. Call emergency services for hospital transport.
4. If necessary, administer 1-2 mg/kg IV methylene blue over 5-10 minutes. Record the time and dose. Occasionally, patients may require a second dose if methemoglobin levels remain >40% as determined by ABG sampling. The second dose of methylene blue is usually given 1 hour after the initial dose.
5. Inform both paramedics and emergency room personnel of a tentative diagnosis of methemoglobinemia and provide pertinent medical history, including information about any local anesthetics or other triggering agents administered by the dentist or the patient.

All cases of suspected methemoglobinemia should be treated as medical emergencies. It is impossible to know how severe the reaction is until an ABG sample is obtained and analyzed, thus immediate action is advised if the patient develops the clinical signs and symptoms of methemoglobinemia, such as cyanosis of the nail beds and perioral region, lethargy, dizziness, confusion, headache, and dyspnea. Patients with more severe reactions may demonstrate signs of shock, respiratory depression and seizures. Death is a possible outcome, should the episode remain unrecognized, undiagnosed, or untreated. Dental professionals should be aware of the clinical signs and symptoms of methemoglobinemia and be prepared to act in the best interest of their patient.

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REFERENCES


Reprint requests:
Dr. Timothy Orr
Stony Brook University
100 Nichols Rd.
Stony Brook, NY 11794
orrmd@gmail.com