



**EDUCATIONAL OBJECTIVE:** Readers will consider methemoglobinemia when there is a discrepancy between the oxyhemoglobin level and oxygen saturation by pulse oximetry

**BHUVNESH AGGARWAL, MD**

Department of Cardiology, Heart and Vascular Institute, Cleveland Clinic

**RUHAIL KOHLI, MD**

Department of Internal Medicine, Cleveland Clinic

**RENDELL ASHTON, MD**

Department of Pulmonary and Critical Care Medicine, Cleveland Clinic

**MOISES AURON, MD**

Departments of Hospital Medicine and Pediatric Hospital Medicine, Cleveland Clinic; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# When the dissociation curve shifts to the left

A 48-YEAR-OLD WOMAN presented to the emergency department after 2 days of nonproductive cough, chest discomfort, worsening shortness of breath, and subjective fever. She had a history of systemic sclerosis. She was currently taking prednisone 20 mg daily and aspirin 81 mg daily.

Physical examination revealed tachypnea (28 breaths per minute), and bronchial breath sounds in the left lower chest posteriorly.

The initial laboratory workup revealed:

- Hemoglobin 106 g/L (reference range 115–155)
- Mean corpuscular volume 84 fL (80–100)
- White blood cell count  $29.4 \times 10^9/L$  (3.70–11.0), with 85% neutrophils
- Platelet count  $180 \times 10^9/L$  (150–350)
- Lactate dehydrogenase 312 U/L (100–220).

Chest radiography showed opacification of the lower lobe of the left lung.

She was admitted to the hospital and started treatment with intravenous azithromycin and ceftriaxone for presumed community-acquired pneumonia, based on the clinical presentation and findings on chest radiography. Because of her immunosuppression (due to chronic prednisone therapy) and her high lactate dehydrogenase level, *Pneumocystis jirovecii* pneumonia was suspected, and because she had a history of allergy to trimethoprim-sulfamethoxazole and pentamidine, she was started on dapsone.

During the next 24 hours, she developed worsening dyspnea, hypoxia, and cyanosis. She was placed on an air-entrainment mask, with a fraction of inspired oxygen of 0.5. Pulse oximetry showed an oxygen saturation of 85%, but arterial blood gas analysis indicated an oxyhemoglobin concentration of 95%.

doi:10.3949/ccjm.82a.14044

## ■ THE 'SATURATION GAP'

1 Which is most likely to have caused the discrepancy between the oxyhemoglobin concentration and the oxygen saturation by pulse oximetry in this patient?

- ☐ Methemoglobinemia
- ☐ Carbon monoxide poisoning
- ☐ Inappropriate placement of the pulse oximeter probe
- ☐ Pulmonary embolism

Methemoglobinemia is the most likely cause of the discrepancy between the oxyhemoglobin levels and the oxygen saturation by pulse oximetry, a phenomenon also known as the “saturation gap.” Other common causes are cyanide poisoning and carbon monoxide poisoning.

Carbon monoxide poisoning, however, does not explain our patient’s cyanosis. On the contrary, carbon monoxide poisoning can actually cause the patient’s lips and mucous membranes to appear unnaturally bright pink. Also, carbon monoxide poisoning raises the blood concentration of carboxyhemoglobin (which has a high affinity for oxygen), and this usually causes pulse oximetry to read inappropriately high, whereas in our patient it read low.

Incorrect placement of the pulse oximeter probe can result in an inaccurate measurement of oxygen saturation. Visualization of the waveform on the plethysmograph or the signal quality index can be used to assess adequate placement of the pulse oximeter probe. However, inadequate probe placement does not explain our patient’s dyspnea and cyanosis.

Pulmonary embolism can lead to hypoxia as a result of ventilation-perfusion mismatch. However, pulmonary embolism leading to low oxygen saturation on pulse oximetry will also

*P jirovecii* pneumonia was suspected, and dapsone was started in light of her allergy to trimethoprim-sulfamethoxazole and pentamidine

lead to concomitantly low oxyhemoglobin levels as measured by arterial blood gas analysis, and this was not seen in our patient.

## ■ BACK TO OUR PATIENT

Because there was a discrepancy between our patient's pulse oximetry reading and oxyhemoglobin concentration by arterial blood gas measurement, her methemoglobin level was checked and was found to be 30%, thus confirming the diagnosis of methemoglobinemia.

## ■ WHAT IS METHEMOGLOBINEMIA, AND WHAT CAUSES IT?

Oxygen is normally bound to iron in its ferrous ( $\text{Fe}^{2+}$ ) form in hemoglobin to form oxyhemoglobin. Oxidative stress in the body can cause iron to change from the ferrous to the ferric ( $\text{Fe}^{3+}$ ) state, forming methemoglobin. Methemoglobin is normally present in the blood in low levels (< 1% of the total hemoglobin), and ferric iron is reduced and recycled back to the ferrous form by NADH-cytochrome b5 reductase, an enzyme present in red blood cells. This protective mechanism maintains methemoglobin levels within safe limits. But increased production can lead to accumulation of methemoglobin, resulting in dyspnea and hypoxia and the condition referred to as methemoglobinemia.<sup>1</sup>

Increased levels of methemoglobin relative to normal hemoglobin cause tissue hypoxia by several mechanisms. Methemoglobin cannot efficiently carry oxygen; instead, it binds to water or to a hydroxide ion depending on the pH of the environment.<sup>2</sup> Therefore, the hemoglobin molecule does not carry its usual load of oxygen, and hypoxia results from the reduced delivery of oxygen to tissues. In addition, an increased concentration of methemoglobin causes a leftward shift in the oxygen-hemoglobin dissociation curve, representing an increased affinity to bound oxygen in the remaining heme groups. The tightly bound oxygen is not adequately released at the tissue level, thus causing cellular hypoxia.

Methemoglobinemia is most often caused by exposure to an oxidizing chemical or drug that increases production of methemoglobin. In rare cases, it is caused by a congenital deficiency of NADH-cytochrome b5 reductase.<sup>3</sup>

**2** Which of the following drugs can cause methemoglobinemia?

- ☐ Acetaminophen
- ☐ Dapsone
- ☐ Benzocaine
- ☐ Primaquine

All four of these drugs are common culprits for causing acquired methemoglobinemia; others include chloroquine, nitroglycerin, and sulfonamides.<sup>4-6</sup>

The increased production of methemoglobin caused by these drugs overwhelms the protective effect of reducing enzymes and can lead to an accumulation of methemoglobin. However, because of variability in cellular metabolism, not every person who takes these drugs develops dangerous levels of methemoglobin.

Dapsone and benzocaine are the most commonly encountered drugs known to cause methemoglobinemia (TABLE 1). Dapsone is an anti-inflammatory and antimicrobial agent most commonly used for treating lepromatous leprosy and dermatitis herpetiformis. It is also often prescribed for prophylaxis and treatment of *P jirovecii* pneumonia in immunosuppressed individuals.<sup>7</sup> Benzocaine is a local anesthetic and was commonly used before procedures such as oral or dental surgery, transesophageal echocardiography, and endoscopy.<sup>8-10</sup> Even low doses of benzocaine can lead to high levels of methemoglobinemia. However, the availability of other, safer anesthetics now limits the use of benzocaine in major US centers. In addition, the topical anesthetic Emla (lidocaine plus prilocaine) has been recently reported as a cause of methemoglobinemia in infants and children.<sup>11,12</sup>

Also, potentially fatal methemoglobinemia has been reported in patients with a deficiency of G-6-phosphate dehydrogenase (G6PD) who received rasburicase, a recombinant version of urate oxidase enzyme used to prevent and treat tumor lysis syndrome.<sup>13,14</sup>

Lastly, methemoglobinemia has been reported in patients with inflammatory bowel disease treated with mesalamine.

Although this adverse reaction is rare, clinicians should be aware of it, since these agents are commonly used in everyday medical practice.<sup>15</sup>

**Patients with clinically significant methemoglobinemia usually have a saturation gap > 10%**

TABLE 1

## Common agents that can cause methemoglobinemia

Class of drugs	Examples
<b>Antibiotics</b>	Dapsone, trimethoprim-sulfamethoxazole, sulfonamide
<b>Anesthetics</b>	Benzocaine, lidocaine, procaine, prilocaine
<b>Analgesics</b>	Acetaminophen
<b>Antimalarials</b>	Primaquine, chloroquine
<b>Anticancer agents</b>	Cyclophosphamide, flutamide
<b>Others</b>	Nitroglycerin, sodium nitroprusside, mesalamine, rasburicase

### RECOGNIZING THE DANGER SIGNS

The clinical manifestations of methemoglobinemia are directly proportional to the percentage of methemoglobin in red blood cells. Cyanosis generally becomes apparent at concentrations around 15%, at which point the patient may still have no symptoms. Anxiety, lightheadedness, tachycardia, and dizziness manifest at levels of 20% to 30%. Fatigue, confusion, dizziness, tachypnea, and worsening tachycardia occur at levels of 30% to 50%. Levels of 50% to 70% cause coma, seizures, arrhythmias, and acidosis, and levels over 70% are considered lethal.<sup>16</sup>

While these levels provide a general guideline of symptomatology in an otherwise healthy person, it is important to remember that patients with underlying conditions such as anemia, lung disease (both of which our patient had), sepsis, thalassemia, G6PD deficiency, and sickle cell disease can manifest symptoms at lower concentrations of methemoglobin.<sup>1,17</sup>

Most patients who develop clinically significant levels of methemoglobin do so within the first few hours of starting one of the culprit drugs.

### DIAGNOSIS: METHEMOGLOBINEMIA AND THE SATURATION GAP

In patients with methemoglobinemia, pulse oximetry gives lower values than arterial blood gas oxygen measurements. Regular pulse oximetry works by measuring light absorbance at two distinct wavelengths (660 and 940 nm)

to calculate the ratio of oxyhemoglobin to deoxyhemoglobin. Methemoglobin absorbs light at both these wavelengths, thus lowering the pulse oximetry values.<sup>1</sup>

In contrast, oxygen saturation of arterial blood gas (oxyhemoglobin) is calculated indirectly from the concentration of dissolved oxygen in the blood and does not include oxygen bound to hemoglobin. Therefore, the measured arterial oxygen saturation is often normal in patients with methemoglobinemia since it relies only on inspired oxygen content and is independent of the methemoglobin concentration.<sup>18</sup>

Oxygen supplementation can raise the level of oxyhemoglobin, which is a measure of dissolved oxygen, but the oxygen saturation as measured by pulse oximetry remains largely unchanged—ie, the saturation gap. A difference of more than 5% between the oxygen saturation by pulse oximetry and blood gas analysis is abnormal. Patients with clinically significant methemoglobinemia usually have a saturation gap greater than 10%.

Several other unique features should raise suspicion of methemoglobinemia. It should be considered in a patient presenting with cyanosis out of proportion to the oxygen saturation and in a patient with low oxygen saturation and a normal chest radiograph. Other clues include blood that is chocolate-colored on gross examination, rather than the dark red of deoxygenated blood.

Co-oximetry measures oxygen saturation using different wavelengths of light to distinguish between fractions of oxyhemoglobin,

The preferred treatment: identify and promptly stop the causative agent, and start methylene blue infusion

deoxyhemoglobin, and methemoglobin, but it is not widely available.

### THE NEXT STEP

**3** What is the next step in the management of our patient?

- ☐ Discontinue the dapsone
- ☐ Start methylene blue
- ☐ Start hyperbaric oxygen
- ☐ Give sodium thiosulfate
- ☐ Discontinue dapsone and start methylene blue

The next step in her management should be to stop the dapsone and start an infusion of methylene blue. Hyperbaric oxygen is used in treating carbon monoxide poisoning, and sodium thiosulfate is used in treating cyanide toxicity. They would not be appropriate in this patient's care.

### MANAGEMENT OF ACQUIRED METHEMOGLOBINEMIA

The first, most critical step in managing acquired methemoglobinemia is to immediately discontinue the suspected offending agent. In most patients without a concomitant condition such as anemia or lung disease and with a methemoglobin level below 20%, discontinuing the offending agent may suffice. Patients with a level of 20% or greater and patients with cardiac and pulmonary disease, who develop symptoms at lower concentrations of methemoglobin, require infusion of methylene blue.

Methylene blue is converted to its reduced form, leukomethylene blue, by NADPH-methemoglobin reductase. As it is oxidized, leukomethylene blue reduces methemoglobin to hemoglobin. A dose of 1 mg/kg intravenously is given at first. The response is usually dramatic, with a reduction in methemoglobin levels and improvement in symptoms often within 30 to 60 minutes. If levels remain high, the dose can be repeated 1 hour later.<sup>19</sup>

A caveat: methylene blue therapy should be avoided in patients with complete G6PD deficiency. Methylene blue works through the enzyme NADPH-methemoglobin reductase, and since patients with G6PD deficiency lack this enzyme, methylene blue is ineffective.

In fact, since it cannot be reduced, excessive methylene blue can oxidize hemoglobin to methemoglobin, further exacerbating the condition. In patients with partial G6PD deficiency, methylene blue is still recommended as a first-line treatment, but at a lower initial dose (0.3–0.5 mg/kg). However, in patients with significant hemolysis, an exchange transfusion is the only treatment option.

### CASE CONCLUDED

Since dapsone was identified as the likely cause of methemoglobinemia in our patient, it was immediately discontinued. Because she was symptomatic, 70 mg of methylene blue was given intravenously. Over the next 60 minutes, her clinical condition improved significantly. A repeat methemoglobin measurement was 3%.

She was discharged home the next day on oral antibiotics to complete treatment for community-acquired pneumonia.

### TAKE-HOME POINTS

- Consider methemoglobinemia in a patient with unexplained cyanosis.
- Pulse oximetry gives lower values than arterial blood gas oxygen measurements in patients with methemoglobinemia, and pulse oximetry readings do not improve with supplemental oxygen.
- A saturation gap greater than 5% strongly suggests methemoglobinemia.
- The diagnosis of methemoglobinemia is confirmed by measuring the methemoglobin concentration.
- Most healthy patients develop symptoms at methemoglobin levels of 20%, but patients with comorbidities can develop symptoms at lower levels.
- A number of drugs can cause methemoglobinemia, even at therapeutic dosages.
- Treatment is generally indicated in patients who have symptoms or in healthy patients who have a methemoglobin level of 20% or greater.
- Identifying and promptly discontinuing the causative agent and initiating methylene blue infusion (1 mg/kg over 5 minutes) is the preferred treatment.

**A caveat: methylene blue should be avoided in patients with complete G6PD deficiency**

## REFERENCES

1. Cortazzo JA, Lichtman AD. Methemoglobinemia: a review and recommendations for management. *J Cardiothorac Vasc Anesth* 2014; 28:1055–1059.
2. Margulies DR, Manookian CM. Methemoglobinemia as a cause of respiratory failure. *J Trauma* 2002; 52:796–797.
3. Skold A, Cosco DL, Klein R. Methemoglobinemia: pathogenesis, diagnosis, and management. *South Med J* 2011; 104:757–761.
4. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. *Medicine (Baltimore)* 2004; 83:265–273.
5. Kanji HD, Mithani S, Boucher P, Dias VC, Yarema MC. Coma, metabolic acidosis, and methemoglobinemia in a patient with acetaminophen toxicity. *J Popul Ther Clin Pharmacol* 2013; 20:e207–e211.
6. Kawasumi H, Tanaka E, Hoshi D, Kawaguchi Y, Yamanaoka H. Methemoglobinemia induced by trimethoprim-sulfamethoxazole in a patient with systemic lupus erythematosus. *Intern Med* 2013; 52:1741–1743.
7. Wieringa A, Bethlehem C, Hoogendoorn M, van der Maten J, van Roon EN. Very late recovery of dapsone-induced methemoglobinemia. *Clin Toxicol (Phila)* 2014; 52:80–81.
8. Barclay JA, Ziemba SE, Ibrahim RB. Dapsone-induced methemoglobinemia: a primer for clinicians. *Ann Pharmacother* 2011; 45:1103–1115.
9. Taleb M, Ashraf Z, Valavoor S, Tinkel J. Evaluation and management of acquired methemoglobinemia associated with topical benzocaine use. *Am J Cardiovasc Drugs* 2013; 13:325–330.
10. Chowdhary S, Bukoye B, Bhansali AM, et al. Risk of topical anesthetic-induced methemoglobinemia: a 10-year retrospective case-control study. *JAMA Intern Med* 2013; 173:771–776.
11. Larson A, Stidham T, Banerji S, Kaufman J. Seizures and methemoglobinemia in an infant after excessive EMLA application. *Pediatr Emerg Care* 2013; 29:377–379.
12. Schmitt C, Matulic M, Kervégant M, et al. Methaemoglobinaemia in a child treated with Emla cream: circumstances and consequences of overdose [in French]. *Ann Dermatol Venerol* 2012; 139:824–827.
13. Bucklin MH, Groth CM. Mortality following rasburicase-induced methemoglobinemia. *Ann Pharmacother* 2013; 47:1353–1358.
14. Cheah CY, Lew TE, Seymour JF, Burbury K. Rasburicase causing severe oxidative hemolysis and methemoglobinemia in a patient with previously unrecognized glucose-6-phosphate dehydrogenase deficiency. *Acta Haematol* 2013; 130:254–259.
15. Druetz A, Rahier JF, Hébuterne X. Methaemoglobinaemia and renal failure following mesalazine for treatment of inflammatory bowel disease. *J Crohns Colitis* 2014; 8:900–901.
16. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999; 34:646–656.
17. Groeper K, Katcher K, Tobias JD. Anesthetic management of a patient with methemoglobinemia. *South Med J* 2003; 96:504–509.
18. Haymond S, Cariappa R, Eby CS, Scott MG. Laboratory assessment of oxygenation in methemoglobinemia. *Clin Chem* 2005; 51:434–444.
19. Jang DH, Nelson LS, Hoffman RS. Methylene blue for distributive shock: a potential new use of an old antidote. *J Med Toxicol* 2013; 9:242–249.

ADDRESS: Moises Auron, MD, Department of Internal Medicine, M2 Annex, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: [auronm@ccf.org](mailto:auronm@ccf.org)