# Clinical Pharmacology & Toxicology Pearl of the Week

# ~ Methylene Blue ~



## Introduction:

Methylene blue (MB) is a solid, odorless, dark green powder at room temperature that yields a blue solution when it is dissolved in water. It is used as a dye/stain. It also has several applications in the management of the poisoned patient:

1. It interacts with the secondary pathway of methemoglobin reduction, where NADPH-Methemoglobin reductase reduces methylene blue to leukomethylene blue using NADPH from the G6PD-dependent hexose monophosphate shunt (Figure from EM Crit).





2. It has been used in refractory hypotension in calcium channel blocker poisoning

- Nitric oxide (NO) is important in the regulation of peripheral vascular tone and is synthesized locally by nitric oxide synthase (NOS) in the endothelium.
- NO then diffuses into the smooth muscle, where it binds to guanylate cyclase.
- Guanylate cyclase activity increases cGMP, and downstream activity results in smooth muscle relaxation.
- MB inhibits guanylate cyclase activity, reducing vasodilation and potentially increasing systemic vascular resistance.

#### Dose:

- Methemoglobinemia: 1-2mg/kg IV over 5 minutes
  - May see transient worsening in oxygen saturation due to blue pigment interfering with sat probe
  - Anticipate clinical improvement within minutes; resolution of cyanosis may take up to an hour
- <u>Shock</u>: 1-2mg/kg IV over 5 minutes. If response occurs, begin infusion at 0.1–2.0 mg/kg/hr.

# **Cautions:**

- Dosing beyond 7 mg/kg
  - Above doses of 7 mg/kg, MB is an oxidizing agent and may paradoxically worsen methemoglobinemia and hemolysis. Poison centres are starting to receive reports of patients with hemolytic anemia secondary to daily methylene blue use for unclear indications
- G6PD deficiency
  - G6PD deficiency causes a deficiency in NADPH, which in turn causes deficiency in glutathione resulting in hemolysis.
  - MB may be ineffective in G6PD patients (due to NADPH deficiency). IV vitamin C is an alternative reducing agent that works independently from NADPH and may be considered in these cases.
- Transient body fluid and skin color change
  - Transient blue discoloration of urine, tears, saliva and skin for about 24 hours
- Risk of serotonin syndrome
  - Methylene blue is a weak monoamine oxidase inhibitor and may increase the risk of serotonin syndrome when combined with other serotonergic medications
- Consequences of long-term use
  - While there have been some studies investigating its potential role in the treatment of neurodegenerative disorders like Alzheimer's, further research is necessary. The long-term consequences of people ingesting methylene blue daily are unknown.

## **References:**

- 1. Jang et al. J. Med. Toxicol. (2013) 9:242–249.
- 2. Warrick et al. (2016): A systematic analysis of methylene blue for drug-induced shock, Clinical Toxicology, DOI: 10.1080/15563650.2016.1180390.
- 3. EM Crit. Methemoglobinemia. https://emcrit.org/ibcc/methemoglobinemia/.
- 4. Hashmi et al. Cureus 2023 Oct 9;15(10):e46732. doi: 10.7759/cureus.46732

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the <u>Alberta</u> <u>Referral Directory</u> (ARD) by searching "Pharmacology" from the ARD home page. Click <u>HERE</u> for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in <u>Alberta Referral Directory</u> (ARD) by searching "Toxicology" from the ARD home page.

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Figure from Jang et al. Regulation of the relaxation of vascular smooth muscle by nitric oxide. Methylene blue inhibits guanylate cyclase activity, reducing vasodilation and potentially increasing systemic vascular resistance.