Chapter 207: Dyshemoglobinemias

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INTRODUCTION

Dyshemoglobinemias are disorders in which the hemoglobin molecule is functionally altered and prevented from carrying oxygen. The most clinically relevant dyshemoglobinemias are carboxyhemoglobin, methemoglobin, and sulfhemoglobin. \(^1\) Carboxyhemoglobin is created during carbon monoxide exposure and, because of its unique importance and prevalence, is usually considered an environmental emergency (see chapter 222, "Carbon Monoxide").

METHEMOGLOBINEMIA

PATHOPHYSIOLOGY

The iron moiety within deoxyhemoglobin normally exists in the ferrous (bivalent or Fe\(^{2+}\)) state. Ferrous iron avidly interacts with compounds seeking electrons, such as oxygen or other oxidizing agent, and in the process is oxidized to the ferric (trivalent or Fe\(^{3+}\)) state. Hemoglobin in the ferric form is unable to bind oxygen for transport and is termed methemoglobin. Under normal circumstances, <1% to 2% of circulating hemoglobin exists as methemoglobin; higher concentrations define the condition of methemoglobinemia.

Methemoglobin accumulation is enzymatically prevented by the rapid reduction of the ferric iron back to the ferrous form. Cytochrome b\(_5\) reductase is primarily responsible for this reduction, in which reduced nicotinamide adenine dinucleotide donates its electrons to cytochrome b\(_5\), which subsequently reduces methemoglobin to hemoglobin (Figure 207-1). This pathway is responsible for reducing nearly 95% of methemoglobin produced under typical circumstances. Methemoglobinemia occurs when this enzymatic reduction is overwhelmed by an exogenous oxidant stress, such as a drug or chemical agent (Table 207-1).
### Drugs Causing Methemoglobinemia

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
</tr>
<tr>
<td>Phenazopyridine</td>
<td>Commonly reported</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>Rarely used</td>
</tr>
<tr>
<td><strong>Antimicrobials</strong></td>
<td></td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Dapsone</strong></td>
<td>Hydroxylamine metabolite formation is inhibited by cimetidine</td>
</tr>
<tr>
<td><strong>Local anesthetics</strong></td>
<td></td>
</tr>
<tr>
<td>Benzocaine</td>
<td>Most commonly reported of the local anesthetics</td>
</tr>
<tr>
<td><strong>Lidocaine</strong></td>
<td>Rare</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Common in topical anesthetics</td>
</tr>
<tr>
<td>Dibucaine</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Nitrates/nitrites</strong></td>
<td></td>
</tr>
<tr>
<td>Amyl nitrite</td>
<td>Cyanide antidote kit and used to enhance sexual encounters</td>
</tr>
<tr>
<td>Isobutyl nitrite</td>
<td>Used to enhance sexual encounters</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>Cyanide antidote kit</td>
</tr>
<tr>
<td>Ammonium nitrate</td>
<td>Cold packs</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>Excessive topical use</td>
</tr>
<tr>
<td>Well water</td>
<td>Problem in infants, due to nitrate fertilizer runoff</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Oxidant | Comments
--- | ---
Sulfonamides | 
Sulfamethoxazole | Uncommon

FIGURE 207-1.
Methemoglobin formation and mechanism of action of methylene blue. G6PD = glucose-6-phosphate dehydrogenase; Hb(Fe²⁺) = hemoglobin; Hb(Fe³⁺) = methemoglobin; NAD⁺ = oxidized nicotinamide adenine dinucleotide; NADH = reduced form of nicotinamide adenine dinucleotide; NADP⁺ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate; PO₄ = phosphate.

Methemoglobin can also be reduced by a second enzymatic pathway using the reduced form of nicotinamide adenine dinucleotide phosphate (or NADPH) and NADPH-methemoglobin reductase.² This pathway is normally of minimal importance and is responsible for less than 5% of total reduction under typical circumstances. However, this enzyme and pathway are crucial for the antidotal effect of methylene blue (Figure 207-1).

The limited role for NADPH partially explains why patients with glucose-6-phosphate dehydrogenase deficiency with a resultant deficiency in NADPH are not at increased risk of developing methemoglobinemia, although they are at risk of developing hemolysis following exposure to an oxidant stress. To a very limited extent,
nonenzymatic reduction systems, such as vitamin C and glutathione, may participate in the reduction of methemoglobin to hemoglobin.

The primary clinical effect of methemoglobin is to reduce the oxygen content of the blood. Because hemoglobin-bound oxygen accounts for the vast majority of an individual's oxygen-carrying capacity, as the methemoglobin concentration rises, oxygen-carrying capacity to the tissues falls. Patients with methemoglobinemia are often more symptomatic than patients who suffer from a simple anemia that produces an equivalent reduction in oxygen-carrying capacity. This is caused by a leftward shift in the oxyhemoglobin dissociation curve, the consequence of which is a reduced release of oxygen from the erythrocyte to the tissue at a given partial pressure of oxygen (Figure 207-2).²

**FIGURE 207-2.**
Oxyhemoglobin dissociation curve.

The oxyhemoglobin dissociation curve of blood with a 50% reduction in erythrocytes (i.e., anemia) follows a curve similar to that of nonanemic blood; although the oxygen content is lower, unbinding of half of the oxygen (50% oxygen saturation) occurs at the same PO₂. With 50% methemoglobin, the leftward shift of the oxyhemoglobin dissociation curve means that hemoglobin is less willing to give up its oxygen, so that tissue hypoxia is more severe than in those with a 50% anemia.

**Acquired Methemoglobinemia**

Drugs in conventional doses rarely produce clinically significant methemoglobinemia, although subclinical methemoglobinemia may go unrecognized (Table 207-1). Benzocaine is the local anesthetic most commonly associated with methemoglobinemia.³,⁴,⁵ Methemoglobin induction with sodium nitrite is a therapeutic goal in the management of patients suffering from cyanide poisoning (see chapter 204, "Industrial Toxins"). Certain compounds, particularly dapsone,⁶ require metabolism to the "active" oxidant, and there may be substantial delay until toxicity is evident. Occupational methemoglobinemia usually involves exposure to aromatic...
compounds, primarily amino- and nitro-substituted benzenes. Routes of absorption are typically dermal or inhalational due to the high lipophilicity and volatility of these compounds, respectively.

Neonates and infants are more susceptible to methemoglobin accumulation because of undeveloped methemoglobin reduction mechanisms. This accounts for the relatively common development of methemoglobinemia in infants given certain nitrogenous vegetables (e.g., spinach) or well water that contains high nitrate levels (generally from fertilizer use). Bacteria within the GI flora convert nitrate to the nitrite form, which is a more potent oxidant. Another common cause of acquired infantile methemoglobinemia is gastroenteritis, which presumably is caused by an increased oxidant burden originating in the GI tract.

Hereditary Methemoglobinemia

Hereditary methemoglobinemia results from either an enzymatic deficiency (i.e., cytochrome b₅ reductase) or from the presence of an amino acid substitution within the hemoglobin molecule itself, termed hemoglobin M. Patients with cytochrome b₅ reductase deficiency develop methemoglobin levels of 20% to 40%. Cyanosis in these individuals begins at birth, but they remain asymptomatic and develop normally.

Hemoglobin M, an abnormal form of hemoglobin, has altered tertiary structure so that the heme iron exists in an environment favoring the ferric form. This disorder only occurs in the heterozygous form, because the homozygous form is incompatible with life. As with cytochrome b₅ reductase deficiency, patients develop profound cyanosis but tolerate the elevated methemoglobin concentrations well due to compensatory mechanisms.

CLINICAL FEATURES

Healthy patients who have normal hemoglobin concentrations do not usually develop clinical effects until the methemoglobin level rises above 20% of the total hemoglobin. At methemoglobin levels between 20% and 30%, anxiety, headache, weakness, and light-headedness develop, and patients may exhibit tachypnea and sinus tachycardia. Methemoglobin levels of 50% to 60% impair oxygen delivery to vital tissues, resulting in myocardial ischemia, dysrhythmias, depressed mental status (including coma), seizures, and lactate-associated metabolic acidosis. Levels above 70% are largely incompatible with life.

Cyanosis associated with methemoglobin is often described as a gray discoloration of skin, with a detection threshold for methemoglobin of 1.5 grams/dL, corresponding to methemoglobin levels between 10% and 15% in a nonanemic individual (Figure 207-3). Methemoglobin levels above 20% will discolor the blood a chocolate brown.

**FIGURE 207-3.** Methemoglobinemia due to dapsone. Gray-blue discoloration of the patient’s fingernails compared with that of the physician. With the patient on supplemental oxygen, the pulse oximeter reported an oxygen saturation of 93%. Arterial blood gas measurement reported a PaO₂ of 307 mm Hg, a calculated oxygen saturation of 99.8%, and a measured methemoglobin of 12%. [Photo Contributed by J. S. Stapczynski, MD.]
Anemic patients may not exhibit cyanosis until the methemoglobin level rises well above 10% because cyanosis detection is dependent on the level of methemoglobin, not the percentage. Anemic patients may likewise suffer significant symptoms at lower methemoglobin concentrations because the relative percentage of hemoglobin in the oxidized form is greater. Patients with preexisting cardiopulmonary diseases that impair oxygen delivery will also manifest symptoms with less significant elevations in their methemoglobin levels. Conversely, compensatory mechanisms that shift the oxyhemoglobin dissociation curve to the right, such as acidosis or elevated 2,3-diphosphoglycerate, may result in somewhat better toleration of methemoglobin.

**DIAGNOSIS**

Consider methemoglobinemia in patients with cyanosis, particularly if cyanosis does not improve with supplemental oxygen (Figure 207-4). A useful clue is that patients with methemoglobin-associated cyanosis generally are less symptomatic than equivalently appearing patients with hypoxemia-induced cyanosis. This is due to the more deeply pigmented color of methemoglobin compared with deoxyhemoglobin; it takes about 5 grams/dL of deoxyhemoglobin to cause cyanosis, which equates to an oxygen-carrying capacity of approximately 67% of normal, compared with the cyanosis visible with a methemoglobin concentration of 1.5 grams/dL, which equates to an oxygen-carrying capacity of 90% of normal. Blood containing methemoglobin has a characteristic "chocolate brown" color when phlebotomized. Detection of this discoloration is improved when compared directly with normal blood.

**FIGURE 207-4.**
Pulse oximetry results are not accurate in patients with methemoglobinemia. The standard pulse oximeter uses two wavelengths of light, 660 nm and 940 nm, to calculate the percentage of oxyhemoglobin. Methemoglobin is also detected by these wavelengths, and light absorption by methemoglobin confounds the calculation for the oxyhemoglobin percentage. In patients with methemoglobinemia, the pulse oximeter will report a falsely elevated value for arterial oxygen saturation percentage. The specific values vary by oximeter, but typically trend to approximately 85%.

Pulse co-oximeters are commercially available that use additional wavelengths of light to measure the total hemoglobin concentration and percentages of carboxyhemoglobin and methemoglobin. When first released, accuracy for methemoglobinemia levels was progressively unreliable with increasing hypoxemia, but the new probes appear to have corrected the problem.

Definitive identification of dyshemoglobinemias requires co-oximetry, a spectrophotometric method capable of differentiating among oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin species. This widely available test can be performed on a venous or arterial specimen.
Arterial blood gas results may be initially deceptive because the partial pressure of oxygen, a measure of dissolved, not bound, oxygen, is normal. Thus, calculation of oxygen saturation from measured partial pressure by the blood gas analyzer will produce a falsely elevated result.

**TREATMENT**

Patients with methemoglobinemia require supportive measures to ensure oxygen delivery and the administration of appropriate antidotal therapy, if indicated (Table 207-2). Gastric decontamination is of limited value, because there often is a substantial time interval between exposure to the toxic agent and the development of methemoglobin. If a source of continuing GI exposure is suspected, decontamination is indicated, and in most stable patients, a single dose of activated charcoal is likely sufficient. Dermal decontamination should be used as indicated. Antidotal therapy with methylene blue is reserved for symptomatic patients or for those asymptomatic patients with methemoglobin levels >25%.

**TABLE 207-2**

Management of Methemoglobinemia

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess airway, breathing, and circulation; exclude other causes of cyanosis</td>
</tr>
<tr>
<td>Insert an IV line</td>
</tr>
<tr>
<td>Administer oxygen</td>
</tr>
<tr>
<td>Attach the patient to a cardiac and pulse oximeter or co-oximeter</td>
</tr>
<tr>
<td>Obtain an ECG</td>
</tr>
<tr>
<td>Decontaminate the patient as needed</td>
</tr>
<tr>
<td>Administer methylene blue: if symptomatic or methemoglobin &gt;25%</td>
</tr>
<tr>
<td>Consider: cimetidine for patients taking dapsone</td>
</tr>
</tbody>
</table>

Methylene blue indirectly accelerates the enzymatic reduction of methemoglobin by NADPH-methemoglobin reductase. NADPH-methemoglobin reductase reduces methylene blue to leucomethylene blue, which is then capable of directly reducing the oxidized iron (Fe³⁺) back to the ferrous state (Fe²⁺) (Figure 207-1). The initial methylene blue dose is 1 milligram/kg (0.1 mL/kg of the 1% solution or approximately 7 mL in an adult) IV over 5 minutes. The infusion should be slow because rapidly administered doses of methylene blue are painful. Clinical improvement should be seen within 20 minutes, and as the methemoglobin level falls, the most severe signs and symptoms will resolve first. Resolution of the cyanosis occurs later only after the methemoglobin concentration falls below 1.5 grams/dL. Repeat dosing of methylene blue is acceptable, if cyanosis has not cleared in 1 hour. Serotonin toxicity (syndrome) is a rare risk when methylene blue is administered to patients on serotonergic drugs such as antidepressants.¹⁴

Treatment failures may result if the patient has glucose-6-phosphate dehydrogenase deficiency, because this enzyme is critical for the production of NADPH by the hexose monophosphate shunt (Figure 207-1). Hemolysis may impede a response to methylene blue, which requires an intact erythrocyte to be effective. Oxidant drugs with long serum half-lives, such as dapsone with a half-life of approximately 50 hours, produce prolonged
oxidant stress to the red blood cell. Therefore, dapsone-exposed patients may require repetitive dosing of methylene blue. Because the hydroxylamine metabolite of dapsone is responsible for the production of methemoglobin, inhibition of its formation by cytochrome P450 with cimetidine, in standard doses, is generally recommended.

In rare instances, patients may be deficient in NADPH-methemoglobin reductase, the required enzyme for methylene blue activation. Lastly, treatment failure may occur in patients with sulfhemoglobinemia, which is clinically indistinguishable from methemoglobinemia, but which is not responsive to methylene blue. Patients who do not respond to methylene blue should be treated supportively. If clinically unstable, the use of packed red cell transfusions or exchange transfusions may be indicated.

**SULFHEMOGLOBINEMIA**

**PATHOPHYSIOLOGY**

Sulfhemoglobinemia is a rare condition that occurs when a sulfur atom irreversibly binds to the porphyrin ring of the heme moiety and induces the permanent oxidation of iron to the ferric (Fe\(^{3+}\)) state. Many of the agents responsible for sulfhemoglobinemia are identical to those associated with methemoglobin. Because many of these drugs or chemicals do not contain sulfur, the origin of sulfur is speculative; hypotheses include alteration of intestinal flora with production and absorption of hydrogen sulfide and/or glutathione. Historically, sulfhemoglobinemia was most often associated with acetanilide, phenacetin, sulfonamide, and a proprietary mixture that contained sodium bromide. Because these drugs are rarely used and the sodium bromide component in the proprietary mixture was removed in 1975, contemporary cases of drug-induced sulfhemoglobinemia are now most often reported with phenazopyridine, dapsone, metoclopramide, and sumatriptan. Sulfhemoglobinemia has been associated with industrial chemicals, such as trinitrotoluene, hydroxylamine sulfate, dimethyl sulfoxide, and hydrogen sulfide.

**CLINICAL FEATURES**

Patients with sulfhemoglobinemia can have a clinical presentation similar to those with methemoglobinemia. However, the disease process itself is substantially less concerning because, although the reduction in the patient’s oxygen-carrying capacity is quantitatively similar, the sulfhemoglobin oxygen dissociation curve is shifted rightward, not leftward as in methemoglobinemia, favoring the release of hemoglobin-bound oxygen to the tissue with sulfhemoglobinemia. Because of the milder symptoms, speculation is that cases of sulfhemoglobinemia are often missed.

**DIAGNOSIS**

The pigmentation of the blood by sulfhemoglobin is substantially more intense than other colored hemoglobin species; only 0.5 gram/dL of sulfhemoglobin is needed to produce a cyanosis equivalent to that produced by 1.5 grams/dL of methemoglobin or 5 grams/dL of deoxyhemoglobin. The color of blood drawn from a patient with sulfhemoglobinemia has been described as dark greenish-black. In sulfhemoglobinemia, standard pulse
oximetry tends to report a falsely low value for arterial oxygen saturation percentage. The diagnosis of sulphhemoglobinemia may be difficult to confirm. Standard co-oximetry may not differentiate sulphhemoglobin from methemoglobin because of similar spectral absorbance, and specialized settings are required to reliably measure sulphhemoglobin concentration.

TREATMENT

Sulphhemoglobin persists for the life of the red cell and the level is not reduced by treatment with methylene blue. Most patients require only supportive care, although exchange transfusion or packed red cell transfusion is occasionally recommended for patients with severe toxicity.

REFERENCES


[PubMed: 22024786]

[PubMed: 3193485]

[PubMed: 23490227]

[PubMed: 20007731]

[PubMed: 20841412]

[PubMed: 20484716]

[PubMed: 17364641]

[PubMed: 15886294]

[PubMed: 19300288]

[PubMed: 18072164]

[PubMed: 9866446]


**USEFUL WEB RESOURCES**


U.S. Food and Drug Administration. FDA Drug Safety Communication: Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications—[http://www.fda.gov/Drugs/DrugSafety/ucm263190.htm](http://www.fda.gov/Drugs/DrugSafety/ucm263190.htm)

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