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Case Report

Cardiogenic Shock secondary to Amlodipine overdose rescued by VA ECMO

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Abstract: - Ingestion of amlodipine beyond the recommended dose can have adverse effects including refractory symptomatic bradycardia, hypotension, shock, pulmonary edema, and circulatory collapse. Management of amlodipine toxicity is challenging but primarily involves supportive management with intravenous fluid hydration, vasopressor support, calcium chloride and insulin infusion. However, in the past few years' cases extracorporeal membrane oxygenation (ECMO) has been successfully utilized as a rescue therapy for acute amlodipine overdose when all conventional treatment measures have failed. Veno-arterial ECMO allows for gaseous exchange, hemodynamic support, and vital organ perfusion until hemodynamically stability is achieved. Here we report a case of a 62-year-old male with 800 mg amlodipine toxicity presenting with refractory hypotension, bradycardia, and severe metabolic acidosis that was successfully managed and rescued with veno-arterial extracorporeal membrane oxygenation (VA-ECMO). With this case we would like to emphasize on utilizing ECMO as a viable option to provide relatively safe, and lifesaving therapeutic option for individuals with refractory shock in lethal drug poisoning

Keywords: Cardiogenic Shock, Amlodipine, overdose

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Introduction

Calcium channel antagonists (non-dihydropyridines and dihydropyridines) are one of the most common drugs used to treat a wide variety of cardiovascular diseases including but not limited to systemic hypertension, cardiac arrhythmias, angina pectoris, Raynaud's syndrome, migraines, and prevention of cerebral vasospasm. Dihydropyridines such as amlodipine, nifedipine, nicardipine, lacidipine, isradipine, nisoldipine, felodipine, block L type calcium channel blockers in vascular smooth muscle cells, making them potent vasodilators and has minimal effect on myocardial contractility at treatment doses. Whereas the non-dihydropyridines such as Verapimil and Diltiazem selectively block L type calcium channels in the myocardium, making them stronger agents affecting cardiac inotropy and cardiac conduction system and weaker vasodilators. However, at higher than standard doses, both dihydropyridines and non-dihydropyridines can have its effects on vasculature, cardiac inotropy, and the conducting system. Of these calcium channel antagonists, dihydropyridines, especially amlodipine is the most prescribed drug for treatment of hypertension. Like any other drug, ingestion of amlodipine beyond the recommended dosage can have adverse effects and untoward toxicities including bradycardia, profound hypotension, circulatory shock, cardiac arrest, pulmonary edema, hyperglycemia, sudden cardiovascular collapse, bowel ischemia and metabolic acidosis. According to the American Association of Poison Control Centers in 2011, 11,764 cases of calcium channel blockers (CCBs) overdoses were reported [1]. CCBs are associated with 48% of deaths related to cardiovascular drug exposure [2]. Amlodipine overdose can be lethal in higher doses that may result in profound hypotension leading to tissue hypoperfusion, metabolic acidosis and end organ damage. Standard treatment modalities for amlodipine overdose consist of intravenous fluid resuscitation, gut decontamination, administration of calcium gluconate, high dose insulin, dextrose and supportive care. In severe cases of persistent hypotension and bradycardia, traditional vasopressors, inotropes and cardiac pacing can be initiated for cardiovascular support. However, cases of refractory hypotension associated with amlodipine toxicity can be very challenging to treat. Limited case studies have been reported utilizing extracorporeal membrane oxygenation (ECMO) in cases of refractory hypotension due to CCB overdose. Here we report a case of a 60-year-old male with amlodipine toxicity that was successfully managed with VA-ECMO after conventional medical therapy failed.

Case presentation

A 62-year-old man, with a history of hypertension, hyperlipidemia and schizophrenia presented to the emergency room 8 hours after ingesting 80 tablets of 10 milligrams amlodipine as a suicidal attempt. Initial vital signs upon presentation were stable with a blood pressure 119/81 mmHg, heart rate 61 beats per minutes. On physical exam patient was alert, awake, oriented to self, place and date. Initial laboratory work showed worsening kidney function with hyperkalemia (6.7 mEq/L), bicarbonate levels (18 mEq/L), and an elevated creatinine (2.8 mg/dL). Chest X Ray was negative for any infiltrates and vascular congestion. EKG showed junctional rhythm with ventricular rate of 75, normal intervals, no ST segment changes.

While waiting for additional labs, the patient became acutely hypotensive with blood pressure 60/33 mmHg. Patient was started on IV fluids, vasopressors, and calcium gluconate 2 g injection however patient neurological status continued to worsen thereby necessitating mechanical ventilation for airway protection. CT head was negative for any intracranial pathology. Patient was then admitted to the intensive care unit for further management.

Upon admission to ICU, the patient was started on an insulin drip at 1 unit/kg, along with dextrose 10% infusion. Patient continued to remain hypotensive and hence was given additional calcium gluconate 2 g in three doses 15 minutes apart followed by calcium drip at 20 mg/kg/hour. A trial of glucagon 5 mg twice did not show any response; hence a drip was not initiated. During the course patient's vasopressor requirements continue to increase incrementally to maximum doses of norepinephrine, vasopressin, dobutamine, and epinephrine in a span of a few hours. Repeat laboratory work revealed worsening metabolic acidosis (ph 7.06) kidney function, and lactic acidosis. Patient was then started on Bicarbonate drip 150 mEq/L at 150 ml/hr. Despite aggressive fluid resuscitation, the patient had minimal urine output and at that time continuous renal replacement therapy (CRRT) was initiated 22 hours after toxic ingestion. Insulin drip was titrated up to 300 units/hour to maintain euglycemic hyperinsulinemia, and

Calcium gluconate drip increased to 30 milligrams/hours/kg to maintain ionized calcium above 4 mg/dL. Patient was being monitored by fingerstick every 1 hours, with basal metabolic profile, lactic acid, arterial blood gas, EKG and ionized calcium every 4 hours.

Despite all above measures, the patient continued to deteriorate, requiring the addition of neo synephrine for blood pressure support. Cardiology team was consulted for device support, and a shared decision was made for VA ECMO placement. Patient was then cannulated 29 hours after toxic ingestion. Cannulation was complicated by moderate blood loss requiring 2 packed red blood cell transfusion. 12 hours after ECMO initiation the patient was only on low dose norepinephrine and dobutamine. Metabolic acidosis resolved and lactic acid normalized. During the course patient developed refractory hypoglycemic events despite on dextrose 10% and decreasing insulin infusion thus prompting discontinuation of insulin drip. Bicarbonate infusion was discontinued 48 hours after toxic ingestion, vasopressor support and calcium infusion at 72 hours post ingestion. Kidney function and urine output improved thus CRRT was stopped on day 4. Patient was then decannulated off of VA-ECMO in OR on day 5, extubated successfully on day 6, and transferred out of the intensive care unit on day 7. During his ICU stay, he developed acute bilateral lower extremity DVT for which he was started on heparin drip and subsequently transitioned to apixaban 5 mg twice a day.

Discussion

Although asymptomatic on presentation, patients with calcium channel blocker overdose can deteriorate rapidly and can lead to significant morbidity and mortality. Amlodipine, dihydropyridine calcium channel blockers that has half-life of 30-50 hours. They are predominantly protein bound and hence have a large volume of distribution (~ 21 L/kg) and are metabolized by the liver [3]. Amlodipine is smooth muscle selective that causes vasodilation at therapeutic doses however at higher doses or in toxic levels, it can lead to myocardial depression and impair cardiac conduction by blocking the sodium channels and causing QT prolongation [4]. Additionally, in toxic concentrations amlodipine can also block L type calcium channels in the beta cells of pancreas resulting in reduced insulin secretion, hyperglycemia and insulin resistance [4]. Noncardiogenic pulmonary edema may also be evident due to precapillary vasodilation [5]. In most cases, renal failure may also occur which is predominantly due to hypoperfusion, resulting in metabolic acidosis, decreased insulin secretion and insulin resistance [5]. At higher concentrations of amlodipine, the pharmacokinetics changes from first order elimination to zero order clearance by the liver, hence resulting in changes in metabolism, which makes it difficult to manage these patients due to the unpredictability of drug clearance [12].

Management and treatment of calcium channel antagonists overdose include supportive care that include airway management, fluid resuscitation and circulatory support via vasopressors and inotropes. Administration of activated charcoal in a dose of 1 gm/kg within 1-2 hours of ingestion can produce beneficial results [3]. There is limited evidence to suggest the use of gastrointestinal decontamination with activated charcoal or whole bowel irrigation with polyethylene glycol in altering clinical outcome in CCBs overdose. However, it is still advocated due to the potentially lethal nature of CCBs overdose and the availability of a specific antidote [6]. Activated charcoal is encouraged if presented early on and might require multiple doses in the setting of a sustained-release preparation [7]. Data has shown that there is decreased efficacy of using activated charcoal as the time from ingestion increases [3]. In our case, the patient presented 6-8 hours post ingestion and hence activated charcoal was not used as a means for decontamination. Beyond initial therapies there is no set algorithm for management of amlodipine or CCBs toxicity.

In cases with persistent hypotension, intravenous vasopressors are administered to maintain a mean arterial pressure of 65 and above (MAP > 65). Intravenous calcium, preferably calcium chloride is also recommended to increase calcium entry into cells and counteract the negative inotropic effects of calcium channel blockers [3]. However, not all patients receiving intravenous calcium respond and the benefit may be temporary [4]. Glucagon is the mainstay treatment modality for beta-blocker overdose however few cases of CCBs overdose implementing glucagon have shown to improve hemodynamics [3]. Hyperinsulinemia euglycemic treatment (HIET) (1unit/kg of regular insulin with 0.5 g/kg dextrose drip) for CCBs overdose was first reported in 1999. HIET showed improvement in circulatory shock in patients with CCBs overdose who had failed initial medical therapy [3]. HIET has been shown to improve cardiovascular parameters and decreasing vasopressor support by increasing smooth muscle contractility by increased carbohydrate uptake and decreasing myocardial free fatty acid extraction [3]. The use of lipid emulsions in concomitance with HIET in

CCBs overdose have recently been shown to improve hemodynamic support [3]. Lipid emulsions provide free fatty acid for HIET therapy and sequester lipophilic CCBs molecules [3]. Recent studies have also coined using methylene blue as a novel approach for management of refractory CCB overdose [3]. Methylene blue reduces vasodilation by decreasing intracellular cyclic guanosine monophosphate (cGMP) and inhibiting nitric oxide synthesis [3].

Some studies had implemented continuous veno venous hemofiltration (CVVH) for CCBs overdose that was refractory to vasopressor support [8]. However, hemofiltration might not be of any benefit as CCBs are predominantly protein bound that are not filtered via CVVH and require a large volume of distribution [2]. In our patient, CVVH was initiated due to acute renal failure and refractory metabolic acidosis.

The use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) as a last line of therapy for refractory hypotension has also been reported. VA-ECMO allows for gaseous exchange and hemodynamic support in individuals presenting with shock in CCBs toxicity. The principle of ECMO in medication toxicity is to support hemodynamics and vital organ perfusion until the medications have been eliminated from the system [11]. Faruqi et al reported a case of amlodipine overdose that was successfully managed via VA-ECMO after multiple medical therapies failed [9]. Few other case reports have also demonstrated successful outcomes with ECMO on patients with antihypertensives toxicity [10-11].

Based on our case and the limited literature available, VA-ECMO should be implemented as a last resort to provide efficient and a relatively safe, efficient and life saving therapeutic option for individuals with refractory shock in lethal drug poisoning when all conventional therapies have failed [10]. However, there are not enough studies to develop criteria for responsiveness to ECMO in patients with drug toxicity who have failed conventional therapies and at this point initiation of ECMO in severe refractory circulatory shock due to drug toxicity is reviewed on a case by case basis based on observational studies [13]. Our case here emphasizes and highlights the potential importance of early initiation of VA-ECMO in severe refractory circulatory shock due to amlodipine and or any other drug toxicity.

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The authors confirm that the data supporting the findings of this study are available within the article.

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