Methylene Blue
An Antidote for Methemoglobinemia and Beyond

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Abstract: Methylene blue has been in medicinal use for centuries and is best known as an antidotal treatment for acquired methemoglobinemia (MetHB). More recently, methylene blue has gained recognition for its efficacious use in the treatment of ifosfamide neurotoxicity and refractory vasoplegic shock in both the pediatric and adult critical care literature, extending its use beyond MetHB. Methylene blue's mechanism of action is somewhat complex and based partly on its oxidizing capabilities, ironically the same mechanism that causes MetHB. This review will examine methylene blue's use in the treatment of acquired MetHB and ifosfamide neurotoxicity and review the current literature regarding its role in critically ill pediatric and adult patients with refractory vasoplegic shock. Methylene blue's pharmacologic actions, dosing, and adverse effects will also be discussed.

Key Words: methylene blue, methemoglobinemia, ifosfamide, vasoplegic shock

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TARGET AUDIENCE

This CME activity is intended for health care providers in the pediatric emergency department, critical care, urgent care, oncology, and primary care settings.

LEARNING OBJECTIVES

After completion of this article, the reader should be able to:

1. Identify the 3 clinical indications for using methylene blue: methemoglobinemia, ifosfamide neurotoxicity, and refractory vasoplegic shock.
2. Explain the dosing and administration of methylene blue.
3. Describe potential adverse effects of methylene blue.

What Is Methylene Blue?

Methylene blue is a basic thiazine dye, tetramethylthionine chloride, and is considered the first synthetic medication used in humans.[1] Methylene blue is an odorless dark green crystalline powder and when mixed in water turns into a blue solution.[2,3] Its first uses in medicine were as an intestinal and urinary antiseptic, as a weak antimalarial, and in 1933 as treatment for aniline-induced methemoglobinemia (MetHB). Methylene blue is rapidly distributed into the brain, lungs, heart, liver, and kidneys.[4] It is eliminated in urine, bile, and feces as leukomethylene blue.[4]

Although methylene blue is primarily used for the treatment of acquired MetHB, it also has diverse uses in medicine including those for medical procedures, such as identifying the ureters in urological surgery and the gland in parathyroid surgery and as treatment for poisonings.[2,5] Interestingly, methylene blue is known in oncologic literature to be an effective treatment for the reversal of ifosfamide-induced encephalopathy, and in the 1990s, methylene blue was studied in vasoplegic shock and noted to improve blood pressure in patients.[6]

METHYLENE BLUE IN MetHB

Methemoglobinemia is a disorder of red blood cells that can be hereditary or acquired.[7] In this disorder, the hemoglobin molecule is adversely affected by the oxidation of iron.

Methemoglobin forms when the iron atom in the hemoglobin molecule is oxidized from ferrous (Fe^{+2}) to ferric (Fe^{+3}) iron.[2] Only the ferrous iron can bind and release oxygen. Methylene blue is an oxidizing agent and in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) is converted to leukomethylene blue.[5] Leukomethylene blue then reduces methemoglobin to hemoglobin.[5] Methemoglobin has strong affinity for its bound oxygen atom, causing a leftward shift in the oxygen dissociation curve, resulting in decreased release of oxygen at the tissue level. Methemoglobin is normally present in very low concentrations in body but is considered abnormal, MetHB, if there is greater than 1% present in the body.[7] Hemolysis can also occur because of oxidant stress and sometimes occurs during or after episodes of MetHB; however, certain protective mechanisms involving NADH and glutathione can reduce the oxidant burden and prevent the concomitant development of both disorders.[7]

Acquired causes of MetHB include medications and other xenobiotic toxins (Table 1). In most cases, methemoglobin concentrations of 1% to 3% do not typically result in clinical symptoms; however, in levels greater than 20%, symptoms can include fatigue, dyspnea, chest pain, headache, dizziness, tachycardia, seizures, central nervous system (CNS) depression, and death.[2,5] Symptoms can occur at lower concentrations in younger patients less than 36 months; those with cardiovascular, pulmonary, or CNS disease; or patients with anemia.[5] Methemoglobinemia is identified in patients with the presence of cyanosis without cardiovascular causes, elevated methemoglobin level (%) on co-oximetry, chocolate-colored blood, and an arterial blood gas with normal P_{O_2} values.[5] Note that the pulse oximetry machines used in most health care facilities are not configured to measure MetHB, and thus, readings will be inaccurate. For patients with mild MetHB and no underlying medical conditions, antidotal treatment is usually not necessary. Removing the offending agents usually results in resolution of MetHB with normal NADH enzymatic reconversion to hemoglobin.

DOSING OF METHYLENE BLUE

Methemoglobinemia is commonly treated with methylene blue as a first-line agent, and it works through its conversion to

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TABLE 1. Common Causes of MetHB

Medications	Xenobiotics	Pediatric
Dapsone	Amyl nitrate (poppers)	Acidosis
Nitric oxide	Aniline dye	Infants <4 mo
Nitroglycerin	Chlorobenzene	(Reduced NADH methemoglobin reductase activity)
Nitroprusside	Copper sulfate	Dehydration
Local anesthetics (benzocaine and lidocaine)	Fires (smoke inhalation)	Diarrhea
Quinine (chloroquine)	Naphthalene	Hyperchloremia acidosis
Sulfonamides (sulfanilamide, sulfathiazide, and sulfamethoxazole)	Nitrates (well water)	Prematurity
	Nitrites (foods)	**Hereditary**
	Nitrophenol	Hemoglobin M
	Nitrogen oxide gases	NADH methemoglobin reductase deficiency
	Organic nitrites (isobutyl nitrite)	
	Silver nitrate	
	Trinitrotoluene	

leukomethylene blue by NADPH (Fig. 1), which then allows reduction of MetHB to hemoglobin.[5,7]

It is recommended to treat symptomatic patients and those with MetHB levels of greater than 20%. The most accepted treatment for MetHB is 1 to 2 mg/kg of intravenous methylene blue infused over 5 to 30 minutes followed by a 15- to 30-mL normal saline flush. Methylene blue is usually given as 0.1 to 0.2 mL/kg of a 1% solution (Table 2). If there is localized pain due to the medication while being infused, it can be diluted in 50 mL of 5% dextrose in water and infused over 5 to 15 minutes. The onset of action of methylene blue is a few minutes with maximum effects occurring in about 30 minutes. This dose can be repeated in 30 to 60 minutes if necessary, based on clinical signs and symptoms, and perhaps a follow-up MetHB level if warranted. If there is no effect after 2 sequential doses, then dosing should be stopped and the diagnosis reexamined. The possibility of glucose-6-phosphate dehydrogenase deficiency should also be considered in patients in which methylene blue does not resolve significant elevations of documented MetHB concentrations. With extremely high MetHB levels accompanied by significant clinical toxicity, skin and/or gut decontamination should be considered based on the exposure. Other treatments such as multiple doses of charcoal, packed red blood cells transfusions, hyperbaric oxygen therapy, and/or exchange transfusion may be beneficial in certain situations.[7]

ADVERESE EFFECTS OF METHYLENE BLUE

There are a variety of adverse effects seen with the use of methylene blue, most commonly chromaturia and skin discoloration.[4] Other adverse effects include extremity pain, dizziness, nausea, headache, shortness of breath, chest discomfort, burning sensation of the mouth and stomach, restlessness, apprehension, and dysgeusia.[1,5,8,9] Paradoxical induction of MetHB by methylene blue can be seen when given at high doses or for long durations of time and is probably related to disequilibrium among enzyme reductase systems involved. Studies show that higher doses of methylene blue can induce hemolytic anemia independent of the presence of MetHB and in the setting of sepsis can result in decrease in splanchnic blood flow.[1,3] Because methylene blue is a dye, it will transiently alter pulse oximeter readings. Large doses can interfere with the ability to detect a clinical decrease in oxygenation (eg, pulse oximeter continues to read 85%), and therefore, repeat co-oximeter measurements along with arterial or venous blood gas analysis should be performed with clinical assessment.[5] In addition, in 2011, the US Food and Drug administration issued a warning against the use of methylene blue while taking serotonergic drugs.[3] Patients who are using serotonergic medications are recommended to discontinue them before use of methylene blue for diagnostic/therapeutic indications due to the risk of serotonin syndrome and worsening MetHB.[5]

OTHER ISSUES

Methylene blue is not beneficial in patients with NADPH methemoglobin reductase deficiency or those who have sulfhemoglobinemia. Patients who have glucose-6-phosphate dehydrogenase deficiency lack NADPH, which is needed for methylene blue to reduce methemoglobin. However, because of variants in disease, it is hard to determine if methylene blue will be beneficial in those patients because of different phenotypic enzymatic expression. Some studies report hemolysis in those patients.[1,5,9] If chronic cyanosis is present and/or methemoglobin levels do not decrease, consider checking a hemoglobin electrophoresis to look for hereditary deficiencies. If the patient's condition worsens after administration

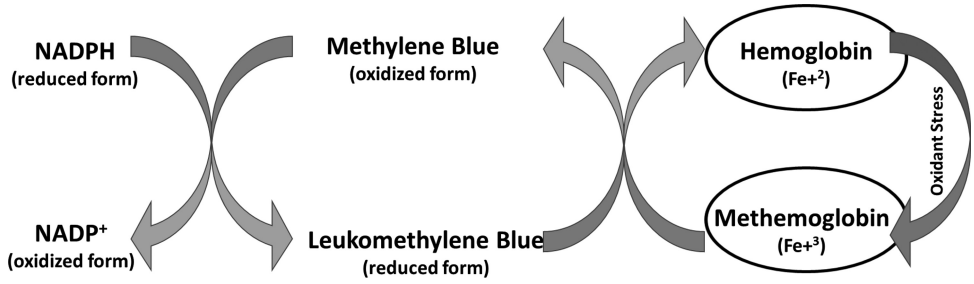

FIGURE 1. Mechanism of action of methylene blue. When methemoglobin is formed because of an oxidant stress, it can be reduced to leukomethylene blue in the presence of NADPH, which is oxidized by NADPH methemoglobin reductase. Leukomethylene blue can then reduce methemoglobin to hemoglobin.

TABLE 2. Methylene Blue Dosing for MetHB

IV: 1–2 mg/kg IV over 5–30 min follow with 15–30 mL flush
Diluted:
IV: 1–2 mg/kg mixed in 50 mL of 5% dextrose; infuse over 5–15 min
Repeat dose if no improvement 30–60 min after first dose with 1 mg/kg dose
Maximum dose of 100 mg regardless of weight
Neonates: 0.3–1.0 mg/kg
Doses can be given via interosseous route, but not by subcutaneous or intrathecal injection.

IV indicates intravenous.

of methylene blue, it is not recommended to continue treatment. It is not recommended to use intravenous methylene blue in pregnant patients unless the risks outweigh the benefits because of potential fetal complications. There is also minimal data available regarding breastfeeding with the use of methylene blue; therefore, the recommendation is to stop breastfeeding for 8 days after use.[5]

IFOSFAMIDE NEUROTOXICITY

Ifosfamide is an alkylating agent that is used for treatment of malignant tumors.[10] There are many well-studied adverse side effects for this drug, notably hemorrhagic cystitis, nephrotoxicity, myelosuppression, and neurotoxicity.[11] The most concerning neurotoxic effect is ifosfamide-induced encephalopathy.

The clinical findings of ifosfamide-induced encephalopathy can be moderate to severe, from somnolence, agitation, confusion, hallucinations, extrapyramidal symptoms, seizures, to CNS depression, coma, and death.[7,10,11] The literature states the incidence of ifosfamide-induced encephalopathy varies between 10% and 40% of patients.[10] The onset of symptoms for this reaction can occur between 2 and 96 hours after the initial administration. Symptoms are usually transient and resolve after 48 to 72 hours; however, studies show that in some cases, long-term serious neurologic dysfunction may persist.[10–12] For patients who do not have resolution, there is no standard medication that has been proven to reverse the neurotoxic effects.[10]

There are various predisposing factors reported for ifosfamide-induced encephalopathy, including hyponatremia, renal failure, female sex with bulky disease, and hypoalbuminemia, and previous cisplatin use.[10,11] Multiple mechanisms have been proposed, and most studies focus on mitochondrial toxicity.[12] It is hypothesized that chloroacetaldehyde, an inactive toxic metabolite of ifosfamide, is responsible for neurotoxicity; however, the exact pathophysiology is unknown.[10,11]

METHYLENE BLUE FOR IFOSFAMIDE-INDUCED ENCEPHALOPATHY

Several investigators have reported the efficacy of methylene blue in reversing ifosfamide-induced encephalopathy.[10–12] It is postulated that methylene blue inhibits the transformation of chloroethylamine into chloroacetaldehyde and inhibits multiple amine oxidase activities, preventing the formation of chloroacetaldehyde. A publication from 2000, by Pelgrims et al[12] suggested that intravenous methylene blue shortened the duration of neurotoxicity in adults, for example, within 48 hours. The authors also suggest that methylene blue could be given orally or intravenously, dosing 50 mg 4 times a day for secondary prophylaxis of ifosfamide-induced encephalopathy.

Another study looking at the management of ifosfamide-induced encephalopathy by Patel et al[11] summarized case reports and 1 retrospective chart review examining both adult and pediatric patients. Dosing regimens of methylene blue varied with patients receiving a single dose of 50 to 60 mg up to 6 doses a day, with favorable neurologic results.[11] In these patients, neurotoxic symptoms improved as rapidly as 10 minutes for some, whereas others took a few days to recover.[11] The authors suggested methylene blue was considered modestly effective, with the greatest benefit for severe neurotoxicity.[11] There was minimal evidence to support the use of methylene blue for secondary prophylaxis.[11] A retrospective study by Abahssain et al[10] reported that 75% of the patients who developed ifosfamide-induced encephalopathy and received methylene blue demonstrated neurological improvement. Based on the literature reviews, methylene blue should be considered as a treatment for severe ifosfamide neurotoxicity. This decision is best made collaboratively with oncologists and medical toxicologists.[10–12]

METHYLENE BLUE IN THE TREATMENT OF VASOPLEGIC SHOCK

Vasoplegic Shock

The term "shock" is defined as an acute circulatory failure leading to widespread cellular hypoxia and end-organ damage. Distributive shock is described as vasodilation with abnormal distribution of blood flow, decrease in systemic vascular resistance (SVR), and normal or increased cardiac output.[13] Distributive shock has multiple etiologies including sepsis, anaphylaxis, and drugs and may progress to states of uncontrolled vasodilation.[2,8] Vasoplegic syndrome results in severe hypotension, with preserved or elevated cardiac output and low SVR, with reduced cardiac filling pressures, and with uncontrolled vasodilation.[2,3] "Vasoplegic syndrome," "vasoplegic shock," and "vasodilatory shock" are all interchangeable terms used in the literature.

There are 2 mechanisms that are responsible for loss of vascular tone: (1) the activation of nitric oxide synthase causing an abnormal nitric oxide synthesis and (2) activation of smooth muscle cell–soluble guanylyl cyclase.[3] Vasoplegia is most likely caused by multiple factors leading to intrinsic vasodilating pathways, decreasing vascular tone leading to decreased end-organ perfusion pressure.[2,3] The mortality rate in patients with vasoplegia can be greater than 50% if untreated.[2] Increasing intravascular volume alone does not improve the hemodynamics of patients with vasoplegic syndrome, and patients may be minimally responsive to vasopressors and other pharmacotherapy that increases SVR. Methylene blue has been reported to increase arterial blood pressure in patients after cardiac surgery on cardiopulmonary bypass, increase survival in these patients after early administration, and improve hypotension in patients with septic shock in numerous publications, and these observations have since been applied to many cases of drug-induced vasoplegia.[3]

Treatment of Vasoplegic Shock

Current treatment regimens for patients with vasodilatory shock (septic shock, distributive shock, and vasoplegic shock) is based on optimizing fluid resuscitation and using vasopressors such as norepinephrine and other vasoactive drugs such as vasopressin and corticosteroids.

Methylene blue has been reported to improve blood pressure by antagonizing the vasodilation seen in vasoplegia. Methylene blue as a vasopressor causes vasoconstriction by inhibiting nitric oxide synthase and preventing the activation of guanylyl cyclase and decreasing responsiveness of the vessels to cyclic GMP in smooth muscle cells.[13–15]

Calcium channel blocker poisonings continue to cause significant mortality and morbidity in patients because of severe hypotension, refractory to standard treatment regimens. Laes et al[14] report a case of dihydropyridine calcium channel blocker poisoning–induced vasodilatory shock, refractory to standard therapy, where methylene blue was a beneficial adjunct in improving the hypotension. Methylene blue usage in such patients was associated with increases in SVR and a decrease in the need for catecholamines.[13–15] Similarly, Fisher et al[6] reported a patient with severe quetiapine poisoning with refractory hypotension to have beneficial effects after methylene blue administration. In addition, methylene blue has been successful in treating shock due to valsartan poisoning.[14] Despite evidence of improvement in blood pressures in hypotension due to drug toxicity, there is currently minimal data that suggest a decrease in mortality with the use of methylene blue in this subset of patients.[2]

Methylene blue should be considered in patients with vasoplegic shock who are unresponsive to standard vasopressor therapy; however, given the limited data on its use, it can only be recommended as an adjunctive or "rescue" therapy.[2]

DOSING OF METHYLENE BLUE FOR VASOPLEGIA

The dose for refractory hypotension due to drug toxicity is not well established. Dosing that has been reported to be beneficial in case reports is 1 to 3 mg/kg bolus over 10 to 60 minutes. The literature also suggests that if there is improvement to follow with continuous infusion at a rate of 0.25 to 1 mg kg^{-1} $hour^{-1}$.[1,3,11] Lower doses of methylene blue have been reported to result favorable outcomes, whereas higher doses such as 7 mg/kg were noted to cause decreases in splanchnic perfusion.

USAGE OF METHYLENE BLUE IN PEDIATRIC INTENSIVE CARE UNIT

There is limited literature available in pediatrics regarding refractory hypotension and the role of methylene blue.[4] Catecholamine-resistant shock is shock refractory to both fluid resuscitation and vasopressor therapy and results in significant morbidity and mortality in the pediatric population.[9] In the last 5 years, there have been multiple published reports on outcomes of critically ill children receiving methylene blue. There have been a limited number of controlled studies that support the efficacy of methylene blue for vasoplegic shock in pediatric patients. In a systematic review by Otero Luna et al,[9] 24 studies involving a total of 102 patients described the use of methylene blue in critically ill children. The findings suggest that methylene blue increased mean arterial pressure and decreased need for catecholamines. Dosing recommendations for methylene blue in pediatric patients were similar to those of adults with vasoplegia—intravenous dosing with a 2 mg/kg bolus and, if needed, followed with an infusion rate of 0.5 mg kg^{-1} $hour^{-1}$.[9]

A retrospective chart review published in 2020 of 7 pediatric cases treated with methylene blue for refractory vasoplegic shock reported favorable hemodynamic responses, with increases in blood pressure in the first hour after a loading dose, although 1 patient showed no improvement and had pulmonary hypertension and later dying.[16] Patients were all given 1 mg/kg over 10 minutes as a loading dose and then a continuous infusion of 0.25 mg kg^{-1} $hour^{-1}$.

CONCLUSIONS

Uses for methylene blue have extended beyond its role as a traditional antidote for clinical toxicity due to acquired MetHB and has renewed uses in modern-day medicine. It remains the first-line agent for treating MetHB and may be also considered for ifosfamide encephalopathy, especially in patients with certain risk factors. Despite a limited number of studies, the use of methylene blue in critically ill adult and pediatric patients should be considered as adjunctive or rescue treatment of drug-induced vasoplegic shock and catecholamine-resistant shock. Dosing is straightforward; however, health care providers should be aware of potential adverse effects and how methylene blue can affect the ongoing evaluation of the patient.

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