

A Case Series of Calcium Channel Blocker Poisoning - Pivotal Role of Hyperinsulinemia-Euglycemia Therapy

Lakshmikanthcharan S^{1*}, Vivekananthan P¹, Sivakumar MN² and Eldho Mathew³

¹Consultant Intensivist, Department of Critical Care, Royalcare Superspeciality Hospital, Coimbatore, India

²Head, Department of Critical Care, Royalcare Superspeciality Hospital, Coimbatore, India

³Clinical Pharmacist, Bareen International Hospital, MBZ City, Abu Dhabi, UAE

***Corresponding Author:** Lakshmikanthcharan S, Consultant Intensivist, Department of Critical Care, Royalcare Superspeciality Hospital, Coimbatore, India.

Received: March 02, 2020; **Published:** March 19, 2020

Abstract

Introduction: Calcium Channel Blockers (CCBs) are commonly used in the management of hypertension. Hyperinsulinemia-Euglycemia Therapy (HET) is a vital intervention in the management of CCB poisoning. We share our experience in three cases of CCB over dosages, who survived with HET.

Objective: To emphasize the effectiveness of Hyperinsulinemia-Euglycemia Therapy along with other conventional measures in the early recovery from Calcium Channel Blocker poisoning induced refractory shock.

Case Presentation: We hereby report three cases of CCB over-dosage with consumption of 75 - 100 mg of amlodipine tablets. They presented with refractory hypotension and tachycardia. Initial management was with decontamination, fluid resuscitation, inotropes, glucagon and calcium gluconate. Later we introduced Hyperinsulinemia-Euglycemia Therapy. Patient's hemodynamics gradually became stable and were weaned off inotropic supports.

Discussion: HET is a potentially life-saving treatment in calcium channel blocker toxicity. We suggest that such therapy should be considered early in patients those who are not responding to conventional treatment.

Conclusion: We conclude that amlodipine (CCB) overdose can be effectively treated with early GI decontamination, fluid resuscitation, calcium and glucagon infusions, and cautious use of inotropes with careful monitoring of possible complications. The use of Hyperinsulinemia-Euglycemia therapy is required in the treatment of Calcium Channel Blocker overdose in non-responders.

Keywords: Amlodipine Overdose; Calcium Channel Blocker; Glucagon; Hyperinsulinemia; Euglycemia Therapy

Abbreviations

HET: Hyperinsulinemia-Euglycemia Therapy; CCB: Calcium Channel Blocker; ICU: Intensive Care Unit; GCS: Glasgow Coma Scale; ABG: Arterial Blood Gas; MAP: Mean Arterial Pressure

Introduction

Calcium channel blockers (CCB) are one of the main anti-hypertensives used for several years. They also can cause refractory bradycardia and hypotension following the accidental or intentional overdose. Toxicity due to over dosage is associated with significant mortality. Incidence quoted include four fifth of CCB poisoning patients resulting in hospitalization and carry a mortality of 2% [1]. Toxicity with regular dosage of these drugs was not reported. In this case series, we are discussing our ICU experiences with calcium channel blocker poisoning either alone or in combination with other drugs.

Cases

Case 1: Calcium channel blocker poisoning

A 19-year-old girl with no comorbidities alleged to have deliberately consumed 10 tablets each of Amlodipine 10 mg and Fexofenadine 120 mg, presented with vomiting and giddiness to a local hospital where gastric lavage was done. The patient was shifted to our hospital in shock by 12 hours from the time of consumption.

She came to us with a BP of 80/50 mm Hg on 0.4 mcg/kg/min nor-adrenaline support. She had a GCS of 15/15, drowsy, tachypneic (35 - 45 breaths/minute), peripheral pulses were feeble. Initial ABG showed compensated metabolic acidosis, lactate was on the higher side (64 mg/dl). Echo showed good Left ventricular function and Inferior vena cava was full.

Enema and activated charcoal were given initially. Vasopressin 2 units/hour was added to augment blood pressure, but not achieved. Inj. Glucagon 2 mg and Inj. Calcium gluconate 3 gm given intravenously as a bolus, followed by continuous infusion of 1mg per hour and 1 gm per hour respectively. 25 ml of 50% Dextrose and 25 units of regular insulin was given per hour and blood sugar level maintained between 180 - 200 mg/dl. Once acidosis was better calcium gluconate changed to calcium chloride since it contains more calcium. Low potassium and Low phosphate level were corrected with intravenous potassium phosphate.

By next day early morning, she became alert, conscious and vitals became normal, weaned off nor-adrenaline and vasopressin. She was shifted to step-down ICU and then to room in 2 days.

Case 2: Combination of calcium channel blocker and beta blocker poisoning

A 36-year-old lady with no known comorbidities alleged to have deliberately consumed 15 tablets of Amlodipine (each 5 mg) and Atenolol (each 50 mg) and 3 other unknown tablets at the middle of a night, the early morning she felt nausea, vomiting, and dizziness. She was brought to our hospital with very low BP (60/30 mm Hg) and feeble pulses. At emergency, she was started on 0.4 mcg/kg/min of nor-adrenaline and given a gastric lavage. Bolus doses of Inj. Glucagon 5 mg, Calcium gluconate 3 gm were given intravenously and shifted to ICU.

She had a GCS of 15/15 with mild dizziness. Lower blood pressure of 60 mmHg systolic was treated with vasopressor and inotropic agents namely noradrenaline, adrenaline, vasopressin and dopamine successively. Peglec (polyethylene glycol) enema and activated charcoal 50 gram were given orally for decontamination. Nausea and vomiting were persisting and managed with ondansetron. ABG showed mild uncompensated metabolic acidosis (serum Lactate - 34 mg/dl). Her Left Ventricular function was good and protecting airway. Calcium gluconate started instead of calcium chloride to avoid further acidosis. Inj. Glucagon infusion started at 2 mg/hr and increased to 3 mg/hr. 25 ml of 50% Dextrose and 25 units of Insulin started per hour to maintain Hyperinsulinemia - Euglycemia and blood sugar level maintained between 180 - 200 mg/dl. Basal ionized calcium was 10 mg/dl, to maintain hypercalcemia, calcium gluconate 30 ml (3 gm) per hour was given. Meanwhile, output was dropped. The patient continued to have metabolic acidosis and treated with sodium bicarbonate infusion and sodium bicarbonate in half normal saline as an infusion. BP did not improve even with maximum doses of inotropes and then started with isoprenaline infusion at a rate of 2.5 mcg/min. BP gradually picked up and Glucagon reduced to 1 mg/hr. Urine output improved. Hypophosphatemia and hypokalemia were treated with potassium phosphate infusion.

Blood pressure improved and later inotropes were weaned. The patient became tachypneic and had breathing difficulty. Chest X-ray showed features of pulmonary edema. Fluids stopped and diuretic therapy was initiated to treat pulmonary edema. Insulin stopped prior to dextrose to avoid rebound hypoglycemia. She improved and was shifted to the ward after 3 days of ICU stay.

Case 3: Combination of calcium channel blocker and paracetamol poisoning

A 38-year-old lady a recently diagnosed hypertensive on amlodipine 5 mg daily alleged to have deliberately consumed 15 tablets of Amlodipine (each 5 mg) and 10 tablets of Paracetamol (each 500 mg). Stomach wash was given outside and came to our emergency with GCS of 15/15 by 8 hours. While receiving in ICU she required 0.4 mcg/kg/min of Nor-adrenaline and 1 Units/hr vasopressin to maintain Blood Pressure of 100/60 mmHg. Fluid resuscitation was given initially and later adjusted based on volume status. Inj. Glucagon 2 mg bolus and 2 mg/hr and Inj. Calcium gluconate 10% 30 mL bolus and 5 mL/hr were initiated. N- Acetyl cysteine infusion started in view of paracetamol over-dosage as per Prescott protocol for 24 hours. Adrenaline infusion of 0.2 mcg/kg/min was also required later to maintain MAP above 65 mmHg. Nausea and Vomiting were managed with Ondansetron. Patient LV function was good and NIV initiated for tachypnoea. ABG showed mild uncompensated metabolic acidosis (Lactate 53 mg/dl). Hyperinsulinemia-Euglycemia therapy was started due to her worsening hemodynamics. Inj. Human actrapid 10 units bolus and 15 units per hour infusion with 50 ml per hour infusion of 25% Dextrose were started. Later dose changed to 20 units per hour of Insulin and 40 ml of 50% dextrose to maintain blood sugar value between 180 - 200 mg/dl. Serum calcium and potassium were monitored periodically. All inotropes were weaned off after 12 hours of infusion of insulin and dextrose.

Discussion

Calcium channel blockers (CCB) are one of the most commonly used antihypertensive. CCBs are of two types dihydropyridines and nondihydropyridines [2,3]. Dihydropyridines (amlodipine) block L-type calcium channels, especially in the vascular smooth muscle, resulting in smooth muscle relaxation. These drugs have slight myocardial depressant activity at therapeutic levels and in fact, may increase cardiac output due to the reflex tachycardia. Dihydropyridines are smooth muscle selective, not smooth muscle-specific, and in toxic concentrations may lead to myocardial depression and impaired cardiac conduction. Our 3 patients had consumption of amlodipine, a dihydropyridine in the over dosage range of 75 - 100 mg.

In a hypotensive patient, the initial intravenous fluid bolus of 1 - 2 liters can be tried if cardiac function is fine. If hypotension persists, conventional intravenous inotropes and vasopressors are warranted. Detoxification includes gastric lavage especially when a patient presents within 1 - 2 hours of ingestion, and activated charcoal in patients presenting within the first two hours of ingestion. And for sustained release formulations, the use of activated charcoal up to 4 hours after ingestion has been documented to be effective. Whole-gut lavage with polyethylene glycol solution may be useful in cases of sustained-release tablets ingestion [4]. All our patients had good left ventricular function and initially received volume boluses and the early decontamination procedures.

Intravenous calcium is a frequently used agent for calcium channel overdose. The goal is to competitively overcome the antagonism of the CCBs. However, not all patients respond to intravenous calcium administration, and the benefit may be temporary [5]. Calcium may be given either as 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. Calcium chloride will increase the metabolic acidosis. Calcium salts can be given in bolus doses or administered as a continuous infusion [5]. A typical dosing would start with a 0.6 mL/kg bolus of calcium gluconate (0.2 mL/kg bolus of calcium chloride), followed by a continuous infusion of 0.6 - 1.5 mL/kg/hr of calcium gluconate (0.2 - 0.5 mL/kg/hr of calcium chloride) and the infusion rate titrated to hemodynamic response. Importantly, ionized calcium levels should be monitored, with the goal being two times the normal.

Glucagon is another commonly mentioned antidote for CCB overdose. Glucagon stimulates adenylyl cyclase via G proteins, resulting in increased intracellular cyclic AMP which in turn leads to stimulation of muscle contraction. Glucagon has positive inotropic and chronotropic effects as recognized in many animal studies [6]. The initial glucagon dose is 50 - 150 mcg/kg given as an intravenous bolus and may be repeated every 3 - 5 minutes, followed by infusions up to 5mg per hour. Main adverse effects are nausea, vomiting, hyperglycemia, and ileus. All 3 of our patients had vomiting and managed with antiemetics. All the above conventional methods of antagonism were tried in our 3 patients but did not improve hemodynamics significantly.

CCB toxicity often results in hyperglycemia from decreased insulin production due to the blockage of the L-type calcium channels in the pancreas [7-9]. Another consequence of hypoinsulinemia is impairment of the myocardial energy supply. In most instances, the myocardium uses free fatty acids for energy. However, in a shock state, the myocardium switches to glucose use, dependent on insulin. With hypoinsulinemia and acquired insulin resistance, myocardial cells are unable to use glucose as an energy source, leading to decreased myocardial contractility and hypotension. HET may lead to the reversal of cardiovascular collapse in CCB toxicity by improving myocardial utilization of carbohydrates as well as by clearing the cytosol of lactic acid and other glycolytic byproducts. In addition, insulin has a direct positive inotropic activity that may contribute to its clinical effects. HET was initiated in all our cases and refractory shock gradually improved. Insulin dose ranging from 0.1 units/kg/hr to 1.0 units/kg/hr and Dextrose 50%, dose ranging from 5g to 15g per hour are usually recommended in HET. Much higher doses might be needed which need to be individualized to clinical effect with appropriate monitoring to negate potential side effects. There is a 1D recommendation by the expert consensus group for management of CCB poisoning in adults for use of HET as first line therapy in the presence of myocardial dysfunction and 2D recommendation for rescue therapy in incremental higher doses of HET in the presence of myocardial dysfunction [10].

HET therapy is associated with deleterious effects like hypoglycemia, hypokalemia, volume overload and hyponatremia requiring intense monitoring. This might be the reason as to why HET therapy may not have been rigorously tested and established as a therapy, suited to be used in all clinical settings. Serum glucose and potassium were closely monitored and corrected in our cases. However, hyponatremia, volume overload was not encountered in our series of patients.

Metabolic acidosis in our patient could be attributed to the acute renal failure and prolonged hypotension leading to lactic acidosis. Decreased insulin secretion and increased insulin resistance may also lead to the metabolic acidosis in CCB poisoning.

The second case was complicated by transient pulmonary edema which might have resulted from the combined effects of the drug itself and fluid resuscitation during the initial phase of therapy. Normal cardiac function on echocardiography excluded myocardial depression as an etiologic factor. Noncardiogenic pulmonary edema following CCB overdose is well described in the literature [11-13]. Precapillary vasodilatation resulting in excessive pulmonary capillary transudation was suggested as the possible mechanism of non-cardiogenic pulmonary edema [11].

When pharmacological measures prove ineffectual, cardiac pacing, intra-aortic balloon counter pulsation, and extracorporeal bypass may play important roles, which were luckily not required for our patients. In our three cases described here, the effect of amlodipine on vascular smooth muscle was evident. All three patients developed profound hypotension requiring prolonged inotropic support without significant effect on cardiac pacemaker or conduction system with preserved systolic function of the heart.

Conclusion

We conclude that Amlodipine (CCB) overdose can be effectively treated with early GI decontamination, resuscitation with fluids, calcium and glucagon infusions, and cautious use of inotropes with careful monitoring of possible complications. The use of Hyperinsulinemia-Euglycemia therapy early in the management of Calcium Channel Blocker over-dosage is beneficial especially in cases of refractory shock.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

Bibliography

1. Christensen MB, et al. "Outcomes following calcium channel blocker exposures reported to a poison information center". *BMC Pharmacology and Toxicology* 19 (2018): 78.
2. M Spedding and R Paoletti. "Classification of calcium channels and the sites of action of drugs modifying channel function". *Pharmacological Reviews* 44.3 (1992): 363-876.
3. DR Abernethy and JB Schwartz. "Calcium-antagonist drugs". *The New England Journal of Medicine* 341.19 (1999): 1447-1457.
4. KL Cumpston, et al. "Whole bowel irrigation and the hemodynamically unstable calcium channel blocker overdose: primum non nocere". *Journal of Emergency Medicine* 38.2 (2010): 171-174.
5. SD Salhanick and MW Shannon. "Management of calcium channel antagonist overdose". *Drug Safety* 26.2 (2003): 65-79.
6. Cumpston K, et al. "Failure of hyperinsulinemia/euglycaemia therapy in severe diltiazem overdose". *Journal of Toxicology: Clinical Toxicology* 40 (2002): 618.
7. Megarbane B, et al. "The role of insulin and glucose(hyper-insulinaemia/euglycemia) therapy in acute calcium channel antagonist and beta-blocker poisoning". *Toxicological Reviews* 23.4 (2004): 215-222.
8. Kline JA, et al. "The diabetogenic effects of acute verapamil poisoning". *Toxicology and Applied Pharmacology* 145.2 (1997): 357-362.
9. Ohtam Nelson J, et al. "Effect of Ca++ channel blocker on energy level and stimulated insulin secretion in isolated rat islets of Langerhans". *Journal of Pharmacology and Experimental Therapeutics* 264.1 (1993): 35-40.
10. Maude St-Onge, et al. "Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults". *Critical Care Medicine* 45.3 (2017).
11. Humbert VH Jr, et al. "Noncardiogenic pulmonary edema complicating massive Diltiazem overdose". *Chest* 99 (1991): 258-259.
12. Saravu K and Balasubramanian R. "Near-Fatal Amlodipine poisoning". *Journal of the Association of Physicians of India* 52 (2004): 156-157.
13. Lam YM, et al. "Continuous calcium chloride infusion for massive nifedipine overdose". *Chest* 119 (2001): 1280-1282.

Volume 8 Issue 4 April 2020

©All rights reserved by Lakshmikanthcharan S., et al.