44. METHEMOGLOBIN

Saralyn R. Williams, M.D.

1. What is methemoglobin?
Methemoglobin is an abnormal hemoglobin in which the iron moiety of oxyggenated hemoglobin is in the ferric (Fe³⁺) state rather than the ferrous (Fe²⁺) state. When hemoglobin contains a ferric iron, it is unable to carry oxygen or carbon dioxide.

2. How does methemoglobin affect oxygen-carrying capacity?
Hemoglobin contains a tetramer of peptide (globin) chains. In adult hemoglobin, the most common peptides are two α chains and two β chains. Each of the globin chains encloses a heme molecule in a hydrophobic pocket. Each heme molecule is capable of carrying oxygen when the iron moiety is in the reduced (ferrous) state. The α and β chains can undergo a conformational change so that the hemoglobin molecule can vary its oxygen affinities. As oxygen binds to the heme molecule, the affinity for additional binding increases, giving the oxyhemoglobin dissociation curve a sigmoidal shape. The binding and release of oxygen vary with temperature, level of 2,3-biphosphoglycerate, and pH of the serum. As the temperature increases, pH decreases or levels of 2,3-biphosphoglycerate increase, and the sigmoid curve shifts to the right, facilitating the release of oxygen and binding of carbon dioxide.

Methemoglobin reduces the oxygen-carrying capacity of the blood by two mechanisms. First, methemoglobin is unable to carry oxygen molecules. Second, the presence of methemoglobin shifts the oxyhemoglobin dissociation curve to the left. This shift increases the affinity of the remaining hemoglobin to oxygen. The remaining hemoglobin is able to bind oxygen molecules more efficiently; however, it is less able to release oxygen to tissues.

3. What are normal methemoglobin levels?
In adults with no hereditary methemoglobinemia, the baseline methemoglobin level is approximately 1% of total hemoglobin.

4. How is methemoglobin reduced or eliminated in the body?
The red blood cell has two mechanisms for reduction of methemoglobin. The dominant pathway uses reduced nicotine adenine dinucleotide (NADH). NADH results from the metabolism of glucose to pyruvate during glycolysis. NADH then becomes the electron donor to the ferric iron of methemoglobin. Originally, one enzyme was thought to be involved in this reaction and was named NADH methemoglobin reductase. More recently, two enzymes have been identified in this reduction process: cytochrome b₅ and cytochrome b₅₉ reductase. In vivo, this dual enzyme system is capable of > 95% of the methemoglobin reduction activity.

The second mechanism for methemoglobin reduction requires the presence of reduced nicotine adenine dinucleotide phosphate (NADPH), which is produced by the hexose monophosphate shunt. The enzymatic conversion of glucose-6-phosphate (G-6-P) to 6-phosphogluconate occurs by the enzyme glucose-6-phosphate dehydrogenase (G-6-PD). With this conversion, NADP⁺ is reduced to NADPH. NADPH uses NADPH methemoglobin reductase to reduce the ferric iron to a ferrous state. This enzymatic system is less efficient and accounts for < 5% of the methemoglobin-reducing capacity of the red blood cell.

5. What is the difference between acquired methemoglobinemia and congenital methemoglobinemia?
Acquired methemoglobinemia is the most common form of methemoglobinemia and most often results from exposure to drugs or toxins that oxidize ferrous iron. Hereditary forms of
methemoglobinemia do occur and are usually due to one of two conditions, hemoglobin M or NADH methemoglobin reductase deficiency. Hemoglobin M is a variant in which the iron is stabilized in the oxidized (Fe\(^{3+}\)) state. One type of this autosomal dominant mutation results from the replacement of a histidine by a tyrosine on either the α or β subunit of the hemoglobin molecule.

The other form of congenital methemoglobinemia occurs from a deficiency in the NADH methemoglobin reductase enzyme system. A deficiency could occur with either enzyme cytochrome b\(_6\) or cytochrome b\(_5\) reductase. Because this trait is autosomal recessive, patients who are homozygous for this deficiency may have clinical cyanosis from elevated methemoglobin levels.

6. Describe common causes for acquired methemoglobinemia.

One of the most common classes of drugs responsible for acquired methemoglobinemia is local anesthetics. Three of the local anesthetics that are most notorious are benzocaine, prilocaine, and lidocaine. Benzocaine-induced methemoglobinemia from topical mucosal membrane application is associated with endoscopy, bronchoscopy, and transesophageal echocardiography. Benzocaine is also found in many over-the-counter products such as hemorrhoid creams and teething gels.

Nitrites are another major class of agents that cause methemoglobinemia. Therapeutic induction of methemoglobin for cyanide poisonings utilizes nitrates. Methemoglobin from ingestion of well water results from contamination by nitrates that are converted to nitrates in vivo.

Other well-known inducers of methemoglobin include sulfonamide antibiotics, phe nazo pyridine, dapsone, aniline dyes, chloroquine, and primates. Benzene derivatives, dinitrophenol, chlorates, and other oxidizing chemicals may also produce methemoglobinemia as well as ingestion of Gyromitra mushrooms. Nitrothane, found in many artificial fingernail removers, also has been reported to cause delayed methemoglobinemia when ingested.

7. What are the signs and symptoms of methemoglobinemia?

One of the first clues is generalized cyanosis. Application of oxygen does not improve the cyanosis. Symptoms may be quite variable depending on the level of the methemoglobin and the patient's ability to handle the loss of the oxygen-carrying capacity. Early symptoms include anxiousness and dizziness, with fatigue and confusion occurring at higher levels. Tachycardia may be seen at lower levels along with cyanosis. With higher levels, tachypnea, altered mental status, dysrhythmias, and acidosis may occur. Death can occur at methemoglobin levels > 70% of the total hemoglobin.

8. What level of methemoglobin is required for a patient to appear cyanotic?

Methemoglobin is usually reported as a percent of hemoglobin in the methemoglobin form. The absolute amount of hemoglobin that must be in the ferric state to cause cyanosis is 1.5 g/dl. Provided that hemoglobin levels are in normal range (12–15 mg/dl), 1.5 g/dl would account for 10–15% of the hemoglobin. If a patient is anemic, 1.5 g/dl will account for a larger percentage of net hemoglobin. Therefore, a larger percentage of the hemoglobin will need to be in the methemoglobin state for the patient to be cyanotic. For example, if a male patient with renal failure has a hemoglobin of only 8 mg/dl, then 1.5 g/dl would account for approximately 19% of his hemoglobin. Thus, the methemoglobin level in this patient would be at least 19% before he would appear cyanotic.

9. How is the diagnosis of methemoglobinemia made in a cyanotic patient?

The most important bedside clue is persistent cyanosis after the administration of high-flow oxygen. The pulse oximeter will read abnormally low saturations in these patients, although the low reading does not correspond with the level of methemoglobin. In addition, methemoglobin-containing blood does not turn bright red with the exposure of oxygen. A drop of the patient's blood placed onto filter paper will appear chocolate colored instead of bright red.

Another clue to the diagnosis of methemoglobinemia is the presence of a normal partial pressure of oxygen (pO\(_2\)) on an arterial blood gas (ABG) sample. The ABG measures the partial
Methemoglobin

The of two conditions, hemoglobin M or hemoglobin N, is a variant in which the iron is sub-
normal dominantly results from the α or β subunit of the hemoglobin molecule. It occurs from a deficiency in the NADH cyto-
chrome oxidase system could occur with either enzyme cyto-
chrome oxidase is autosomal recessive, patients who are anemic from elevated methemoglobin levels.

Therapeutic indication for acquired methemoglobinemia is rare and not usually benzocaine, prilobinemia from topical mucosal mucous membranes, and transesophageal echocardiography, products such as hemorphoid creams and nitrites. Methemoglobin from ingestion of any artificial fingernail removers, also has been reported.

Therapeutic indications for methemoglobinemia include sulfonamide antibiotics, phenazopyridine, Benzenedivinylamine, dinitrophenol, methemoglobinemia as well as ingesting nitrites in vivo.

10. What is the treatment for methemoglobinemia?

The treatment of the patient with methemoglobinemia begins with supportive care. Oxygen supplementation is initiated using a non-rebreather face mask. Decontamination with activated charcoal may be necessary if the condition is the result of an ingestion of a long-acting substance such as dapsone. In a patient with significant symptoms or signs, reduction of the methemoglobin level by administration of methylene blue should be considered. Methylene blue is administered intravenously, 1 mg/kg, over 3–5 minutes. The dose of methylene blue may be repeated in 30 minutes if cyanosis does not improve. The methemoglobin level should be significantly reduced within an hour of the infusion of methylene blue.

11. How does methylene blue enhance the reduction of methemoglobin?

Methylene blue acts as a cofactor that accelerates the efficiency of the NADPH methemoglobin reductase. Instead of accounting for the usual 5% of the reduction capacity of the erythrocyte, the addition of methylene blue allows this pathway to become the predominating mechanism for reduction of methemoglobin. Methylene blue is converted to leukomethylene blue, which is actually colorless. Leukomethylene acts as an electron donor to the ferric iron, reducing it back to the ferrous state.

12. Are there contraindications to the administration of methylene blue?

The primary contraindication to the administration of methylene blue is G-6-PD deficiency. G-6-PD is an enzyme used in the first step of the hexose monophosphate shunt. This enzymatic reaction reduces NADP to NADPH. NADPH is used by methemoglobin reductase for the reduction of methylene blue. In the absence of G-6-PD, the secondary pathway using NADPH methemoglobin reductase to reduce methemoglobin is useless because no NADPH is created. In this setting, red cells may be subject to hemolysis because methylene blue can create oxidative stress.

13. What is the differential diagnosis if the administration of methylene blue does not reverse the methemoglobinemia?

The primary element in the differential is G-6-PD deficiency. Additional causes include NADPH methemoglobin reductase deficiency or sulhemoglobinemia.

14. What is sulhemoglobin?

Sulhemoglobin results from the incorporation of a sulfur atom into the porphyrin ring of hemoglobin. Sulhemoglobin will cause the patient to appear cyanotic and may be incorrectly interpreted by co-oximeters as methemoglobin. Sulhemoglobin also is unable to carry oxygen molecules; however, the patient usually tolerates sulhemoglobin better. Only 0.5 gm/dl of hemoglobin must be sulhemoglobin in order to cause cyanosis. Sulhemoglobin also shifts the oxygen dissociation curve to the right, thus allowing oxygen to be more easily released into tissues.

Sulhemoglobin lasts for the life cycle of the individual red blood cell. It is not reversed by the administration of methylene blue because the sulfuration process is permanent. Detection of sulhemoglobin requires spectrophotometric techniques.
15. What is the treatment for methemoglobinemia when methylene blue is contraindicated or is not working?
Exchange transfusions or infusions of packed red blood cells may be used in a patient who has G-6-PD deficiency or in whom methylene blue is not reducing the methemoglobin. This treatment is reserved for patients with very high concentrations of methemoglobin or very low total hemoglobin concentrations.

16. Is there any indication for a continuous infusion of methylene blue?
Recurrence of methemoglobinemia has been reported with longer acting oxidizing agents such as dapsone, nitroethane, and aniline dyes. In these cases, repetitive dosing of methylene blue or possibly an infusion drip may be required to keep the hemoglobin in the reduced state.

17. Extra credit: In 1947, Berton Roueche, a writer for *The New Yorker* magazine, wrote of the medical detective work involved in a classic 1944 incident, in which a group of men suffered from methemoglobinemia when sodium nitrite was accidentally added to their oatmeal instead of table salt. What is the title of this now classic toxicologic story?
“Eleven Blue Men.”

BIBLIOGRAPHY