

## Benzocaine-Induced Methemoglobinemia

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There have been 58 reported cases of benzocaine-induced methemoglobinemia since Bernstein (1) first described the condition in 1950. Although it occurs infrequently, benzocaine-induced methemoglobinemia is a potentially fatal complication if not promptly diagnosed and treated. We report a case of methemoglobinemia after topical use of benzocaine in preparation for bronchoscopy and subsequent endotracheal intubation.

### Case Report

A 71-yr-old, 53-kg woman was admitted to the cardiovascular intensive care unit (CVICU) because of increasing lethargy 2 days after undergoing a Collis-Belsey repair of a large paraesophageal hernia.

The patient had a history of anemia with hemocult positive stools, but no overt bleeding. She required two unit transfusions on three separate occasions during the past 3 yr, the last approximately 3 mos before admission. The examination for this had been unrevealing, except for multiple linear ulcerations in the paraesophageal hiatal hernia sac, suggestive of sac gastritis that was thought to be the source of her persistent anemia.

On admission to the CVICU, her temperature was 36.9°C, heart rate 112 bpm, arterial blood pressure 99/57 mm Hg, and respirations 20 breaths/min. The results of a physical examination were normal, except there was diminished air entry in the right base on auscultation of the chest. Results of laboratory investigations were normal, except for a white blood cell count of 13,800/mm<sup>3</sup> and a hematocrit of 31.8%. Results of analysis of arterial blood gases (ABG) were arterial pH (pHa) 7.28, Paco<sub>2</sub> 69 mm Hg, Pao<sub>2</sub> 116 mm Hg, base excess +5 mEq/L, HCO<sub>3</sub><sup>-</sup> 32, and Sao<sub>2</sub> 98% while the patient was breathing from a nonrebreather mask at an oxygen flow rate of 15 L/min. At that time, the Spo<sub>2</sub> was 96%. The fraction of inspired oxygen (Fio<sub>2</sub>) was reduced to 0.50, and noninvasive, intermittent positive-pressure breathing was started. A patient-controlled analgesia (PCA) pump (morphine 2 mg/mL, no basal rate, 1-mg demand bolus, and 6-min bolus interval) that was being used for postoperative

pain management was discontinued. The PCA demand bolus had been decreased from 1.0 mg to 0.5 mg the day before the patient's CVICU admission. The total opioid (morphine) use in the 24-h period before CVICU admission was 19 mg.

A chest radiograph showed a right lower lobe infiltrate. An IV combination of piperacillin and tazobactam (3.375 gm/6 h) was started. Because of a large amount of pulmonary secretions and the possibility of aspiration of gastric contents, an awake bronchoscopy was performed after a 1-s spray of 20% benzocaine to the oropharynx. A large amount of secretions was found, sent for culture, and later returned as mixed flora. Subsequent respiratory cultures grew *Pseudomonas aeruginosa*. Over the next 2 h, the patient became increasingly lethargic, hypercarbic, and hypoxemic. The results of ABG analysis 2h after bronchoscopy were pHa 7.20, Paco<sub>2</sub> 81 mm Hg, Pao<sub>2</sub> 52 mm Hg, base excess +4 mEq/L, HCO<sub>3</sub><sup>-</sup> 32, Sao<sub>2</sub> 77% while the patient was breathing from a 50% Venturi mask. At this point, it was decided to endotracheally intubate the patient. Review of the anesthesia record revealed a history of difficult endotracheal intubation because of an anterior glottic aperture and a short thyromental distance. Awake intubation of the trachea was performed by direct laryngoscopy with one attempt, after a 1-s spray to the oropharynx with 20% benzocaine. The interval between the two benzocaine doses was approximately 2 h. Synchronized intermittent mandatory ventilation at a rate of 14 breaths/min was instituted with a positive end-expiratory pressure of 8 cm H<sub>2</sub>O, and a Fio<sub>2</sub> of 1.00. The results of postintubation ABG analysis were pHa 7.51, Paco<sub>2</sub> 35 mm Hg, Pao<sub>2</sub> 289 mm Hg, base excess of +4 mEq/L, HCO<sub>3</sub><sup>-</sup> 27, and Sao<sub>2</sub> 100%. A continuous fentanyl infusion was started.

The patient remained hemodynamically stable and maintained a normal Pao<sub>2</sub> and Sao<sub>2</sub>; however, she developed central cyanosis and had a gradual decrease in Spo<sub>2</sub> to a low of 84%, despite increasing the Fio<sub>2</sub> to 0.85. A repeat chest radiograph revealed worsening of the right lower lobe infiltrate. An ABG sample (pHa 7.43, Paco<sub>2</sub> 40 mm Hg, Pao<sub>2</sub> 201 mm Hg, base excess +1 mEq/L, HCO<sub>3</sub><sup>-</sup> 25 mEq/L, Sao<sub>2</sub> 99%, SpO<sub>2</sub> 90%, on an Fio<sub>2</sub> of 0.75) appeared dark. The arterial percent o<sub>2</sub> saturation gap (Sao<sub>2</sub> - Spo<sub>2</sub> = 9%) suggested the presence of a nonoxygen transporting hemoglobin derivative. The methemoglobin level measured by coximetry was 22.5%. Methylene blue (1% tetramethyl thionine chloride, 1 mg/kg) was administered IV for 5 min. Approximately 1 h later, the results of ABG analysis were pHa 7.40, Paco<sub>2</sub> 41 mm Hg, Pao<sub>2</sub> 129 mm Hg, base excess 0, HCO<sub>3</sub><sup>-</sup> 25 mEq/L, Sao<sub>2</sub> 99%, Spo<sub>2</sub> 96%, on 0.45 Fio<sub>2</sub>. The

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methemoglobin level was 2.4%. Approximately 165 min after the administration of the methylene blue dose, the  $SaO_2$  and  $SpO_2$  were 98% with an  $FIO_2$  of 0.40, and the methemoglobin level was 2.0%. The central cyanosis had resolved. IV antibiotics and mechanical ventilatory support were continued for treatment of the pneumonia. The patient did not have recurrent methemoglobinemia, and she recovered uneventfully.

## Discussion

Our patient's initial lethargy can be explained by  $CO_2$  retention, possibly related to PCA use. This lethargic state may have led to aspiration, hypoxemia, and a right lower lobe infiltrate and was likely prolonged by methemoglobinemia. Although the results of her initial respiratory cultures were negative, she later developed pneumonia from *P aeruginosa* that responded to antibiotic therapy. The dark arterial blood and low  $SpO_2$  can be explained by hypoxemia secondary to a developing pneumonia. However, the  $PaO_2$  and  $SaO_2$  were not similarly decreased, and this inconsistency suggested the presence of a hemoglobin derivative, in this case methemoglobin.

Benzocaine (ethyl aminobenzoate) is a topical anesthetic routinely used for endotracheal intubation, endoscopy, transesophageal echocardiography, bronchoscopy, and other minor surgical and cannulation procedures. A one-second spray of 20% benzocaine delivers the recommended dose of 200 mg. Absorption of topical benzocaine is believed to occur mainly through systemic exposure, favored by broken skin or mucosa, and by absorption through the gastrointestinal tract.

Although methemoglobinemia is rare, it can be fatal if unrecognized. It is characterized by central cyanosis that is refractory to supplemental oxygen. The refractory cyanosis is caused by a higher than normal methemoglobin concentration and a decrease in oxygen-carrying capacity. In erythrocytes, the heme iron of unoxygenated hemoglobin is continually oxidized by various oxidant substances from the ferrous ( $Fe^{2+}$ ) to the ferric ( $Fe^{3+}$ ) state to form methemoglobin. The oxidized form of hemoglobin, methemoglobin, cannot bind oxygen or carbon dioxide, and therefore, the hemoglobin molecule loses its transport function. Methemoglobin normally constitutes less than 1% of the total hemoglobin. Reductive metabolic pathways regulate the amount of oxidant substances that oxidize heme iron to the ferric state, and nicotinamide adenine dinucleotide (NADH) methemoglobin reductase and nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase directly reduce the ferric hemoglobin to ferrous hemoglobin. Disruption of these regulatory pathways results in methemoglobin levels of greater than 1%.

Methemoglobinemia has two forms: acquired and congenital. In acquired methemoglobinemia, exposure

to certain drugs or chemicals may cause oxidation of hemoglobin to methemoglobin faster than methemoglobin is reduced to hemoglobin. Commonly reported oxidant substances include amyl nitrite, aniline dyes, benzocaine, bismuth subnitrate, Cetacaine (a combination preparation of 14% benzocaine, 2% tetracaine, and 2% butamben), dapson, lidocaine, nitroglycerin, p-aminosalicylic acid, phenytoin, prilocaine, primaquine, pyridine, silver nitrate, and sulfonamides (2). Prachal and Gregg (3) provide a comprehensive review of substances associated with methemoglobinemia. Aniline derivatives, such as lidocaine, prilocaine, and nitrites are the most common methemoglobin-inducing drugs.

Hereditary causes are extremely rare and include the M-hemoglobinopathies and NADH/NADPH dependent enzyme deficiencies. Methemoglobinemia has occurred in patients without predisposing factors or excessive doses of benzocaine. More than half of the reported cases involve infants and the elderly (4).

Symptom development depends on the ratio of methemoglobin to total hemoglobin. Central cyanosis usually occurs with methemoglobin concentrations of greater than 15%, although in anemic individuals, as in this case, it can occur with levels as low as 2.5% (2). Anxiety, headaches, weakness, dyspnea, nausea, and vomiting may occur with levels of greater than 30%. Lethargy, stupor, bradycardia, acidosis, and paralysis occur as methemoglobin levels approach 55%, but may occur at lower levels in patients who are anemic. Higher levels may cause coma, generalized seizures, arrhythmias, and hemodynamic instability (5). Levels of 70% are usually fatal (6). Concurrent or delayed (up to five days) hemolytic anemia may occur and produce jaundice or renal failure.

The diagnosis of methemoglobinemia is suggested by the presence of chocolate-brown arterial blood that does not change color when exposed to air in a patient with central cyanosis (7). There is usually no respiratory distress, and the  $SpO_2$  is typically low, despite high  $FIO_2$  and a normal  $PaO_2$  and  $SaO_2$ . The presence of a nonoxygen transporting hemoglobin derivative is suggested by a difference between the calculated ( $SaO_2$ ) and measured ( $SpO_2$ ) percent  $O_2$  saturation (arterial percent  $O_2$  saturation gap). The diagnosis is confirmed by qualitative measurements of methemoglobin by co-oximetry.

Once the diagnosis is confirmed, prompt treatment is mandatory. Therapy is directed to increasing the oxygen-carrying capacity of the blood by converting methemoglobin to hemoglobin. Treatment begins with general supportive care, including airway maintenance, supplemental oxygen, and hemodynamic support. Exposure to the methemoglobin-inducing drug or chemical should be stopped to prevent further absorption. Treatment of severe methemoglobinemia requires IV methylene blue (1% tetramethyl thionine

chloride, 1–2 mg/kg) administered for five minutes. Methylene blue is reduced to leukomethylene blue by accepting electrons from NADPH in the presence of NADPH methemoglobin reductase. Leukomethylene blue then acts as an electron donor and nonenzymatically reduces methemoglobin to hemoglobin. With larger doses, methylene blue can produce side effects including precordial pain, dyspnea, sweating, restlessness, and tremors. To avoid these toxic effects, the total dose should not exceed 7 mg/kg (8). Exacerbation of methemoglobinemia may occur with methylene blue doses of greater than 15 mg/kg by direct oxidation of hemoglobin to methemoglobin (8). Large doses can also cause blue discoloration of the skin, despite resolution of cyanosis. The average adult requires only two 100-mg ampules of methylene blue.

Normal levels of methemoglobin should be achieved within 20 minutes to one hour after methylene blue is administered. If cyanosis persists beyond one hour, a second dose may be given and repeated every four hours as necessary to the maximal dose of 7 mg/kg. Lack of response, because of deficiency of glucose-6-phosphate dehydrogenase or of NADPH methemoglobin reductase, or because of extremely increased methemoglobin levels (>70%), may require transfusion, exchange transfusion, or hemodialysis. Methemoglobinemia can recur because benzocaine is highly lipophilic and may continue to enter the bloodstream from adipose tissue stores after methylene blue blood concentrations are no longer therapeutic (4). The majority of these cases resolved within 24–72 hours after clearing residual benzocaine. All patients should be checked for the presence of hemolysis

within three to five days after methemoglobinemia resolves.

In conclusion, benzocaine-induced methemoglobinemia is a rare, but potentially fatal complication if unrecognized. In the intensive care setting in particular, the diagnosis of methemoglobinemia may be delayed while more common causes of a low  $S_pO_2$  and cyanosis in a critically ill patient are being eliminated. It is obviously important to be aware of the methemoglobinemia-inducing drugs that are frequently used in clinical practice and of the clinical presentation and laboratory changes that are characteristic of methemoglobinemia, in order to recognize this rare complication when it occurs.

## References

1. Bernstein BM. Cyanosis following use of anesthesia (ethylaminobenzoate). *Rev Gastroenterol* 1950;17:123–4.
2. Clary B, Skaryak L, Tedder M, et al. Methemoglobinemia complicating topical anesthesia during bronchoscopic procedures. *J Thorac Cardiovasc Surg* 1997;114:293–5.
3. Prachal JT, Gregg XT. Red cell enzymopathies. In: Hoffman R, Banz EJ, Shattil SJ, eds. *Hematology basic principles and practice*. 3rd ed. New York: Churchill Livingstone, 2000:561–75.
4. Rodriguez LF, Smolik LM, Zbehlik AJ. Benzocaine-induced methemoglobinemia: report of a severe reaction and review of the literature. *Ann Pharmacother* 1994;28:643–9.
5. Goldfrank LR, Kirsstein RK. *Toxicological emergencies: a handbook in problem solving*. New York: Appleton-Century-Crofts, 1978.
6. Curry S. Methemoglobinemia. *Ann Emerg Med* 1982;11:214–21.
7. Harley JD, Celermajer JM. Neonatal methaemoglobinaemia and the “red-brown” screening test. *Lancet* 1970;2:1223–5.
8. Guerriero SE. Methemoglobinemia caused by topical benzocaine. *Pharmacotherapy* 1997;17:1038–40.