

# Critical Management of Severe Hypotension Caused by Amlodipine Toxicity Managed With Hyperinsulinemia/Euglycemia Therapy Supplemented With Calcium Gluconate, Intravenous Glucagon and Other Vasopressor Support: Review of Literature

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## Abstract

Calcium channel blocker (CCB) overdose, whether intentional or accidental, is a common clinical scenario and can be very lethal. Conventional treatments for CCB overdose include intravenous (IV) fluids, calcium salts, dopamine, dobutamine, norepinephrine, phosphodiesterase inhibitors, and glucagon. However, the conventional therapies are unsuccessful in reversing the cardiovascular toxicity of CCB, so they commonly fail to improve the hemodynamic condition of the patient. Blockade of the L-type calcium channels that mediate the antihypertensive effect of CCBs also decreases the release of insulin from pancreatic  $\beta$ -islet cells and reduces glucose uptake by tissues (insulin resistance). By targeting this insulin-mediated pathway, hyperinsulinemia/euglycemia therapy (HIET) appears to have a distinct role, and its clinical potential is underrecognized in the management of severe CCB toxicity. We present a case of young man with amlodipine toxicity successfully managed with high dose of IV insulin therapy.

**Keywords:** Calcium channel blocker toxicity; Hyperinsulinemia/euglycemia therapy; Shock

## Introduction

Calcium channel blocker (CCB) overdose, whether intentional or accidental, is a common clinical scenario and can be very

lethal. Conventional treatments for CCB overdose include intravenous (IV) fluids, calcium salts, dopamine, dobutamine, norepinephrine, phosphodiesterase inhibitors, and glucagon. Most of these therapies are intended to increase transmembrane calcium flow (calcium salts) or increase cyclic adenosine monophosphate (cAMP) concentration by stimulating production of adenylate cyclase (with norepinephrine and glucagon) or by inhibiting production of phosphodiesterase (with amrinone and milrinone). However, the conventional therapies are unsuccessful in reversing the cardiovascular toxicity of CCB, so they commonly fail to improve the hemodynamic condition of the patient. Blockade of the L-type calcium channels that mediate the antihypertensive effect of CCBs also decreases the release of insulin from pancreatic  $\beta$ -islet cells and reduces glucose uptake by tissues (insulin resistance). By targeting this insulin-mediated pathway, hyperinsulinemia/euglycemia therapy (HIET) appears to have a distinct role, and its clinical potential is underrecognized in the management of severe CCB toxicity. There is growing experimental and clinical evidence of the value and the safety of HIET in the management of CCB poisoning. Although the mechanism of this beneficial action is not fully explained, HIET should be considered in patients with CCB-induced cardiovascular compromise. Additional clinical research and prospective clinical studies are needed to confirm the safety and efficacy of HIET and to support more formal guidelines and therapeutic regimens, but some rational recommendations can be made based on the available data. Author suggested careful monitoring of blood glucose, serum potassium concentrations and electrocardiogram is required.

## Case Report

An 18-year-old obese man was brought to our emergency department after inadvertent intake of anti-hypertensive medications under the influence of alcohol which were originally prescribed to his mother. According to patient, he took pills around 12:30 am after returning home and remembered waking up at 4:00 am with episodes of non-bilious, non-bloody vomiting.

Manuscript submitted December 3, 2017, accepted December 12, 2017

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doi: <https://doi.org/10.14740/cr646w>

Patient reports being drunk when he ingested multiple pills of amlodipine 5 mg, metformin 500 mg and combination pill of lisinopril 20 mg/hydrochlorothiazide 25 mg which were half bottle full as per family. However, he continues to deny suicidal attempt or intentional intake of prescribed medication. He has no history of suicidal attempt, mood disorder or any other past psychiatric illness. He has no medical problem and does not take any medication at home. He admits smoking marijuana and tobacco and drinks alcohol regularly. On presentation, his temperature was 98.7 °F, blood pressure was 68/50 mm Hg, pulse was 82 beats per minute, respiratory rate was 14 cycles per minute and BMI was 41.1 kg/m<sup>2</sup>. Chest exam showed bilateral air entry without any adventitious sounds. The cardiovascular exam showed normal heart sounds without murmurs, gallops, or rubs. The abdomen was soft, with no visceromegaly and with normal bowel sounds. Extremities were without edema, cyanosis, or clubbing. Electrocardiogram showed sinus tachycardia with no evidence of any conduction delays. In the emergency room, he received intravenous bolus of normal saline with transient improvement in his blood pressure; however, his blood pressure remained low requiring vasopressor support. Initially he was treated with activated charcoal, aggressive intravenous hydration and calcium infusion. Poison control was consulted and suggested HIET. He was started on high dose insulin of 250 units/h that was increased to 450 units/h, dose was up titrated based on blood pressure response along with up titrating doses of intravenous dextrose to avoid hypoglycemia. Blood sugar levels were checked every 30 min during the time of insulin/dextrose administration. Although most of the time while receiving intravenous insulin/dextrose therapy his blood sugar levels were at higher sides, he developed total of three episodes of asymptomatic hypoglycemia range from 47 to 61 mg/dL well responded to increasing dose of dextrose. Beside serum glucose, serum lactic acid, serum creatinine, serum potassium, serum calcium, PH and intake/output were closely monitored. Echocardiogram showed normal wall motion, contractility and valvular functions. He received insulin therapy for about 42 h and intravenous glucagon therapy at rate of 10 mg/h for about 30 h. During the period of refractory hypotension, he received vasopressor support with phenylephrine and norepinephrine. He required total of 3 days monitoring in critical care unit without airway compromise or need of positive pressure ventilation. Subsequently patient was transferred to inpatient psychiatry unit to evaluate for undiagnosed underlying psychiatric; however, he remained asymptomatic and subsequently discharged home with outpatient follow-up for the management of substance dependency.

## Discussion

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 system and pacemaker cells. CCBs are used extensively to treat angina pectoris, hypertension, Raynaud's syndrome, supraventricular tachycardia and migraine headaches. CCBs are divided based on their primary physiologic

effects. Dihydropyridine CCBs (DHPs) such as amlodipine and nifedipine, preferentially block calcium channels in the vasculature, acting as vasodilators and in toxic doses leading to myocardial depression, impairing cardiac conduction and QRS prolongation [1-3]. All other CCBs are grouped together as non-dihydropyridine (non-DHP) CCB. The most common are verapamil and diltiazem. These act on cardiomyocytes to reduce vascular permeability and affect cardiac contractility and conduction, though they also have some mild vasodilatory action [4].

Conventional therapy for CCB poisoning included the administration of fluids, calcium salts, glucagon, and vasopressor [5, 6]. Intravenous calcium has been a frequently used agent for calcium channel overdose. The goal is to competitively overcome the antagonism of the CCB. Calcium may be given as either calcium gluconate or calcium chloride. While calcium chloride contains three times more calcium for the same volume, calcium gluconate is less irritating to the veins and is preferred in most instances. Ionized calcium levels should be monitored, with the goal being two times the normal [1]. Glucagon is another frequently recommended antidote for CCB overdose. Glucagon stimulates adenyl cyclase via G proteins, resulting in increased intracellular cyclic AMP, which in turn leads to stimulation of muscle contraction. The clinical effect of glucagon resides in its positive inotropic and chronotropic effects as confirmed in multiple animal studies, but not in human clinical trials [2]. The main side effects of this therapy are nausea, vomiting, hyperglycemia, and ileus. The significant incidence of vomiting mandates ensuring a protected airway prior to glucagon administration [1]. In severe symptomatic bradycardia not responding to atropine or isoprenaline infusion other modalities of treatment described in literature are transvenous pacing [7], plasma exchange [8] and extracorporeal membrane oxygenation [9]. Extracorporeal elimination by conventional hemofiltration and dialysis is not recommended because these agents bind to plasma proteins and have a large volume of distribution. In our case, the patient presented with severely decreased blood pressure, which was reversed after administration of the HIET along with conventional therapy and tapering dose of vasopressors (norepinephrine and phenylephrine). HIET is considered to be the most advanced therapy first reported in humans in 1999, that showed improvement in circulatory shock [10, 11] interrupting the vicious cycle that is responsible for progressive hemodynamic deterioration and, ultimately, patient death. The efficacy and safety of this treatment have been demonstrated in several cases of CCB poisoning [6, 12, 13].

CCB overdose is frequently complicated by metabolic acidosis secondary to renal failure from prolonged hypoperfusion and end-organ ischemia [4], though in our patient renal failure and lactic acidosis were partly contributed by overdose of metformin and lisinopril. Another pathophysiologic mechanism for acidosis in patients with calcium channel toxicity decreases insulin production due to the blockage of the L-type calcium channels in the pancreas leading to impairment of the myocardial energy supply. In normal circumstances, myocardial cells use the oxidation of free fatty acids as an energy substrate for aerobic metabolism. However, in a shock state, the myocardium switches to glucose use which requires the presence of

**Table 1.** Various Treatment Methods Used in CCB Overdose

1) Decontamination
a) Activated charcoal: single dose of 50 g for adults
b) Polyethylene glycol whole bowel irrigation: 2 L/h in adults until rectal effluent is clear
2) Supportive therapy
a) Intravenous fluids
b) Atropine: 1 mg IV (can be repeated up to 3 mg total)
3) Antidotes
a) Calcium salts: i) calcium chloride: 10 - 20 mL of a 10% solution administered over 10 min (can repeat dose if no effect); ii) calcium gluconate: 30 - 60 mL of a 10% solution (dose can be repeated if no effect); iii) continuous infusion with either salt: 0.5 mEq of Ca/kg/h
b) Glucagon: 5 mg IV bolus, can be repeated twice at 10 min intervals
4) Phosphodiesterase inhibitor (e.g., amrinone and milrinone)
5) Adrenergic agents (e.g., norepinephrine and dopamine, etc.)
6) HIE
a) Regular insulin bolus of 0.1 U/kg IV and then continuous infusion of 0.2 - 0.5 U/kg/h
b) Dextrose 25 - 50 g bolus followed by a continuous infusion of 0.5 g glucose/kg/h that can be titrated to appropriate blood glucose.
7) Invasive therapy
a) Transvenous pacing
b) Intraaortic balloon pump
c) Cardiopulmonary bypass
d) Extracorporeal membrane oxygenation

insulin in order to enter the cell. Therefore, CCB toxicity causes decrease insulin release from pancreas hence during a state of hypoinsulinemia and acquired insulin resistance, myocardial cells are unable to use glucose as an energy source, leading to decreased myocardial contractility and hypotension. The lack of energy substrate exacerbates cardiovascular depression, which is already compromised by the blocking of the calcium channels. Non-cardiogenic pulmonary edema is also one of the complications secondary to CCB overdose [14-16]. HIET may lead to reversal of cardiovascular collapse in CCB toxicity by improving myocardial utilization of carbohydrates, increasing plasma levels of ionized calcium, improving hyperglycemic acidotic state, as well as by clearing the cytosol of lactic acid and other glycolytic byproducts [2, 17, 18]. In addition, insulin has a direct positive inotropic activity that may contribute to its clinical effects [2, 17-19]. Boyer and colleagues proposed a protocol for the initiation of HIET wherein an initial insulin bolus of as much as 1 IU/kg is given, followed by insulin infusions of 0.5 IU/kg/h and 10% dextrose in half-normal saline. Blood glucose must be checked at least once every 30 min and hypertonic glucose must be infused to maintain blood glucose in the upper normal range. Up to 20 - 30 g/h may be needed in adults. Supplemental potassium is required only to prevent severe hypokalemia [20]. The duration of HIET should be guided by the clinical response, especially hemodynamic parameters: the goal should be hemodynamic stability after the withdrawal of vasoactive agents [20, 21]. Methylene blue has been used as a novel approach to treat refractory CCB overdose based on reports of its use to counteract post-coronary artery bypass vasoplegia when added to vasopressors and

HIET. Methylene blue resolves vasoplegia by decreasing intracellular cyclic guanosine monophosphate (cGMP), scavenging nitric oxide, and inhibiting nitric oxide synthesis, all in direct opposition to the action of CCBs [22, 23]. There is no definitive evidence that either gastrointestinal decontamination in the form of activated charcoal or whole bowel irrigation alters the clinical outcome in the CCB overdose. However, gastrointestinal (GI) decontamination is still advocated because of the potential lethal nature of this overdose and lack of a specific efficacious antidote. But potential risks of GI decontamination should be kept in mind, e.g. gastric lavage should probably be withheld in patients who are already bradycardic or have conduction disturbances [15]. There are case reports that have suggested the importance of whole bowel irrigation in patients who ingested sustained release preparations of calcium channel blockers [3, 24] (Table 1).

## Conclusion

CCB overdose, whether intentional or accidental, can be lethal. There is growing experimental and clinical evidence of the value and the safety of HIET in the management of CCB poisoning. Although the mechanism of this beneficial action is not fully explained, HIET should be considered in patients with CBB-induced cardiovascular compromise. Although not effective in all cases, HIET often improves arterial blood pressure, myocardial contractility and metabolic acidosis. Whatever the main hemodynamic effect involved, observations support the value of HIET in patients with CCB intoxication and

circulatory compromise and suggest that this therapy should probably be considered earlier in the management of the condition rather than being used as a rescue option. Indeed, some cases in which HIET was introduced late in the treatment and failed to improve the patient's condition have also been reported. The effectiveness of HIET is often limited to an improvement of hypotension and acidosis that is observed within 30 - 45 min of starting insulin administration. Direct actions on bradycardia and cardiac conduction are variable and are hardly differentiated from effects due to the improvement of hemodynamic status. Additional clinical research and prospective clinical studies are needed to confirm the safety and efficacy of HIET and to support more formal guidelines and therapeutic regimens, but some rational recommendations can be made on the basis of the available data. Author suggested careful monitoring of blood glucose, serum potassium concentrations and the electrocardiogram is required.

### Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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