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Case Report

CALCIUM CHANNEL BLOCKER (AMLODEPINE) POISIONING MANAGED BY HYPERINSULINEMIC EUGLYCEMIC THERAPY--A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Amlodepine poisioning is rare. Amlodepine toxicity presents as hypotension, pulmonary oedema both cardiogenic and non-cardiogenic. Standard approaches to the management of calcium channel blocker overdoses, including fluid resuscitation, gut decontamination, administration of calcium, as well as supportive care, are often ineffective. pWe report a case of amlodepine poisioning with acute respiratory distress syndrome, successfully managed with hyperinsulinemic eugycemia therapy (HIE).

Key Words: *Amlodepine Poisioning, Acute Respiratory Distress Syndrome, Hyperinsulinemic Eugycemia Therapy*

INTRODUCTION

Calcium channel blockers are widely used in the management of diverse cardiovascular conditions, including hypertension, arrhythmias, and angina. Calcium channel blockers (CCB) are the leading cause of overdose death among all cardiovascular medicines. Clinical toxicity of calcium channel blockers usually begins within 30-60 minutes of ingestion of an overdose of 5-10 times the therapeutic dose (Bruce DA *et al.*, 1998). Amlodipine is a newer dihydropyridine CCB with half-life of 30-58 hours, several times longer than other CCB.

Complications like hypotension, pulmonary oedema both cardiogenic and non-cardiogenic, are responsible for major morbidity. Pulmonary oedema, may be noncardiogenic, often occurs as a complication of an overdose of calcium channel blocker and may require treatment with diuretics or even mechanical ventilation.

Central nervous system effects like drowsiness, confusion, and seizures are rare. However, toxicity associated with overdose may produce serious, life-threatening complications, including bradycardia, hypotension, metabolic acidosis, and shock. In 2004, 10,513 cases of CCA toxicity were reported in the United States, resulting in 62 deaths (Watson *et al.*, 2005).

Standard approach to the management of CCB overdose consists of intravenous fluid resuscitation, gut decontamination, administration of calcium, glucagon, and atropine, and supportive care. In severe cases, the development of bradycardia and hypotension may require placement of a temporary pacemaker and administration of vasopressors and inotropes. In many cases, however, the shock is refractory to inotropes and vasopressors, leading to cardiovascular collapse and death. Interestingly, recent case reports have described novel, successful management of CCA toxicity with euglycemic insulin therapy. We present our experience with a case of amlodepine poisioning with acute respiratory distress syndrome, successfully managed with high-dose hyperinsulinemia-euglycemia (HIE therapy).

CASE

A 23 years female married, lost her husband a year back, was brought with history suicidal ingestion of 30 tablets of Amlodipine 5 mg (150-mg). There was no history of chest pain, palpitation, dyspnoea, cough, loss of consciousness or convulsions. On examination patient was restless, no pallor, ictreus, cyanosis was present. Her pulse rate was 110 beats/min, regular. Blood pressure recorded was 110/80 mm of Hg on admission (supine), respiratory rate was 28cycle /minute and JVP was normal. Systemic examination was unremarkable. ECG showed sinus tachycardia. Chest X-ray PA was normal. Oxygen

saturation was 99% on room air. Investigations revealed Anemia (7.8 d/dl), counts of 14,000/cmm with 68 % neutrophils and raised ESR (80 mm/hr). Her liver function tests, renal functions, calcium and phosphorus were normal. Gastric lavage was given along with activated charcoal. IV fluids was started and patient was admitted in medical ICU . After 6 hours patient developed hypotension and Inj.dopamine was started and titrated according systolic BP. Her blood pressure was maintained on inotropes. On day 3 of admission patient developed dysnea and examination showed tachycardia and tachypnoea with respiratory rate of 54 cycles/min, normal JVP and respiratory system examination showed bilateral basal crepitations on auscultation. Patient was desaturated even with oxygen inhalation of 6 lit/ min. A diagnosis of acute pulmonary oedema was considered and patient was intubated and shifted to ICU for mechanical ventilation, Inj. Furosemide and broad-spectrum antibiotics were continued. Repeat CXR on day 3 showed acute respiratory distress syndrome like picture, with normal 2D echo. A diagnosis of non-cardiogenic pulmonary oedema was made.

Her Repeat Calcium was 7.6 mg.dl and calcium gluconate 10% , 10 ml bolus and then infusion 2ml/hr was continued. Hyperinsulinemia euglycemia technique therapy was instituted. Intravenous insulin Infusion of 5 IU/hr along with Infusion Inj. 10% dextrose was started and titrated to maintain an appropriate glucose concentration. Within six hours after starting the insulin infusion, her blood pressure increased to 130/80□mmHg, and vasopressor requirements decreased. She was weaned off the norepinephrine within 10 hours after starting the insulin infusion, weaned off the dopamine within 11 hours after starting the insulin infusion. The insulin drip was continued for two days. No significant adverse effects were noted from the insulin therapy, and renal replacement therapy was not required. Calcium infusion was stoped after 36 hrs. She improved gradually over the next 6 days and was extubated on Day 5 of admission. Her repeat chest X-ray PA was and other parameters were normal.

DISCUSSION

Since being introduced almost fifty years ago, CCBs have become one of the most frequently prescribed class of medications. This significant usage has led to increasing reports of toxicity and in 2004, a national survey of poison control centers found 10,513 cases of CCA toxicity with 62 subsequent deaths. (Watson *et al.,* 2005).

Pharmacology of CCB

CCBs can be divided into two major categories: dihydropyridines and nondihydropyridines (Spedding M *et al.,* 1992). Dihydropyridines (amlodipine, felodipine, nicardipine, and nifedipine) block L-type calcium channels, preferentially in the vascular smooth muscle, resulting in smooth muscle relaxation. These drugs have little myocardial depressant activity at therapeutic levels and in fact may increase cardiac output due to the reflex tachycardia Nondihydropyridines (diltiazem and verapamil) block myocardial and smooth muscle L-type calcium channels, leading to myocardial depression and inhibition of electrical activity. However, two important points need to be noted. First, dihydropyridines are smooth muscle selective, not smooth muscle-specific, and in toxic concentrations may lead to myocardial depression and impaired cardiac conduction. Secondly, CCB, especially at high doses, can block sodium channels and can cause QRS prolongation, similar to tricyclic antidepressants (Shiwan *et al.,* 2012).

In addition to actions on the heart and vascular smooth muscle, CCBs often have an effect on the pancreas. Calcium entry into the pancreatic beta cells via L-type calcium channels is essential for insulin release. Thus, CCA toxicity frequently results in hyperglycemia with relative hypoinsulinemia.

Amlodipine is a newer dihydropyridine CCB with half-life of 30-58 hours, several times longer than other CCB. Well-absorbed following oral administration. It is extensively metabolized and metabolites are excreted in the urine. Onset of drug action is gradual.

CCB Toxicity

Patients who overdose on CCBs often present with hypotension and bradycardia. The hypotension results from vasodilation and decreased cardiac output (due to the bradycardia and myocardial depression). The

bradycardia is often secondary to sinus arrest, and patients often have an AV or ventricular escape rhythm. Due to the myocardial depression, patients may present with pulmonary edema.

Electrophysiological effects seen in overdoses of calcium channel blockers include sinus bradycardia, accelerated atrioventricular node conduction, second and third degree heart block, sinus arrest with nodal escape rhythms, and asystole (Kenny *et al.*, 1994).

Non cardiogenic pulmonary odema has associated with CCB overdose (Salej *et al.*, 2011). The proposed explanation can be to include capillary leak syndrome due to prostacyclin inhibition as well as inflammatory cytokine release leading to ARDS-like picture. However popular theory is the selective precapillary dilatation resulting in pulmonary capillary transudation.

Treatment of CCB toxicity

Management of CCB toxicity aims on restoring cardiac function and systemic blood pressure. Supportive care and gastrointestinal decontamination are the standard approaches. In addition specific treatment modalities available for CCB overdose include calcium, glucagon, adrenergic agents, and sodium bicarbonate. When pharmacological measures are ineffective, cardiac pacing and intra-aortic balloon counterpulsation may play important modes of treatment.

Initial treatment consists of securing the airway as many patients with CCB toxicity have an altered mental status. In a hypotensive patient, an intravenous fluid bolus of 1-2 liters is given, especially in the absence of pulmonary edema. If hypotension persists, intravenous inotropes and vasopressors are warranted. Detoxification may include gastric lavage especially when a patient presents within 1-2 hours of ingestion. Other useful detoxification measures include the use of activated charcoal in patients within the first two hours of ingestion. Whole-gut lavage with polyethylene glycol solution may be useful in selected cases of ingestion of sustained release tablets, although adverse outcomes have been reported with this treatment modality, especially in patients who are already hemodynamically unstable or who have ileus (Salhanick *et al.*, 2003).

Intravenous calcium is commonly used in 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. Calcium may be given either as calcium gluconate or calcium chloride. Calcium salts can be given in bolus doses or administered as a continuous infusion (Salhanick *et al.*, 2003). A typical dosing would start with a 0.6mL/kg bolus of calcium gluconate (0.2mL/kg bolus of calcium chloride), followed by a continuous infusion of 0.6–1.5mL/kg/hr of calcium gluconate (0.2–0.5mL/kg/hr of calcium chloride), and the infusion rate titrated to hemodynamic response. Ionized calcium levels should be monitored, with the goal being two times the normal. While calcium salt administration is recommended for treatment of CCB toxicity, significant overdose with cardiovascular instability rarely responds to calcium as a single agent, and other measures are instituted (Shiwan *et al.*, 2012).

Glucagon is another agent which is commonly used, which 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 is due to positive inotropic and chronotropic effects seen in animal studies, but have not been confirmed in human clinical trials (Kerns *et al.*, 2007). The initial glucagon dose is 50–150 microgram/kg given as intravenous bolus or 3 to 10mg in a 70kg patient. The bolus may be repeated every 3–5 minutes to clinical effect, followed by infusions of the effective dose every hour. Main side effects of this therapy are nausea, vomiting, hyperglycemia, and ileus.

Sodium bicarbonate is another potentially useful therapy in treatment of CCB overdose in patients with acidosis, where CCB binding to the L-type calcium channel is increased. Thus, treatment of the acidosis may improve the hemodynamic status. In addition, CCBs, especially in high doses, may also inhibit fast sodium channels, leading to QRS prolongation (Kerns *et al.*, 2007). If the QRS duration is longer than 120 milliseconds, a 1-2mEq/kg bolus of sodium bicarbonate may be given.

In spite of the supportive care alredy mentioned above, many patients often continue to experience clinical deterioration. In the past several years, hyperinsulinemia-euglycemia (HIE) therapy has gained

wider acceptance as part of the treatment for CCB toxicity as described in multiple case reports and animal studies (Engebretsen *et al.,* 2011; Shiwan *et al.,* 2012). CCB toxicity often results in hyperglycemia from decreased insulin production due to the blockage of the L-type calcium channels in the pancreas. Hypoinsulinemia causes impairment of the myocardial energy supply. Usually, the myocardium uses free fatty acids for energy. Whereas, in a patient with shock, 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. HIE therapy may lead to reversal of cardiovascular collapse in CCB toxicity by improving myocardial utilization of carbohydrates. In addition, insulin has direct positive inotropic activity that may contribute to its clinical effects (Kerns II *et al.,* 2007 and Engebretsen *et al.,* 2011)

No randomized controlled trials have yet been performed to evaluate the role of high-dose insulin therapy in human subjects with CCB overdose. Most of the human data for HIE therapy in CCB toxicity is limited to published case reports (Boyer *et al.,* 2001 and Smith *et al.,* 2008). These cases have involved the treatment of overdoses of diltiazem (9 cases), verapamil (10 cases), and amlodipine CCAs (9 cases). The dosing of the insulin bolus ranged from 0 to 1000IU though only about half of the patients received a bolus, and the maintenance insulin infusion ranged from 0–2.64IU/kg/hr. Current recommendations for the use of insulin therapy in CCB overdose consist of intravenous bolus administration of 1IU/kg followed by an infusion of 0.5IU/kg/hr. The duration of therapy ranged from 6 to 96 hours. In these reports and as well as in our case, hyperinsulinemia therapy resulted in hemodynamic improvement. Some authors have suggested that late onset of hyperinsulinemia-euglycemia is associated with lack of survival, in our patient; improvement was demonstrated up to 48 hours post presentation (Kerns II *et al.,* 2007 and Cumpston *et al.,* 2002).

Hypoglycemia and hypokalemia are the main adverse effects of HIE therapy; therefore, serum glucose and electrolytes should be closely monitored. As suggested by Boyer, it is reasonable to administer 25 grams of glucose (1 ampule of D50) prior to initiation of HIE therapy if the blood glucose is less than 200mg/dL, and similarly, to administer 40mEq of potassium chloride intravenously if the potassium level is less than 2.5meq/L (Shiwan *et al.,* 2012).

Although no definitive guidelines regarding HIE therapy in human CCA overdose have been published, there is enough empirical evidence to warrant strong consideration of this therapy for treatment of CCA overdose. More research is warranted to answer questions such as which patient populations would benefit most from this treatment, at what point in the treatment timeline should this therapy be instituted, and what are the optimal doses.

CONCLUSION

CCB overdose, whether intentional or accidental, can be lethal. Due to a long elimination half-life and delayed onset of effects, patients with amlodipine overdose should receive aggressive decontamination therapy and may require extended clinical monitoring and supportive care if they are hemodynamically unstable. . Hyperinsulinemia-euglycemia therapy should be considered in cases of of CCB toxicity in order to improve cardiac contractility and hemodynamics. Close monitoring of serum glucose and electrolytes is advised to prevent potential adverse effects.

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