A multifaceted approach to calcium channel blocker overdose: a case report and literature review

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KEY CLINICAL MESSAGE
Calcium channel blocker toxicity can be devastating. Initial therapy with fluid, calcium, and adrenoreceptor agonists should be prompt and novel therapies can be added if no response. Determining cardiogenic shock versus vasoplegia with echocardiogram or other hemodynamic monitoring may guide treatment options.

INTRODUCTION
Calcium channel blockers are widely prescribed cardiovascular medications with potentially dire consequences at toxic doses. Treatment of cardiovascular collapse is complex in the acute setting and data on treatment modalities are minimal. Often, the best course of action is to support the patient’s cardiovascular system with traditional vasopressors and employ any number of novel therapies based on observational evidence.

CASE
We present a 60-year-old white female with a history of borderline personality disorder, hypertension (outpatient records indicate office readings for systolic blood pressure ranging from 120 to 130 mmHg on treatment), and chronic lumbago who reported to the emergency department with nausea and vomiting for 2 days and intentional amlodipine overdose. She reported taking approximately 300 mg of amlodipine 10 h prior to admission. The patient’s other medications included oxycodone, docusate, ibuprofen, and pantoprazole, all of which she reported taking as prescribed. On presentation, the patient was alert and oriented with a Glasgow Coma Score (GCS) of 15. Vital signs showed a noninvasive blood pressure of 90/56 mmHg with no other abnormality. Examination revealed equal and mildly diminished radial pulses, normal heart rate and rhythm, clear lung fields, sluggish bowel sounds, no peripheral edema and no pallor. Initial laboratory results included an unremarkable complete blood count, a basic metabolic panel showing a sodium of 136 mmol/L, potassium of 5.3 mmol/L, chloride of 102 mmol/L, bicarbonate of 17 mmol/L, urea nitrogen of 22 mg/dL and a creatinine of 1.58 mg/dL (baseline 0.44 mg/dL). Further, urinalysis on admission was remarkable for the presence of ketones. Urine and serum toxicology including salicylate and acetaminophen were negative. Procalcitonin was 0.1 ng/mL and lactic acid was 2 mmol/L. Cardiac troponins were trended and were not elevated. Activated charcoal was not administered on admission due to the amount of time that had passed from ingestion to presentation. The patient was admitted to the medical transitional care unit for observation.

The medical intensive care team was notified 7 h after admission when the patient’s noninvasive mean arterial pressure (MAP) fell to the low 50s and was not responsive to fluid resuscitation and her mental status deteriorated to a GCS of 7. She was transferred to the medical intensive care unit where she required intubation for airway protection,
had two central lines placed for medication compatibility concerns, and had an arterial line placed. In the ICU, lactic acid was found to be 6.4 mmol/L, and arterial blood gas showed a pH of 6.95, partial pressure of carbon dioxide (pCO₂) of 43 mmHg, a partial pressure of oxygen (pO₂) of 79 mmHg, and calculated bicarbonate of 9 mmol/L on 60% fraction of inspired oxygen (FiO₂). Electrocardiogram at 79 mmHg, and calculated bicarbonate of 9 mmol/L on 60% of 180 mmol/L. Hemodynamic state was monitored using istered per hospital ICU protocol targeting blood glucose recommended starting an insulin drip which was admin-

1L) in 1L D5W were subsequently started. After central access was obtained, calcium carbonate (12 mg/hr), nor-
epinephrine (starting at 75 µg/min titrated up to 100 µg/ min at maximum), epinephrine (5 µg/min titrated up to 10 µg/min), dobutamine (10 µg/kg/min titrated up to 25 µg/kg/min), methylprednisolone (100 mg every 8 h), and phenylephrine (100 µg/min) were started in rapid succession. Despite these interventions, arterial line MAPs were ranging between 45 and 60. Poison control was con-
sulted and recommended continuing calcium carbonate while monitoring ionized calcium every 2 h, along with the bicarbonate drip in D₃W, and glucagon drip. They also recommended starting an insulin drip which was admin-
istered per hospital ICU protocol targeting blood glucose of 180 mmol/L. Hemodynamic state was monitored using an arterial line and target MAP was >65.

Cardiology was consulted and performed a stat two-
dimensional transthoracic echocardiogram, which showed mildly reduced left ventricular contractility with the ejection fraction measured at 51%. Methylene blue (2 mg/kg administered over 1 h) and vasopressin (0.04 units/min at set rate) were started per cardiology’s recommendations.

Within 18 h of these therapies, the patient’s MAP stabi-
lized above 65, and vasopressors were slowly weaned starting with dobutamine, as echocardiogram result made cardiogenic shock unlikely. Phenylephrine, dopamine, and vasopressin were also weaned off on the first day. Epineph-
rine, insulin, and steroids were discontinued in ICU day 2. On day 3, the patient required only norepinephrine and glucagon drips to maintain a MAP >65. By day 4, the patient was requiring no vasopressors, was following com-
mands, and was extubated. She was transferred to the floor the next day for treatment of acute kidney injury and aspi-
ration pneumonia. She was discharged without sequelae on hospital day 7.

**Discussion**

Calcium channel blockers (CCBs) are a heterogeneous group of chemicals that inhibit L-type calcium channels. These channels control myocardial and vascular smooth muscle contractility as well as the cardiac conduction sys-
tem and pacemaker cells. CCBs are used extensively to treat angina pectoris, hypertension, Raynaud’s syndrome, supra-
ventricular tachycardias, and migraine headaches. CCBs are divided based on their primary physiologic effects. Di-
hydropyridine CCBs (DHP’s), such as amlodipine and nifedi-
pine, preferentially block calcium channels in the vasculature, acting as vasodilators with little to no effect on cardiac contractility or conduction. All other CCBs are grouped together as nondihydropyridine (non-DHP) CCBs. The most common are verapamil and diltiazem. These act on cardiomyocytes to reduce vascular permeabil-
ity and affect cardiac contractility and conduction, though they also have some mild vasodilatory action [1].

In 2010, the American Association of Poison Control Centers reported 3298 CCBs overdoses in adults, causing the second highest number of overdose deaths of any cardio-
vascular medication [2]. CCBs are highly protein bound, have a large volume of distribution, and are metabol-
ized by the liver. As the dose increases, there is a change in pharmacokinetics from first-order elimination to zero-
order clearance by the liver, which results in accumulation of the drug systemically. This change in metabolism is fur-
ther confounded by CCBs action of splanchnic vasocon-
striction, reducing drug delivery to the liver [3]. The unpredictability of drug clearance at toxic levels makes car-
ing for these patients in a standardized fashion difficult.

Initial treatment for CCBs overdose patients includes airway maintenance, crystalloid fluid boluses, and atro-
pine for symptomatic bradycardia. Activated charcoal can be administered to an intubated patient or a patient able to protect their airway within 1–2 h of overdose. Despite favorable gastrointestinal clearance of CCB at 2 h or less with charcoal, efficacy declines as time from ingestion increases and carries risk for aspiration obtunded patients [4–7]. Whole bowel irrigation may be beneficial early after ingestion prior to hemodynamic compromise, but becomes dangerous after hypotension develops because CCBs slow gut motility and increase risk of obstruction or perforation [8].

Following these initial therapies, there is no set treat-
ment algorithm. Intravenous calcium, preferably calcium chloride through a central line, is recommended to increase calcium entry into cells via nonblocked channels, counteracting negative inotropy, and vasoplegia. Glucagon increases intracellular cyclic adenosine monophosphate (cAMP) and contraction of smooth muscle via a beta-receptor independent pathway. While this has become a mainstay in the treatment of beta-blocker overdose, glucago-
on is of questionable usefulness in CCBs overdose mech-
anistically, but there are case reports of improved hemodynamics with glucagon administration [9]. Further,
glucagon is associated with dose-dependent nausea and vomiting and increased risk of aspiration, diarrhea, hypokalemia, and theoretical tachyphylaxis [10].

Hyperinsulinemia euglycemia treatment (HIET) (1 unit/kg bolus of regular insulin with 0.5 g/kg dextrose push followed by 0.5–1 unit/kg/hr of regular insulin with concomitant dextrose drip) was originally shown to improve survival in dogs poisoned with verapamil in a controlled environment [11]. First reported in humans in 1999, HIET therapy showed improvement in circulatory shock in five CCBs overdose patients who did not adequately respond to “standard” treatment which was variable amongst the reported patients [12]. HIET has been described stabilizing cardiovascular parameters, decreasing vasopressor support, and improving patient outcomes when instituted early because of delayed onset-of-benefit [10, 13]. The proposed mechanism involves improved smooth muscle contractility by increased efficiency of carbohydrate uptake and utilization which counteracts CCBs blockade of indigenous insulin release and decreased myocardial free fatty acid extraction. This optimizes the glucose-dependent energy formation required to overcome CCBs overdose [14]. Both glucose and potassium should be frequently monitored on this therapy and potassium should be replaced if the level falls below 3 mmol/L [10].

A case series in non-DHP CCBs overdose found that the use of fluid challenge and alpha- and beta-adrenoreceptor agonists (classic vasopressors and dobutamine) without HIET in hypotensive overdose patients was not detrimental to outcomes. This study did not standardize the agents used, the order in which they were employed, or the maximum dose of each agent. However, it did show that an approach consisting solely of early administration of adrenoreceptor agonists alone may lead to successful outcomes [15]. Further, the addition of vasopressin has been reported to improve MAP and improve cardiac function in patients’ refractory to a combination of other vasopressors, insulin, and glucagon [16].

There is no recommended gold standard for hemodynamic monitoring during the resuscitation of these patients. However, opinion suggests that differentiating between negative inotropy and vasopedia may be useful for choosing between adrenoreceptor agonists alone [17]. Observing signs of cardiogenic shock would suggest that inotropic agents such as dobutamine and dopamine would be beneficial and will prevent exposure to the side effects of arrhythmia and cardiac ischemia in patients with preserved inotropic performance [17, 18].

A recent report of two cases using lipid emulsions in CCB overdose shows promise for yet another therapy directed at hemodynamic support. Lipid emulsions add free fatty acid substrate for HIET therapy and sequester free lipophilic CCBs molecules. In both cases, lipid emulsion (1.5 mL/kg bolus followed by 0.25 mL/kg/min for 60 min) was initiated after vasopressors and HIET had been started, and were followed by discontinuation of vasopressors at 1 and 10 h, respectively [19]. Lipid emulsion therapy was not shown to enhance HIET without simultaneous vasopressor treatment.

Methylene blue has been used as a novel approach to treat refractory CCB overdose based on reports of its use to counteract postcoronary artery bypass vasopedia when added to vasopressors and HIET. Methylene blue resolves vasopedia by decreasing intracellular cyclic guanosine monophosphate (cGMP), scavenging nitric oxide, and inhibiting nitric oxide synthesis, all in direct opposition to the action of CCBs [20, 21].

A single case report describes success with using continuous venovenous hemodiafiltration and concomitant charcoal hemoperfusion in the treatment of hypotension secondary to CCBs overdose that was refractory to multiple vasopressors and HIET therapy [22].

It is difficult to recommend one specific strategy to address the complicated issue of CCBs overdose. Urgent administration of fluids, calcium, atropine, vasopressors, and HIET therapy seem to be the most well validated initial approaches to treatment, with the addition of the novel adjunct therapy being added into treatment based on necessity. However, because of the unpredictable and often dire nature of CCBs overdose, it is beneficial to be aware of all reported therapies as potential treatment modalities.

Consent

The patient was deemed decisional and not psychotic by psychiatry while in the hospital. Approximately 1 month after her discharge and hospital follow-up with her primary care physician she was contacted by telephone and the nature of this case report was described to her. She was agreeable to the use of her information in this report and returned a signed consent by mail, which can be made available to the editors of this journal upon request.

Conflict of Interest

Neither Dr. Wendorf nor Dr. Burkes have any conflict of interest to report.

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