A Novel Use of Methylene Blue in the Pediatric ICU

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Methylene blue (MB) is a medication commonly used to treat methemoglobinemia, reducing methemoglobin to hemoglobin. A novel use of MB, as detailed here, is in the treatment of refractory hypotension. A number of reports have detailed use of MB for this purpose in adults, but few data in pediatrics. A 22-month-old girl with Noonan syndrome, biventricular hypertrophic cardiomyopathy, and chronic positive pressure ventilation developed shock with tachycardia, hypotension, and fever after 3 days of diarrhea. She was critically ill, with warm extremities, bounding pulses, and brisk capillary refill. Laboratory tests revealed metabolic acidosis, low mixed venous oxygen saturation, and leukocytosis with bandemia. Treatment of severe septic shock was initiated with fluid resuscitation, inotropic support, sedation, and paralysis. She remained hypotensive despite norepinephrine at 0.7 μg/kg per minute, dopamine at 20 μg/kg per minute, and vasopressin at 0.04 U/kg per hour. Her vasoplegic shock worsened, despite aggressive conventional therapy. Intravenous MB was initiated, with a loading dose of 1 mg/kg followed by a continuous infusion at 0.25 mg/kg per hour. Upon initiation of MB, her systolic blood pressure increased by 33 points (40% increase), and diastolic blood pressure increased by 20 points (46% increase). She was able to wean off all inotropes quickly after initiation of MB. MB should be considered in the setting of refractory vasoplegic shock in the PICU.

Septic shock is a known cause of significant morbidity and mortality in children, with an incidence of 0.56 cases per 1000 children and a national mortality rate of 10.3% (6.2 per 100 000 population).1 The primary goals in treatment of septic shock are rapid restoration of hemodynamic stability and treatment of the underlying infection. Therapy for correcting hemodynamic instability includes aggressive fluid resuscitation followed by vasoactive infusions for fluid refractory shock. Vasoactive agents commonly used include dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin. Methylene blue (MB) is a potentially useful adjunct in a subset of patients with fluid-refractory, catecholamine-refractory, warm shock. MB is commonly used to treat methemoglobinemia by reducing methemoglobin to hemoglobin. A novel use of MB, as detailed in this case report, is in the treatment of refractory vasoplegia and hypotension. A number of reports have detailed the use of MB for this purpose in adults,2 but there is a paucity of pediatric data.

A 22-month-old girl with Noonan syndrome, biventricular hypertrophic cardiomyopathy, failure to thrive, and chronic respiratory failure necessitating long-term ventilation developed fever with uncompensated shock after 3 days of diarrhea. Her initial vital signs and laboratory data are detailed in Tables 1 and 2. She was ill-appearing, with warm extremities, bounding pulses, and flash capillary refill (<2 seconds). Her medications at
this time included calcium gluconate, fluconazole, lansoprazole, propranolol, and verapamil. Arterial blood gas demonstrated metabolic acidosis. Electrolyte abnormalities included hypernatremia, hypokalemia, and hyperchloremia. Renal function demonstrated disproportionate elevation of blood urea nitrogen compared with creatinine. Complete blood cell count revealed leukocytosis with a significant elevation in band forms (12%). Cultures of blood, urine, and trachea were obtained. A *Clostridium difficile* culture was also obtained, given her history of diarrhea. Broad-spectrum antimicrobial therapy was initiated with vancomycin, meropenem, gentamicin, and micafungin. A transthoracic echocardiogram, unchanged from her baseline, showed severe biventricular hypertrophy, dynamic left ventricular outflow tract obstruction (peak left ventricular outflow tract gradient, 52 mm Hg), normal biventricular systolic function (left ventricular ejection fraction, 65.3%), and moderate pulmonary valve stenosis.

She was initially resuscitated with 100 mL/kg of fluids to restore her depleted intravascular volume, as suggested by preceding diarrhea, hypernatremia, and azotemia. Her central venous pressure was measured during resuscitation and was adequate at 12 to 18 mm Hg after fluids. Despite an adequate central venous pressure she remained hypotensive, so norepinephrine was added for warm shock. We decreased metabolic demand with sedation, paralysis, mechanical ventilation, and aggressive control of fever with a cooling blanket. After transient improvement, she worsened and became refractory to 1 µg/kg per minute of norepinephrine, 0.04 U/kg per minute of vasopressin, and 20 µg/kg per minute of dopamine. MB was added for severe refractory vasoplegia and hypotension. A loading dose of 1 mg/kg was administered, followed by an infusion of 0.25 mg/kg per hour 4 hours after the loading dose, with dramatic improvement. Her systolic blood pressure (BP) increased by 33 mm Hg (40% increase), and diastolic BP increased by 20 mm Hg (46% increase) (Fig 1).

After the bolus of MB, BP improved significantly. Dopamine was weaned off in 6 hours and norepinephrine in 14 hours. MB was infused for a total of 25 hours. Although the BP was adequate, the clinical decision was made to discontinue MB (without weaning) before stopping vasopressin. Vasopressin was able to be discontinued 5 hours after MB was stopped. She was unparalyzed 1 day after MB was discontinued and returned to her baseline. Her infectious workup was negative. She was eventually transferred from the PICU to the chronic ventilator unit on a laptop ventilator for additional inpatient care.

### DISCUSSION

MB is a dye most commonly recognized for its treatment of methemoglobinemia but has been found to have diverse uses in medicine. More esoteric indications include anaphylaxis, malaria, hepatopulmonary syndrome, vasoplegic syndrome, and refractory hypotension.3 MB owes this extensive repertoire to its effects on multiple physiologic pathways. In methemoglobinemia, MB reduces methemoglobin to hemoglobin via its interaction with reduced nicotinamide adenine dinucleotide phosphate (NADPH).4 Additionally, it inhibits inducible nitric oxide synthase (iNOS), an enzyme that is activated by endotoxins and cytokines. Activation of iNOS in endothelial and vascular smooth muscle results in increased generation of nitric oxide (NO), which activates guanylate cyclase to increase cyclic guanosine monophosphate and causes smooth muscle relaxation, vasodilatation, and increased vascular permeability.5 This is the mechanism of action of MB in reversing refractory vasoplegia in conditions that can result in exuberant production of NO, such as sepsis,
systemic inflammatory response syndrome, or anaphylaxis.

MB is rapidly distributed into the brain, heart, lungs, liver, and kidneys. It rapidly enters erythrocytes and is quickly reduced to leucomethylene blue. Its half-life has been estimated from 30 minutes to 6.6 hours. It is eliminated in the bile, feces, and urine as leucomethylene blue.6–9

Dosing guidelines for MB in refractory hypotension in adults have been previously published. Paciullo et al5 summarized the trials that evaluated MB in septic shock and reported bolus doses of 1, 2, 3, and 4 mg/kg, including 2 studies that used infusions of 0.25 mg/kg per hour up to 2 mg/kg per hour. They reported that MB administration is associated with increases in mean arterial pressure while reducing catecholamine requirements in patients in septic shock, but its effects on morbidity and mortality are unclear.2,5,10 Dumbarton et al11 also reported a case of prolonged MB infusion for 120 hours at doses titrated from 0.12 to 0.5 mg/kg per hour in an adult with refractory septic shock. Another dose finding study infused 1, 3, or 7 mg/kg over 20 minutes in adults with septic shock. Improved hemodynamics were reported with doses as low as 1 mg/kg, with more adverse effects at higher doses.12

**DOsing in PEDIATRICS**

Limited literature is available for dosing of MB in children with refractory hypotension. Taylor and Holtby13 reported a child with vasoplegia who received 2 doses of MB at 2 mg/kg intravenously for hypotension in relation to bypass. Another study used similar doses of 1 to 2 mg/kg in neonates for sepsis and acquired methemoglobinemia.9 Driscoll et al14 described 5 neonates with refractory hypotension due to septic shock who received 1 mg/kg intravenously infused over 1 hour and had subsequent improvement in BP. Prasad et al15 compared intermittent and continuous MB infusions in 11 children for methemoglobinemia using the same overall dose of 2 mg/kg; these investigators found the continuous infusion to be more effective than intermittent boluses.
Our patient received a 1-mg/kg bolus of undiluted MB to treat vasodilatory shock. Clinical improvement occurred after the MB bolus, and an MB continuous infusion was started ~4 hours after the bolus at a rate of 0.25 mg/kg per hour for a total of 25 hours. The final concentration of the MB infused was 0.05%. MB is stable when diluted in normal saline or 5% dextrose in water; the length of stability is uncertain.

ADVERSE EFFECTS OF METHYLENE BLUE

The most common adverse effect of MB administration is self-limiting blue-green discoloring of skin or urine, which our index patient demonstrated. Confusion, fever, headache, nausea, abdominal pain, vomiting, and diaphoresis have been reported. Some studies have noted pulmonary vasoconstriction and decreases in oxygenation as well as cardiac arrhythmias, decreased cardiac output, and decreased renal and mesenteric blood flow. These more serious adverse effects reportedly did not occur with doses <2 mg/kg. Also, because of the ability of MB to absorb light at wavelengths close to the wavelengths emitted by some oximetry devices, case reports have highlighted a decrease in oximetry readings, whereas others have reported no significant changes. Our patient’s hemodynamics were monitored throughout the infusion. Her heart rate decreased mildly during infusion, an effect thought to be secondary to improved blood pressure. Her oxygen saturations were followed on arterial blood gases, and there was no change in pulse oximetry readings during infusion. She was ventilated with a pressure-regulated volume control-pressure support mode. There were no changes in her ventilation strategy around the time of the MB infusion. Because the patient in this case report had a history of pulmonary valve stenosis and was also chronically dependent on mechanical ventilation, the potential for MB to cause pulmonary vasoconstriction and possibly worsen the patient’s respiratory condition was given much consideration before it was decided that the risk/benefit ratio was favorable.

MB is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. NADPH is critical to the reduction of MB to leucomethylene; patients with glucose-6-phosphate dehydrogenase deficiency have low levels of endogenous NADPH, putting them at a higher risk of hemolytic anemia. Because MB may alter cyclic guanosine monophosphate accumulation in platelet aggregation, there is concern about deleterious effects on platelet count; however, it has been postulated that this may be an effect of septic shock rather than MB treatment because at least 1 study has shown no significant effects on platelets.

In pediatric patients, doses >2 mg/kg have been associated with methemoglobinemia, hemolytic anemia, and hyperbilirubinemia. Our patient received a cumulative dose higher than that but had no such side effects.

COST

As mentioned in the case narrative, because of profound vasoplegia, continuous infusions of vasopressin, norepinephrine, and dopamine were administered. Overall, the daily cost for the MB infusion was ~$7 more than the cost of vasopressin, norepinephrine, dopamine, and epinephrine; however, it provided a decreased drip burden for the nursing staff and allowed the discontinuation of all vasoactive drugs after 1 day.

CONCLUSIONS

Through its effect on iNOS, MB has a potential role in reversing vasodilation in conditions associated with exuberant production of NO. Its benign side effect profile renders it a good option in the treatment of catecholamine refractory vasoplastic states including septic shock.

ABBREVIATIONS

BP: blood pressure
iNOS: inducible nitric oxide synthase
MB: methylene blue
NADPH: nicotinamide adenine dinucleotide phosphate
NO: nitric oxide

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