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Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

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The Maryland Poison Center's Monthly Update: News, Advances, Information

G6P Deficiency? No Problem

Methemoglobinemia is a rare disorder that occurs when iron atoms in hemoglobin become oxidized. An iron atom loses an electron to an oxidant during oxidation and is thus converted from the ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}). Normal methemoglobinemia levels are less than 2%. Methemoglobinemia can occur due to various factors, including exposure to drugs, chemicals, or congenital enzyme deficiencies (Table 1). Severity of symptoms is dependent upon the patient's methemoglobin level, cardiovascular reserves, and baseline hemoglobin functionality (Table 2).

Table 1: Common Causes of Methemoglobinemia
Local anesthetics: Benzocaine, lidocaine, prilocaine
Nitrates: Nitroglycerin, nitroprusside
Antibiotics: Rifampin, dapsone, sulfonamides
Others: Rasburicase, metoclopramide, cyclophosphamide

Table 2: Symptoms Based on Methemoglobin Levels
3-15%: Asymptomatic: Cyanosis can occur at levels > 5%
20-30%: Moderate symptoms: Fatigue, dyspnea, chest pain,
>40%: Severe symptoms can occur: Seizure, coma, arrhythmias, hyperlactatemia, death

If the clinical scenario is highly suggestive of methemoglobinemia in a critically ill patient, it is reasonable to initiate methylene blue as administration can be both diagnostic and therapeutic. Methylene blue is the treatment of choice for methemoglobinemia and is indicated in symptomatic patients and when the methemoglobin level is greater than 30%.

Methylene blue has a listed contraindicated with glucose-6 phosphate dehydrogenase (G6PD) deficiency which may give some clinicians hesitancy. But should it? G6PD deficiency diminishes NADPH to varying degrees leading to reduced glutathione and risk for subsequent hemolysis. Methylene blue, an electron shuttle, facilitates use of NADPH to reduce methemoglobin back to functional hemoglobin, theoretically exacerbating NADPH deficiency, increasing risk of hemolysis, and potentially being ineffective due to the limited NADPH available.

In methemoglobinemia patients with G6PD deficiency, there is limited literature supporting the optimal treatment approach which leaves clinicians discussing the risk-benefit of either supportive care and observation versus methylene blue administration or alternative modalities. Intravenous (IV) vitamin C, ascorbic acid, is a potential alternative as a reducing agent that does not require NADPH. However, the delayed onset of action of vitamin C has prolonged onset to clinical improvement up to 24 hours. Alternative explored therapies of riboflavin, plasma exchange, and hyperbaric oxygen therapy also have limited data to support use over methylene blue.

Given that no individual is completely void of G6P functionality, unknown G6PD status or confirmed deficiency can still proceed with a low-dose trial of methylene blue at 1 mg/kg IV. A recent study showed that methylene blue is generally well tolerated in either of these scenarios (Rothenberg et. Al). If sequela of hemolytic anemia does develop, supportive care with transfusion remains an option.

If you have a patient with methemoglobinemia due to medications or poisoning, call the Maryland Poison Center at 1-800-222-1222

Did you know?

The utility of methylene blue for the treatment of methemoglobinemia was discovered serendipitously in 1933 and the mechanism of action was elucidated by 1950.

For more on methemoglobinemia:

1. Rothenberg R, Biary R, Hoffman RS. Effectiveness and tolerability of methylthioninium chloride (methylene blue) for the treatment of methemoglobinemia: twenty-four years of experience at a single poison center. Clin Toxicol (Phila). 2025 Apr;63(4):284-291. doi: 10.1080/15563650.2025.2470428.
2. Cortazzo JA, Lichtman AD. Methemoglobinemia: a review and recommendations for management. J Cardiothorac Vasc Anesth. 2014 Aug;28(4):1043-7. doi: 10.1053/j.jvca.2013.02.005.

Madison Savidge, PharmD, MBA
PGY2 Emergency Medicine Pharmacy Resident
Kayla Bourgeois, PharmD, DABAT
Clinical Toxicologist

@MPCToxTidbits