Intraoperative Detection of Methemoglobinemia in a Patient Given Benzocaine Spray to Relieve Discomfort From a Nasogastric Tube: A Case Report

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A 27-year-old man who had 2 admissions 1 month apart for abdominal surgery had a high methemoglobin (MHb) level secondary to liberal use of benzocaine oral spray. A co-oximetry level for MHb of greater than 0.30 proportion of total hemoglobin (30.1%) was detected intraoperatively. The patient was successfully treated with methylene blue intravenously and recovered uneventfully.

When the arterial blood gas with a normal partial pressure of oxygen is inconsistent with a low pulse oximeter reading and with the physical appearance of the patient, methemoglobinemia should be considered as a differential diagnosis. This case illustrates the acquired form of methemoglobinemia. Adequate oxygen delivery to the tissues in the body is compromised when MHb overwhelms the capacity of the red blood cells to carry oxygen. If methemoglobinemia is left untreated, it may be fatal.

Keywords: Benzocaine spray, methemoglobinemia, methylene blue.

As anesthesia providers, one of our major responsibilities is to ensure adequate oxygen delivery to the tissues of the body. When cyanosis occurs, we focus on the airway and pulmonary and cardiovascular systems in search of the cause. If the condition is not readily diagnosed and corrected, it is also important to consider the role of hemoglobin in oxygen transport. Methemoglobinemia should always be considered in the differential diagnosis when the pulse oximeter displays a low saturation that cannot be attributed to another cause.

There is a special risk of masking early signs and symptoms in patients who are under general anesthesia or of overlooking methemoglobinemia as a differential diagnosis on airway management calls outside the operating room. Early recognition during the intraoperative period may be the first step in diagnosing and treating methemoglobinemia. The observation of "chocolate-brown blood" in the surgical field and known exposure to agents capable of causing methemoglobinemia such as nitrates, nitrites, sulfonamides, and the local anesthetics benzocaine and prilocaine may provide clues that will lead to the correct diagnosis.[1] Methemoglobinemia may also result from congenital deficiencies of enzymes that normally convert methemoglobin (MHb) to hemoglobin or from an alteration in the hemoglobin molecule itself.[2]

There is some concern that cardiopulmonary bypass (CPB) may have an effect in causing methemoglobinemia.[3] An impaired reduction of MHb in red blood cells after CPB, because of either a lack of energy substrates for the different MHb-reducing enzymes or reduced activity of the enzymes themselves, could be a cause. This hypothesis is supported by the decrease of enzyme activity with cell aging that might be accelerated by CPB.[3] This theory would also be in accordance with morphologic studies showing "sublethal damage" of the erythrocytes as a result of CPB, possibly as a consequence of the well-known inflammatory response to extracorporeal circulation.[4] In addition, patients who have major cardiac or pulmonary disease, or who are anemic, may be more likely to suffer from the consequences of methemoglobinemia.

Case Summary

The patient was a 27-year-old man, with a weight of 63 kg and a height of 160 cm. He had no known drug allergies, health problems, or previous surgeries and reported occasional ethanol use. He was admitted to the hospital from home by the local emergency medical system providers after sustaining a fall of about 3.6 m from a ladder while working on his roof. The patient was not intoxicated, and he did not lose consciousness. He underwent an exploratory laparotomy. The injuries consisted of blunt trauma only. He had positive findings from a computed tomography (CT) scan and underwent a primary surgical repair of a bladder rupture. During his 5-day hospital stay, he had a nasogastric (NG) tube in place for 4 days. For the discomfort of the NG tube he was allowed to use benzocaine (Hurricane) spray orally. Specifically, his orders read, "Hurricane spray prn [as needed] while NG in place." He had an uneventful recovery and was discharged.

However, a month later the patient returned because he was experiencing abdominal discomfort as well as nausea and vomiting. A follow-up cystogram revealed a leak and diffuse dilatation in the small bowel. An abdominal CT showed an obstructing lesion near the mid-jejunum and a leak in the wall of the bladder. He was admitted, an NG tube was placed, and he was kept at nothing-by-mouth (NPO) status and given intravenous (IV) fluids. Again, the orders read, "Hurricane spray 1-2 puffs every 4-6 hours as needed and Cepacol [nonprescription numbing] lozenges, as needed." He underwent another exploratory laparotomy, lysis of adhesions, bladder repair, and small-bowel resection. On the evening of surgery he was classified as an ASA class IIE. His vital signs were blood pressure 130/98 mm Hg and a heart rate of 100/min. The laboratory results were as follows: alkaline phosphatase, 1.3 μkat/L (77 U/L); bilirubin, 12.0 μmol/L (0.7 mg/dL); lipase, 2.5 μkat/L (152 U/L); international normalized ratio, 1.13; sodium, 134 mmol/L (134 mEq/L); potassium, 3.9 mmol/L (3.9 mEq/L); serum urea nitrogen, 5.0 mmol/L (14 mg/dL); hemoglobin, 137 g/L (13.7 g/dL); amylase, 3.50 μkat/L (210 U/L); alanine aminotransferase, 0.53 μkat/L (32 U/L); and aspartate aminotransferase, 0.48 μkat/L (29 U/L).

Further examination revealed a very pale, almost "gray" skin color; tachypnea; gray nailbeds; and pale lips. The patient had a low oxygen saturation of 89% and was given a 100% non-rebreather mask, with oxygen saturation rising to only 90%. He was taken to the operating room, standard monitoring was placed, and he was preoxygenated. A rapid-sequence intubation was done with 90 mg of succinylcholine, 140 mg of propofol, and 50 mg of lidocaine, and he was intubated orally with a 7.5-mm endotracheal tube. Bilateral breath sounds were confirmed, and he was placed on the ventilator with oxygen at 2-L flow and sevoflurane at 1.8%. Vecuronium, 6 mg, was given for muscle relaxation after the succinylcholine was no longer present by a train-of-four. After intubation and positive tube placement, the anesthetist confirmed that oxygen saturations were still only 91% by pulse oximetry. Postinduction blood pressure was 110/60 mm Hg, and the heart rate was 90/min. The incision was made, and the first comment by the surgeons was, "His blood is brown."

An arterial blood gas was sent to the laboratory, and the results were: pH, 7.31; P_{CO_2}, 5.3 kPa (40 mm Hg); P_{O_2}, 71 kPa (533 mm Hg); bicarbonate (HCO_3), 13 mmol/L (mEq/L); base excess, –16 mmol/L (–16 mEq/L); and a calculated oxygen saturation of 100%. Because the arterial blood gas result revealed a Pa_{O_2} that was not consistent with the low pulse oximetry reading and the appearance of "brown blood," methemoglobinemia was suspected and a co-oximeter analysis was done. Most respiratory departments and laboratories where blood gas analysis is done on a regular basis will usually have a spectrophotometer that can do direct measurement of oxyhemoglobin, carboxyhemoglobin, and MHb. The patient's MHb level was 0.30 proportion of total hemoglobin (30.1%) (normal, <0.01 [<1.0%]). He was treated with methylene blue, 65 mg (dosing 1-2 mg/kg) IV. Within 30 minutes of treatment, the oxygen saturations were 98% to 99%, his heart rate was 80/min, blood pressure was 120/60 mm Hg, and the blood in the surgical field appeared "normal" again. The rest of the surgery was uneventful, as was his recovery.

Discussion

This case illustrates acquired methemoglobinemia, undoubtedly acquired from the liberal use of benzocaine (Hurricane) spray. There is also a congenital or hereditary form of methemoglobinemia, and it is important to be aware of both causes.

Hemoglobin consists of 4 heme groups, each containing an iron atom. Each atom is capable of binding with oxygen only if the iron is in the reduced, or ferrous (Fe^{2+}), state. When an iron atom is oxidized, an electron is removed to make the ferric (Fe^{3+}) state of iron.[5] Methemoglobin, the form of hemoglobin that contains Fe^{3+}, cannot transport oxygen because the ferric hemoglobin is shaped differently. Thus, administered oxygen is unable to bind to the MHb molecule, and oxygen transport is impaired, despite adequate arterial oxygen tension.[6]

In the normal physiological state, small amounts of MHb form during the reaction between oxygen and hemoglobin. These amounts are approximately 1%, and such a low level is well tolerated. Typically, the MHb that does exist is rapidly converted back to hemoglobin unless there is a deficiency of the enzyme cytochrome-b_5 reductase and NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) MHb reductase.[7] There could also be a deficiency in glucose-6-phosphate dehydrogenase (G6PD), a major source of NADPH needed for reduction of oxidized cytochrome b_5. Cytochrome-b_5 reductase is responsible for more than 95% of the reducing capacity of erythrocytes. In contrast, NADPH MHb reductase accounts for less than 5% of normal erythrocyte-reducing capacity.[8]

Methemoglobinemia is caused by deficiencies in these reducing pathways (most notably the NADPH–MHb reductase pathway) or abnormal hemoglobin structure that tends to promote the formation of MHb from hemoglobin.[9] Patients who have inherited this deficiency in an autosomal recessive pattern may exhibit lifelong cyanosis.

The case presented illustrates the error in the perception that benzocaine is a benign product with a short half-life and minimal systemic absorption. The spray is intended most commonly for use on the mucosal tissues, typically in connection with preintubation bronchoscopy or endoscopy.[10] Benzocaine acts as an indirect oxidant,

converting the iron in erthrocytes from the ferrous to the ferric form, which impedes the hemoglobin's oxygen-carrying capability.

The packaging of benzocaine (Hurricane) states under the administration of product to "apply aerosol for 1 second or less for normal anesthesia; spray in excess of 2 seconds is contraindicated." No maximum dose is specified, but precautions include sensitization and an association with the occurrence of methemoglobinemia. Correct dosing includes guesswork because delivered quantities of the spray depend on many variables. These variables include canister tip orientation (upright, inverted, or horizontal), and the residual volume in the canister—a decreased volume would result in a reduction in spraying volume each time. This patient had the benzocaine spray and Cepacol lozenges "as needed" while the NG tube was in place during both admissions.

Although underlying cardiac or respiratory conditions may exacerbate the symptoms of methemoglobinemia, there are some risk factors that may predispose patients to methemoglobinemia. The obvious risk factor would be patients with a known hereditary lack of MHb reductase, as mentioned previously. There is an age-related risk affecting infants and the elderly. An increased systemic exposure and absorption through a break in the mucosal barrier or absorption through the gastrointestinal tract may be the main route of systemic access, as in this patient who had the NG tube and underwent a bowel resection. He may also have had an oropharyngeal abrasion or gastritis, areas of inflamed tissues, tissue hyperemia, and hypoxia, all which presumably facilitate the absorption of the drug. In addition, there may have been absorption through the respiratory membranes.

The previously mentioned risk factors and lack of appropriate dosing certainly put this patient at risk for acquiring methemoglobinemia. Reexposure to an offending agent has been documented in the literature as a risk for acquiring methemoglobinemia. This patient had 2 admissions, both with an NG tube and benzocaine spray and Cepacol lozenges as needed. During the first exposure, he may have developed a low level of MHb. The symptoms associated with methemoglobinemia roughly correlate with the proportion of MHb to total hemoglobin. This patient had a hemoglobin level lower than normal, at 13.7 g/L, on his second admission. Clinical cyanosis becomes evident at a MHb concentration of greater than 0.15 proportion of total hemoglobin (> 15%). Weakness, tachycardia, dyspnea, and nausea and vomiting are seen with MHb concentrations greater than 30%. Lethargy, dizziness, and stupor are seen at concentrations greater than 55%.[11] With concentrations of approximately 55% to 70%, individuals may experience circulatory failure, cardiac arrhythmias, seizures, and coma.[11] Death may occur with concentrations exceeding 70%.[12-14]

This patient was tachycardic, nauseated with vomiting, cyanotic, and hypoxic. His MHb level was greater than 0.30 proportion of total hemoglobin (> 30%). The patient's leak in the bladder and bowel obstruction with subsequent nausea and vomiting may have made him malnourished. Although the plasma albumin level was not tested, it may have been lower due to his nutritional state giving rise to more free benzocaine molecules. The higher concentration of free benzocaine may have tipped the balance for the formation of methemoglobinemia.[15] It is possible this patient was heterozygous with a low MHb reductase pathway and a reduced ability to convert MHb back to hemoglobin. Methemoglobinemia may not develop in a heterozygous patient in the presence of one trigger, but the combination of several triggers may overwhelm the low level of MHb reductase and push the patient into severe methemoglobinemia.[15]

Treatment of methemoglobinemia should be directed at restoring the oxygen-carrying capability of the blood and removing the oxidizing agent. Supportive therapy should be started concurrently, with special concern for airway patency, hemodynamic support, and administration of supplemental oxygen.[11]

Treatment of severe methemoglobinemia requires IV administration of methylene blue, 1 to 2 mg/kg over a period of 5 to 10 minutes. The total dose should not exceed 7 mg/kg.[16] In asymptomatic patients with methemoglobinemia, usually a MHb concentration of less than 0.15 (< 15%), only close observation is necessary. The half-life of MHb is approximately 55 minutes.[16] Most cases resolve within 24 to 72 hours after clearing of residual benzocaine.[16] When methylene blue is given, it augments the reducing potential of the NADPH–MHb reductase system by serving as a cofactor in the transfer of an electron from NADPH to the ferric heme ion.[17]

A diagnosis is confirmed by co-oximetry measurement of MHb concentrations and a good clinical response after methylene blue administration.[11] The patient in this case responded well to treatment with methylene blue, with a subsequent increase in oxygen saturation and a return to normal-appearing blood color in the surgical field.

An often overlooked measure in the treatment of methemoglobinemia is the administration of dextrose. Methylene blue is the gold standard of treatment; however, dextrose is a substrate necessary to form NADPH via the hexose monophosphate shunt pathway. For the endogenous reducing enzymes and methylene blue therapy to be effective, glucose must be present in adequate supply.[18]

A poor clinical response to methylene blue administration should arouse suspicion of an enzymatic deficiency and prompt an alternative treatment approach.[11] Patients with a G6PD deficiency would require transfusion and/or dialysis because methylene blue can cause hemolytic anemia in these patients.[19] Alternatives to methylene blue include riboflavin and ascorbic acid, but

these agents have a delayed onset of action and thus are not useful in the emergency situation.[20] N-acetylcysteine has been studied as an alternative to methylene blue, as have cytochrome P-450 inhibitors such as cimetidine. However, there is only limited information on these alternative agents, and further research is warranted.[21]

Conclusion

As anesthesia providers, we use several different medications in our practice that have been associated with methemoglobinemia. The most commonly used medications are local anesthetics (prilocaine, lidocaine, and benzocaine), metoclopramide, nitric oxide, nitroglycerin, and sodium nitroprusside. We may also be involved in heart surgeries using CPB, which has an attendant risk of producing excessive quantities of MHb.

Methemoglobinemia results from the oxidation of the ferrous iron in hemoglobin to the ferric state. High levels of MHb may be inherited or acquired. If acquired, methemoglobinemia may be caused by drugs or toxins, by deficiency of enzymes that normally convert MHb back to hemoglobin, or by a substitution of the hemoglobin molecule structure in itself.

Perioperative care includes arrival at the correct diagnosis when there is a discrepancy between pulse oximetry and clinical findings. Removal of the offending agent, treatment with methylene blue, and maintenance of oxygen delivery to tissues are the treatment goals.

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