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A case report on the effect of plasmapheresis in the treatment of severe calcium channel blocker toxicity

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ABSTRACT

Overdose by calcium channel blocker (CCB) antihypertensive agents has been shown to be a cause of significant morbidity and can often be fatal. (1) Although overdoses of calcium-channel blockers and beta blockers are uncommon, they have a high mortality rate, and management may be complicated. (2) Amlodipine, a dihydropyridine CCB, can cause prolonged hypotension in overdose. (3) We report a case of severe Amlodipine/Atenolol overdose that was refractory to multiple therapeutic approaches but rapidly responded to plasmapheresis. We describe the case of a previously healthy 25-year-old lady presented after ingesting 30 tablets of Amlodipine 5 mg/Atenolol 50 mg in a suicide attempt. The patient was initially managed with fluid resuscitation, calcium boluses, glucagon bolus, methylene blue boluses and multiple vasoactive agents. Hyperinsulinemic euglycemic therapy was initiated when hypotension persisted despite conventional treatments but was stopped later due to life threatening hypoglycemia and hypokalemia. Refractory hypotension prompted the use of plasmapheresis in an attempt to lower serum amlodipine levels as knowing that amlodipine is highly protein bound. Plasmapheresis is a procedure used to remove pathologic substances from a patient's blood that has proven useful in some cases of drug overdose. (1) A dramatic improvement of cardiovascular stability was already observed during plasmapheresis. The primary outcomes were to reduce mortality and improve hemodynamic parameters. The secondary outcomes included reduce length of stay in intensive care unit, duration of vasopressor use and functional outcomes. (4) Conclusion: This case demonstrates that a Plasmapheresis can be effective in restoring hemodynamic stability in severe calcium channel blocker toxicity and recommend its use in patients with calcium channel blocker toxicity that is not responsive to traditional therapies.

Keywords:

plasmapheresis, calcium channel blocker toxicity

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Case report:

A 25-year old lady with no past medical history or psychiatric issues presented to the emergency department with history of drug overdose of 30 tablets of beta blocker and calcium channel combination (Amlodipine 5 mg/Atenolol 50 mg) and 45 tablets of rosuvastatin 10 mg. In the emergency department, the patient noted to be hypotensive 82/49 mm Hg with heart rate 55/min and normal oxygen saturation. At time of presentation (5 hours post ingestion), she started to complain of

severe dizziness, inability to walk, nausea and vomiting. She was conscious and oriented with a GCS of 15, but her clinical condition started to deteriorate (bradycardic, hypotensive with ECG Changes) (Figure 1). As the patient condition is worsening, it is likely that a significant amount of the drug had been absorbed and in view of a large amount of the tablets ingested, decision was made to electively intubate the patient suspecting further worsening in her clinical condition.

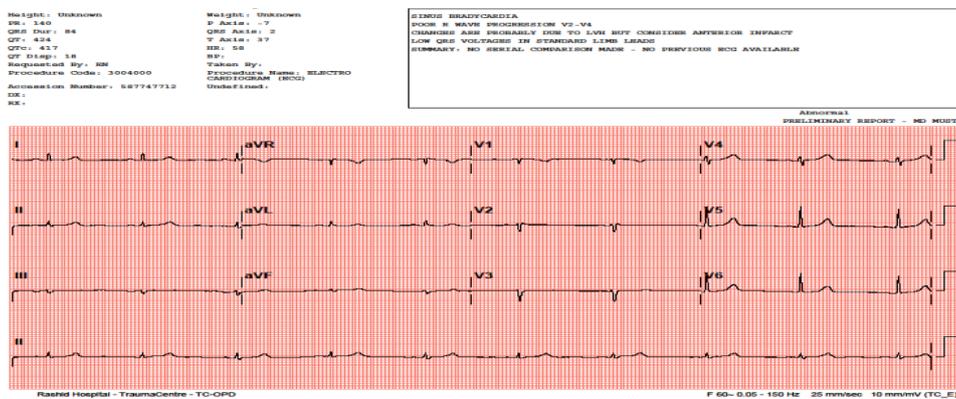


Figure 1. The 12-lead ECG on admission to the intensive care unit showing sinus bradycardia.

For further worsening in her condition due to cardiogenic shock and bradycardia, central line was inserted and noradrenaline and dopamine infusion started. She reviewed by toxicology team who started her on activated charcoal, sodium bicarbonate, insulin infusion and methylene blue. Also received stat dose of Epinephrine, calcium, glucagon and referred to ICU team for further management.

On examination, there was no skin rash or any signs of physical abuse assault. Pupils are 4 mm very sluggish bilaterally, normal CNS reflexes and no clonus. Regular heart sound, no murmur with sinus bradycardia. There was bilateral wheezes and ronchi for which started on ipratropium and salbutamol nebulization for beta-blocker overdose related wheezes. Arterial blood gas showed pH 7.31, pCO2 37.6, pO2 93, HCO3 18.6. Chest x-ray showed right basal pulmonary infiltrates. ECG showed sinus bradycardia (57/min) and in between there was

junctional rhythm. CT abdomen angiogram done and showed features are consistent with shock bowel secondary to systemic hypotension.

There was high creatine phosphokinase level (2563 u/l) which may due to rhabdomyolysis associated with rosuvastatin overdose and there was severe hypophosphatemia (0.7 mg/dL) and hypokalemia secondary to high dose insulin infusion which optimized by electrolyte replacement.

On admission in ICU, she was intubated and ventilated, On maximum inotropic support with noradrenaline, dopamine and dobutamine infusion. Her Blood pressure still low (89/50 mm hg) with minimal urine output. She was on high dose insulin euglycemia therapy up to 10 units/kg (500units/hour insulin) with Dextrose 50% infusion through central line to maintain blood glucose level above 200 mg/dl. Glucose and potassium values were monitored every

hour, and the infusion was adjusted accordingly but high dose insulin/dextrose infusion therapy was stopped due to suspected brain oedema as the patient developed dilated non-reactive pupils and to avoid life threatening hypoglycaemia and hypokalemia. CT scan brain ordered but the patient was unstable to be moved and hence mannitol was given once. Previous CT brain on admission was normal. later after stopping high dose insulin infusion, the pupil became reactive and no signs of increase ICP.

There was a refractory hypotension (cardiogenic shock) with the above management associated with multi organ failure (hypoxic respiratory failure, oliguric renal failure, coagulopathy and encephalopathy) due to systemic hypoperfusion.

Plasmapheresis started to treat severe calcium channel blocker toxicity; although the evidence available is only from case reports but knowing that amlodipine is highly protein bound keeps plasmapheresis is a good option especially if there was persistent hypotension with the above management.

A dramatic improvement of cardiovascular stability was already observed during plasmapheresis; after first session of plasmapheresis the heart rate restores to the normal rhythm, gradually tapering from inotropic and chronotropic support and start to pass an adequate urine output.

Chest X ray initially was normal then there was a progression of pleural effusion. Bilateral Thoracentesis done which improve the oxygenation and facilitate weaning from the mechanical ventilation.

After four daily sessions of plasmapheresis, the patient extubated, weaned off from vasopressors and was discharged from ICU after few days in good health after a psychiatry consultation.

Discussion:

Overdose by calcium channel blocker antihypertensive agents has been shown to be a cause of significant morbidity and can often times prove fatal. ⁽¹⁾ CCB exert their therapeutic

and toxic effects by the direct blockade of L-type calcium channels causing relaxation of the vascular smooth muscle with subsequent vasodilation. ⁽⁵⁾ Shock and metabolic acidosis result from the persistent hypotension. In high doses, calcium channel blocking agents cause insulin resistance. ⁽¹⁾ Calcium channel blockade concurrently triggers the heart to switch to preferential carbohydrate metabolism as opposed to the free fatty acid oxidation that occurs in the myocardium in the non-stressed state. The effects of calcium channel antagonism are also seen in other parts of the body. For example, in the beta-islet cells of the pancreas, calcium channel antagonism inhibits insulin secretion, producing insulin resistance and hyperglycemia. ⁽⁵⁾

Amlodipine is dihydropyridine calcium channel blocker which causes mainly peripheral vasodilation and reflex tachycardia. Unlike non-dihydropyridine CCBs like Verapamil and Diltiazem, dihydropyridines as a group have predominant effect on vascular smooth muscle cells with little effect on cardiac pacemaker cells or contractility. ⁽⁶⁾ In large doses it also affects myocardial contractility and causes cardiogenic shock. fatalities had occurred with doses more than 140 mg (the patient took 150 mg). Amlodipine is a potent vasodilator with a long half-life and delayed onset of action that is particularly concerning after an overdose. ⁽⁷⁾

Atenolol is selective beta 1 adrenergic blocking agent that causes myocardial depression and conduction delays (negative inotropic effect and negative chronotropic effect). β -blockers act on beta-receptors through competitive inhibition, indirectly decreasing the production of cAMP and thereby limiting calcium influx through L-type calcium channels with a resulting negative effect on heart rate and cardiac contractility. ⁽⁵⁾

The combined effect of amlodipine and atenolol is associated with severe myocardial depression specially with abolishing the mitigating effect of reflex tachycardia caused by the amlodipine. The symptoms start to appear four hours post

ingestion. Life-threatening cardiovascular effects such as profound vasodilation with decreased systemic vascular resistance, bradycardia, conduction delay, hypotension, and resulting cardiogenic shock have been well established in BB and CCB overdose. Other adverse effects include hyperglycemia (more common in CCB overdose) and lactic acid accumulation leading to metabolic acidosis. In addition, altered mental status, dysrhythmias, seizures⁽⁵⁾

Management:

1) Activated charcoal can be considered if patients present to the ED within 1 to 2 hours of ingestion of a non-sustained release product. charcoal administration was found to decrease absorption by nearly 50% at 2 hours from ingestion. The effect was lost if charcoal was given at 6 hours post ingestion.⁽⁸⁾

In this case the patient presented in the emergency department five hours post ingestion so, activated charcoal mostly was ineffective.

2) Although calcium seems like a natural reversal agent (particularly for calcium-channel blocker toxicity), the evidence for calcium is weak. There are case reports describing both efficacy and lack of efficacy in giving calcium for calcium-channel blocker overdose.⁽⁹⁾ We do not recommend more than a single dose of calcium, as its efficacy is uncertain and too much calcium can be deleterious.⁽²⁾

3) Sodium bicarbonate may be indicated if there is a widened QRS, indicating the presence of sodium channel blockade; however, it is not used routinely in management of either calcium-channel blocker or beta blocker overdose.⁽²⁾

4) Vasopressor agents are commonly used in the management of the hypotension found in calcium-channel blocker or beta blocker overdose. A wide variety of agents, including epinephrine, norepinephrine, vasopressin, dopamine, and dobutamine have been used, with variable success. Standard dosing of these agents may not be adequate, and higher doses (as well as the use of multiple agents) may be

required in the severely poisoned patient. Selecting which vasopressor to use depends on the provider's comfort level, as no single agent has been shown to be superior to another when treating calcium-channel blocker or beta blocker toxicity.⁽²⁾

In this case there was a refractory hypotension (cardiogenic shock) on maximum inotropic support with noradrenaline, dopamine and dobutamine infusion.

5) Methylene blue is another option that can be used in amlodipine overdose as it counteracts the vasodilatory effect of amlodipine through inhibiting nitric oxide synthesis. Methylene blue 2 mg/kg IV over 20 minutes followed by methylene blue 1mg/kg over an hour. Methylene blue can be used for refractory shock in a patient with amlodipine toxicity.⁽⁷⁾

6) Glucagon is produced in the pancreas and plays a key role in glucose homeostasis. Its role as a chronotropic and inotropic agent has been studied since the 1960. Glucagon exerts its effect by increasing cyclic adenosine monophosphate (cAMP). During calcium-channel blocker or beta blocker toxicity, the amount of cAMP is reduced, leading to negative inotropic and chronotropic effects.⁽¹⁰⁾

Several case reports indicate its use early in the management of the toxic patient^{(10) (11)} but the Glucagon which were used in these previous studies were obtained from mammalian pancreatic extract, contained insulin until recombinant glucagon was available in 1998. Glucagon therapy has largely been replaced by insulin/glucose administration.⁽²⁾

Our patient also received stat doses of calcium gluconate, sodium bicarbonate, methylene blue and glucagon but still in severe hypotension and hypoperfusion.

7) For the patient severely poisoned with a calcium-channel blocker or a beta blocker, high-dose insulin euglycemic therapy has become a mainstay of treatment. Several case series and reports showing good success with its use which

have made insulin/glucose a first-line intervention in the treatment of the unstable calcium-channel blocker toxic or beta blocker-toxic patient. ⁽²⁾

Most notably, a number of studies have demonstrated that insulin administered in higher doses has strong positive inotropic properties. ⁽⁵⁾ High dose insulin is beneficial in cases of CCB/BB overdose, through the following mechanism:

- 1) Insulin supports the heart metabolically during shock states as it provides a glucose as substrate to the shocked heart and using insulin will facilitate glucose use by stressed heart. When cardiac myocytes are under physiologic stress, their metabolism converts from free fatty acids to glucose. Insulin further promotes carbohydrate metabolism by increasing glucose uptake into the myocyte as well as increasing lactate uptake and providing further substrate for energy. ⁽⁹⁾
- 2) There is insulin resistance with CCB overdose and by giving high insulin dose, it overcomes this resistance. ⁽⁵⁾
- 3) High dose insulin increases lactate removal via oxidation during shock and increases left ventricular function without increasing myocardial oxygen requirement.
- 4) High dose insulin produces vasodilation, which improves local microcirculation and aids systemic perfusion ⁽⁵⁾

A recent animal study comparing insulin therapy to vasopressin and epinephrine found that insulin therapy was superior, producing a better blood pressure and heart rate response. ⁽¹²⁾

There are no official guidelines regarding insulin dosing in Poison induced cardiogenic shock and wide practice variation exists. Doses (1-10 unit/kg) has been reported to be safe and effective in CCB overdose. ⁽⁵⁾ Potential complications of high-dose insulin therapy are hypoglycemia and hypokalemia. ⁽²⁾ Monitor blood glucose and potassium levels and optimize electrolyte replacement as necessary is

essential (insulin will drop potassium and glucose levels).

A hyperinsulinemic euglycemic therapy was initiated in our patient when hypotension persisted despite above conventional treatments but was interrupted due to suspected for brain oedema, persistent euglycemic status of the patient and to avoid life threatening hypoglycemia and hypokalemia.

8) Intravenous lipid emulsion (ILE) is thought to act through several mechanisms including shifting of lipophilic drugs from tissue into circulation, providing energy for heart muscle from lipid acids, or enabling calcium influx into myocardium. Experimental studies showing that ILE is effective in cases of certain lipophilic substances. However, ILE was not always superior to standard treatment protocols in attenuating toxicity of some other drugs, including CCBs. ⁽¹³⁾ Lipid emulsion was associated with improved hemodynamic parameters and survival in animal models of intravenous verapamil poisoning, but not in models of oral verapamil poisoning. ⁽⁴⁾ The evidence for the use of ILE in calcium channel blocker overdose is weak, coming mainly from animal studies and human case reports. Studies are heterogeneous and so are difficult to compare. ^{(4) (14)}

In a recent study showed that intravenous lipid emulsion may be ineffective in acute poisonings with amlodipine. Although intravenous lipid emulsion may be life-saving treatment of poisonings with certain calcium channel blockers or beta blockers, like verapamil and propranolol, it may be ineffective in some other circumstances, including toxicity of amlodipine, nifedipine and metoprolol. ⁽¹³⁾

There are possible problems associated with the use of ILE, including respiratory distress and the inability to measure serum electrolytes. In one case report, adverse effects such as hypertriglyceridemia and hypoxemia were observed with lipid emulsion when used at exceptionally high doses. Hyponatremia, extreme lipemia, and inability to obtain reliable

arterial blood gas, or electrolyte levels were also noted in one case report. ⁽⁴⁾

9) Atropine is used in the management of a bradycardic, hypotensive patient, it is rarely effective with either calcium-channel blocker or beta blocker overdose. ^{(9) (15)} Pacing either transthoracic or transvenous pacing may be considered if the patient remains refractory to other therapies; however, its efficacy is uncertain. ^{(2) (16)}

10) Haemodialysis is not routinely indicated in the management of either calcium-channel blocker or beta blocker overdose. Because calcium-channel blockers are highly protein bound and have a large volume of distribution, haemodialysis is not indicated or useful. ⁽²⁾

11) Refractory hypotension with the above management prompted the use of plasmapheresis in an attempt to lower serum amlodipine levels.

Plasmapheresis is a procedure used to remove pathologic substances from a patient's blood that has proven useful in some cases of drug overdose. ⁽¹⁾

Amlodipine is a dihydropyridine group of calcium channel blockers (CCBs) having a half life of 30-50 hours and a large volume of distribution (21 L/Kg). ^{(6) (16)} Plasmapheresis is an option to treat severe calcium channel blocker toxicity; although the evidence available is only from case reports but knowing that amlodipine is highly protein bound keeps plasmapheresis an essential option especially if there is persistent hypotension on high dose vasopressors in addition to high dose of insulin.

Verapamil (90% protein bound) and diltiazem (77-93% protein bound) were successfully removed by plasma exchange in overdose situations. ^{(17) (18)}

Therapeutic plasma exchange may also utilized in the management of certain cases of amlodipine overdose as approximately 93% of the circulating drug is bound to plasma proteins. ^{(1) (19)}

In our case study a dramatic improvement of cardiovascular stability was already observed during plasmapheresis; after first session of plasmapheresis the heart rate restores to the normal rhythm, gradually tapering from inotropic and chronotropic support and after fourth session of plasmapheresis, the patient weaned off from vasopressors and extubated.

12) In case of failure of the high insulin, vasopressors and plasmapheresis, Extracorporeal membrane oxygenation (ECMO) is an option that can be considered if available.

There are a few case reports of good outcomes using an intra-aortic balloon pump in severely poisoned calcium-channel blocker or beta blocker patients. Also, ECMO has been used in the management of refractory shock in calcium-channel blocker or beta blocker overdose in several case reports. ⁽²⁰⁾ Both modalities usually require a tertiary care hospital setting to provide the necessary services, thus limiting their routine use. These treatments should be reserved for patients with refractory shock despite optimal medical treatment. ⁽²⁾

Conclusion:

Conventional therapies, including, atropine, cardiac pacing, calcium, glucagon, and vasopressors often fail to improve hemodynamic status in severe calcium channel blockers toxicity. ⁽⁵⁾ Plasmapheresis can be effective in restoring hemodynamic stability in severe calcium channel blockers toxicity; although the evidence available is only from few case reports but knowing that amlodipine is highly protein bound that recommend its use in patients with calcium channel blockers toxicity that is not responsive to traditional therapies.

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