

CASE REPORTS

Use of Methylene Blue for Refractory Septic Shock During Continuous Venovenous Hemodiafiltration

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As an inhibitor of nitric oxide, methylene blue has been investigated as an alternative vasopressor in patients with septic shock refractory to catecholamine vasopressors and as an agent to maintain hemodynamic stability in patients receiving intermittent hemodialysis. However, to our knowledge, the use of methylene blue as a vasopressor in patients receiving continuous renal replacement therapy has not been evaluated. We describe a 56-year-old man who was receiving continuous venovenous hemodiafiltration (CVVHDF) for acute renal failure secondary to sepsis. After a difficult hospital stay for injuries sustained from a motor vehicle accident, the patient developed sepsis and subsequent renal failure. On hospital day 47, after an adequate course of antibiotics, the patient developed refractory shock while receiving norepinephrine, phenylephrine, vasopressin, and hydrocortisone. He was then given a continuous infusion of methylene blue, which increased his mean arterial pressure and allowed for weaning of the catecholamine vasopressors. Eight hours after the start of methylene blue, the CVVHDF filter failed, and the hemodiafiltration was stopped. Because the filter was blue, a sample of the patient's effluent was analyzed by using ultraviolet-visible spectroscopy. No methylene blue was detected in the sample, suggesting that the drug was not being removed by CVVHDF. Clinicians should use caution when they are considering the use of methylene blue in patients with refractory shock who are also receiving CVVHDF.

Key Words: methylene blue, sepsis, continuous renal replacement therapy, CRRT, continuous venovenous hemodiafiltration, CVVHDF, shock, hypotension.

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The treatment of refractory shock in patients with sepsis is a topic of great debate. The use of methylene blue as an alternative vasopressor in patients with severe septic shock was first described in 1992.¹ Since that time, numerous animal studies, case reports, and clinical trials have described the effects of methylene blue on hemodynamic parameters and inflammatory

markers in septic shock.^{2–12} However, we know of no studies or case reports that address the use of methylene blue in patients receiving continuous venovenous hemodiafiltration (CVVHDF).

Continuous venovenous hemodiafiltration is a form of continuous renal replacement therapy (CRRT) that uses both convection and diffusion to remove solute. Unlike filters for traditional intermittent hemodialysis, those for CVVHDF are made of synthetic materials such as polysulfone polyamide, polyacrylonitrile, or polymethylmethacrylate, which are more permeable and allow for clearance of higher molecular weight solutes. The clearance of higher molecular weight solutes accounts for the increase in drug

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removal when a drug has a high sieving coefficient. Although no sieving coefficient has been documented for methylene blue, its molecular properties suggest at least partial clearance during CVVHDF.^{13,14}

We describe a patient who was treated with methylene blue while receiving CVVHDF after he developed refractory septic shock while hospitalized for injuries sustained from a motor vehicle accident.

Case Report

A 56-year-old Caucasian man (height 72 in., weight 195 kg, body mass index 58 kg/m²) was brought to the emergency department after a motor vehicle accident. Injuries included fractures of the right tibia and fibula; fractures of the C3, C4, and T4 vertebral bodies; multiple rib fractures; sternal fracture; kidney laceration; retroperitoneal hemorrhage; and multiple scalp lacerations. His medical history was remarkable only for untreated hypertension and obesity. The patient was hemodynamically stable, with a blood pressure of 104/74 mm Hg and mean arterial pressure of 84 mm Hg. The patient developed a sudden change in mental status and respiratory failure requiring intubation. Computed tomography showed no acute intracranial abnormalities.

The patient was transferred to the trauma intensive care unit. He developed hemodynamic failure with a blood pressure of 44/29 mm Hg and mean arterial pressure of 34 mm Hg. A norepinephrine infusion was started, but his response was minimal even after titration to 70 µg/minute. Vasopressin 0.04 U/minute was added, which increased the patient's mean arterial pressure into the 80-mm Hg range.

During the patient's first days in the intensive care unit, vasopressor support with norepinephrine and vasopressin was stopped and restarted several times, as the patient underwent surgical procedures to repair his injuries. He continued to have difficulty maintaining adequate oxygen saturation and eventually required rotational bed therapy, short courses of neuromuscular blockade with vecuronium, inhaled epoprostenol, and brief use of an oscillating ventilator.

On hospital day 12, a chest radiograph indicated pneumonia, and microbiologic cultures from a bronchoalveolar lavage grew a multidrug-resistant *Acinetobacter calcoaceticus-baumannii* complex susceptible only to colistimethate.

Intravenous colistimethate sodium 300 mg every 12 hours (3 mg/kg/day) and nebulized amikacin 500 mg every 8 hours were started. The dosing was based on the patient's estimated creatinine clearance (using the Cockcroft-Gault equation) of approximately 30 ml/minute.

The patient's condition continued to deteriorate. On hospital day 13, the patient developed acute renal failure with fluid overload, non-anion gap metabolic acidosis, and hyperkalemia. Continuous venovenous hemodiafiltration was started (Prisma System; Gambro, Lakewood, CO) by using a Hospal AN69 acrylonitrile and sodium methallyl sulfonate copolymer hollow fiber hemofilter (surface area 0.9 m², creatinine sieving coefficient of 1). The blood flow rate was 100 ml/minute, dialysate flow rate 1500 ml/hour, and the replacement fluid rate 1500 ml/hour. The patient's hemodynamic status stabilized, and vasopressor agents were no longer needed. The *Acinetobacter* pneumonia was treated for 21 days. However, other infections developed, and progress toward weaning supportive measures was further impeded.

On hospital day 32, colistimethate and amikacin were stopped, and the next day, the patient became septic. Broad-spectrum antimicrobial coverage was started with meropenem, colistimethate, vancomycin, and caspofungin; their dosages were appropriately adjusted for the CVVHDF. Drotrecogin alfa therapy was also begun. Sputum and bronchial wash cultures grew methicillin-resistant *Staphylococcus aureus*. A tissue culture of a sample from a decubitus ulcer grew methicillin-resistant *S. aureus* and *A. calcoaceticus-baumannii*. Despite treatment and supportive measures, the patient continued to need increasing hemodynamic support with norepinephrine titration.

On hospital day 47, the patient developed severe hypotension despite a norepinephrine infusion at 40 µg/minute, a vasopressin infusion at 0.04 U/minute, and intravenous hydrocortisone 100 mg every 8 hours. A phenylephrine infusion was started and titrated to 200 µg/minute, with only a minimal increase in the patient's blood pressure from 68/51 to 86/67 mm Hg after 1 hour.

At this point, the patient had developed refractory shock, and methylene blue was chosen as the next vasopressor. An initial bolus dose of 0.5 mg/kg (100 mg) was given over 10 minutes, with a blood pressure response to 107/59 mm Hg. A continuous infusion of methylene blue 100 mg/hour (0.5 mg/kg/hr) was started.¹⁰ The

patient's blood pressure increased, allowing for a reduction of the norepinephrine and phenylephrine infusion rates. Because the elimination of methylene blue during CVVHDF is unknown, the patient's effluent was analyzed by using ultraviolet-visible spectroscopy (UV160U; Shimadzu, Kyoto, Japan). Methylene blue was not detected (Figure 1). The effluent itself was not blue; however, the CVVHDF filter was bright blue.

After 8 hours of the methylene blue infusion, failure of the CVVHDF filter was detected, indicated by high transmembrane and filter pressures, and dialysis was stopped. The transmembrane and filter pressures had already been increasing before the methylene blue bolus dose was administered, so it was unclear if the methylene blue was the cause of the filter failure. After discussions with the family, the decision was made not to restart CVVHDF and to consider conventional hemodialysis if hemodynamically tolerable. However, during the night, the patient became asystolic and died. The family refused autopsy. Throughout the patient's hospitalization (days 17–48), multiple attempts had been made to wean hemodynamic, ventilator, and continuous renal replacement support; however, these attempts had failed.

Discussion

Methylene blue is a potent inhibitor of nitric oxide production and a scavenger of nitric

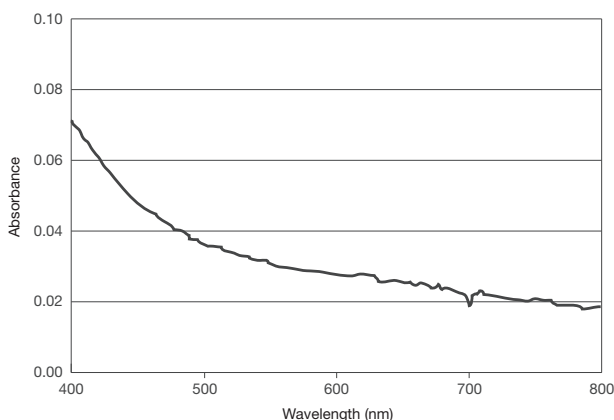


Figure 1. Analysis of the patient's effluent fluid by ultraviolet-visible spectroscopy shows that methylene blue, with reported absorption peaks of 688 and 609 nm, was not detected after an 8-hour methylene blue infusion during continuous venovenous hemodiafiltration (CVVHDF). This suggests that the methylene blue was not being eliminated during CVVHDF.

oxide.^{15–17} Through the production of a superoxide anion, methylene blue prevents nitric oxide-associated hypotension during septic shock. This action may make methylene blue an acceptable alternative vasopressor in patients with shock refractory to conventional treatment.

The prevention of intradialytic hypotension could be of major importance to both patients undergoing hemodialysis and those receiving CRRT. It is common for patients who are hemodynamically stable before hemodialysis or CRRT to decompensate, which requires intervention to maintain acceptable hemodynamic parameters and allow patients to continue the therapy. In our patient, methylene blue was used to improve his hemodynamic parameters while he was in septic shock and receiving CRRT. Although CRRT may be more appropriate than hemodialysis for hemodynamically unstable patients, our patient's blood pressure decreased during CRRT. We believe that our patient was hypotensive secondary to septic shock; however, contribution from CRRT cannot be ruled out.

Use of methylene blue for hypotension related to hemodialysis was reported in an open-label trial.¹⁸ Of 41 subjects, 18 were patients receiving hemodialysis but experiencing recurrent episodes of hypotension, 18 were patients receiving hemodialysis and had no hypotension, and five were healthy volunteers. All were given methylene blue as a 1-mg/kg bolus dose and 0.1-mg/kg continuous infusion lasting 210 minutes. In the patients with recurrent hypotension, no further episodes of hypotension were reported. No changes in blood pressure were observed in the healthy volunteers, and only slight increases in blood pressure were observed in the patients receiving hemodialysis who had no hypotension. Adverse events related to the methylene blue included injection-site pain and bluish discoloration of the lips. The authors concluded that the inflammatory response due to hemodialysis may have increased the release of nitric oxide. In the patients who responded to treatment, methylene blue may have blunted the overproduction of nitric oxide and the associated hypotension. This trial illustrated the ability of patients receiving hemodialysis to safely receive infusions of methylene blue, with no discussion of equipment failure.

Once infused, methylene blue is metabolized to leucomethylene blue, and it is excreted slowly in the urine as more than 50% metabolites. Based on methylene blue's molecular weight of 373.9 g/mol, low protein binding,¹⁹ volume distribution

of approximately 40 ml/kg,²⁰ and increased solute clearance with larger surface area filters for CVVHDF, methylene blue should have a better clearance rate with CVVHDF than with hemodialysis. However, the lack of detectable methylene blue in the patient's effluent fluid, as analyzed by ultraviolet-visible spectroscopy, and the bright blue appearance of the filter suggested that methylene blue was not passively diffusing through the filter or being removed by convection. Because of the increasing transmembrane and filter pressures that occurred before the methylene blue bolus dose was administered, it is unclear if methylene blue caused the patient's CVVHDF filter to fail. However, we recommend using great caution if methylene blue is considered for patients receiving CRRT who have septic shock unresponsive to conventional vasopressors.

Conclusion

To our knowledge, this is the first case report of the use of methylene blue for refractory shock in a patient receiving CRRT. Patients with acute renal failure and hemodynamic instability are increasingly treated with modes of CRRT. Clinicians should be cautious when prescribing methylene blue in these patients.

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