

Methylene Blue

Methemoglobinemia occurs when iron atoms in hemoglobin become oxidized. During oxidation, the iron atom loses an electron to an oxidant and is converted from the ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}). Normal methemoglobin levels are 1-3%. A variety of medications and other xenobiotics (Table 1) can cause elevated methemoglobin level, leading to decreased oxygen-carrying capacity and oxygen delivery. This can result in cyanosis, dizziness, fatigue, headache, dyspnea on exertion, and tachycardia; at levels above 50% seizures, dysrhythmias, hypotension, acidosis, coma, and death can occur. Methylene blue is an oxidizing agent that is the treatment of choice for acquired methemoglobinemia.

Table 1. Common Causes of Methemoglobinemia

Benzocaine, lidocaine, and prilocaine
Dapsone
Organic nitrites/nitrates: amyl nitrate, nitroglycerin, nitroprusside
Inorganic nitrates: fertilizers, contaminated well water, preservatives
Chlorates
Phenazopyridine
Quinones: chloroquine, primaquine
Sulfonamides

Mechanism/Indications: Methylene blue is reduced to leukomethylene blue by erythrocyte methemoglobin reductase in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). Leukomethylene blue then reduces methemoglobin to oxyhemoglobin. Methylene blue is indicated in patients with methemoglobin levels >20-25%, or who have lower levels but are symptomatic.

Dosing: Adults and children should receive 1-2 mg/kg (0.1-0.2 ml/kg of 1% solution) intravenously infused over 5 minutes. Methylene blue has a rapid onset of action; maximal effects are normally seen within 30 minutes. The dose may be repeated in 1 hour if cyanosis persists.

Adverse Effects/Contraindications: Toxicity of methylene blue is dose-related. At doses of 2-4 mg/kg, hemolytic anemia and skin desquamation may occur in infants. At doses of 7 mg/kg, nausea, vomiting, chest pain, fever, and hemolysis have been described. Hypotension may occur at doses of 20 mg/kg, and bluish discoloration of the skin can occur at 80 mg/kg. Neonates exposed to methylene blue may also experience hyperbilirubinemia, methemoglobin formation, respiratory distress, and phototoxicity. Patients with G6PD deficiency are more likely to develop hemolysis and methemoglobin production with methylene blue. Judicious use of methylene blue is recommended in G6PD deficient patients, though G6PD status is not often readily available. Caution should also be taken in patients with severe renal impairment. Methylene blue is contraindicated in patients with a history of hypersensitivity to the product. Intraspinal injection is contraindicated.

Elizabeth Anne Sinclair, Pharm.D.
PGY2 Pediatric Pharmacy Specialty Resident
The Johns Hopkins Hospital

(cont. on page 2)

Methylene Blue (continued)

For more on methylene blue:

- Clifton J, Leiken JB. Methylene blue. *Am J Ther.* 2003;10:289-291.
- El-Husseini A, Azarov N. Is threshold for treatment of methemoglobinemia the same for all? A case report and literature review. *Am J Em Med.* 2010;28:748.e5-748.e10.
- Price DP. Methemoglobin inducers. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. *Goldfrank's toxicologic emergencies.* 9th ed. New York: McGraw Hill; 2011:1698-1707.
- Lexi-Comp Online, Lexi-Drugs Online [Internet]. Hudson (OH): Lexi-Comp, Inc.; 2011. Methylene blue [cited 2011 May 3]. Available from: <http://online.lexi.com> .

May 2011 (reviewed February 2013)