LEVOSIMENDAN AS A RESCUE ADJUNCT IN AMLODIPINE INTOXICATION

– A Case Report –

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Introduction

Calcium channel blockers (CCB) are the cardiovascular medicines most commonly associated with overdose death[1]. Amlodipine, a dihydropyridine CCB, can cause shock at overdose levels. The hemodynamic shock is likely caused by calcium channel blockade in myocardial smooth muscle and beta cells. This blockade leads to peripheral vasodilatation, hyperglycemia, hypoinsulinemia, metabolic acidosis and shock[2]. Here we describe the use of levosimendan, a calcium sensitizing agent, to treat a 16-year old woman who ingested 500 mg of amlodipine and failed to respond to conventional therapies including calcium salts, inotrope infusions and hyperinsulinemia-euglycemia therapy.

Case Report

A 16-year old woman with no past medical history or psychiatric disorders was admitted to the intensive care unit of Private Hospital (Istanbul, Turkey) approximately 15 hours after attempting suicide by ingesting 50 tablets of amlodipine 10 mg (500 mg total). She was a student living with her family and denied tobacco and alcohol use. She had no known allergies and took no regular medications.

She received gastric lavage and activated charcoal in the emergency department four hours after ingestion. She was admitted to the intensive care unit with a blood pressure of 75/34 mm Hg and a pulse of 125 bpm. She received intravenous crystalloid, intravenous dopamine 10 µg·kg-1·min-1, and intravenous insulin 0.5 U·kg-1·h-1. Chest x-ray revealed pulmonary infiltration suggestive of pulmonary edema. During her seven-hour intensive care unit stay, she had received 2700 mL of crystalloids, but her urine output was only 50 mL. Her blood glucose was normal at each hourly check. For financial and logistics reasons, she was then transferred to the anesthesia intensive care unit of our hospital.

Upon transfer, the patient was awake and conversant, with a Glascow Coma Scale (GCS) score of 15. Her blood pressure was 87/36 mm Hg, heart rate was 112 bpm, temperature was 36.0ºC, and oxygen saturation was 99% on oxygen 4 L/min by face mask. Her pupils were equal, round and reactive to light. Her neurological, cardiovascular and gastrointestinal systems were unremarkable. Laboratory tests disclosed the following values: sodium, 137 mmol/L (normal range 136-142);

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potassium, 4.71 mmol/L (3.5-5.0); total calcium, 2.43 mmol/L (2.05-2.55) [9.7 mg/dL (8.2-10.2)]; ALT, 41 UL (10-14); AST, 40 (20-48). Her renal function values and other liver function values were normal. An electrocardiogram showed sinus tachycardia. Arterial blood gas analyses showed a mild metabolic alkalosis. Plasma amlodipine level was not measured.

Hyperinsulinemia-euglycemia (HIE) therapy was provided with increasing rates of dopamine 10 µg·kg-1·min-1 and norepinephrine 0.2 µg·kg-1·min-1 delivery. Calcium chloride 10 g in serum saline over 3 hours was also given with the HIE therapy. On day three, the patient developed shortness of breath and subsequent respiratory arrest. Endotracheal intubation and mechanical ventilation were performed. A repeat chest x-ray showed uniform, diffuse pulmonary infiltrates with a normal-appearing heart. Continious ventilatory support and diuretic therapy for one day were successful in resolving the pulmonary infiltrates, metabolic alkalosis and fever.

On the same day, the patient developed a leucocytosis of 28 cells/mL. Tracheal aspirates were pink and foamy, suggesting pulmonary edema. An echocardiogram revealed normal left ventricular function, minimal aortic insufficiency, and mild mitral insufficiency, making a cardiogenic cause for pulmonary edema unlikely. The ejection fraction was 50% and cardiac enzymes were within normal ranges. A subclavian catheter was inserted on the same day and her central venous pressure (CVP) was 21 mm Hg. Because the patient did not respond to initial treatment, she underwent plasma exchange to clear the amlodipine from her circulation. Dopamine 20 µg·kg-1·min-1 and norepinephrine 15 µg·kg-1·min-1 were administered for hemodynamic support.

On day four, she received levosimendan 12 µg·kg-1·min-1 for 10 min as a loading dose, then levosimendan 0.1 µg·kg-1·min-1 for 12 hours, then levosimendan 0.2 µg·kg-1·min-1 for 12 hours. The patient responded to levosimendan therapy (blood pressure and heart rate returned to normal levels) and inotropes were decreased. On day five, inotropes were stopped, and the patient was succesfully weaned from the ventilator on day six. She was transferred to the Internal Medicine ward after psychiatric consultation.

Discussion

In treating this patient, we searched the published literature and found that HIE therapy is the generally recommended treatment for CCB toxicity in the critical care setting[6-12]. Supportive care including the use of phosphodiesterase inhibitors, adrenergic agents, cardiac pacing, balloon pump or extracorporeal bypass is indicated if antidotal thearpy is ineffective[17-19]. Because our patient did not respond to HIE therapy and supportive treatment, we searched for alternative treatement strategies.

A study by Buckley et al.[20] discussed the use of calcium to overcome amlodipine's competitive blockade of calcium channels in the cardiac conducting system. The degree of hypercalcemia required to overcome blockade depends on the degree of CCB intoxication and the body's response[20]. Buckley et al.[20] recommend administering one gram of calcium salts every two to three minutes until the cardiac block is reversed on electrocardiogram. In their experience, patients who were refractory to calcium therapy were refractory to other treatments as well[20,21].

Our patient received 14 g of calcium chloride, with a resultant serum calcium level of 15 mg/dL (3.75 mmol/L). However, we found no obvious response to this calcium therapy. Because CCBs are highly protein-bound, extensively distributed in tissues, and rapidly metabolized by the liver to inactive metabolites[22], hemofiltration and dialysis are ineffective in the management of overdose. One case report by Ezidiegwu at al.[23] described successful treatment of amlodipine overdose with plasma exchange after non-responsiveness to conventional therapy. However, plasma exchange had no effect in our patient.

After four days of treatment, our patient remained in shock with no evidence of improvement. We decided to use levosimendan, a calcium-sensitizing agent indicated for use in patients with acutely decompensated heart failure[26]. Levosimendan sensitizes contractile proteins to calcium by interacting with troponin in cardiac muscle, which prolongs troponin's effect on contractile proteins[26]. Levosimendan also vasodilates via ATP-dependent potassium channels[27]. We used the intravenous levosimendan loading dose and infusion rates that are approved for the short-term treatment of acute severe decompensated heart failure[26,28], and

observed blood pressure effects soon after initiating treatment.

Conclusion

To the best of our knowledge, this is the first report of using levosimendan to treat amlodipine intoxication. In our opinion, levosimendan can be used as a rescue adjunct in paitents with CCB overdoses who fail to respond to conventional therapies such as calcium salts, inotropes, and hyperinsulinemia-euglycemia therapy. Given the long half-life of CCB agents, levosimendan may be a useful alternative to invasive therapies like intra-aortic balloon pump in CCB overdoses[17]. Further clinical research is needed to support the current findings opinion and evaluate the role of levosimendan in calcium channel blocker intoxication.

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