

Two cases of methemoglobinemia

In a military community hospital

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Acquired methemoglobinemia is a rare but potentially life-threatening condition that is frequently associated in the primary care setting with topical anesthetics, dapsone, and antimalarial agents.¹ As illustrated by the cases of 2 patients who presented to Fort Belvoir Community Hospital in Virginia in the span of 3 weeks, health care providers must maintain a heightened index of suspicion for methemoglobinemia involving clinical presentations of persistent hypoxia or cyanosis.

Case 1

A 22-year-old woman presented to the emergency department with post-tonsillectomy bleeding. Her vital signs were within normal limits and included an oxygen saturation of 99% on room air. The patient was promptly evaluated by the on-call otorhinolaryngologist. Following multiple applications of nonmetred doses of 20% benzocaine topical aerosol spray, localized cauterization was performed. After hemostasis was achieved, the patient was transferred back to the emergency department for observation and intravenous rehydration.

Forty-five minutes later, the patient was noted to be profoundly cyanotic and diaphoretic, with a room air oxygen saturation of 89%. Despite use of a non-rebreathing face mask, the patient remained hypoxic, with oxygen saturations of around 88%. A portable chest x-ray scan taken immediately showed no relevant findings, an electrocardiogram had normal findings, and both blood pressure and heart rate remained within normal limits. Arterial blood gas was measured expeditiously; the blood was noted to be chocolate brown in colour, with a pH of 7.38, a P_{CO_2} of 37.2 mm Hg, a bicarbonate level of 24 mmol/L, and a P_{O_2} of 33.6 mm Hg. Portable co-oximetry was then performed, which identified a methemoglobin level of 23%. An infusion of 100 mg of methylene blue was given for 5 minutes, with immediate improvement in the patient's oxygen saturation. Repeat co-oximetry showed a methemoglobin level of 12%, and a second 100-mg dose of methylene blue was administered. Within minutes, the patient's colour had returned to normal and her oxygen saturation was 100% on room air.

The patient was subsequently admitted to the intensive care unit for close monitoring with continuous pulse oximetry and serial methemoglobin level checks. During the next 18 hours the patient remained hemodynamically stable, with good oxygenation on room air and a normal methemoglobin level.

Case 2

A 32-year-old man presented to the emergency department with acute onset of light-headedness, nausea, and paresthesia of the upper extremities. Symptoms started approximately 1 hour after drinking a large amount of "metallic-tasting" water from a fountain located at the Warrior Transition Battalion building in which he resided.

Initial vital signs were normal except for a room air oxygen saturation of 92% via pulse oximetry. Physical examination findings were notable for acrocyanosis, and he was given 2 L of oxygen via nasal cannula. Portable co-oximetry revealed a methemoglobin level of 15%. Arterial blood gas was measured and showed a pH of 7.40, a P_{CO_2} of 39.9 mm Hg, a bicarbonate level of 25 mmol/L, and a P_{O_2} of 103.0 mm Hg. Additional bloodwork results were unremarkable, and the patient was subsequently admitted for overnight

EDITOR'S KEY POINTS

- Presentations of methemoglobinemia in the primary care setting remain a real possibility, particularly with routine use of topical anesthetics. A heightened index of suspicion must be maintained in cases of hypoxia or cyanosis that are refractory to supplemental oxygen use.
- While co-oximetry can help provide an immediate diagnosis, blood colour alone might be the only "diagnostic tool" available in resource-limited or remote settings.
- Treatment is largely dependent on the degree of methemoglobinemia and presence or absence of symptoms. Methylene blue is the first-line treatment. Given the possibility of rebound methemoglobinemia, close follow-up in the primary care setting is recommended.



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observation. Because the patient was no longer symptomatic, methylene blue was not administered and his room air oxygen saturation steadily improved with supplemental oxygen.² The following morning, his methemoglobin level was 1.3% and he remained asymptomatic. Subsequent analysis of the drinking water revealed high levels of nitrates.

Literature search

A literature search using the terms *methemoglobinemia* and *co-oximetry* was performed in the PubMed and MEDLINE databases. Multiple potentially relevant studies were reviewed and considered for inclusion. References from selected articles were also searched. Inclusion criteria comprised, but were not limited to, articles published within the past 10 years regarding acquired methemoglobinemia and methemoglobinemia related to local anesthetics or environmental agents.

Discussion

Pathophysiology. Methemoglobin is an altered conformation of hemoglobin in which the ferrous (Fe^{2+}) state is oxidized to the ferric (Fe^{3+}) state. The ferric heme in methemoglobin is unable to bind oxygen, resulting in an altered structure. Additionally, there is increased oxygen affinity of the molecule, causing a left shift of the oxygen dissociation curve, interfering with oxygen delivery to tissues.³ Methemoglobinemia is either congenital or acquired. Congenital methemoglobinemia is due to a deficiency of the enzyme cytochrome b_5 reductase, which reduces methemoglobin to hemoglobin, maintaining a steady-state methemoglobin level of less than 1.0%. However, in individuals with normal cytochrome b_5 reductase levels, exposure to oxidizing agents might result in increased production of methemoglobin to the extent that enzymatic reduction cannot compensate for this acute increase.

Signs and symptoms. Patients with an elevated methemoglobin concentration might initially develop relatively mild symptoms such as dyspnea, headache, lethargy, and fatigue. However, at higher methemoglobin levels, profound cyanosis might develop and symptoms might progress to respiratory distress, altered mentation, seizure, dysrhythmias, and death.⁴ Patients with comorbidities, such as anemia or the presence of other abnormal hemoglobin species (eg, sickle cell anemia), cardiovascular disease, lung disease, or sepsis, might experience moderate to severe symptoms at much lower methemoglobin levels.¹ Young infants (<6 months of age) might be particularly susceptible to methemoglobinemia in the context of gastroenteritis and dehydration owing to low gastric acid production, a large number of nitrite-reducing bacteria, and relative ease of fetal hemoglobin oxidation.⁵

Pathogenesis and diagnosis. Acquired methemoglobinemia is most often caused by exposure to exogenous oxidizing substances. While many substances have been implicated, topical anesthetics, dapsone, and antimalarial medications are the most common.¹ Methemoglobinemia has also been identified in patients exposed to various environmental agents (ie, nitrogen-containing compounds) and in certain medical conditions such as sepsis.^{1,6}


Noninvasive methods of estimating methemoglobin levels have been developed. When methemoglobin levels rise above 20%, the blood develops a chocolate-brown colour.^{7,8} A low-cost quantitative test—a blood colour chart—was developed by Shihana et al and can be used at the bedside.⁸ By using this colour chart, clinicians can estimate the methemoglobin level based on the colour of the blood. Pulse oximeters that can estimate methemoglobin levels have also been developed, now commonly known as co-oximeters. Earlier models of co-oximeters were inaccurate in patients with oxygen saturation levels less than 95%; however, newer models used for humans were shown to be efficacious in the presence of oxygen saturation levels as low as 74%.⁹ When compared with arterial blood gas analysis—considered to be the criterion standard test—co-oximeters have been shown to accurately detect methemoglobin levels of 15% or less.^{10,11} Given their accuracy at low levels, co-oximeters are useful screening tools, but more studies are needed to validate them at methemoglobin levels greater than 15%.

Management. Primary treatment of methemoglobinemia involves removal of the inciting agent whenever possible. Methylene blue is generally the first-line treatment of moderate to severe cases and should be infused in asymptomatic patients with methemoglobin levels greater than 30% and in symptomatic patients with levels greater than 20%.¹ Observation with serial monitoring of methemoglobin levels might be reasonable in asymptomatic patients with methemoglobin levels less than 20%.¹² Patients whose methemoglobin levels do not improve with methylene blue infusion might require exchange transfusion.^{1,5} Owing to the risk of rebound methemoglobinemia in patients receiving methylene blue, close observation for up to 24 hours is recommended.^{11,13} Caution should be taken when administering methylene blue, as high doses (>7 mg/kg) can paradoxically increase methemoglobin production.¹⁴

Conclusion

As illustrated by these case reports, presentations of methemoglobinemia in the primary care setting remain a real possibility, particularly with routine use of topical anesthetics. A heightened index of suspicion must be maintained in cases of hypoxia or cyanosis that are

refractory to supplemental oxygen use. Fortunately, the diagnosis was expeditiously considered in both cases and these patients recovered fully.

While co-oximetry can help provide an immediate diagnosis, blood colour alone ("chocolate-brown" blood) might be the only "diagnostic tool" available in resource-limited or remote settings. Treatment is largely dependent on the degree of methemoglobinemia and presence or absence of symptoms. Methylene blue remains the first-line treatment. Given the possibility of rebound methemoglobinemia, close follow-up in the primary care setting is recommended. 

At the time of the presenting cases, **Drs Wall, Wong, and Kinderknecht** were family medicine residents at Fort Belvoir Community Hospital in Fort Belvoir, Va. **Ms Farrior** was a nurse in the Department of Emergency Medicine at Fort Belvoir Community Hospital. **Dr Gabbay** was the staff emergency medicine physician in the Department of Emergency Medicine at Fort Belvoir Community Hospital.

Competing interests

None declared

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