



Case Report

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Non-cardiogenic pleural effusion after amlodipine intoxication and hyperinsulinemic therapy

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Abstract

We report a patient with amlodipine intoxication who presented to hospital 30 hours after suicidal intake of the drug. Admitted to the intensive care unit, the patient had profound hypotension and need for fluid replacement and infusion of dopamine and noradrenaline. The patient was also administered insulin and calcium gluconate. In addition to profound hypotension, massive non-cardiogenic pleural effusion also complicated the clinical picture. Bilateral pleurocans were placed and non-invasive ventilation was administered in continuous positive airway pressure (CPAP) mode. Hyperinsulinemic euglycemic therapy was also applied. Following the onset of insulin therapy mean blood pressure increased and need for vasopressors was reduced. Possible positive inotropic action of insulin therapy in this patient suffering calcium channel blocker intoxication is in accordance with previous reports. It has been suggested that hyperinsulinemic euglycemic therapy may be considered as a first-line therapy in amlodipine intoxication.

Keywords: Amlodipine, hyperinsulinemia, pleural effusion

Introduction

Amlodipine is a dihydropyridine calcium channel blocking agent used in the treatment of essential hypertension and angina pectoris. It is a drug with a long serum half-life that, following ingestion and absorption, is highly protein-bound, and that forestalls the entry of extracellular calcium into the cardiac and smooth muscle cells through voltage-dependent L-type calcium channel inhibition [1], by that means inhibiting intracellular electric conduction leading to impairment of myocardial function and marked vasodilation accompanied with systemic hypotension and metabolic acidosis [2]. Literature reports have shown that, while a maximum oral amlodipine dose of 1000 mg can produce signs of intoxication, even 50 mg drug was associated with a plasma concentration of 88 µg/L, exceeding the reported therapeutic plasma level of 5-18 µg/L. Herein, we aimed to report a case of non-cardiogenic massive pleural effusion following 300 mg amlodipine intake, which dramatically responded to hyperinsulinemic euglycemic therapy.

Case Report

A 23-year-old woman was admitted to our intensive care unit with nausea, vomiting, and headache 30 hours after suicidal amlodipine intake at a dose of 300 mg.

She had no known illnesses or history of psychiatric disorders. She was living with her family. She was not

married. She had no history of smoking or alcohol intake alcohol. She also had no known drug allergy or regular medication use.

On physical examination she was conscious and had a Glasgow coma score of 15; she had tachypnea (>40 breaths/minute), tachycardia (140 bpm), and hypotension (80/35 mmHg); her oxygen saturation was 95% and body temperature was 36°C. Her pupillae were isochoric and bilateral light reflexes were positive. Respiratory sounds were inaudible in lower zones bilaterally. Her heart rate was regular, with no murmurs. She had no cyanosis but had edema in both upper and lower extremities. The electrocardiogram showed sinus tachycardia at 140 beats/min. There were no conduction abnormalities or rhythm disorders. Gastrointestinal decontamination was not performed. Arterial blood gas analysis revealed the following: pH: 7.39 pCO₂: 25.6 pO₂: 54.6 SpO₂: 82.3% lactate: 1.9 HCO₃: 15.4 base excess: -6.8 mmol/L. Plasma amlodipine was not measured. A central venous catheter was placed in the right subclavian vein for central venous pressure monitoring and a catheter was placed in the right radial artery for blood pressure monitoring.

Central venous pressure was measured 1-2 mmHg. She received 5000 ml isotonic fluid via central catheter within 4 hours. Her blood pressure decreased despite aggressive volume replacement. Calcium gluconate 10 mL of 10% solution was administered intravenously over 10 minute and repeated every 15 minutes for a total of four doses, followed by an intravenous infusion at a rate of 5 mL/h. It was aimed to keep serum calcium level between 1.2-1.95 mmol/L without causing a side effect. Dopamine was started at 10 µg/kg/min and its dose was

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increased since the patient remained hypotensive. She had bilateral pleural effusion in chest X-Ray (Figure 1).

Figure1.



She was consulted by cardiology department and found to have an ejection fraction of 60%, non-cardiogenic bilateral pleural effusions, and no attendant cardiomegaly. A thoracic computerized tomography confirmed bilateral pleural effusions and, additionally, bilateral atelectatic areas in lungs, with left sided involvement being more prominent. Despite removal of a total of 1500 cc pleural fluid from both sides by means of pleurocans, the patient remained tachypneic with an oxygen saturation of 68%. Therefore, non-invasive ventilation was intermittently applied by continuous positive airway pressure (CPAP) for 3 days. Dopamine infusion (20 µg/kg/min) did not succeed in increasing blood pressure, and norepinephrine infusion (10 µg/kg/min) was also administered. Despite dual vasopressor treatment and I.V. hydration, a decent blood pressure could not be attained; hence, dextrose-insulin infusion was started. She received 10 IU insulin IV bolus followed by an continuous infusion of 10 IU insulin in 100 mL 25 % dextrose over 2-4 hours with careful laboratory monitoring to avoid hypoglycemia and hypokalemia. Approximately 3 hours after the onset of dextrose-insulin therapy, mean arterial blood pressure increased to 110–120 mm Hg and heart rate normalized. The patient was soft weaned from pressors 3 hours after insulin therapy. After inotropes and dextrose-insulin infusion, urine output increased to 100 mL/hr. although it was only 30 ml/hr. at admission. Insulin infusion also normalized lactate elevation and increased base excess in blood gas analysis (Table 1). Insulin was stopped when arterial blood pressure was stabilized 30 hours after insulin infusion. The patient was transferred to psychiatry department for psychiatric treatment 5 days later.

Table 1. Serial arterial blood gas analyses

	In emergency department	2 nd day	3 rd day	4 th day	5 th day
pH	7.39	7.36	7.38	7.42	7.45
pCO ₂	25.6	25.7	30.6	28.9	30.3
pO ₂	54.6	39.5	68.3	61	83.6
SpO ₂ %	82.3	67.2	90.2	87.6	95.5
Lactate	1.9	2.8	2.4	1.3	1.1
HCO ₃	15.4	14.4	17.8	18.7	23.4
Base excess	-8.5	-10	-6.3	-4.8	-1.2
Administered therapies		CPAP Hyperinsulinemic therapy			euglycemic

Discussion

In this case report we aimed to report a case of bilateral non-cardiogenic pulmonary edema requiring respiratory support due to amlodipine intoxication. We also reported an improvement in hemodynamic status and acidosis by dextrose-insulin therapy after failure of I.V. hydration, calcium, and dual vasopressor therapy.

Unlike other calcium channel blockers, amlodipine binds to proteins at high doses and thus has a substantially lower metabolic clearance and a longer plasma half-life (35-65 hours) [1,3]. Our patient presented to hospital with nausea and vomiting approximately 30 hours after the intake of 300 mg amlodipine. At admission she had a pulse rate of 40 bpm and a blood pressure of 58/38 mmHg. This suggested that the drug was absorbed through gastrointestinal system and had a prolonged clearance, producing ongoing signs and symptoms. As she presented late in the course and no clinical signs were observed, we did not perform gastrointestinal decontamination since it was reported that whole bowel irrigation is not effective beyond 24 hours after CCB overdose [4].

Despite I.V. hydration, calcium, and vasopressor support, our patient suffered non-cardiogenic pleural effusion requiring mechanical ventilator assistance and resistant hypotension without any attendant cardiac conduction defect. Amlodipine prevents calcium entry into vascular smooth muscle cells and myocytes by inhibiting voltage-dependent L type Ca²⁺ channels. Hypodynamic shock caused by amlodipine is characterized by peripheral vasodilatation, hyperglycemia, hypoinsulinemia, metabolic acidosis, and it is a result of calcium channel blockade by amlodipine in myocytes, smooth muscle cells, and pancreatic beta cells. Normally, myocytes and smooth muscle cells oxidize free fatty acids for energy metabolism. However, they use glucose for energy in the state of shock, and this pathway is prevented by hypoinsulinemia caused by amlodipine, leading to cardiac mechanical inefficiency, poor tissue perfusion, and acidosis [5]. Amlodipine exerts a weaker effect on cardiac contractility and pacemaker cells while it has more profound effects on vascular smooth muscle cells. Precapillary vasodilatation resulting in excessive pulmonary capillary transudation has been implicated as the aetiology of non-cardiogenic pleural effusion [6]. The above-discussed pathophysiological process completely explains

hypotension, acidosis, peripheral edema, and respiratory failure requiring ventilatory support lasting for days in our patient.

Calcium has variable effects on cardiac conduction, contractility, and hypotension. It has been reported that calcium has no demonstrable action in some cases of CCB overdose while it proved successful in others. The required dose of IV calcium is unclear [7]. Kenny et al. recommended using 10% calcium chloride or 20-30 mL of calcium gluconate for up to four times by monitoring clinical response and serum calcium level [8]. We administered low dose calcium and observed no side effect.

The principle difficulty with amlodipine intoxication is its low metabolic clearance and the resultant prolonged hypotension owing to a prolonged half-life. We administered vasopressors in suitable doses [9] but could not obtain desired blood pressure response. We therefore started hyperinsulinemic euglycemic therapy and observed a stabilized blood pressure, increased urine output, and improved acidosis thereafter. To date, many studies have reported supportive data for hyperinsulinemic euglycemic therapy as a first step treatment for CCB overdose [10]. CCBs antagonize pancreatic L type calcium channels and limit insulin secretion, leading to a hyperglycemic clinical state in which cells cannot utilize glucose for energy metabolism. Insulin increases plasma level of ionized calcium, corrects hyperglycemic acidotic medium, improves carbohydrate use by myocardial cells, and produces an indirect inotropic action [7]. In addition to treatment of CCB intoxication, insulin has also been reported to reduce rates of complication and death in critical patients without CCB intoxication [11].

Former studies have reported the use of therapeutic plasma exchange and intravenous lipid emulsion (ILE) therapy in addition to intravenous fluid, vasopressors, and insulin infusion in CCB overdose. Ezidiegwu et al. showed that total plasma exchange therapy was life-saving by clearing toxins from circulation even 36 hours after amlodipine intake [2]. Meaney et al. [12] showed that ILE therapy was effective in CCB overdose unresponsive to multiple vasopressor support.

In conclusion, management of amlodipine intoxication is still difficult, and conventional therapies may fail in many cases. Hyperinsulinemic euglycemia therapy can be considered either as a first-line therapy or when conventional measures fail to correct hemodynamic instability.

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