

Acute Dapsone-Induced Methemoglobinemia in a 24-Year-Old Woman with Ulcerative Colitis

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Methemoglobin, a unique form of hemoglobin (Hb) with diminished oxygen affinity, is formed and metabolized roughly at equivalent rates under normal physiologic conditions. However, when methemoglobin generation supersedes compensatory physiologic reductive capacity, methemoglobinemia may result. Potential etiologies of methemoglobinemia include a variety of heritable metabolic defects and acquired insults, with the latter commonly a consequence of exposure to exogenous oxidizing agents. This article reviews the case of a 24-year-old woman who acutely developed methemoglobinemia while being treated with dapsone during an ulcerative colitis (UC) exacerbation. Hb physiology as well as the pathogenesis, diagnosis, and treatment of methemoglobinemia are discussed.

CASE PRESENTATION

Initial Presentation and History

A 24-year-old woman with a 7-year history of biopsy-confirmed UC presented to the emergency department with progressive abdominal cramping and bloody diarrhea over the past 4 months. She noted that her symptoms had become more severe over the prior 2 weeks. She also reported a 15-lb weight loss over the past 2 weeks accompanied by anorexia and intermittent nonbloody emesis. Review of symptoms was otherwise remarkable for increased arthralgia in her hips and wrists bilaterally, which she noted to be typical of her UC exacerbations. The patient denied fever, chills, shortness of breath, dysuria, and dizziness. Medications included mesalamine 1600 mg twice daily, 6-mercaptopurine (6-MP) 50 mg daily, and prednisone 40 mg daily. She noted a history of allergic reaction to sulfa antibiotics.

Physical Examination

Physical examination revealed a blood pressure of 142/90 mm Hg, heart rate of 90 bpm, respiratory rate of 18 breaths/min, temperature of 98.4°F, and oxygen

saturation of 100% on room air measured via pulse oximetry. Her abdomen was diffusely tender to palpation, particularly in the mid-epigastric region, without rebound or guarding. Clinically significant laboratory tests included a white blood cell count of $24.2 \times 10^3/\mu\text{L}$ with 85% neutrophils (normal, $4.5\text{--}11.0 \times 10^3/\mu\text{L}$), Hb level of 15.7 g/dL (normal, 11.6–15.4 g/dL), and a C-reactive protein level of 8.62 mg/L (normal, 0.08–3.1 mg/L). Blood cultures, polymerase chain reaction studies for cytomegalovirus, and stool studies, including analysis for *Clostridium difficile* toxin, ova and parasites, and culture, were unremarkable. Flexible sigmoidoscopy revealed moderate patchy inflammation in the rectum and sigmoid colon as well as characteristic pseudopolyps.

Hospital Course

The patient was admitted to the hospital for a presumptive UC exacerbation and was started on intravenous (IV) methylprednisolone 20 mg twice daily, metronidazole 500 mg by mouth twice daily, mesalamine 1600 mg by mouth twice daily, and 6-MP 50 mg by mouth daily. After 5 days with only marginal clinical improvement, IV cyclosporine therapy was initiated along with dapsone prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP), given that this was the patient's first course of cyclosporine and her known allergy to sulfa antibiotics. Despite improvement in UC-associated symptoms, the patient became cyanotic and dyspneic on day 8 of dapsone therapy. Pulse oximetry at this time revealed an oxygen saturation of 64%, at which point the patient was immediately placed on supplemental oxygen. A subsequent arterial blood gas (ABG)

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sample was dark brown in color and revealed the following: pH, 7.54; PaCO₂, 32 mm Hg; PaO₂, 216 mm Hg; bicarbonate, 27.4 mEq/L; base excess, 5.9 mEq/L; and oxygen saturation, 100% on 4 L/min by nasal cannula. Considering the color of the ABG sample in addition to the patient's clinical symptoms and history of recent dapsone therapy, methemoglobin levels were assessed using absorption spectra analysis and returned at 27.8% (normal, 0.4%–1.5%). The patient was administered methylene blue (MB) 50 mg intravenously for presumptive dapsone-induced methemoglobinemia. The patient's respiratory symptoms displayed rapid and dramatic improvement, with a repeat ABG 1-hour post-MB therapy revealing a methemoglobin level of 1.9%. No further testing for methemoglobin was obtained. Results of reflex glucose-6-phosphate dehydrogenase (G6PD) activity testing following the event were within normal limits.

After completing a 2-week course of IV cyclosporine without additional PCP prophylaxis, the patient was discharged in stable condition on oral cyclosporine, mesalamine, 6-MP, and a prednisone taper after 19 days in the hospital. Prior to discharge, the patient was counseled extensively regarding the nature of her adverse drug reaction. At no point during her hospital course did the patient require admission to the intensive care unit. Aside from medications mentioned previously, the only additional medications given to the patient during her hospital course were lansoprazole 30 mg daily by mouth and acetaminophen/hydrocodone 500/5 mg by mouth every 6 hours as needed for adequate analgesia. Of note, the patient did not receive any metoclopramide during admission and had never received PCP prophylaxis in the past.

METHEMOGLOBINEMIA

Hemoglobin Physiology

Hb is a protein that increases the body's oxygen carrying capacity by nearly 70-fold at normal plasma concentrations. Structurally, Hb is a globular protein consisting of 4 subunits, each of which contain a heme moiety (iron-containing porphyrin) and a polypeptide chain. In adults, the majority of Hb is designated as $\alpha_2\beta_2$, with 2 subunits carrying the α polypeptide and the remaining 2 subunits carrying the β polypeptide. Iron within each heme binds oxygen, and each Hb protein may bind a total of 4 oxygen molecules. In turn, efficient oxygen binding is dependent upon iron's cationic valence within each heme group. Specifically, iron in the ferrous state (Fe²⁺) may readily bind oxygen. However, the addition of another positive charge via ferrous oxidation markedly reduces the

ferric ion's (Fe³⁺) affinity for oxygen, thereby making Hb an inadequate oxygen transporter, subsequently referred to as methemoglobin.^{1,2} The remaining ferrous groups within the Hb tetramer enhance their oxygen-binding affinity when methemoglobin is generated, which shifts the Hb–oxygen dissociation curve to the left and further deprives vital tissues of oxygen.

Methemoglobin is formed at a constant rate under normal physiologic conditions. As oxygen departs from Hb at sites of capillary exchange, a small amount leaves as a superoxide radical (O₂⁻) rather than molecular oxygen, capturing an electron normally destined for return to the ferric ion (formed during Hb oxygenation).³ Similarly, normal erythrocytes possess the ability to reduce methemoglobin back to Hb by way of the soluble nicotinamide adenine dinucleotide (NADH) cytochrome *b5* reductase.⁴ This enzyme, which accounts for roughly 99% of daily methemoglobin reduction, is a flavoprotein that occurs in both a membrane-bound form in somatic cells and a soluble form in erythrocytes.⁵ In both cases, the enzyme is encoded by a single gene located on chromosome 22.⁶ Additional minor pathways of methemoglobin reduction include those involving glutathione, ascorbic acid, tetrahydropterin, cysteamine, reduced flavin, and reduced cysteine on protein molecules.⁷ Under physiologic conditions, the aforementioned mechanisms of methemoglobin formation and reduction occur roughly at equal rates, allowing for the maintenance of steady state methemoglobin levels.

Pathogenesis

Methemoglobinemia occurs when methemoglobin generation supersedes compensatory physiologic reductive capacity. Etiologies can be broadly characterized as genetic or acquired, with the latter being much more common than the former. Hereditary methemoglobinemia may be due to cytochrome *b5* reductase deficiency (CBRD), which occurs in 2 variants. Type I CBRD involves deficiency of the soluble enzyme in erythrocytes and results in cyanosis. Type II CBRD involves lack of the membrane-bound form of cytochrome *b5* reductase, which results in deficiency within all somatic tissues and subsequent neurologic impairment with the potential for premature death.^{8,9} In individuals with G6PD deficiency, oxidative stress leads to the production of oxidized glutathione, which is cytotoxic and freely diffuses out of cells unless rapidly reduced. This subsequently results in diminished intracellular glutathione reserves, which, as described earlier, are critical in the minor pathways of methemoglobin reduction.⁷ Finally, hereditary methemoglobinemia may result from a variety of Hb mutations,

Table. Selected Agents Capable of Inducing Methemoglobinemia

Acetanilid	Naphthalene
Aniline dyes	Nitrites
Benzene derivatives	Nitroglycerin
Benzocaine	Phenacetin
Chlorates	Phenazopyridine
Chloroquine	Phenytoin
Clofazimine	Prilocaine
Dapsone	Primaquine
Dimethyl sulfoxide	Resorcinol
Dinitrophenol	Rifampin
Ferricyanide	Smoke inhalation
Lidocaine	Sodium valproate
Methylene blue*	Sulfasalazine
Metoclopramide	Sulfonamides

*Both a cause and treatment of methemoglobinemia.

collectively designated as HbM disease. Such mutations may involve either the α or β Hb peptides and typically involve tyrosine substitution for either proximal or distal histidine residues.¹⁰

The majority of methemoglobinemia cases result from exposure to exogenous oxidizing agents. Many agents induce methemoglobinemia (Table), including aniline dyes, chloroquine, dapsone, benzocaine, lidocaine, metoclopramide, nitrites, nitroglycerin, phenytoin, rifampin, sodium valproate, and sulfonamides. All of these agents may cause methemoglobinemia at either toxic or standard doses, and the relative risk is enhanced in patients with underlying partial CBRDs.¹¹ Nonpharmacologic agents such as chlorates, which are used in a variety of industrial and commercial products (eg, explosives, matches, dyes), are also potent oxidizing agents and must be kept in mind in instances of accidental chemical exposures.⁷

Dapsone can be used to treat a variety of conditions, ranging from leprosy and malaria to *P. jiroveci* and *Toxoplasma gondii* infection. Dapsone has both antibacterial (via its antagonistic effects on folate synthesis as a para-aminobenzoic acid analogue) and anti-inflammatory (via direct neutrophil inhibition) properties.¹² Even when dapsone is administered at standard doses of 100 mg daily, methemoglobinemia may be significant in biochemically normal patients and severe in those with genetic predispositions to oxidative damage. The oxidative toxicity of dapsone has been shown to be related to the production of its hydroxylamine intermediate via *N*-hydroxylation catalyzed by a variety of hepatic en-

zymes¹³ or via myeloperoxidase in circulating leukocytes.¹⁴

Diagnosis

In patients with acquired methemoglobinemia, diagnosis is dependent upon clinical suspicion and a thorough history of medication intake. First, direct observation may reveal blood that is chocolate-brown in appearance. Second, the presence of cyanosis in an individual with a normal P_{aO_2} level may suggest the diagnosis. Due to the spectral properties of methemoglobin, oxygen saturations recorded by pulse oximetry may not correlate well with the actual percentage of methemoglobin in the blood.⁷ Third, clinical symptomatology varies depending upon methemoglobin concentration. Cyanosis begins to develop at levels greater than 1.5 g/dL, whereas anxiety and tachycardia are noted at levels between 3 g/dL and 4 g/dL. As methemoglobin concentrations begin to exceed 4.5 g/dL, confusion, fatigue, and dizziness may result. Finally, at levels greater than 7.5 g/dL, seizures, coma, arrhythmia, and death may ensue. However, it should be noted that the onset of symptoms does not always correlate with particular methemoglobin concentrations.⁷

Absorption spectra analysis (peak absorption of methemoglobin, 631 nm) is used to confirm the diagnosis of methemoglobinemia. Both type I and type II CBRD can be identified by clinical phenotype and/or enzymatic activity assay. Finally, HbM may be identified by absorption spectra analysis or protein electrophoresis at a pH of 7.1.¹⁵

Return of methemoglobin levels to normal range may not represent complete reversal of oxidative damage. For example, certain agents such as dapsone and aniline have been known to produce rebound methemoglobinemia within 4 to 12 hours of successful MB therapy.¹⁶ Hence, patients with methemoglobinemia caused by these agents may benefit from additional monitoring of methemoglobin levels even after return to normal ranges.

Treatment

Treatment of methemoglobinemia is dependent upon the etiology (genetic versus acquired) and time course (acute versus chronic). For acute methemoglobinemia due to drug exposure, treatment includes discontinuation of the offending agent. Additionally, care must be taken not to allow methemoglobin levels to exceed 50%, at which point life-threatening oxygen deprivation may occur. MB has traditionally been administered at 1 to 2 mg/kg intravenously over 5 minutes

to promote methemoglobin reduction via an NADPH-dependent process.^{17,18} Dextrose should be coadministered in order to increase NADPH formation. In general, clinicians should expect a rapid response to MB therapy; however, MB may be readministered after 1 hour if necessary. Co-oximetry is not a reliable marker for methemoglobin reduction, as MB itself will be detected as methemoglobin with this method. It should also be noted that MB is actually an oxidant and its metabolite, leukomethylene blue, is the reducing agent. Further, the G6PD pathway enhances the efficacy of MB by producing NADPH. Thus, MB therapy may paradoxically result in both hemolysis and worsening methemoglobinemia in G6PD-deficient patients.¹⁸ Nevertheless, MB therapy may be attempted first in patients with partial enzyme deficiencies. If MB therapy is ineffective and life-threatening shock is imminent, exchange transfusion should be initiated. Ascorbic acid, part of the minor reduction pathway of methemoglobin, may be useful in patients in whom MB therapy is contraindicated. Additionally, activated charcoal may be useful in instances of dapsone-induced methemoglobinemia, as this is believed to disrupt dapsone's enterohepatic circulation.⁷

Current studies suggest that methemoglobin levels may potentially be reduced in patients requiring chronic dapsone therapy with coadministration of either cimetidine or *N*-acetylcysteine. As a P450 inhibitor, cimetidine is believed to block the formation of dapsone's hydroxylamine intermediate, which is a significant metabolite in the generation of methemoglobinemia.^{7,19} *N*-acetylcysteine, a mucolytic agent commonly used to treat acetaminophen poisoning, is believed to restore intracellular glutathione and may be capable of serving as a glutathione substitute capable of directly reducing oxidized agents.^{20,21}

Individuals with genetic predispositions to methemoglobinemia should avoid oxidant agents and may also be treated with either MB or ascorbic acid for cosmetic purposes. There is no known effective therapy for HbM disease at present.

CONCLUSION

Methemoglobinemia constitutes a medical emergency and may result in significant mortality if treatment is delayed. Successful diagnosis primarily relies upon a high index of suspicion when administering implicated pharmacologic agents as well as a basic understanding of Hb and methemoglobin pathophysiology. Further, health care providers should be aware that pulse oximetry alone is not reliable in detecting the severity of methemoglobinemia. Cases of suspected drug-induced methemoglobinemia should be treated

with immediate removal of the suspected offending agent and prompt administration of MB. **HP**

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