Acute Methemoglobinemia Secondary to Topical Benzocaine Spray

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ABSTRACT

Benzocaine spray is a frequently used local anesthetic, capable of attenuating the gag reflex and diminishing discomfort during procedures requiring access to the oropharynx. However, it is also a potent oxidizing agent that can induce methemoglobinemia, with potentially lethal cyanosis. An 82-year-old woman with ileus developed acute methemoglobinemia secondary to a 3-second dose of topical benzocaine spray after nasogastric tube placement. Within several minutes, she became dyspneic and syncopal, developing a cyanotic appearance. Her symptoms failed to respond to oxygen. Pulse oximetry revealed a saturation of 86%, despite an essentially normal arterial blood gas, and co-oximetry revealed an elevated methemoglobin level. Methylene blue (1 mg/kg) was administered, resulting in the rapid and dramatic resolution of symptoms. Strict supervision of patients receiving benzocaine spray is warranted, along with careful monitoring for any signs/symptoms of cyanosis.


Benzocaine is a very effective topical local anesthetic that is present in a number of products including Baby Oragel® for teething and Vagisil® for diaper rash, as well as Americaine hemorrhoidal ointment®, Orajel®, and Solarcaine aerosol® for use in adults. Over the past half century, Hurricane Spray® has become a very popular form of benzocaine used for local anesthesia of the oropharynx.

CASE REPORT

An 82-year-old white woman with a history of hypertension, paroxysmal atrial tachycardia, and hypothyroidism underwent laparoscopic left adrenalectomy for possible adrenal carcinoma. On the third postoperative day, the patient's course was complicated by a paralytic ileus. A nasogastric tube was placed, preceded by a 3-second dose of Hurricane spray (20% benzocaine, approximately 600- to 885-mg total dose) to the oropharynx. Within several minutes, the patient developed lethargy and confusion. She then became dyspneic and syncopal, and developed a cyanotic appearance. She did not respond to 100% O₂ by non-rebreather mask despite an arterial blood gas (ABG) with a PaO₂ of 310 mm Hg and an
oxygen saturation of 99.7%. A simultaneous pulse oximetry revealed an oxygen saturation of 86%. The arterial blood was extremely dark in appearance. An electrocardiogram revealed supraventricular tachycardia with a rate of 170 to 180 and ST-depression in the lateral leads. A sinus rhythm resulted after 6 mg of intravenous adenosine, with a rate of 120 and resolution of the ischemic changes. A diagnosis of methemoglobinemia was confirmed by co-oximetry, which revealed a methemoglobin level of 30.9% (normal = 0%). A 50-mg dose of methylene blue was administered intravenously, and over the course of 1 hour her confusion and cyanosis resolved. Methemoglobin levels decreased to 6.4%, 3.7%, and 2.4% over the next 1, 3, and 6 hours, respectively (Figure 1).

**DISCUSSION**

Methemoglobin refers to iron within the hemoglobin moiety that has been oxidized from the ferrous (Fe++) to the ferric (Fe+++ ) state. This change in the oxidation state results in a diminished oxygen-carrying capacity. Methemoglobin is normally present within the red blood cell at concentrations less than 1% to 2%. Under normal conditions, methemoglobin is reduced by a number of enzymatic pathways. The major pathway is via NADH cytochrome b5 methemoglobin reductase. In methemoglobinemia, the hemoglobin moiety is oxidized at a rate that overwhelms the compensatory enzymatic reduction systems, resulting in a rapidly declining oxyhemoglobin level and subsequent cyanosis.

Benzocaine is an ester-type local anesthetic available in a number of topical applications (eg, Hurricane spray) that has been widely implicated as a causative agent of methemoglobinemia. The current hypothesis is that benzocaine indirectly oxidizes O2 to produce the O2-free radical, which acts as a potent oxidizing agent on the hemoglobin moiety (Figure 2). Although the recommended dosage for Hurricane spray is a 1- to 2-second spray, standard clinical practice has shown that adequate local anesthesia to the oropharynx often requires at least a 3- to 4-second dose. Methemoglobinemia has been reported with doses at and above the standard recommended 1-second dose. However, there appears to be no correlation between published doses and methemoglobin levels (Table).

**SYMPTOMS**

The severity of the symptoms of methemoglobinemia correlate directly with the level of methemoglobin. Symptoms typically become apparent when the methemoglobin concentration reaches 10% to 30% of total hemoglobin. These symptoms can range from some cyanotic skin discoloration to anxiety, lightheadedness, headache, and tachycardia. As the concentration rises above 30%, signs and symptoms also may include worsening fatigue, confusion, dizziness, and tachypnea. Patients can experience seizures, coma,
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Arrhythmias, and acidosis as concentrations rise above 50%. Death typically ensues at levels greater than 70%. In patients with underlying comorbidities, the symptoms may be more severe than expected for a given level of methemoglobin.

**DIAGNOSIS**

Early suspicion for and treatment of methemoglobinemia is crucial in preventing serious morbidity or mortality. In the rapid assessment of a cyanotic patient, the history of events prior to the onset of symptoms, as well as the pathognomonic clinical findings, provide critical clues for making the diagnosis. In this assessment, one must realize the futility of pulse oximetry. The pulse oximeter reads O\(_2\) saturation as a ratio of oxy- to deoxyhemoglobin based on light absorption at their specific wavelengths (oxyhemoglobin = 660 nm; deoxyhemoglobin = 940 nm). Ratios of 0.43 and 3.4 correspond to 100% and 0% saturation, respectively. Methemoglobin absorbs equally at 660 nm and 940 nm. This ratio of 1 corresponds to an oxygen saturation (by pulse oximeter) of 85%. Thus, as methemoglobin levels rise, there is a steady decline in the pulse oximeter reading until it stabilizes in the 82% to 86% range despite an oxyhemoglobin level that may be much lower. Therefore, pulse oximetry is a useless tool in the monitoring of the oxygen status of a patient with methemoglobinemia.

ABG measurement, however, can be useful. Methemoglobin prevents binding of O\(_2\) to hemoglobin, but there is no decline in O\(_2\) dissolving capacity, resulting in an essentially normal ABG with a normal to slightly elevated PaO\(_2\). Thus, ABG is a poor tool for ruling in methemoglobinemia. However, severely decreased PaO\(_2\), increased PaCO\(_2\), and acidosis in a cyanotic patient provide significant evidence for ruling out methemoglobinemia. Because of poor binding of O\(_2\) to the hemoglobin moiety, the arterial blood during methemoglobinemia may appear as a dark purple to chocolate color. Moreover, exposure of the sample to normal room air fails to increase the redness of the blood. The latter finding may provide immediate evidence that a venous blood draw was not inadvertently performed and that a process is inhibiting O\(_2\) binding.

**DIAGNOSTIC TEST OF CHOICE**

The diagnostic test of choice for methemoglobinemia is co-oximetry. Co-oximetry provides a spectrophotometric analysis that is capable of providing specific measurement of methemoglobin levels in the arterial blood. In addition, by using a variety of absorbance wavelengths, co-oximetry can accurately measure specific levels of oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and hemoglobin. Thus, co-oximetry is not only a vital tool when diagnosing methemoglobinemia, but it is also useful for monitoring arterial oxygenation status and for accurately monitoring the success of the treatment protocol.

**TREATMENT**

Intravenous methylene blue is the treatment of choice for methemoglobinemia. Methylene blue is reduced to leukomethylene blue via the enzyme NADPH methemoglobin reductase (Figure 2). This reduced molecule then donates an electron to methemoglobin, effectively reducing it to hemoglobin. In the process, leukomethylene blue is oxidized back to methylene blue. The typical initial dosage is 1 to 2 mg/kg intravenously; clinical improvement is typically noted within 15 to 30 minutes. If no improvement is seen, a repeat dosage can be administered. However, caution must be taken when giving dosages ranging from 4 to 7 mg/kg, as methylene blue can actually become an oxidizing agent and worsen methemoglobinemia. Side effects include nausea, vomiting, diarrhea, abdominal discomfort, and anxiety. A Heinz body hemolytic anemia is a rare

Table. Published Case Reports of Benzocaine-Induced Methemoglobinemia

<table>
<thead>
<tr>
<th>Case Study</th>
<th>Age/Gender</th>
<th>Benzocaine Dose (Seconds)</th>
<th>Methemoglobin Level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckley and Newman, 1987</td>
<td>57 M</td>
<td>4</td>
<td>48.5</td>
</tr>
<tr>
<td>Collins, 1990</td>
<td>41 M</td>
<td>3-4</td>
<td>29.7</td>
</tr>
<tr>
<td>Linares et al, 1990</td>
<td>73 M</td>
<td>4</td>
<td>48.5</td>
</tr>
<tr>
<td>Bhutani et al, 1992</td>
<td>15 F</td>
<td>3-4</td>
<td>54</td>
</tr>
<tr>
<td>D’Inneen et al, 1994</td>
<td>84 M</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>Grauer and Giraud, 1996</td>
<td>68 M</td>
<td>6</td>
<td>47.2</td>
</tr>
<tr>
<td>Guerriero, 1997</td>
<td>77 F</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Present Case Report</td>
<td>82 F</td>
<td>3</td>
<td>30.9</td>
</tr>
</tbody>
</table>

Review of the published case reports of benzocaine-induced methemoglobinemia in which actual benzocaine dose and methemoglobin level (as determined by co-oximetry) were reported. There appears to be no statistical correlation between dosage and methemoglobin level (correlation coefficient = 0.393).
but potentially fatal side effect found in patients with a history of glucose-6-phosphate dehydrogenase deficiency. Other treatments including exchange transfusion, N-acetylcysteine, ascorbic acid, and hyperbaric oxygen have also been shown to have limited benefit.

A number of cases of methemoglobinemia have been reported secondary to topical benzocaine spray. Most cases have occurred in elderly patients who may have a decrease in either functional enzyme load or normal enzyme level with decreased enzyme activity, thus making it difficult to handle the oxidant load caused by a typical anesthesia dose. Patients should be closely monitored during administration of benzocaine (or any local anesthetic) for signs or symptoms of developing cyanosis, and intravenous methylene blue should be readily available on all crash carts and in any area where benzocaine is stored or used.

REFERENCES