Prolonged methylene blue infusion in refractory septic shock: a case report

Perfusion prolongée de bleu de méthylène dans un cas de choc septique réfractaire: une présentation de cas

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Abstract

Purpose Methylene blue (MB) has been advocated for the treatment of refractory hemodynamic instability in patients with septic shock. However, the use of MB infusions in septic shock is not considered standard treatment, and the available literature describes infusions of short duration, typically less than six hours.

Clinical features We report a case of septic shock in a 67-yr-old male who required maximal vasopressor support with norepinephrine, epinephrine, and vasopressin. Despite standard protocols for the treatment of septic shock, the patient's hemodynamic status was refractory 80 hr post admission. However, initiation of a MB infusion resulted in the rapid restoration of hemodynamic stability and a subsequent decrease in vasopressor requirements.

Multiple attempts to discontinue the MB infusion resulted in immediate and repeated increases in vasopressor requirements, necessitating a continuous infusion with a slow taper of MB for 120 hr. Ultimately, the patient survived the illness and was discharged home. We observed no adverse events that could be attributed to the use of MB.

Conclusion In our patient, the use of MB resulted in hemodynamic stability unattained with standard vasopressor support. Further research is warranted on the use of MB in patients with septic shock.

Résumé

Objectif Le bleu de méthylène (BM) a été proposé par certains chercheurs comme traitement de l'instabilité hémodynamique réfractaire chez les patients en choc septique. La perfusion de BM n'est toutefois pas considérée comme un traitement standard du choc septique, et la littérature publiée décrit des perfusions de courte durée, en général de moins de six heures.

Éléments cliniques Nous rapportons un cas de choc septique chez un homme de 67 ans qui a eu besoin d'un soutien vasopresseur maximal avec de la norépinéphrine, de l'épinéphrine et de la vasopressine. Malgré l'application des protocoles normalisés pour le traitement du choc septique, l'état hémodynamique du patient demeurait réfractaire 80 h après son admission. L'amorce d'une perfusion de BM a toutefois permis de rétablir rapidement la stabilité hémodynamique du patient et a entraîné une réduction subséquente de ses besoins en vasopresseurs. Les nombreuses tentatives d'interruption de la perfusion de BM ont entraîné des augmentations immédiates et répétées des besoins en vasopresseurs, c'est pourquoi une perfusion continue à un débit plus bas de BM durant 120 h a été mise en place. Le patient a finalement survécu à la maladie et reçu son congé de l'hôpital. Nous

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n'avons pas observé d'événements indésirables qui auraient pu être liés à l'utilisation de BM.

Conclusion *Chez notre patient, l'utilisation de BM a permis d'atteindre une stabilité hémodynamique qui n'avait pas été obtenue lors de l'utilisation standard de vasopresseurs. Des recherches plus approfondies sont nécessaires concernant l'utilisation du BM chez les patients en choc septique.*

Standard care of patients with severe sepsis/septic shock includes early diagnosis, antimicrobial administration, and aggressive resuscitation to restore hemodynamic instability.^{1,2} Although uncommon, methylene blue (MB) administration in patients with septic shock has been described with rapid reversal of sepsis-induced vasodilation.³⁻¹² Little is known about the clinical utility, optimal dose, or duration of MB administration in patients with septic shock. The relatively few reports available on the use of MB in septic shock describe relatively short infusions. Most reports describe infusions less than six hours in length,^{7,9,11,13} with the longest reported infusion less than 44 hr.¹²

We report the administration of MB to a patient with profound hemodynamic instability secondary to septic shock that was refractory to conventional vasopressor support. The novel element of this report is the prolonged 120-hr infusion of MB required to restore and maintain hemodynamic stability in a case of septic shock.

The patient provided written consent for the publication of this article.

Case report

A 67-yr-old male with a history of Wegener's granulomatosis, splenectomy, and chronic prednisone and azathioprine use was transferred to the Queen Elizabeth II Health Sciences Centre Emergency Department (ED) after a temporary loss of consciousness. The Emergency Medical Service found the patient to have wide complex tachycardia (150 beats·min⁻¹), non-palpable pulses, and a temperature of 38.4°C. His systolic blood pressure was 45 mmHg by non-invasive blood pressure monitoring. He weighed approximately 100 kg on presentation. The patient's home medications were: risedronate 35 mg weekly, prednisone 7 mg daily, furosemide 40 mg daily, gabapentin 1,200 mg three times per day, azathioprine 25 mg daily, folate 1 mg daily, extra strength Tylenol two tabs three times per day, multivitamin one tab daily,

glucosamine two tabs twice per day, and omega fatty acids four tabs daily.

Treatment was initiated in the ED following standard guidelines for the management of severe sepsis, and ceftriaxone was administered within 20 min of arrival.^{1,2,14,15} Intravenous crystalloid fluid resuscitation was initiated; normal saline 4.5 L was administered over the initial two hours, and norepinephrine at 0.1 µg·kg⁻¹·min⁻¹ was titrated to maintain a mean arterial pressure (MAP) ≥ 65 mmHg. Serum lactate was 8.3 mmol·L⁻¹ when measured 15 min after presentation. The patient was anuric with initial creatinine and blood urea nitrogen of 229 µmol·L⁻¹ and 8.9 mmol·L⁻¹, respectively.

Due to a decreased level of consciousness (Glasgow Coma Scale 9-11) and ongoing hemodynamic instability, the patient required emergent endotracheal intubation and ventilation (controlled mechanical ventilation - rate 23, positive end expiratory pressure 14, fraction of inspired oxygen 75%). Measurement of the patient's mixed venous oxygen saturation was 73%, and further antimicrobials were administered (meropenem 500 mg dosed for renal function). In addition, hydrocortisone 100 mg was administered in the ED due to the initial refractory nature of the shock.

The patient was transferred to the medical/surgical intensive care unit (ICU) within 2.5 hr, where the norepinephrine infusion was rapidly escalated to 1 µg·kg⁻¹·min⁻¹ to maintain a MAP > 65 (Fig. 1). In addition to a vasopressin infusion of 0.04 U·min⁻¹, an epinephrine infusion was then initiated and titrated up to 1 µg·kg⁻¹·min⁻¹ due to ongoing hemodynamic instability. The patient's central venous pressure was 21 mmHg, suggesting adequate fluid resuscitation. Seven hours after initial presentation, the patient's serum lactate level was 7.8 mmol·L⁻¹, and creatinine had risen to 324 µmol·L⁻¹. A transthoracic echocardiogram demonstrated a hyperdynamic left ventricle with preserved function, a moderate pericardial effusion, and mild ventricular volume under-filling, but no evidence of cardiac tamponade. In addition to the meropenem, vancomycin was added to cover the possibility of methicillin resistant *Staphylococcus aureus*. Subsequently, antimicrobial coverage was broadened with intravenous levofloxacin for atypical bacterial pathogens and fluconazole for fungal coverage, although cultures remained negative at this point. Hydrocortisone 50 µg four times per day was continued for the next seven days and then weaned over the following seven days.

Over the next two days, the patient remained hemodynamically unstable with a systolic blood pressure of < 100 mmHg despite the vasopressor infusions. A test dose of MB 100 mg *iv* bolus was administered 80 hr after first admission (Fig. 1, arrow). Rapid hemodynamic stability and subsequent decrease in vasopressor requirements

Fig. 1 **A** Heart rate, systolic blood pressure, and mean arterial pressure of the patient during the course of treatment. **B** Infusion rates of methylene blue (MB) and the vasopressors, vasopressin, epinephrine, and norepinephrine, over a period of seven days in a patient with septic shock. Arrows indicate attempts to wean MB that were followed by increases in adrenergic vasopressor requirements. Data have been smoothed to depict the running average using Sigmaplot 10.0 software (Systat software Inc, San Jose, CA, USA), and thus the immediate and brief increases in adrenergic vasopressor dosages are not represented

ensued, and a continuous infusion at $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ was administered through a central venous catheter. The immediate effect of the infusion was an increase in blood pressure, allowing for a decrease in norepinephrine and epinephrine levels (Fig. 1B). A subsequent attempt was made to reduce the infused dose of MB to $0.12 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$; however, the patient became increasingly hemodynamically unstable and epinephrine and norepinephrine requirements increased (Fig. 1A). The dose of MB was subsequently titrated to $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$, which successfully maintained hemodynamic stability.

Over the course of the next 12 hr, epinephrine and norepinephrine requirements decreased, and we were able to discontinue the epinephrine and vasopressin infusions, utilizing lower doses of norepinephrine (0.05 to $0.2 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Once the dose of epinephrine and norepinephrine had been decreased, the patient's heart rate also decreased from $130 \text{ beats} \cdot \text{min}^{-1}$ to $< 80 \text{ beats} \cdot \text{min}^{-1}$ (Fig. 1A).

During the following four days, several attempts were made to discontinue MB, but each attempt led to immediate hypotension that resolved with re-initiation of the MB

infusion. However, stepwise weaning of the MB infusion was sufficient to maintain appropriate hemodynamics, resulting in a prolonged infusion of 120 hr.

As the patient's hemodynamic status stabilized, his serum lactate levels fell to a low of $2.1 \text{ mmol} \cdot \text{L}^{-1}$. Central venous pressure remained stable (14 to 21 mmHg) throughout treatment. Due to anuria and a steady rise in the patient's creatinine to a peak level of $641 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$ within 52 hr of presentation, the patient required continuous renal replacement therapy (CRRT), which was started on the second day of admission without complication. Continuous renal replacement therapy was discontinued 16 days after admission after creatinine and blood urea nitrogen levels normalized, although hemodialysis was continued three times per week. No bacteria were cultured from the patient's urine, serum, sputum, and cerebrospinal fluid, although stool did subsequently become positive for *Clostridium difficile*, which was treated with metronidazole.

No clinically significant adverse events were appreciated that could be attributed to MB, apart from significant blue/green discoloration of the skin and mucosa, particularly noticeable in his extremities (Fig. 2).

Fig. 2 Patient's hand demonstrating obvious blue discoloration of the skin, edema, and disseminated intravascular coagulopathy-associated purpura. Note the hand of a caregiver for colour reference

The patient's course in the ICU was complicated by the above-mentioned infection with *C. difficile* as well as cholestasis that required a percutaneous drain placement. However, he recovered sufficiently to be transferred from the ICU after a 24-day admission. He remained a hospital inpatient for more than 150 days after the end of the MB infusion and was then discharged to a rehabilitation centre. He was discharged to home one month later. His lengthy stay was due primarily to delirium, a subsequent *C. difficile* infection, poor renal function requiring dialysis three times per week, and a flare of his Wegener's disease that required plasmapheresis.

Discussion

The use of MB to treat septic shock is not considered a standard of care and often remains a therapy of last resort. In this case, we report the need for a prolonged infusion of MB over a period of 120 hr in a patient with intractable septic shock. Previous research has demonstrated that MB may be efficacious in septic shock when given by intravenous bolus or short-term (≤ 6 h) infusions,^{3,4,9,11,16–18} although a case report of a longer-term infusion of 44 hr has been described.¹² Despite standard treatment for septic shock with early goal-directed therapy, conventional vasopressors, including norepinephrine, epinephrine, and vasopressin, our patient responded only to the administration of MB. While anecdotal, this case highlights the potential utility of prolonged infusions of MB in the treatment of refractory septic shock.

The mechanism of action of MB has not been described fully, although it is an inhibitor of both inducible nitric oxide (NO) synthase and soluble guanylate cyclase in vascular smooth muscle cells.^{19,20} Inhibition of these enzymes results in decreased production and efficacy of

NO, a vasodilatory paracrine hormone.^{19–21} Cytokines and inflammatory factors present during sepsis are thought to induce endothelial NO production in smooth muscle cells, leading to systemic vasodilation and shock.²² Nitric oxide is also thought to decrease the sensitivity of endothelial adrenergic receptors to sympathetic vasoconstrictory stimuli, exacerbating the vasodilation that NO causes.²¹ By blocking both the production and effect of NO in the vasculature, MB is thought to mitigate the vasodilatory response in refractory septic shock.

Relatively few adverse events have been associated with the use of MB in bolus and short-term infusion dosing.⁴ Common side effects previously described include green urine and body fluids and blue discoloration of the skin, potentially affecting the evaluation of cyanosis.^{3,4,16,23} In patients with septic shock, bolus doses of MB have been associated with increases in pulmonary vascular resistance,⁵ and caution has been advised in patients with acute respiratory distress syndrome.¹⁸ Additionally, while little is known about the appropriate dose of MB, a recent study demonstrated that bolus doses of $7 \text{ mg} \cdot \text{kg}^{-1}$ may compromise splanchnic perfusion, while maintaining dose-dependent hemodynamic properties.²⁴ In addition, the safety of MB for patients undergoing CRRT has not been adequately studied. A recent report suggested that MB did not passively diffuse through the filter, and it was not being removed by convection when continuous venovenous hemodiafiltration was used.²⁵ Other than discoloration of our patient's skin, we noted no significant adverse events associated with the use of MB.

We report a case of refractory septic shock in which prolonged administration of intravenous MB resulted in an immediate and profound decrease in vasopressor support requirements. Attempts to wean the MB infusion resulted in additional hemodynamic instability that resolved with re-administration of MB, therefore necessitating a 120-hr infusion. Except for skin discoloration, MB infusion was associated with no obvious significant adverse events. Further studies are warranted to explore the efficacy and safety of MB in the treatment of septic shock.

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Conflicts of interest None declared.

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