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# Benzocaine-Induced Methemoglobinemia: A Case Report

Keith T. Veltri, PharmD; and Ellen Rudnick, MS, BPharm

## INTRODUCTION

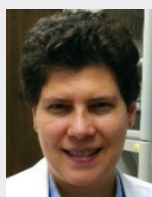
Local anesthetics are classified by their chemical structures, with the two major categories being esters and amides (Table 1). The agent of choice depends on the method of administration, the length of time for which the affected areas require local anesthesia, and potential adverse effects.

Esters include benzocaine (Cepacol, Reckitt Benckiser; Dermoplast, Prestige Brands Holdings; Chloraseptic, Prestige Brands Holdings; HurriCaine, Beutlich Pharmaceuticals; Lanacane, Reckitt Benckiser; Orabase, Colgate-Palmolive Company; Orajel, Church & Dwight; and Zilactin, Blairex Laboratories); chloroprocaine (Nesacaine, APP Pharmaceuticals); procaine (Novocaine, Colgate-Palmolive Company); and tetracaine.<sup>1</sup>

Amides include bupivacaine (Marcaine, Hospira; Sensorcaine, AstraZeneca); dibucaine (Nupercainal, Nucere Pharma); levobupivacaine (Chirocaine, Purdue Pharma); lidocaine (Dilocaine, Shire; Solarcaine, Bayer; Lidoderm, Endo Pharmaceuticals; and Xylocaine, Fresenius Kabi USA); mepivacaine (Carbocaine, Cooke-Waite; Isocaine, Novocol Pharmaceutical; Polocaine, Novocol Pharmaceutical); prilocaine (Citanest, Dentsply Pharmaceutical); and ropivacaine (Naropin, Fresenius Kabi).<sup>1</sup>

Some combination products contain both amides and esters; the most com-

Welcome to the Pharmacovigilance Forum, where we report on interesting adverse drug reactions (ADRs), including drug-induced disease. ADRs are a leading cause of morbidity and mortality. The Institute of Medicine has estimated that



44,000 to 98,000 deaths occur annually from medical errors, with 7,000 due to ADRs. Studies suggest that 6.7% of hospitalized patients have a serious ADR; about 0.5% die as a consequence. ADRs are a significant, preventable public health problem that we can help mitigate through education.

Drug approvals in the U.S. continue to grow. In 2015, the Food and Drug Administration (FDA) approved 45 novel drugs—up from an average of about 28 per year from 2006 through 2014. This is a significant increase, especially since

many of these approvals involved complex biologic agents. Yet all pharmaceuticals carry a risk of ADRs, whether they are new and improved, generic agents, older brand products, complex biologics, or biosimilars. Publishing ADR cases is a great way to educate others about little-known reactions, unique patient management of a reaction, or interesting presentations of known reactions to a drug or drug class.

Each Pharmacovigilance Forum will discuss noteworthy topics related to ADRs in the clinical realm. Every medication has the potential to cause disease, but clinicians are often slow to recognize drug therapy as an etiological factor. I encourage anyone with a potentially interesting case to contact me, to publish ADRs here or elsewhere, and to report ADRs to the FDA MedWatch program.

—Michele B. Kaufman

monly used of these agents include lidocaine/prilocaine (Emla, Akorn, Inc.) and benzocaine/tetracaine/butamben (Cetacaine, Cetylite Industries).<sup>1</sup>

Amides have largely replaced the esters because they produce fewer adverse effects and generally have a longer duration of action.<sup>1</sup>

Pramoxine (Analpram, Sebela Pharma-

ceuticals; Itch-X, B. F. Ascher & Company; Pramegel, Pharmaderm; Pramoxone, Sebela Pharmaceuticals; Prax, Ferndale Laboratories; and Tronolane, Abbott Laboratories) is a local anesthetic that does not belong to either the amide or ester class.<sup>1</sup>

Local anesthesia can be achieved by various methods, including topical administration, infiltration, field block, nerve block, and intravenous regional injection. The method by which a local anesthetic is administered aids its effectiveness by delivering the agent directly to the area that is causing or will cause pain. This decreases systemic absorption and related toxic effects. Systemic absorption could produce toxic effects on both the cardiovascular and nervous systems.<sup>1</sup>

Recently, topical anesthetics have been reported to cause methemoglobinemia, an elevated fraction of methemoglobin (an unstable type of hemoglobin within erythrocytes). The popularity of benzocaine as

**Table 1 General Anesthetic Agents<sup>1</sup>**

Esters
<ul style="list-style-type: none"> <li>• Benzocaine</li> <li>• Chloroprocaine</li> <li>• Procaine</li> <li>• Tetracaine</li> </ul>
Amides
<ul style="list-style-type: none"> <li>• Bupivacaine</li> <li>• Dibucaine</li> <li>• Levobupivacaine</li> <li>• Lidocaine</li> <li>• Mepivacaine</li> <li>• Prilocaine</li> <li>• Ropivacaine</li> </ul>
Miscellaneous
<ul style="list-style-type: none"> <li>• Pramoxine</li> </ul>

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a topical anesthetic has diminished as a result of increasing concerns regarding its potential to induce this hematological disorder. Numerous case reports have been published.<sup>2-17</sup> As of 2009, a review of 242 published cases implicated benzocaine in 66% of methemoglobinemia related to local anesthesia, while lidocaine accounted for only about 5% of cases.<sup>13</sup>

**PATHOPHYSIOLOGY**

Hemoglobin is composed of four heme groups: deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin. Each group contains an iron atom capable of binding oxygen. This binding, however, can occur only if the iron is in the reduced state (Fe<sup>+2</sup>). The removal of an electron from reduced iron—oxidizing it from Fe<sup>+2</sup> to Fe<sup>+3</sup>—produces methemoglobin. In addition, the production of a ferric (Fe<sup>+3</sup>) heme group interferes with oxygen unloading by the other ferrous (Fe<sup>+2</sup>) heme groups on the hemoglobin molecule. Red blood cells are continuously under stress by oxidative processes and undergo numerous structural changes that result in the formation of methemoglobin. The development of methemoglobin is regulated by various enzymatic processes, which include the major pathway nicotinamide adenine dinucleotide methemoglobin reductase and the minor pathway nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase.<sup>2,4,7,9</sup> A small amount of methemoglobin is reduced via nonenzymatic pathways, such as by ascorbic acid, reduced glutathione, riboflavin, and cysteine.<sup>5</sup> During these major and minor processes, iron is in the ferrous form (Fe<sup>+2</sup>) and combines with oxygen for transportation to the tissues.<sup>2,4,7-9</sup>

Because methemoglobin prevents oxygen transport to cells, patients presenting with methemoglobinemia become cyanotic despite an adequate respiratory status. Increased oxygenation has no effect on either the cyanotic state or oxygen saturation. Pulse oximetry will most likely be inaccurate, and readings will be inconsistent with the patient’s increasing cyanosis.<sup>5</sup> Oxygen saturation measured by pulse oximetry is typically in the range of 80% to 85% regardless of the severity of methemoglobinemia.<sup>4</sup> Routine analysis of arterial blood gas is used to determine the partial pressure of oxygen (PO<sub>2</sub>), which is then used to calculate

oxygen saturation in the blood. However, the measurement of PO<sub>2</sub> is not affected by the presence of methemoglobin, and as a result, pulse oximetry readings that are inconsistent with oxygen saturation are suggestive of methemoglobin.<sup>4,5</sup>

A pulse oximeter is a noninvasive device attached to the finger, earlobe, or nose that emits two separate wavelengths of light, red (660 nm) and infrared (940 nm). A co-oximeter is used to measure the absorbance of oxyhemoglobin and deoxyhemoglobin circulating throughout the capillaries. It reflects the amount of oxygen in the blood, expressed as a percentage, measuring light absorbance at four different wavelengths, correlating to the absorption characteristics off all four heme groups.<sup>18</sup> Carboxyhemoglobin has an almost identical absorption spectrum (660 nm) to that of oxyhemoglobin.<sup>18</sup> Methemoglobin absorbs light at both wavelengths (660 nm and 940 nm) that standard oximeters emit.<sup>18</sup> Therefore, a definitive diagnosis should be confirmed by co-oximetry in patients who present with cyanosis of an uncertain cause.

A “filter paper test” provides a rapid bedside method for diagnosing methemoglobin. In patients with this disorder, arterial blood, when drawn and placed on the filter paper, is often chocolate brown or black and does not change color when exposed to oxygen.<sup>4,5,9</sup>

The clinical manifestations of methemoglobinemia directly correlate with the level of measured methemoglobin. Symptoms can be worse in those at age extremes (e.g., very young or very old) or with multiple comorbidities. Elderly and pediatric patients, as well as hypoxic patients, are more prone to the formation of methemoglobin. Neonates express low levels of functional NADPH methemoglobin reductase, and this enzyme becomes less efficient in the elderly.<sup>17</sup> A normal methemoglobin level is less than 1% to 3% of the fraction of hemoglobin in healthy individuals. When the methemoglobin level indicated through arterial co-oximetry is 15% to 20%, patients are usually cyanotic, but they may be asymptomatic. When methemoglobin levels reach 20% to 50%, the patient may experience headache and lightheadedness, weakness, chest discomfort, palpitations, and dyspnea. Death can occur when methemoglobin levels exceed 70%.<sup>2,5-7,10</sup>

Methemoglobinemia usually results from exposure to an external oxidizing

agent that compromises the physiological cellular defenses of red blood cells. The disorder can also be hereditary. It is associated with the production of abnormal hemoglobin, which usually presents as cyanosis at birth or as a secondary feature of NADH reductase deficiency.<sup>5,12</sup> Exogenous agents that pose a risk for methemoglobinemia are listed in Table 2.

Table 2 Selected Agents Associated With Methemoglobinemia <sup>5-7, 9, 11</sup>	
<b>High Risk</b>	
<ul style="list-style-type: none"> <li>• Benzocaine</li> <li>• Chloroquine</li> <li>• Ciprofloxacin</li> <li>• Dapsone</li> <li>• Flutamide</li> <li>• Isosorbide dinitrate</li> <li>• Metoclopramide</li> <li>• Naphthalene</li> <li>• Nitrofurantoin</li> </ul>	<ul style="list-style-type: none"> <li>• Nitroglycerin</li> <li>• Nitric oxide</li> <li>• Phenazopyridine</li> <li>• Phenelzine</li> <li>• Phenobarbital</li> <li>• Prilocaine</li> <li>• Primaquine</li> <li>• Quinine sulfate</li> <li>• Sulfonamides</li> <li>• Trimethoprim</li> </ul>
<b>Moderate Risk</b>	
<ul style="list-style-type: none"> <li>• Acetaminophen</li> <li>• Aspirin</li> <li>• Bupivacaine</li> <li>• Etidocaine</li> </ul>	<ul style="list-style-type: none"> <li>• Fentanyl</li> <li>• Lidocaine</li> <li>• Mepivacaine</li> <li>• Nitrous oxide</li> </ul>
<b>Low Risk</b>	
<ul style="list-style-type: none"> <li>• Benzodiazepines</li> <li>• Ibuprofen</li> <li>• Inhalational anesthetics</li> <li>• Meperidine</li> </ul>	<ul style="list-style-type: none"> <li>• Phenothiazines</li> <li>• Propofol</li> <li>• Succinylcholine</li> <li>• Thiopental</li> </ul>

**PRINCIPLES OF TREATMENT AND REPLACEMENT**

The topical anesthetics benzocaine 20% (HurriCaine spray) and lidocaine are readily available in most emergency departments and are commonly used to anesthetize a patient’s airway before elective endotracheal intubations or endoscopic procedures.<sup>14</sup> Both agents have been reported to cause methemoglobinemia. A recent review of the literature indicated that methemoglobinemia was reported more frequently with spray benzocaine used during dental or endoscopic procedures (such as for transesophageal echocardiography).<sup>14</sup> The potentially fatal effects of benzocaine may be due to a toxic metabolite, an N-hydroxy derivative that has an aniline group incorporated into its structure.<sup>6,14</sup> This compound has oxidizing properties.

From November 1997 through March 2002, 132 cases of methemoglobinemia associated with benzocaine administration were reported to the FDA. In 123 of these cases (93%), the product was a spray; in two cases, the product was a benzocaine-containing lozenge; and in one case, it was a gel.<sup>14</sup> These percentages may not accurately represent actual occurrence rates because cases were likely underreported. For example, patients with mild methemoglobinemia may be asymptomatic or may present with only mild symptoms, which may not be recognized as potential cases of drug-induced methemoglobinemia. Differences in absorption and metabolism may explain the variability of benzocaine-induced methemoglobinemia in these individuals.<sup>6,14</sup>

Mild methemoglobinemia can be treated with supplemental oxygen to maximize the oxygen-carrying capacity of the remaining normal hemoglobin after removal of the causative agent. These cases generally do not require specific treatment.<sup>4,5</sup> Symptomatic patients with methemoglobin levels exceeding 20% to 30% should receive methylene blue, which acts as a cofactor for the enzyme NADPH methemoglobin reductase. Electrons are transferred from NADPH to methylene blue, which leads to a reduction of the heme iron to deoxyhemoglobin.<sup>9</sup> Methylene blue should be administered at an initial intravenous dose of 1 mg/kg to 2 mg/kg over five minutes.<sup>4,5,9</sup> If there is no response, a repeat 1-mg/kg dose may be administered after 30 to 60 minutes.<sup>5,9</sup> The adverse effects of methylene blue include bluish skin discoloration (which can complicate the assessment of cyanosis), hemolysis, gastrointestinal distress, bladder irritation, and rebound methemoglobinemia, particularly with doses that exceed 7 mg/kg.<sup>4,5,9</sup> Methylene blue should not be administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or with congenital abnormal hemoglobin or NADH reductase deficiency. Low levels of NADPH are present in these patients, and as a result, methylene blue will be ineffective and will ultimately cause hemolysis. Exchange transfusions should be considered in these individuals.<sup>4,5,7,9</sup>

**Case Report**

The following report describes a patient with benzocaine-induced methemoglobinemia who was seen at our hospital.

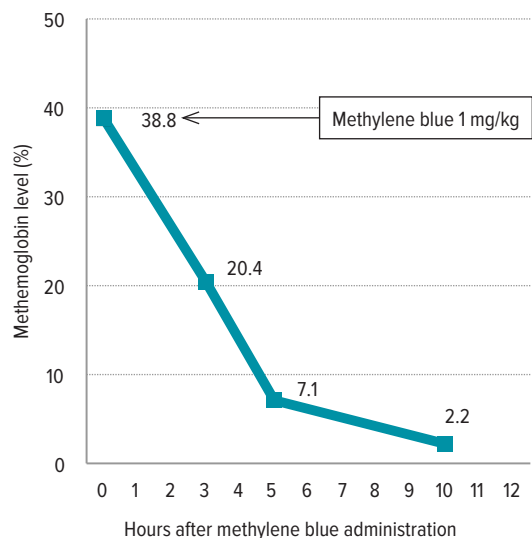
A 46-year-old woman with a medical history of hypertension, anemia, depression, and morbid obesity (which persisted after a gastric bypass in 2003) presented on April 3, 2013, for laparoscopic fistula repair and revision of her 2003 gastric bypass. She felt well at discharge, but soon afterward she experienced chest pain that “felt as though an elephant was sitting on her chest.” She presented to the emergency department on April 12. An upper gastrointestinal series and computed tomography revealed free air in the upper abdomen and a large extraluminal contrast collection posterior to the gastric pouch, with free air bubbles in the upper quadrant. She decompensated, and a nasogastric (NG) tube was temporarily placed. After removal of the NG tube, benzocaine 20% topical oral spray (HurriCaine) was ordered, with nursing instructions to apply one spray to the back of the throat. The order also included instructions to repeat the spray every six hours for pain relief. The following day, the nurse accidentally left the HurriCaine spray canister at the patient’s bedside, and the patient subsequently overdosed as the result of continuous excessive administration of the anesthetic over the next four days.

On the morning of April 17, the patient was found to be cyanotic and “blue.” The patient stated that she felt short of breath, dizzy, and fatigued. She was immediately placed on 2 L of oxygen via nasal cannula. Later that morning, she desaturated to 83% and was placed on 100% fraction of inspired oxygen (FiO<sub>2</sub>). An arterial blood gas (ABG) was ordered “stat.” The ABG showed a methemoglobin level of 38.8%.

At this point, the medical team contacted the hematology service regarding therapeutic management for this patient. The hematology service recommended immediate treatment with methylene blue 1 mg/kg, with a repeat dose one hour later

if the methemoglobin level remained above 20%. The patient ultimately received two doses of 70 mg in two hours before there was an initial decline in the methemoglobin level (Figure 1). The patient became less cyanotic, and her oxygenation improved (Table 3). Hematology further recommended that the medical team continue trending the patient’s methemoglobin levels over the next 24 hours. This was advised because of the potential for a rebound effect, which could occur secondary to the presence of the circulating oxidant. Repeat methylene blue doses were not recommended unless the patient’s methemoglobin level exceeded 20%.

**Figure 1 Level of Methemoglobin Before and After Methylene Blue Treatment**



**DISCUSSION**

Numerous case reports have described methemoglobinemia after gastrointestinal endoscopy, endotracheal intubation, bronchoscopic NG tube placement, and other inpatient procedures that involve prescription topical anesthetics. However, many over-the-counter (OTC) topical anesthetic gels, throat lozenges, or sprays can cause methemoglobinemia. The easy access to OTC benzocaine products, such as Cepacol anesthetic troches (Reckitt Benckiser) and Sucrets maximum-strength lozenges (Prestige Brands Holdings), may lead clinicians to believe that these products are free from adverse effects, including methemoglobinemia.

Methemoglobinemia often occurs when the doses of benzocaine spray (or other local anesthetic agents) exceed

**Table 3 Arterial Blood Gases and Co-Oximetry Values**

	Normal Values	Time of Diagnosis	Time after Administration of Methylene Blue		
			3 hours	5 hours	10 hours
<b>Arterial blood gas</b>					
pH	7.350–7.450	7.490	7.398	7.434	7.404
PCO <sub>2</sub> (mm Hg)	35.0–45.0	31.7	43.1	38.8	46.0
PO <sub>2</sub> (mm Hg)	80–100	180.0	57.3	71.5	139.0
HCO <sub>3</sub> (mmol/L)	22.0–28.0	23.9	26.0	25.6	28.1
SaO <sub>2</sub>	94–100	96.3	88.2	92.9	97.8
<b>Arterial co-oximetry</b>					
O <sub>2</sub> Hb	60–90	59.6	69.9	85.7	94.3
Carboxy Hb	< 9.1	0.0	0.4	0.7	1.4
MetHb	< 1.6	38.8	20.4	7.1	2.2
Deoxy Hb (%)	< 2	2.3	9.3	6.5	2.2
FiO <sub>2</sub> (%)		4L NC	6L NC	4L NC	80%

Carboxy Hb = carboxyhemoglobin; deoxy Hb = deoxyhemoglobin; FiO<sub>2</sub> = fraction of inspired oxygen; Hb = hemoglobin; HCO<sub>3</sub> = plasma bicarbonate; metHb = methemoglobin; NC = nasal canula; O<sub>2</sub>Hb = oxyhemoglobin; PCO<sub>2</sub> = partial pressure of carbon dioxide; PO<sub>2</sub> = partial pressure of oxygen; SaO<sub>2</sub> = arterial saturation of oxygen.

**Table 4 Minimizing the Risk of Methemoglobinemia When Using Topical Anesthetics<sup>21</sup>**

- Affix labels to topical anesthetic spray bottles warning staff of the danger of excessive patient use.
- Identify risk factors while obtaining the patient’s medical history.
- Document the amount of drug administered, including measuring and recording the number of sprays applied. The use of a reference chart with maximum recommended doses of anesthetics may be helpful.
- Supplemental oxygen and methylene blue should be kept handy whenever topical anesthetics are used.
- Use delivery devices that provide more precision in drug administration, such as atomizers (many are available).
- Stock only one topical anesthetic product to reduce dosing confusion. Lidocaine may be safer than benzocaine.

the manufacturers’ recommendations. Clinicians have long pointed out that ambiguous package instructions for use of the spray canisters of benzocaine products can be easily misinterpreted and can lead to potential overdoses. Package instructions commonly suggest that the user should “activate the spray with the forefinger for approximately one second. Maximum anesthesia is produced in one minute.”<sup>19</sup> This direction could easily be misinterpreted to mean that a continuous spray of up to one minute is permitted and even desirable for maximum anesthesia.<sup>19</sup> OTC benzocaine formulations may contain up to 20% benzocaine, and sprays containing benzocaine deliver 45 mg to

60 mg of the anesthetic in one second. Adverse events related to topical anesthetics usually involve the use of multiple sprays or of sprays lasting longer than the recommended duration.<sup>3,11,20</sup> Table 4 lists several strategies to reduce the risk of methemoglobinemia when using topical anesthetics.<sup>21</sup>

After discussing the potential for methemoglobinemia in patients treated with topical anesthetics, our pharmacy department decided to remove the HurriCaine spray canister from the formulary and replace it with unit-dose nonspray benzocaine (HurriCaine One), thus making it easier to control the amount of drug being administered. We continue to see benzo-

caine spray ordered for “sore throat.” Our staff has been educated on contacting the prescriber to recommend an alternative agent, such as benzocaine troches or lozenges, or phenol 0.5% spray (Chloraseptic, Prestige Brands Holdings), which can be administered to both adults and pediatric patients over the age of 2 years.

**CONCLUSION**

Methemoglobinemia is a persistent and significant clinical condition that can result from the use of topical anesthetics, among other causes. Although it is treatable, its detection has been complicated by a general lack of awareness in the medical community and by the limited availability of standard co-oximetry for an accurate diagnosis in the inpatient setting. Clinicians should be on the alert for this potentially serious disorder if patients show an inconsistency between the oxygen saturation of arterial blood and the saturation calculated from partial pressure of oxygen. In addition, methylene blue should be readily available in facilities where topical anesthetics are administered.

**REPORTING ADVERSE DRUG REACTIONS**

All ADRs should be reported to MedWatch at 1-888-INFO-FDA, 1-888-463-6332, or online. The FDA 3500 Voluntary Adverse Event Report Form can be accessed easily online for reporting ADRs at [www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm](http://www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm).

The FDA is interested in serious reports that include any of the following patient outcomes: death; life-threatening condition; initial hospitalization; prolonged hospitalization; disability or permanent damage; congenital anomalies or birth defects; and other serious conditions for which medical or surgical intervention is needed to prevent one of the aforementioned outcomes. The FDA is also interested in any unlabeled ADRs for new drugs.

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