Methylene Blue for Refractory Hypotension: A Case Report

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Methylene blue has multiple indications for use, but recently it has been shown to be useful in treating refractory hypotension. Anaphylaxis results in widespread vasodilation and hypotension. Epinephrine has been described as the drug of choice in the treatment of hypotension for anaphylaxis, but the increased heart rate may be poorly tolerated by some patients.

This case report describes a 79-year-old man with a history of diastolic dysfunction who was admitted for elective coronary artery bypass graft surgery. After induction of general anesthesia, symptoms of anaphylaxis developed with urticaria and decreased mean arterial pressure. The hypotension was refractory to vasoactive agents and volume repletion. Methylene blue was primed in the cardiopulmonary bypass pump and was effective in restoring hemodynamic stability. Furthermore, the patient required a decreased amount of vasoactive agents in the postoperative course.

The suspected mechanism of action of methylene blue is inhibition of the enzyme nitric oxide synthase, which ultimately prevents the smooth muscle dilation that accompanies anaphylaxis. Methylene blue may be a valuable adjunct in the treatment of anaphylaxis and other causes of refractory hypotension.

Keywords: Anaphylaxis, hypotension, methylene blue, nitric oxide.

Anaphylaxis can lead to severe hypotension, which is often managed with both fluid boluses and catecholamine infusions. The etiology for hypotension during allergic reactions is a combination of immunologic and inflammatory responses to an allergen. Antibiotics are one of the most common causes of this exaggerated response, which is attributed to a type I immediate hypersensitivity reaction. Chemical mediators of this reaction are released by mast cells within minutes of surface antigen exposure to immunoglobulin E. These chemicals include leukotrienes, prostaglandins, kinins, and histamine. Recognized symptoms of these mediators during anesthesia include hypotension, edema, urticaria, flushing, tachycardia, and bronchospasm. The onset and severity of allergic reactions vary and individual clinical symptoms differ according to the extent of allergen exposure. The following case report discusses the use of methylene blue in a patient undergoing coronary artery bypass graft surgery who remained hypotensive refractory to traditional vasopressor infusions before bypass initiation because of a possible anaphylaxis reaction.

Case Summary

A 79-year-old man, 60 kg, ASA physical status IV, was admitted for a coronary artery bypass graft surgery for severe coronary artery disease. His medical history included hypertension, gout, benign prostatic hypertrophy, noninsulin dependent diabetes, mild aortic stenosis, and previous myocardial infarction with an ejection fraction of 35%. The patient's surgical history included a right carotid endarterectomy. He had no known drug allergies. His current medications included allopurinol, omeprazole, clopidogrel, and aspirin. The clipidogrel and aspirin were discontinued 10 days before surgery. The patient's vital signs were blood pressure, 136/76 mm Hg, and heart rate, 79/min.

After the patient's arrival in the operating room, standard monitors including a 16-gauge intravenous catheter and a 20-gauge radial arterial line were administered. A preoperative antibiotic, cefazolan, 1 g, and midazolam, 2 mg, were administered intravenously. In addition, a left internal jugular pulmonary artery catheter was inserted. Initial pulmonary artery catheter values were pulmonary artery pressure, 27/17 mm Hg; cardiac index, 2.5 L/min per m^2; systemic vascular resistance, 1,231 dynes-sec/cm^{-5}; and mixed venous oxygen saturation, 72%. The patient was preoxygenated and a smooth induction of anesthesia was performed with fentanyl, 250 µg; thiopental, 100 mg; and vecuronium, 10 mg. An 8.0-mm endotracheal tube was inserted under direct laryngoscopy, and after verification of correct placement, was secured at a depth of 21 cm measured at the lip. General anesthesia was maintained with isoflurane titrated to an end-tidal concentration of 1%, and an additional 750 µg of fentanyl was titrated. During the surgical skin scrub, new skin eruptions resembling hives were observed on the patient's torso. The arterial line blood pressure showed a decreased blood pressure of 70s to 80s/40s to 50s mm Hg, and peak airway pressures remained unchanged. Breath sounds remained clear on auscultation

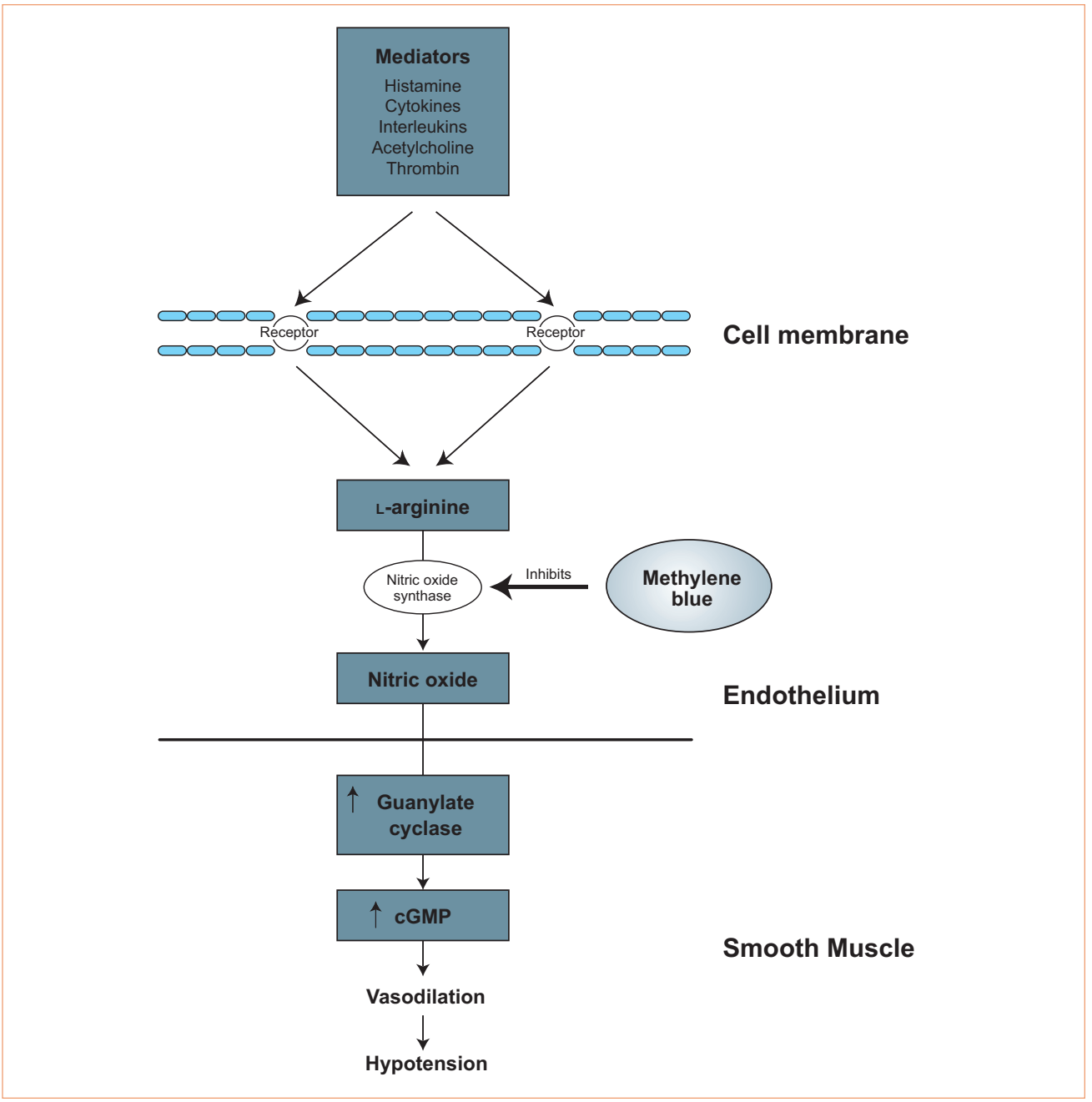

Figure. How Methylene Blue Inhibits Vasodilation and Hypotension by Blocking Nitric Oxide Synthase
cGMP indicates cyclic guanosine monophosphate.

in all fields. Diphenhydramine, 50 mg, and a 500-mL lactated Ringer's bolus were given intravenously for suspected anaphylaxis. Phenylephrine, norepinephrine, nitroglycerin, and insulin infusions were titrated to maintain normotension, dilate coronary vessels, and treat hyperglycemia. Phenylephrine was replaced with a vasopressin infusion after escalating doses and presumed tachyphlyaxis. The surgery proceeded and the vessels were cannulated.

Despite treatment the patient remained hypotensive, and therefore the bypass was initiated with methylene blue, 35 mg (0.5 mg/kg), primed into the bypass pump. All infusions of norepinephrine and vasopressin were discontinued 20 minutes later as the patient's mean arterial pressure returned to a normal 60 mm Hg. Hemostatis was ensured after grafting the obtuse marginal and left anterior descending coronary arteries. Cardiac bypass was discontinued and the patient was decannulated with infusions of milrinone, 1 µg/kg per minute; nitroglycerine, 1 µg/kg per minute; vasopressin, 0.04 U/min; and norepinephrine, titrated to effect. The overall requirement for vasopressors was noted to be lower than before the bypass. Protamine, 350 mg, was given intravenously

during the next 10 minutes. The final pulmonary artery catheter values were pulmonary artery pressure, 51/36 mm Hg; cardiac index, 3.25 L/min per m^2; systemic vascular resistance, 899 dynes-sec/cm^{-5}; and mixed venous oxygen saturation, 71%. Urine output total was 300 mL and the estimated blood loss was 400 mL. The patient was transported, while intubated and monitored, to the cardiac intensive care unit.

Discussion

Methylene blue has proven valuable for multiple indications. It is the treatment of choice for methemoglobinemia, used as a surgical tissue marker, and within the past decade, as a vasopressor for refractory hypotension.[1] There are case reports of success in treating hypotension, particularly in the face of sepsis, anaphylaxis, and vasoplegia syndrome after discontinuation of cardiopulmonary bypass, particularly when norepinephrine treatment has failed.[1-6] Case reports have also shown that methylene blue improved hemodynamics, or even prevented expected hypotension during liver transplantation, hemodialysis, and treatment of cirrhotic patients.[7-9] Methylene blue therapy also has been used for patients who are chronically treated with angiotensin-converting enzyme inhibitors with refractory hypotension on induction of anesthesia.[4]

The proposed mechanism of action is prevention of smooth muscle vasodilation due to blockade of nitric oxide synthase.[2-3,10] Nitric oxide, also known as endothelium derived relaxing factor, is formed from L-arginine by nitric oxide synthase in response to agonists such as acetylcholine, bradykinin, histamine, and thrombin. Nitric oxide is released from vascular endothelium and activates the enzyme guanylyl cyclase, increasing cyclic guanosine monophosphate concentrations intracellularly. The end result is vascular smooth muscle relaxation and vasodilation. Therefore, nitric oxide plays a pivotal role in the maintenance of systemic vascular resistance and as a mediator in the inflammatory response (Figure).

This case report demonstrates hypotension secondary to anaphylaxis that was refractory to treatment and that showed improvement with a gradual decrease in vasopressor requirement after methylene blue administration. Although the use of cardioplegia and protamine reversal of heparin may also contribute to postbypass hypotension, this treatment resulted in more stable blood pressure than expected after cardiopulmonary bypass was discontinued. Although vasopressors were used, the doses were lower than before cardiopulmonary bypass surgery. Compared to other case reports, the methylene blue dose used for this patient was low, at 0.5 mg/kg, which further demonstrates its efficacy. This dose was based on experience of the anesthesia provider, although previous studies show that a therapeutic dose of 1.5 to 2 mg/kg bolus followed by a continuous infusion of 0.5 mg/kg per hour.[1-3] Epinephrine was not administered in this case because of severe diastolic dysfunction and the goal of keeping the heart rate slow to maintain adequate ventricular filling times.

Observable adverse effects of methylene blue include falsely low readings on pulse oximetry and blue-tinged urine. Other adverse effects such as changes in alveolar gas exchange, abdominal pain, diaphoresis, nausea, headache, and cardiac dysrhythmias have been described, but according to this literature review, are infrequently reported.[6] The only observed adverse effect that the patient demonstrated was blue-tinged urine for approximately 5 days. Furthermore, the oxygen saturation value was unaffected by methylene blue administration, which is consistent with another recent case study.[11] The minimal side effects observed here may have been dose related.

In conclusion, the clean adverse effect profile of methylene blue makes this a valuable adjunct to the anesthetist's armamentarium for treatment of hypotension. The hemodynamic response is a reliable increase in blood pressure that can be used to treat hypotension refractory to other medications. This is consistently shown in both human and animal studies.[12] The efficacy has been demonstrated with the cardiothoracic anesthesia community and may be reproducible in other surgical populations.

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