Methylene Blue to Treat Refractory Latex-Induced Anaphylactic Shock: A Case Report

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Anaphylaxis occurs in 1/5000–1/20,000 of anesthesia cases and may evolve with shock and cardiovascular collapse in up to 54% of cases. Mortality varies from 3% to 10%. Latex is the second leading cause of anaphylaxis during the perioperative period. We report a case of latex-induced anaphylactic shock refractory to the usual catecholamine treatment that was reversed with the aid of methylene blue. Exaggerated activation of the nitric oxide–cyclic guanosine monophosphate pathway is observed in refractory shock. Methylene blue selectively inhibits this pathway. (A&A Case Reports. 2017;XXX:00–00.)

Anaphylaxis is a generalized, rapid onset, and severe hypersensitivity reaction that can lead to death.[1] The incidence is estimated to be from 1/5000 to 1/20,000 of anesthesia cases with mortality ranging from 3% to 10%.[2–4] Latex is reported to be the second leading cause of anaphylactic reactions during anesthesia.[5] Anaphylactic shock is one of the most serious manifestations of anaphylaxis. Methylene blue has successfully been used as an adjuvant in the treatment of refractory anaphylactic shock.[3,6,7] We describe a case of a latex-induced anaphylactic shock that was refractory to conventional treatment and reversed with the aid of methylene blue.

The patient's written and informed consent was obtained for this case report, which was also approved by the Research Ethics Committee of University for the Development of the Alto Vale do Itajaí (CAAE: 47962215.1.0000.5676).

CASE DESCRIPTION

A 49-year-old woman, American Society of Anesthesiologists physical status I, with no history of allergies and a history of 3 previous surgeries, underwent open cholecystectomy under combined epidural and general anesthesia. She was monitored by pulse oximetry, cardioscopy (DII and V5), and noninvasive blood pressure measurements; capnography and gas analysis were added after intubation. The individual was sedated with midazolam and fentanyl. An epidural catheter was placed for analgesia only in the T8–T9 interspace and 0.125% levobupivacaine with epinephrine (17 mL = 21.25 mg), fentanyl (100 µg), and morphine (1 mg) injected. For intravenous (IV) induction of general anesthesia, propofol (200 mg), fentanyl (200 µg), and atracurium (40 mg) were administered. Isoflurane 1% was used for maintenance. Cephalothin (IV) was given 30 minutes before surgery; dexamethasone, ondansetron, and dipyrone were given after induction.

Within 20 minutes of administration of the last IV medication and 5 minutes of beginning the surgery, the patient presented a severe anaphylactic reaction with erythema, bronchospasm, and shock (Figure 1). Surgery was stopped and isoflurane administration was discontinued. Volume expansion with crystalloid was performed. Administration of ephedrine and metaraminol followed by epinephrine 100 µg every 2–3 minutes (5 times) did not improve blood pressure. Initiation of a norepinephrine infusion caused a slight increase in blood pressure. Hydrocortisone, ranitidine, diphenhydramine, terbutaline, and aminophylline were also administered. The erythema and bronchospasm improved, but the shock persisted.

Methylene blue 1%, 2 mg/kg IV, improved the blood pressure and produced a marked drop in arterial lactate levels (Figures 1 and 2). The dose of norepinephrine was then decreased. The patient was transferred to the intensive care unit (ICU), sedated, and intubated with a low dose of norepinephrine (0.08 $\mu g \cdot kg^{-1} \cdot m^{-1}$). The patient was extubated 4 hours later without sequelae.

Blood samples were collected at 1 hour after the onset of symptoms for the first tryptase level (trip 1) and at 24 hours after the second tryptase level (trip 2) for immunoglobulin E (IgE) reactions. A high result was observed for trip 1 (27.5 µg/L), though trip 2 was normal (6.53 µg/L). Negative IgE results (radioallergosorbent test) were obtained for dipyrone and the local anesthetic.

The patient remained hospitalized for 2 days in the intensive care unit and was then discharged. Four weeks later, the patient was referred for an evaluation by an allergist, who performed IgE assessment (when possible) and skin tests, which revealed a high-degree latex allergy and the exclusion of other causes. The patient returned later for the cholecystectomy in a latex-free environment. Subarachnoid analgesia with sufentanil and morphine associated with general anesthesia was performed using the same medications from the previous procedure without complications.

DISCUSSION

IgE-mediated hypersensitivity reactions can evolve with shock and cardiovascular collapse in up to 54% of cases[5] and lead to organ deterioration and death. Methylene blue, although not part of the routinely used treatment, is a possible and effective adjuvant in the treatment of catecholamine-refractory anaphylactic shock.

Among the causes of intraoperative anaphylaxis, the use of neuromuscular blockers, antibiotics, and latex are commonly implicated.[2,5] Indeed, latex is responsible for almost

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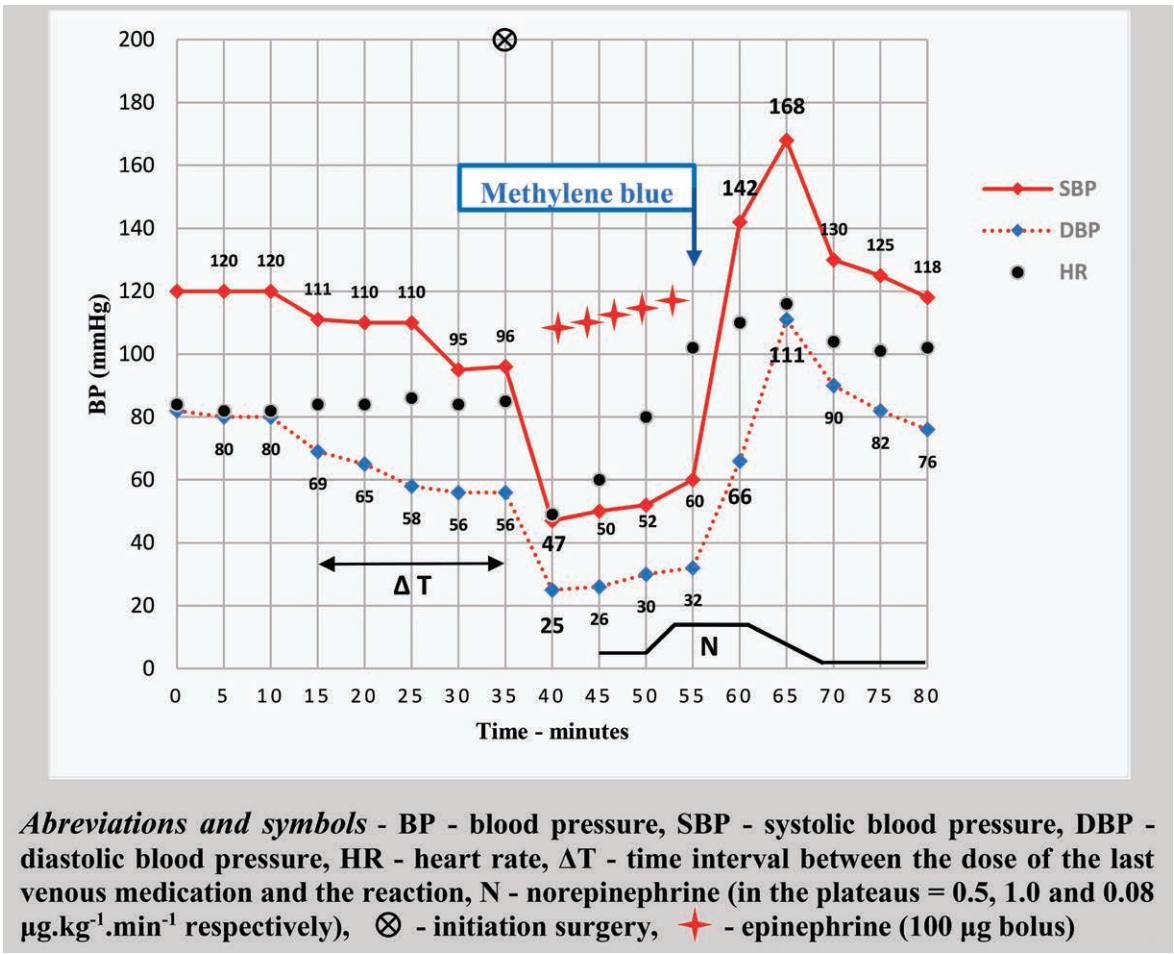

Figure 1. Hemodynamic variables before and after the use of methylene blue.

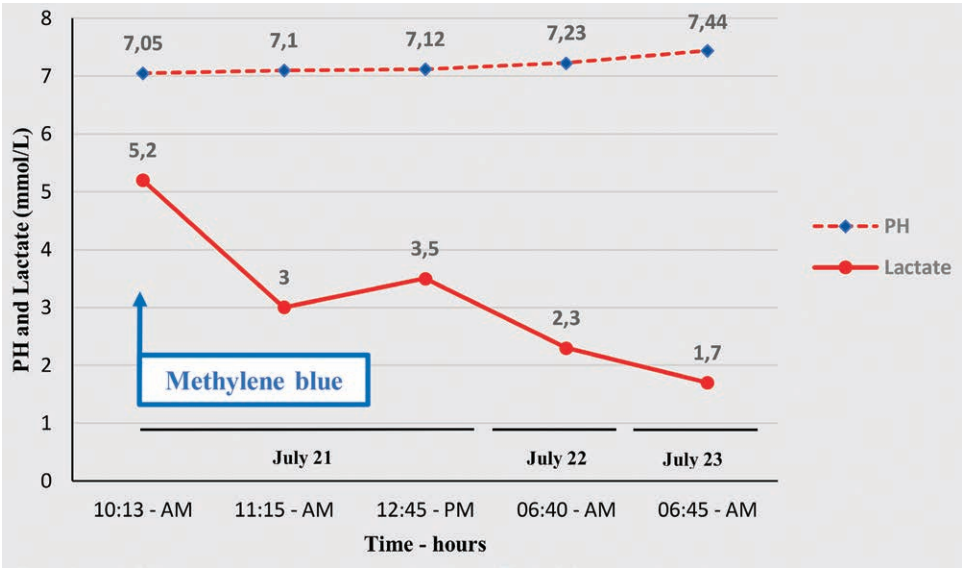

Figure 2. pH levels and arterial lactate concentrations after the use of methylene blue.

20% of anaphylaxis cases under anesthesia and is considered to be the second major cause.[5] Latex reactions occur from within a few minutes to up to 30–60 minutes after anesthesia induction; in contrast, reactions from medications more typically occur immediately or soon after their administration.[2,8,9] The route of administration or contact with the allergen is directly related to the onset and severity of symptoms. For example, IV administration or intimate mucosal contact causes a more rapid onset and more severe reactions.[2,10] In the case presented herein, the anaphylactic

reaction occurred approximately 20 minutes after induction of anesthesia and approximately 5 minutes after beginning the surgery and coincided with entry into the abdominal cavity and intimate contact between the surgeon's latex glove and the abdominal viscera. In addition, the patient had a history of 3 previous surgeries with antigen exposure, which may have led to sensitization.

A latex reaction is typically mediated by IgE. Antigens binding to antibodies produced due to previous exposure leads to degranulation of mast cells and basophils, with formation and release of chemical mediators, such as prostaglandins, leukotrienes, and histamine, with the last being the most important and responsible for most effects of anaphylaxis.[8,10] Induction of nitric oxide (NO) production has been described as the mechanism of action of histamine in the development of anaphylactic shock, which increases activation of guanylate cyclase with a consequent increase in cyclic guanosine monophosphate (cGMP), causing relaxation of the vascular smooth muscle and marked vasodilation.[7,11]

The anaphylactic reaction can be classified into 4 degrees according to the severity of symptoms. The reactions of degrees III and IV are considered to be serious and life threatening. A degree III reaction is characterized by the presence of cutaneomucosal signs, bronchospasm, gastrointestinal disorders, tachycardia or bradycardia, hypotension and shock, and a grade IV reaction by cardiorespiratory arrest.[2] In the case reported, the patient presented with generalized erythema, bronchospasm, bradycardia, and shock, and therefore exhibited a grade III reaction.

Tryptase is a protease that is primarily released by mast cells[2,4,10,12]; its normal value is below 12 μg/L,[12] and an increase above 25 μg/L is highly suggestive of anaphylaxis.[2,4,10,12] In degree III and IV reactions, serum tryptase levels are increased, with a peak between 30 minutes and 2 hours, and return to baseline levels within 24 hours.[2] The patient's trip 1 and trip 2 levels were 27.5 and 6.53 μg/L, respectively. These results supported the diagnosis.

Anaphylaxis treatment consists of calling for assistance, suspending or removing the suspicious agent, interrupting the surgery (if possible), securing the airway, administration of oxygen, discontinuing all anesthetic administration, performing volume expansion, and administering IV epinephrine as follows: 100–200 μg every 2 minutes for degree III reactions, 1 mg every 3–5 minutes (associated with cardiorespiratory resuscitation) for degree IV, and a continuous infusion of 0.05–0.1 $\mu g \cdot kg^{-1} \cdot m^{-1}$ in the case of repeated bolus.[2,4,9] As adjuvant therapy, the following may be used: corticosteroids, H1 and H2 receptor blockers, β-2 agonists, and aminophylline.[2,4,9,10] In cases in which epineprhine is ineffective, vasopressin and norepinephrine may be used.[2,4] Some authors mention the use of methylene blue in refractory cases.[2–4,6,7,13]

Methylene blue has been successfully used in cases of refractory shock due to vasoplegia after extracorporeal circulation, sepsis, and anaphylactic shock[3,6,7,14]; however, its mechanism of action that results in shock reversal has yet to be fully elucidated. Excessive activation of the NO-cGMP pathway occurs in refractory shock,[6,14] and studies indicate that methylene blue inhibits guanylate cyclase, which interrupts this pathway and reverses vasodilation, causing hemodynamic improvement.[7,11] Methylene blue is a selective inhibitor of the NO-cGMP pathway[7] and does not have the side effects of nonselective inhibitors of NO release.[3,7] The dose used in cases of shock is 1–2 mg/kg,[3,7] but additional doses or continuous infusion may be required due to its short half-life.[7,14] Regardless, there is no solid evidence to support the use of methylene blue as a single drug in cases of anaphylaxis; it is rather applied as an adjuvant in treatment with catecholamines.[3,6,15] The usual treatment was used in this case with an unsatisfactory effect; the patient remained in shock for approximately 15 minutes even with high doses of catecholamines. Methylene blue administration was associated with an immediate improvement in hemodynamics and tissue perfusion. The immediacy of improvement suggests that the effect was due to its use and not a late and unique effect of the catecholamines.

Methylene blue in high doses may cause adverse effects such as serotonergic syndrome (mainly in patients using other serotonergic agents),[6,7,14] hemolytic anemia,[7,11] and pulmonary hypertension.[6,7,14] Moreover, it may interfere with pulse oximetry with apparent desaturation.[11] In addition, it paradoxically has been reported as a cause of anaphylaxis.[2,4,5] Such effects are rare,[7,14] and the risk of organ damage and death from untreated shock is much greater.[14] A monitored administration of a low dose (<4 mg/kg) has been considered safe.[14]

Did epidural analgesia contribute to the patient's hypotension? We consider this hypothesis to be improbable. First, no intercurrences in the performance of the technique were observed. Second, the low concentration of anesthetic used in the epidural is unlikely to have led to such severe and persistent hypotension in which the action of catecholamines is ineffective. Finally, hypotension was only one of several symptoms presented by the patient that were clearly due to anaphylaxis.

In conclusion, in cases of shock involving the NO-cGMP pathway, such as in catecholamine-refractory anaphylactic shock, methylene blue is a useful and viable alternative as an adjuvant medication. ■

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DISCLOSURES

Name: Paulo Sergio Da Silva, MD.
Contribution: This author helped conceive and design the study, analyze and interpret the data, execute the study, and prepare and review the manuscript.
Name: Paula Furtado, MD.
Contribution: This author helped acquire and analyze the data, and prepare and review the manuscript.
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