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Case report

Rapid reversal of vasoplegia with methylene blue in calcium channel blocker poisoning

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ABSTRACT

Introduction: Calcium channel blockers (CCBs) are a potent class of medications that exert its action by blocking 'L-type' calcium channels. CCB overdose can be fatal even with appropriate and aggressive therapy. Death ensues from heart block, myocardial suppression, vasoplegia, and shock. Early use of methylene blue (MB) might provide additional means to improve outcomes.

Case presentation: A 25-year-old female presented after an attempted suicide. The patient ingested a substantial amount of diltiazem, promethazine, and trazodone. Seven hours following the ingestion, she became profoundly vasoplegic and hypotensive. Despite guideline-based therapy and high doses of vasopressors, she suffered from worsening lactic acidosis and multiorgan failure. Administration of an intravenous bolus dose of MB resulted in a rapid and sustained improvement of vasoplegia, and the patient subsequently went on to make a complete recovery.

Discussion: In addition to calcium channel blockade, CCBs cause vascular smooth muscle relaxation by the production of nitric oxide (NO). In cases of overdose, NO production can be significant. MB is a safe and inexpensive medication with the potential to reverse NO-mediated vasoplegia that is responsible for CCB induced shock state. In parts of the world where access to advanced medical care is not readily available, early use of MB might have a significant role in the management of CCB overdose.

African relevance

- Methylene blue is an inexpensive, safe, and widely available medication that can help in the reversal of NO-mediated vasoplegia from calcium channel blocker overdose.
- Methylene blue might have a significant role in parts of the world where access to advanced life support might not be readily available.
- Methylene blue remains stable in aqueous solution indefinitely, even when exposed to sunlight. This property makes methylene blue extremely cost-effective.

Introduction

Calcium channel blockers (CCBs) are commonly used as antihypertensive, antianginal and antiarrhythmic medications. They have been used in clinical practice since the 1960s, and unfortunately, intentional or accidental overdose is not rare. Based on their molecular structure, CCBs are divided into two groups, 1) Dihydropyridine (DHP) and 2) Non dihydropyridine (NDP). DHP CCBs include nifedipine, amlodipine, nimodipine and felodipine among others. NDP group consists of verapamil; a phenylalkylamine, and diltiazem; a benzothiazepine. CCBs exert their action by blocking 'L type' calcium channel. DHPs primarily cause vasodilation and reduced peripheral vascular resistance, whereas NDPs are associated with negative chronotropic, inotropic and dromotropic effects. When ingested in massive doses, the tissue selectivity of the CCBs might be lost. Profound vasoplegic shock in the absence of bradyarrhythmia from NDP CCBs is rare [1]. We present a case of diltiazem overdose induced vasoplegic shock in the absence of bradyarrhythmia and successful treatment of the patient with methylene blue (MB).

Case presentation

A 25-year-old female was brought to the hospital following an attempted suicide. She reported ingesting ninety sustained release tablets

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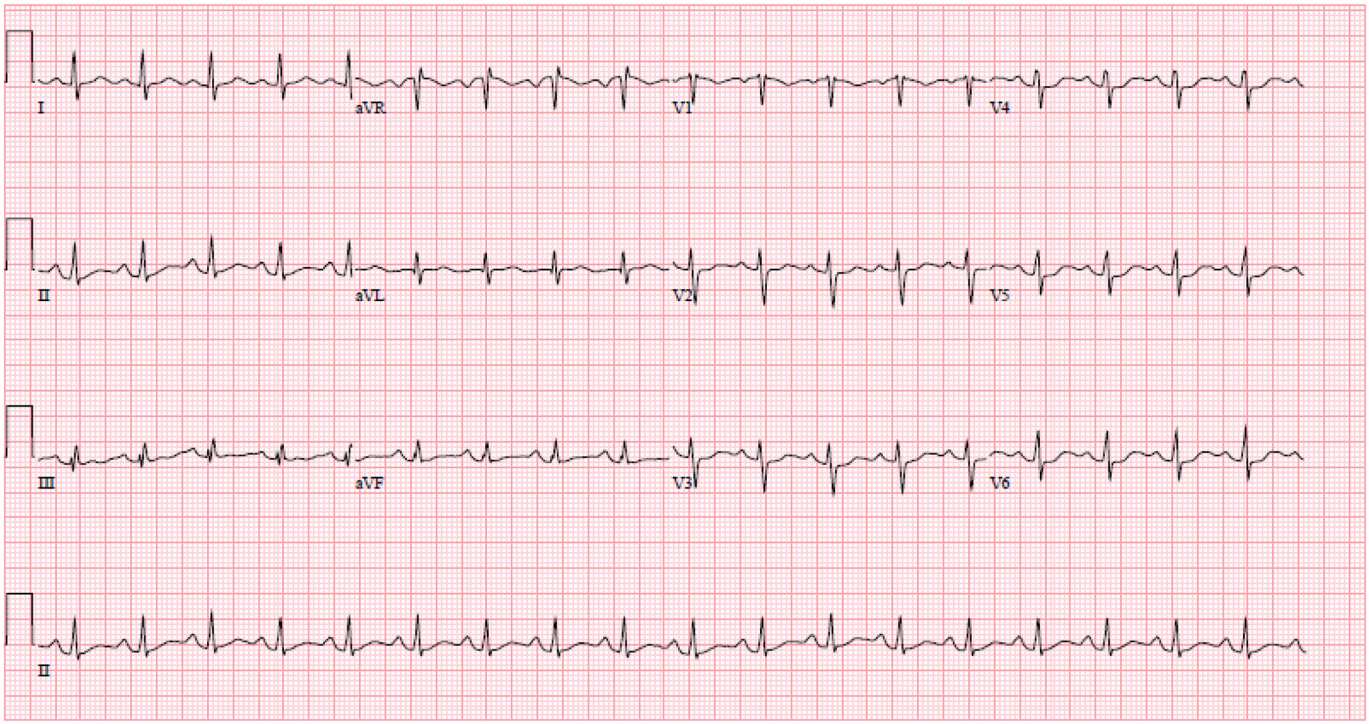


Fig. 1. EKG showing sinus tachycardia and prolonged QTc.

of diltiazem180 mg, a total of 16.2 g (186 mg/kg), trazodone (3 g, 35 mg/kg), and promethazine (1.5 g, 17 mg/kg) 1 h before presenting to the ER. Her past medical history was notable for supraventricular tachycardia requiring cardiac ablation therapy and severe depression. Her vital signs on arrival were, blood pressure-136/66 mmHg, pulse-116 beats per minute, temperature-36.1 ˚C, respiratory rate-21 breaths per minute and oxygen saturation of 96% on room air. Physical examination revealed a drowsy but arousable woman with tachycardia. Within a period of thirty minutes, her mental status worsened rapidly. The patient underwent rapid sequence intubation with 20 mg of etomidate and 100 mg of succinylcholine. Optimal sedation post-intubation was achieved with propofol and fentanyl infusion. Blood work was unremarkable (shown in annexure). Urine toxicologic screening and toxic alcohol panel were negative. EKG showed sinus tachycardia with prolonged QTc (Fig. 1).

Therapy with activated charcoal and whole bowel irrigation was initiated. An echocardiogram demonstrated normal ejection fraction (Fig. 2). As the patient ingested extended-release preparation of diltiazem, it was thought to be too early to see any effect from the CCB overdose. The encephalopathy and tachycardia were attributed to the promethazine and trazodone overdose. The patient was emergently brought to the ICU with the expectation of worsening hemodynamic status.

Seven hours post overdose, she developed hypotension that quickly became refractory to multiple pressors. She received treatment with intravenous calcium gluconate, glucagon, and high dose insulin. Incrementing doses of vasopressors (phenylephrine and norepinephrine) and low dose vasopressin were simultaneously administered to maintain acceptable hemodynamic parameters (dosing regimen is shown in Table 1).

The patient, however, suffered from worsening lactic acidosis and multiorgan dysfunction syndrome. Intravenous MB bolus (2 mg/kg over

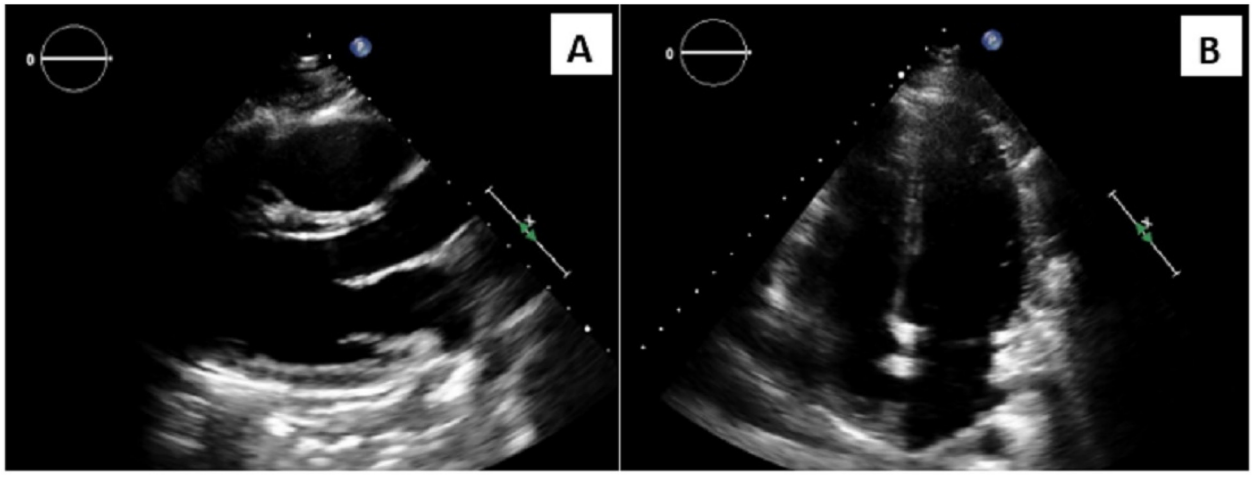
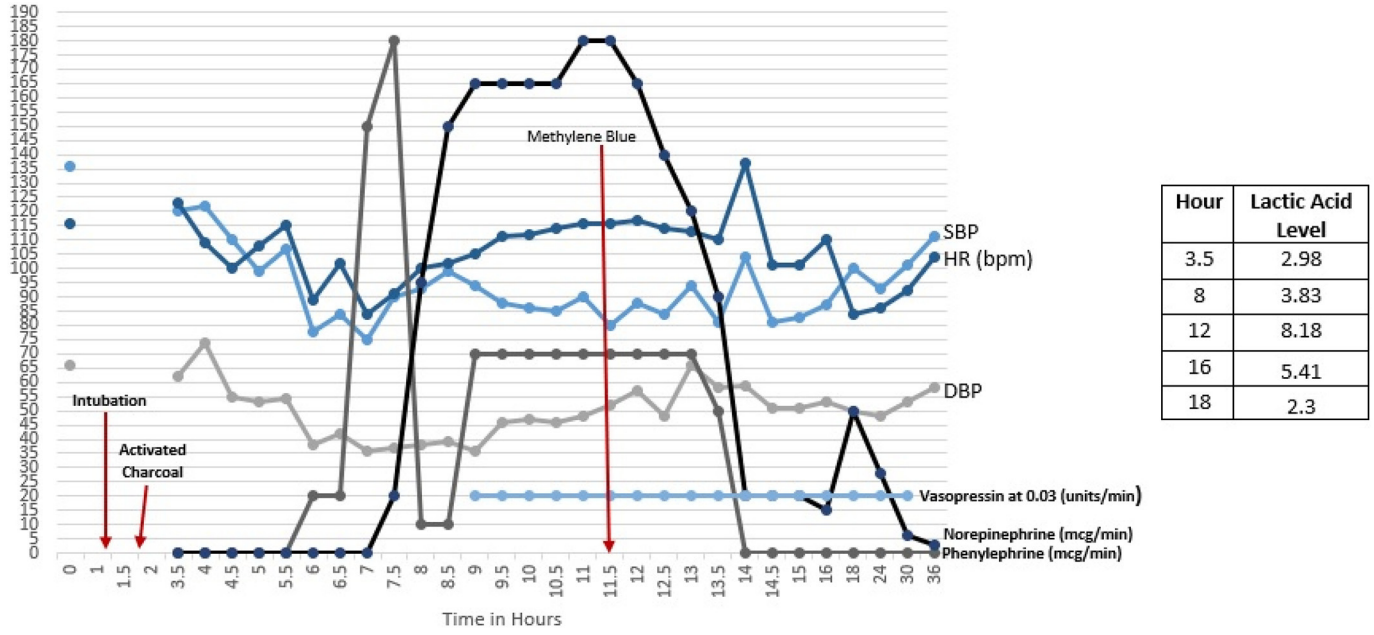


Fig. 2. Echocardiogram with parasternal long axis (A) and apical four chamber (B) views demonstrated normal right and left ventricular architecture, wall thickness and function.

Table 1
Admission electrocardiogram.

Medication	Dose used
Calcium gluconate (10%)	Bolus: 30 ml intravenous over 10 min × 3 (20 min apart), followed by Infusion: 1 ml/kg/h
Glucagon	Bolus: 5 mg intravenous, followed by Infusion: 5 mg/h
High dose regular insulin	Bolus: 1 unit/kg intravenous Infusion: initiated at 0.5 units/kg/h, titrated up to 5 units/kg/h Dextrose (10%) infusion and dextrose (50%) intravenous push to maintain blood glucose > 150 mg/dL Potassium chloride (KCl) infusion to maintain serum potassium > 3 meq/L
Norepinephrine	Infusion: initiated at 2 mcg/min and was titrated up to 180 mcg/min
Phenylephrine	Infusion: initiated at 20 mcg/min and was titrated up to 180 mcg/min
Vasopressin	Infusion: 0.03 units/min
Methylene blue	Bolus: 2 mg/kg intravenous over 30 min Infusion: none

Medication dosing regimen.



Hour	Lactic Acid Level
3.5	2.98
8	3.83
12	8.18
16	5.41
18	2.3

Fig. 3. Trend in hemodynamic parameters and lactic acid following diltiazem overdose and interventions. There was a significant reduction in pressor requirements (both norepinephrine and phenylephrine) following the administration of intravenous bolus dose of methylene blue (red arrow). The maximum vasoconstrictor effect lasted about 4 h. The vasopressor requirements went up subsequently but to a much lesser extent. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

30 min) was administered as the last resort before initiating veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Following the administration of MB, the patient experienced rapid and sustained improvement in her hemodynamics as well as a reduction of the vasopressor requirement by more than 75% (Fig. 3). Thirty-six hours post overdose, the patient required minimal pressor support and went on to make a full recovery with supportive therapy.

Discussion

We have reported a case of severe vasoplegic shock from diltiazem overdose that was rapidly and almost entirely reversed with MB. A cause and effect is established by the observed temporal relationship between the administration of MB and reduction of pressor requirements as well as the necessity to up titrate vasopressors after 4 h, which would be the expected duration of peak effect following a bolus dose of MB. Amlodipine was the most common DHP CCB that caused vasoplegic shock in the previously reported cases where MB was used as rescue therapy. In contrast, our patient suffered from profound vasoplegia with an NDP CCB in the absence of any bradyarrhythmia. We believe that the tachycardia observed in this patient stemmed from the co-ingestion of promethazine and trazodone, medications known to have anticholinergic and serotonergic effects, respectively. The other possibility could be compensatory tachycardia in the setting of profound vasodilation.

A diagnosis of CCB poisoning can usually be attained by history alone. Identification of the correct formulation (immediate release versus sustained release) and quantification of the ingested medication is important. An extensive effort should be made to find potential evidence suggestive of other prescription or nonprescription substance abuse. The onset of symptoms is variable based on the medication formulation. Sustained release preparation of diltiazem takes 6-11 h to reach its peak action [2]. Patients usually suffer from hypotension, bradycardia, heart block, vasodilatory shock, and multiorgan failure. Cardiogenic and sometimes non-cardiogenic pulmonary edema secondary to pulmonary arterial vasodilation can result in respiratory failure. Complete atrioventricular block refractory to chronotropic agents or intravenous pacing can ensue. Laboratory data is usually normal when obtained early, except hyperglycemia which may develop due to calcium channel blockade in pancreatic islet cells and relative

hypoinsulinemia.

The treatment of CCB poisoning starts with the administration of activated charcoal and bowel decontamination in a time-dependent fashion. Intravenous fluid is used for volume expansion in patients with hypotension. Intravenous calcium is used in an attempt to overcome competitive antagonism [3]. Intravenous glucagon has been used to reverse both bradycardia and hypotension from CCB poisoning [4]. Vasopressors and ionotropic agents are used as necessary, with norepinephrine being the preferred agent. The norepinephrine requirements in CCB overdose might be higher compared to septic shock. Hyperinsulinemia-euglycemia therapy, which involves the use of large doses of IV insulin therapy (1–10 unit/kg), and glucose to prevent hypoglycemia, have been shown to be beneficial and safe [5]. Hyperinsulinemia-euglycemia therapy has been recommended as a single therapy when there is evidence of myocardial depression or in combination with vasopressors and intravenous calcium, even in the absence of myocardial dysfunction. There are also cases of successful use of IV lipid emulsion. A guideline based on expert opinion recommends the use of lipid emulsion in cases of refractory shock or cardiac arrest [6]. It is important to emphasize that no randomized control trial has prospectively evaluated these interventions, and most data come from case series, observational, and small animal studies. The level of evidence for these recommendations is fair to poor [6].

MB is a novel therapy for CCB overdose. MB does not affect the calcium channels or bypass it to increase intracellular cyclic adenosine mono phosphate (cAMP), rather, represents a clinical approach directed towards one of the underlying pathobiologies of vasoplegia in CCB overdose. Successful therapy with rapid improvement of hemodynamic status has been reported in a few cases [7]. CCBs upregulate endothelial nitric oxide synthase activity (eNOS) and increase the production of nitric oxide (NO) [8–9]. Thus, a significant quantity of NO production is expected with massive CCB overdose. This NO activates cytosolic guanylate cyclase (GC) and results in the generation of cyclic guanosine monophosphate (cGMP) that culminates in smooth muscle relaxation and vasoplegia. MB is a potent inhibitor of GC; it prevents the generation of cGMP and causes vasoconstriction [9]. MB also improves catecholamine sensitivity. MB has been effective in all shock states that are mediated by NO overproduction, e.g., septic, anaphylactic and circulatory shock following coronary artery bypass graft surgery [10].

The recently published expert opinion did not recommend the use of MB for CCB overdose. This is likely due to the scarcity of definitive evidence, as only a few case reports exist in the literature where MB was utilized in CCB overdose refractory to traditional therapy [6]. We postulate that in cases of vasoplegic shock from CCB poisoning, it would be beneficial to use MB early rather than using it as a last resort. It addition, MB is inexpensive, safe and associated with rare side effects [10]. A bolus dose of MB followed by prolonged low dose infusion has proven to be safe in a patient with CCB overdose [11]. Minimal toxicity occurs when MB is used at low doses. The common and expected side effect is the blue discoloration of body fluids, and sometimes the skin. Methemoglobinemia is insignificant, even with a cumulative dose up to 7 mg/kg. The other potential side effects include hemolytic anemia (especially with glucose 6-phosphate dehydrogenase deficiency), coronary vasoconstriction, cardiac arrhythmia, serotonin syndrome and anaphylaxis [10]. These more serious side effects are uncommon when the medication is used cautiously and judiciously. A false reading on pulse oximetry may also occur [12].

CCB poisoning can be fatal despite aggressive and appropriate therapy. Vasoplegic shock and complete heart block are terminal events that result in circulatory failure. Vasoplegia in CCB overdose is usually managed by high dose of vasopressor therapy. As NO precipitates profound vasodilatation in CCB poisoning, we believe that early use of MB will likely result in a reduction of vasopressor requirement and minimize overall complications. MB is easily available, inexpensive, and has a long history of being safe. In parts of the world where access to advanced medical care is not readily available, MB might have a significant role in the management of CCB overdose. Prospective studies are necessary to establish the utility of MB in CCB overdose definitively.

Dissemination of results

Results from this report were shared with the house staff members of emergency medicine, internal medicine, and pulmonary and critical care medicine at the data collection site through formal presentation.

Authors' contribution

Authors' contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content. BKS contributed 65%; AB 25%; and WC contributed 10%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afjem.2020.06.014.

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