

Virtual Mentor

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CLINICAL PEARL

Biochemistry, Diagnosis, and Treatment of Nitrate Toxicity

Amir Miodovnik, MD

Pediatric review books often contain a case of a previously healthy infant who comes to a clinic or ER with a recent history of diarrhea and vomiting followed by the onset of central cyanosis that does not improve with supplemental oxygen. The salient background information centers on the water source used to prepare the child's feedings, which often derives from a private well rather than a municipal water source. Cyanosis refractory to standard oxygen therapy suggests that the hypoxia does not stem from a congenital or acquired cardiac or respiratory defect. The dramatic improvement reported following treatment with the correct antidote belies the complex biochemical pathways underlying the condition known as methemoglobinemia. What I hope to do in this brief clinical pearl is highlight an important environmental cause of pediatric methemoglobinemia.

Background

Methemoglobinemia is a disorder in which the hemoglobin molecule is functionally altered and cannot transport oxygen. There are both hereditary and acquired forms of the disorder. The hereditary types are rare and usually show up in the first days of life, so I will not discuss them here. Most cases of reported methemoglobinemia are drug-induced, the major pharmaceutical culprits being benzocaine (a topical anesthetic often found in teething gels) and dapsone (an oral antibiotic used to treat certain skin conditions) [1]. Our discussion centers on environmental sources. Nitrate and nitrite are the chemicals most often implicated in epidemic methemoglobinemia as depicted in our clinical case.

The association between nitrate-contaminated well water and blue baby syndrome was first described in the early 1940s. Agricultural fertilizers containing nitrogen in the form of ammonia or ammonium nitrate are responsible for sustaining one-third of the Earth's population. Runoff from these fertilizers contains high levels of nitrates which leach into the groundwater that supplies shallow wells; additional sources of nitrate contamination include septic systems and manure storage or spreading operations [2]. Federal standards for public water supplies do not apply to private wells. Approximately 15 million families in the United States obtain their drinking water from unregulated, domestic wells, and an estimated 2 million of those homes may fail to meet the federal water-safety standard for nitrate of 10 ppm (mg/L) [3].

Babies consume large quantities of water relative to their body weight, particularly if water is used to mix powdered or concentrated formulas or juices. Nitrates are converted to nitrites by gastrointestinal bacteria, especially in young infants in whom

the lower acidity of gastric secretions allows for bacterial proliferation and increased production of nitrites. Nitrites react with oxygen to form oxygen-free radicals which are powerful oxidizers of cellular substrates, including hemoglobin. Events resulting in metabolic acidosis, such as severe diarrhea, dehydration, or sepsis in young infants may increase methemoglobin levels independent of nitrate ingestion. Given that infants begin with lower levels of protective enzymes against methemoglobin, they can develop severe symptoms after only brief exposure to contaminated well water [4].

Pathophysiology

- Methemoglobin (MetHb) occurs when the hemoglobin molecule becomes oxidized in the absence of molecular oxygen. In this oxidized ferric state, hemoglobin can no longer react with oxygen molecules.
- Red blood cells have multiple mechanisms to maintain the normal concentration of methemoglobin at less than 1 percent.

Newborn infants usually have around 1 to 2 percent concentration of methemoglobin. A serum MetHb concentration above 2 percent is termed methemoglobinemia [1]. Under normal circumstances, the most important reductive system involves nicotinamide adenine dinucleotide (NADH), a byproduct of cellular glycolysis. This enzyme system enables the rapid conversion of oxidized methemoglobin back to hemoglobin and clears more than 95 percent of the methemoglobin formed under normal circumstances.

- The enzyme system, however, is not fully active in normal infants until about 4 months of age; therefore, infants are more susceptible to conditions that favor the formation of excess methemoglobinemia [4].
- Methemoglobinemia occurs when the primary enzymatic mechanisms for eliminating methemoglobin are overwhelmed by an exogenous oxidizing drug or chemical agent.

Excessive levels of methemoglobin reduce the oxygen content of blood by reducing the oxygen-carrying capacity of hemoglobin. First, the oxidized ferric ion has a reduced affinity for binding oxygen. Second, methemoglobin results in a leftward shift of the oxygen dissociation curve causing normal hemoglobin to bind oxygen more tightly and preventing the oxygen from unloading freely at the peripheral tissues.

- The key clinical endpoint in methemoglobinemia is the severe tissue hypoxemia and metabolic acidosis (lactic acidosis) resulting from diminished oxygen delivery to peripheral tissues [5].

Presentation

- Patients with methemoglobinemia may have profound cyanosis but only minimal respiratory distress.

The classic chocolate-brown coloration of blood is usually seen at concentrations of 15 to 20 percent. Although patients may have clinical signs of cyanosis at this level,

they are typically asymptomatic. At methemoglobin concentrations between 20 to 50 percent, symptoms include anxiety, headache, weakness, and lightheadedness, and patients may exhibit tachypnea and sinus tachycardia. Infants may demonstrate generalized symptoms such as poor feeding, lethargy, and irritability. Methemoglobin concentrations of 50 to 70 may result in myocardial ischemia, dysrhythmias, depressed mental status (including coma), seizures, and severe metabolic acidosis. Levels above 70 percent are largely fatal [5].

Diagnosis

- The arterial partial pressure of oxygen in methemoglobin may be normal, reflecting the fact that the tissue hypoxemia is not a result of a cardiorespiratory defect.

In general, pulse-oximeter oxygen-saturation values drop linearly with increasing methemoglobin concentrations until the MetHb levels reach 30 to 35 percent, at which point the pulse-oximeter reading becomes stable in the low-to-mid 80s [4]. Further increases in MetHb do not lower the pulse oximeter oxygen saturation and supplemental oxygen does not increase the oxygen saturation.

- Significant MetHb levels are underestimated by conventional pulse-oximeter readings.
- Definitive identification of methemoglobinemia relies on co-oximetry.

Co-oximetry uses four wavelengths of light to measure the absorptive characteristics of oxy- and deoxyhemoglobin, methemoglobin, and carboxyhemoglobin species. It requires a sample of venous or arterial blood and is the most accurate method for determining the oxygen saturation of blood and the percentage of MetHb.

Treatment

- Patients who have methemoglobin concentrations below 20 percent and are asymptomatic require only admission and close observation, as their hemoglobin levels should normalize within 24 to 72 hours.

A methemoglobin concentration alone may not be an adequate indication of the need for therapy. Initial treatment is essentially supportive and involves maximizing the saturation of the remaining functional hemoglobin by providing oxygen. In general, the yield of gastric decontamination is limited because there is often a substantial time interval between exposure to the toxic agent and the development of methemoglobin.

A relatively minor pathway for reducing methemoglobin exists within the red blood cell, consisting of nicotinamide-adenine dinucleotide phosphate (NADPH) and the enzyme NADPH methemoglobin reductase [1].

- In the presence of an electron donor such as the pigment methylene blue, the NADPH methemoglobin reductase system is accelerated and becomes the primary method for reducing methemoglobin.

- Antidotal therapy with methylene blue is reserved for patients with symptomatic methemoglobinemia, usually at methemoglobin concentrations greater than 20 percent.

Symptoms may occur at lower concentrations in anemic patients or those with cardiovascular, pulmonary, or central nervous system compromise. Unstable patients with a presentation highly suspicious for methemoglobinemia should receive methylene blue empirically. All patients (especially infants and young children) with significant methemoglobinemia requiring therapy with methylene blue should be admitted to an ICU for continuous monitoring and supportive care.

The initial dose of methylene blue—1 to 2 mg/kg IV (0.2mL/kg of a 1 percent solution)—given over 5 minutes has a rapid onset of action; maximal effects usually occur within 20 to 30 minutes. Infants with methemoglobin resulting from diarrhea and acidosis may improve with aggressive hydration and correction of the acidosis [5].

Conclusion

Approximately 40,000 infants less than 6 months of age live in homes that have nitrate-contaminated water supplies [3]. Recognition of this unique route of exposure and clinical presentation are paramount for prompt diagnosis and proper management of methemoglobinemia. If your patient's family uses a private water supply, inform them that private water sources are not routinely tested for nitrates. Recommend that they have their water tested for nitrates at least annually if the source is surface water and at least once every 3 years if the source is groundwater [2]. If the water has elevated nitrate levels, advise them to purchase bottled water or find an alternative water supply for drinking and cooking. Little if any nitrate gets into breast milk, unless the mother is consuming very large quantities of nitrate.

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Amir Miodovnik, MD, is an attending physician in pediatrics and community and preventive medicine at The Mount Sinai Hospital in New York City, and a medical doctor for the Pediatric Environmental Health Specialty Unit of New York State and New Jersey. He received his medical training at The Ohio State University College of Medicine and completed his pediatrics residency at Northwestern University/Children's Memorial Hospital in Chicago. Dr. Miodovnik served in the U.S. Navy for 2 years where he was stationed at the U.S. Naval Hospital in Okinawa, Japan.

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