

# Methemoglobinemia: Cyanosis and Street Methamphetamines

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Methemoglobin is a type of hemoglobin in which the ferrous ion has been oxidized to the ferric state. It is therefore incapable of combining with or transporting the oxygen molecule, which is replaced by a hydroxyl radical. Methemoglobinemia can be acquired or inherited. Most cases are acquired and are primarily due to exposure to certain drugs and chemicals, such as nitrates, nitrites, quinones, and chlorates. Inherited methemoglobinemia can result from a structural abnormality of the globin chains, or it can occur as a result of a red blood cell enzyme defect in which the methemoglobin formed cannot be converted back to the reduced form of hemoglobin. Methemoglobin is normally present in the blood in concentrations of 1 to 2 percent and its formation is reversible.<sup>1</sup> I came across a particularly interesting case of methemoglobinemia in which the patient had acute cyanosis.

## Case Report

A 31-year-old woman had brought her son, who had nausea and vomiting, to the After-hours Urgent Care clinic, where they were triaged to the urgent care section. While she was sitting in the waiting room with her son and her husband, the husband noticed that his wife was looking weak and saw that her fingernails and lips were turning blue. The husband called a nurse to look at his wife. Immediately noticing the cyanosis, the nurse brought the patient to the emergency department across the hall, where she was seen by the physician. The patient denied any concerns at the time except for feeling weak and almost fainting while registering her son with the clinic upon arrival. She thought it was just because it was late,

and she had not gotten much sleep during the last couple of days.

Her medical history was notable only for mild asthma since childhood, and she denied any breathing difficulties for the past several days. She was a mother of two boys, worked as a secretary, and lived with her husband of several years. She denied taking any medications (over-the-counter or prescription) or street drugs.

Upon initial examination, although she was awake and alert and answered questions appropriately, she appeared dyspneic and slightly agitated. Her temperature, pulse, and blood pressure were normal, but her respirations were 56/min, and a pulse oximetry reading was 88 percent on room air. Her lungs were clear by auscultation, and she had good air exchange and appropriate thoracic expansion. There was no tactile fremitus or unusual response to percussion. Findings on a heart examination were normal except for a slight tachycardia. Her fingers were cyanotic in the nail beds, and she had perioral cyanosis. There were no clubbing changes on her distal digits.

While she was being examined, the patient's pulse oximetry readings were gradually decreasing. She was given a 100 percent oxygen nonrebreather mask, but her readings continued to fall dramatically. She was told she needed to be intubated for full oxygen support, to which she agreed. Immediately after she was intubated, I was asked to help care for the patient as she was being admitted into the hospital.

Her arterial blood gases before intubation were pH 7.44, pCO<sub>2</sub> 26 mmHg, and pO<sub>2</sub> 109 mmHg, and her oxygen saturation was 52 percent. The measured methemoglobin was 50.6 percent. A repeat blood gas measurement was obtained after intubation and was pH 7.45, pCO<sub>2</sub> 24 mmHg, and pO<sub>2</sub> 321 mmHg, with 65 percent oxygen saturation, and the methemoglobin was still elevated at 40.3 percent. When the patient had her blood drawn for both the arterial blood and peripheral

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blood tests, it appeared to have a brown hue. The rest of her laboratory studies were normal. She was given two doses of 120 mg of methylene blue dye 1 hour apart. She was then transferred to the intensive care unit. After methylene blue was given, her values returned to normal on the next blood gas analysis, with a methemoglobin of 2.8 percent. She was extubated the next morning and was not given any more methylene blue dye. The remainder of her hospital stay was uneventful. Her oxygen saturation was 99 percent on room air. Her husband called her work and apparently nobody else there had been ill. No one in her home had experienced similar symptoms as well.

After the patient was extubated, she admitted to using some methamphetamines that her brother had given her the day before admission. She did not know where he obtained the methamphetamines, but he had sold the same product to other people. She did not know of anyone else having a reaction similar to hers. She had used methamphetamines occasionally in the last 2 years, but she believed her brother had used the same methamphetamines and had not had any similar effects. She denied abusing any other drugs at any time. She did not smoke cigarettes or abuse alcohol.

### Discussion

Methemoglobinemia decreases the oxygen-carrying capacity of blood, because the oxidized iron cannot reversibly bind oxygen. Moreover, when one or more iron atoms have been oxidized, the conformation of hemoglobin is changed to increase the oxygen affinity of the remaining ferrous heme groups. In this way methemoglobinemia exerts a dual effect in impairing the supply of oxygen to tissues.<sup>2-4</sup>

### Toxic Methemoglobinemia

Hemoglobin is continuously oxidized in vivo from the ferrous to the ferric state. The rate of such oxidation is accelerated by many drugs and toxic chemicals, including sulfonamides, lidocaine and other aniline derivatives, and nitrates. A great number of chemical substances can cause methemoglobinemia. The following are some of the agents that are responsible for clinically serious methemoglobinemia in current clinical practice: phenazopyridine, sulfamethoxazole, dapsone, aniline, paraquat-monolinuron, nitrate, nitroglyc-

erin, amyl nitrite, isobutyl nitrite, sodium nitrite, and local anesthetics (benzocaine, prilocaine).<sup>3</sup>

### Diagnosis

A bluish discoloration of the skin and mucous membranes, designated cyanosis, has been recognized since antiquity to be a manifestation of lung or heart disease. Cyanosis resulting from drug administration has also been recognized since before 1890.<sup>3</sup> Toxic methemoglobinemia occurs when various drugs or toxic substances either oxidize hemoglobin directly in the circulation or facilitate its oxidation by molecular oxygen.<sup>4</sup>

Cyanosis that is unresponsive to oxygen therapy,<sup>5</sup> in conjunction with a history of drug or chemical exposure, should lead to the consideration of methemoglobinemia. Blood with more than 15 percent methemoglobin appears dark red or brown and does not become bright red on exposure to oxygen (representing the conversion of deoxyhemoglobin to oxyhemoglobin). Methemoglobin levels of up to 20 percent are usually well tolerated in previously healthy adults. As levels approach 40 percent, patients complain of headache, dizziness, fatigue, and shortness of breath. Levels of 60 percent produce lethargy, stupor, and coma.<sup>6</sup> Patients with cardiovascular compromise or anemia will manifest symptoms at lower methemoglobin levels.<sup>7,8</sup>

The definitive diagnosis is made by arterial blood gas analysis with co-oximetry. Usually methemoglobin is seen with a normal  $pO_2$  level and a low measured oxygen saturation. The  $pO_2$  reading is unaffected, because it is a measure of dissolved oxygen in the plasma.<sup>5</sup> Similarly, the calculated oxygen saturation is expected to be normal, as it is derived from the  $pO_2$ . Because pulse oximetry is widely used in emergency departments, its lack of usefulness in diagnosing methemoglobinemia is noteworthy. Pulse oximeters overestimate the oxygen saturation in the presence of methemoglobin. They also show a diminished response to a change in oxygen saturation when methemoglobin is present.<sup>9,10</sup> As a result, arterial blood gases must be obtained in a patient with cyanosis.

### Laboratory

With methemoglobinemia,  $pO_2$  levels are normal, but measured oxygen saturation is reduced. Laboratories that calculate oxygen saturation

from pO<sub>2</sub> levels (rather than directly measure it) will report normal oxygen saturation levels.<sup>11</sup> In some laboratories arterial blood gas is also used to measure the methemoglobin level in percentages, which should help with the diagnosis.<sup>12</sup>

Methemoglobinemia can be detected with a simple office test. After placing 1 drop of the patient's blood on a piece of filter paper next to a drop of blood from a normal individual, when dry, the methemoglobin-containing blood will turn a deep chocolate-brown or slate-gray color. Another screening test involves partially filling a tube with whole blood, shaking it, and then observing the color. Methemoglobin-containing blood will not turn red but will remain dark when shaken in air or when oxygen is bubbled through it.<sup>9</sup>

Benzocaine and other local anesthetics are commonly used as cocaine adulterants by drug dealers to increase profit from a given quantity of drug.<sup>13</sup> As with cocaine, methamphetamines can be similarly altered to increase profit when sold. Local anesthetics are ideal for this purpose, as they give the user a sense of increased potency because of the anesthetic effect on nasal passages. The clinical effects of these adulterants are not often apparent when the substance is inhaled.<sup>14</sup>

### Treatment

Treatment involves symptomatic support for the patient. The most important step would be to provide 100 percent oxygen to keep the blood oxygen saturation as high as possible. It might be necessary to resort to mechanical intubation to give the maximum forced inspiratory oxygen. The patient most likely will need short-acting paralytics for intubation and sedation while on artificial breathing. The patient should also receive maintenance fluids intravenously while being mechanically ventilated.

The computer program Poisindex Toxicology Management, by Micromedex, is an excellent aid to the physician in treatment of methemoglobinemia.<sup>15</sup> Every hospital should be equipped with this database. There is even a section for animals with methemoglobinemia. When "methemoglobinemia" is typed, the computer retrieves adequate information to help the physician. Emergency therapy for acquired methemoglobinemia consists of an intravenous injection of 1 mg/kg methylene blue. Subsequent management

and management of less severe cases are accomplished by oral methylene blue (60 mg three or four times a day) or ascorbic acid, 300 to 600 mg/d. In patients with glucose-6-phosphate deficiency, methylene blue can provoke hemolysis.<sup>16</sup>

Upon resolution of the methemoglobinemia and the improvement of oxygen saturation, the patient should be easily extubated as sedation wears off. In general, there is no need to give repeated doses of methylene blue once improvement is established. Once extubated, the patient should be questioned again as to possible ingestions or drug use to establish a cause.

### Conclusion

In the case of our patient, we are assuming that she might have been exposed to a benzocaine cutting substance in the methamphetamine. She denied any other exposure or ingestion. None of her co-workers or family members, including her brother, had known of any other similar episodes. I am assuming that my patient might be more sensitive to converting to methemoglobin and should carefully monitor use of nitrites or local anesthetics.

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