Case Letter

Hemodynamic improvement using methylene blue after calcium channel blocker overdose

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Dear editor,

Calcium channel blocker overdoses are often fatal despite standard treatment. Methylene blue is a novel adjunct that should be considered in refractory cases. Currently accepted therapeutic modalities include intravenous fluids, calcium, vasopressors and high-dose insulin euglycemic therapy, however shock may persist despite these treatment options.^[1]

Methylene blue has been utilized in sepsis, shock after cardiac surgery and other non-poisoning causes of shock. However, there are only ten human case reports and one animal study regarding its utility. The case reports describe its use in shock caused by quetiapine, valsartan and dihydropyridine calcium channel blockers, and measure the outcomes of hemodynamics and mortality. The animal study used a rat-model with thirty subjects treated with a lethal dose of amlodipine, followed by methylene blue or normal saline. Results revealed an increase in heart rate, mean arterial pressure (MAP) and median survival time in those treated with methylene blue.^[2]

Expert consensus recommendations for the management of calcium channel blocker poisoning in adults were recently assembled and did not recommend the use of methylene blue as first-line treatment, given that the experience was limited to a small number of case reports.^[1] However, with additional case reports attesting to its efficacy, there may be a role for methylene blue in the treatment of drug-induced vasodilatory shock.

We present a case where methylene blue was administered to a patient suffering from refractory vasodilatory shock following toxic ingestion of amlodipine, resulting in subsequent hemodynamic improvement.

CASE

A 50-year-old Caucasian male with past medical

history of hypertension, diabetes mellitus type 2 and bipolar disorder presented to the emergency department via an advanced life support (ALS) paramedic unit after known overdose just prior to arrival. While at home the patient took sixteen tablets of Amlodipine (80 mg each), thirty tablets of Metformin (500 mg each), twenty tablets of Sertraline and an unknown amount of Methocarbamol. He denied vision changes, chest pain, palpitations, shortness of breath, abdominal pain, nausea, vomiting, headache or dizziness after ingestion.

On initial evaluation, the patient was in no acute distress with a blood pressure of 133/90 mmHg, pulse 114 beats/minute, respiratory rate 22 beats/minute, pulse oximetry 94% on room air and temperature within normal limits. There were no focal physical exam findings.

At this time, electrocardiogram (ECG) demonstrated sinus tachycardia with normal axis, mild QT prolongation at 468 msec and T wave inversion in aVR, V1 and V2. Laboratory studies including a complete blood count, chemistry panel, acetaminophen level, alcohol level, aspirin level and urine toxicology showed no abnormalities. Venous blood gas revealed pH 7.26, and was otherwise unremarkable. Chest X-ray was normal.

Management began with one liter of normal saline intravenous fluids, 10 mL 10% calcium gluconate IVP, and 1 mg glucagon IV. A second normal saline bolus was started, and after ninety minutes blood pressure dropped to 71/46 mmHg, with persistent tachycardia. Patient required a Levophed titration and high-dose-insulin-euglycemic therapy (1 unit insulin/kg bolus, followed by an infusion of 0.5 units·kg⁻¹·hour⁻¹) at that time. Patient was then treated with one liter of 5% dextrose-normal saline, yet remained hemodynamically unstable.

Toxicology was consulted and emergently evaluated

the patient. Methylene blue treatment was advised due to refractory hypotension. Four hours after arrival the patient was started on $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hour}^{-1}$ methylene blue. Repeat labs at that time revealed an arterial blood gas with a lactic acid of 3.9 mmol/L and pH 7.31. Blood pressure was $82/57 \text{ mmHg}$ and the patient was subsequently admitted to the intensive care unit.

During the hospital course, the patient received 100 mg hydrocortisone and additional intravenous fluids. His lactic acid was found to be elevated at 6.5 mmol/L fifteen hours after arrival and dropped to 0.9 mmol/L by twenty-four hours. Blood pressure also stabilized to $135/81 \text{ mmHg}$ after 24 hours. The patient was subsequently weaned off vasopressors and high-dose insulin-euglycemic therapy, and methylene blue was discontinued. The patient was followed by a psychiatrist throughout his admission and transferred to the psychiatric unit once stable.

DISCUSSION

This case report highlights the importance of considering methylene blue in patients with persistent hypotension that is refractory to standard therapeutic modalities.

In particular, shock secondary to toxic ingestion of calcium channel blockers results in significant morbidity and mortality. Shock develops after amlodipine blocks L-type voltage gated calcium channels, thereby inhibiting calcium influx into cells. By inhibiting the influx of calcium in smooth muscle cells, amlodipine prevents calcium-dependent myocyte contraction and vasoconstriction.^[3] The site of action of dihydropyridine calcium channel blockers is primarily in the vasculature, thereby resulting in potent vasodilatory effects. The half-life of amlodipine is 30–50 hours, and the highest bioavailability is noted at 6–12 hours, therefore particular attention should be paid within the first few hours of ingestion.

Current therapeutic modalities recommended include first line treatment with intravenous fluids, calcium to increase contractility and blood pressure (1D), norepinephrine to increase blood pressure (1D), epinephrine to increase contractility and heart rate (1D), high-dose insulin to increase contractility (1D) and blood pressure (2D), dobutamine or epinephrine to increase contractility if in cardiogenic shock (2D) and atropine if bradycardia or conduction disturbances are present (2D).^[1] If there is evidence of myocardial dysfunction, incremental doses of high-dose insulin (2D) and lipid emulsion therapy (2D) should be considered.^[1] Finally,

rescue treatment with venoarterial extracorporeal membrane oxygenation (VA-ECMO) (2D) should be considered, if necessary.^[1] Given that all of the therapeutic modalities were exhausted in our patient, aside from lipid emulsion therapy and VA-ECMO, methylene blue warranted consideration.

Vasodilatory shock develops when nitric oxide stimulates soluble guanylyl cyclase to increase endothelial smooth muscle relaxation.^[4] Methylene blue exhibits pharmacologic effects by inhibiting guanylyl cyclase, resulting in decreased cGMP production, thereby decreasing endothelial smooth muscle relaxation.^[3] Therefore, it is logical that there is great utility for methylene blue use in this setting.

The current literature includes ten case reports and one animal study discussing the use of methylene blue in drug-induced vasodilatory shock.^[1] The clinical parameters previously assessed include pulse rate, mean arterial pressure, median survival time, acidemia and systemic vascular resistance.^[2] The parameters assessed have also been studied in patients treated with methylene blue for shock secondary to sepsis and coronary artery bypass surgery. It is interesting to note that similar hemodynamic outcomes were seen in all patient populations after utilizing methylene blue. Increases in pulse rate, mean arterial pressure, survival time, and systemic vascular resistance were noted.^[2]

The use of and timing of various interventions in previous case reports should also be considered. A chart to summarize such interventions may be reviewed below (Table 1).

No adverse effects of methylene blue have been documented after administration in therapeutic doses ($<2 \text{ mg/kg}$).^[4] However, effects of toxicity include cardiac arrhythmias, coronary vasoconstriction, decreased cardiac output, renal blood flow and mesenteric blood flow.^[4] It may also rarely cause hemolytic anemia and falsely depress oxygen saturation readings.^[14] Interaction with selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase (MAO) inhibitors may lead to serious serotonin toxicity.

It is important to note that the clinical applicability of this case may be limited due to the presence of co-ingestants. It is also difficult to discern whether the patient may have become hemodynamically stable without the use of methylene blue. However, it should be noted that our patient did also co-ingest Sertraline, an SSRI. Effects of serotonin syndrome include hypertension and tachycardia, and the mean peak plasma concentrations of sertraline occur between 4.5–8.4 hours,

correlating with the mean peak plasma concentrations of amlodipine. Although unlikely, the hemodynamic stability of our patient may be a result of the additive effects of sertraline and amlodipine. Alternatively, the hemodynamic stability may have been a result of the calcium, glucagon, high-dose insulin and vasopressor effects. However, the temporal relationship to the hemodynamic improvement strongly suggests that methylene blue was of critical clinical benefit.

CONCLUSION

Our case demonstrates that patients with drug-induced vasodilatory shock refractory to standard therapy may still be prime candidates for methylene

blue treatment. Although studies are limited, there are no known contraindications to utilizing methylene blue in this setting. Patients who do not respond to standard treatment modalities, and are located in a facility without VA-ECMO capabilities, may find great benefit from methylene blue treatment. Given that the potential for morbidity and mortality is high in calcium channel blocker toxicity, it is critical to closely monitor hemodynamic parameters and consider this adjunct agent.

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Table 1. The use of and timing of various interventions in previous case reports

Reference	Age/gender	Clinical presentation	Time to treatment	Interventions prior to methylene blue	Outcome
3	61-year-old/male	Alert and oriented, stable vital signs	Known overdose several hours prior to arrival	Calcium gluconate, glucagon, fluids, pressors, high-dose insulin, fat emulsion therapy, continuous veno-venous hemodialysis. Methylene blue was started 40 hours after initial presentation.	Survival
5	69-year-old/female	Somnolent, vomiting, hypotensive and minimally responsive	Known overdose 5 hours prior to arrival	Fluids, glucagon, calcium chloride, pressors, dextrose-insulin drip. Methylene blue was started 11 hours after initial presentation.	Survival
6	25-year-old/female	Alert and oriented, tachycardic	Known overdose 1 hour prior to arrival	Activated charcoal, fluids, calcium gluconate, glucagon, pressors, high-dose insulin-euglycemia therapy. Methylene blue was started 16 hours after initial presentation.	Survival
7	41-year-old/male	Comatose, intubated, hypotensive	Known overdose 2 hours prior to arrival	Activated charcoal, fluids, pressors. Methylene blue was started 12 hours after initial presentation.	Survival
8	60-year-old/female	Alert and oriented, vomiting, hypotensive	Known overdose 10 hours prior to arrival	Fluids, pressors, glucagon, sodium bicarbonate, calcium carbonate, methylprednisolone, insulin. Methylene blue was started within 18 hours of initial presentation.	Survival
9	53-year-old/male	Alert and oriented, stable vital signs	Not disclosed	Fluids, calcium gluconate, glucagon, pressors, lipid emulsion therapy, hyperinsulinemic euglycemic therapy. Methylene blue was started approximately 9 hours after initial presentation.	Expired
10	62-year-old/male	Vomiting, hypotensive	Known overdose within 24 hours prior to arrival	Fluids, pressors, insulin, antibiotics. Methylene blue was started 4 hours after initial presentation.	Survival
11	15-year-old/male	Altered, hypotensive, tachycardic	Known overdose 1.5 hours prior to arrival	Fluids, calcium gluconate, activated charcoal, pressors. Methylene blue was started 6.5 hours post-ingestion.	Survival
12	58-year-old/female	Alert and oriented, hypotensive, tachycardic	Known overdose 2 hours prior to arrival	Fluids, calcium, pressors, hyperinsulinemia-euglycemia therapy, lipid emulsion, continuous venovenous hemofiltration. Methylene blue was started within 24 hours after initial presentation. Molecular Adsorbent Recirculating System therapy started thereafter.	Survival
13	50-year-old/male	Alert and oriented, Tachycardic	Not disclosed	Fluids, pressors, calcium gluconate, glucagon, hyperinsulinemia-euglycemia therapy, fat emulsion. Methylene blue was started less than 19 hours after initial presentation. VA-ECMO started thereafter.	Survival

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