CASE REPORT

Successful Treatment with Integrated Chinese and Western Medicine for Severe Overdose of Amlodipine: A Case Report

LAI Fang (赖 芳), ZHANG Yan (张 燕), XIE Dong-ping (谢东平), LI Fang (李 芳), and HAN Yun (韩 云)

Introduction

Amlodipine is a dihydropyridine calcium channel blocker (CCB) that inhibits calcium influx into cardiac, vascular smooth muscle cells, and pancreatic beta cells, leading to dilation of arteries and arterioles and reduction in insulin secretion. Oral administration of amlodipine is absorbed slowly but almost completely, with a high oral bioavailability up to 60%–80%. It has a large volume of distribution (21 L/kg) and a long elimination phase ($t_{1/2}$ 35–48 h).[1-3] Severe amlodipine poisoning can lead to potential life-threatening complications such as profound hypotension, acute renal failure, noncardiogenic pulmonary edema, metabolic acidosis, and even cardiac arrest. As per the literature, in severe overdose cases of amlodipine, the taken doses ranged from 50 to 1,000 mg, with plasma concentrations of 67–393 ng/mL and a minimum lethal dose of 70 mg. However, there were cases where the overdose of amlodipine did not always lead to severe symptoms.[4-6] Clinical experience of amlodipine intoxication is limited. This report describes a severe case of overdose of amlodipine successfully treated by integrated Chinese and Western medicine.

Case Presentation

A 28-year-old female was found unconscious by her parents in her bedroom, with 4 empty boxes of amlodipine besylate (21 tablets per box at 5 mg each for a total of 420 mg) lying aside. She had a medical history of depression for nearly 10 years and refused to take any regular medications. During the preceding 2 months, she had several previous failed suicide attempts by cutting her wrist and burning charcoal. In this attempted suicide, she regained consciousness several minutes later and was transferred to the emergency department, who allegedly ingested 420 mg of amlodipine besylate tablets. In the emergency department, she was pale with cold clammy extremities, with a heart rate of 133 beats/min and a blood pressure of 86/47 mm Hg. She showed no signs of respiratory distress at that time. No abnormality was detected in her initial liver and renal function tests, arterial blood gas (ABG) levels, electrolytes levels and chest X-ray (CXR) scan, and the results of the initial hemogram was unremarkable. She was given emergency gastric lavage, magnesium sulfate, intravenous volume expansion, a bolus of 5 mg Alamine, and 20 mL of 10% calcium gluconate.

She presented to the intensive care unit (ICU) approximately 4 h after the ingestion of amlodipine. She developed symptoms of respiratory distress, cough with white sputum, dizziness, palpitations, bilateral extremities edema, and oliguria. The respiratory rate increased to 30 breaths/min and the blood pressure remained low around 85/40 mm Hg. The serum calcium level and serum lactate level were 1.92 mmol/L (reference range: 2.08–2.60 mmol/L) and 7.28 mmol/L (reference range: 0.9–2.3 mmol/L), respectively. Results of repeat ABG revealed hypoxia and metabolic acidosis with a pH of 7.229, pCO_2 of 29 mm Hg, pO_2 of 55.3 mm Hg and a BE-ecf of –11.3 mmol/L. White blood cell (WBC) count increased to 15.1×10^9/L, with 83.7% of neutrophils. Results of a repeat CXR scan showed signs of bilateral pulmonary infiltrates without cardiomegaly (Figure 1A and 1B). Echocardiography revealed mild enlargement of the right ventricle with normal left ventricular function. Her Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score was 23. As she was still in shock, became acute shortness of breath, and developed signs of noncardiogenic pulmonary edema and hypoxia, she was commenced on noninvasive ventilation with bi-level positive airway pressure (BiPAP) to maintain good oxygen saturation, restricted fluid administration with central venous pressure (CVP) monitoring, continuous intravenous infusion of norepinephrine with infusion pump, infusions

Intensive Care Unit, Fangcun Branch Hospital, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou (510145), China
Correspondence to: Prof. HAN Yun, Tel: 86-20-81499399, E-mail: hy660960@126.com
DOI: 10.1007/s11655-015-2130-5

of calcium gluconate based on her repeat blood results of serum calcium level (up to 20–80 mL of 10% calcium gluconate every 24 h), and intravenous diuretics as necessary (started at 120 mg over 6 h, which was then increased to 120 mg over 3 h). Her blood pressure remained low despite continuous intravenous infusion of norepinephrine, and she was commenced on dopamine at the same time. She was also given multiple doses of magnesium sulfate and broad spectrum antibiotics.

For the initial treatment of Chinese medicine (CM), the patient recieved acupuncture and hot compress with *Evodia rutaecarpa* on her abdomen to relieve nausea, vomiting and abdominal pain. She was also given Gancao Ludou Fengmi Decoction (甘草绿豆蜂蜜汤) to remove toxic substances, rice soup cooked with *Pericarpium citri reticulatae* to regulate the Spleen (Pi) and Stomach (Wei), and Xiao Poge Jiuxin Decoction (小破格救心汤, XPJD) to warm yang and solid doff as her symptoms indicated deficiency of yang-qi. The XPJD comprised the following Chinese medicinal herbs: predecocting *Radix Aconiti lateralis* 15 g, *Rhizoma Zingiberis* 15 g, *Radix Glycyrrhizae Preparata* 30 g, *Fructus Corni* 15 g, predecocting *Os Draconis* 30 g, *Rhizoma Pinelliae Praeparatum* 15 g, predecocting *Magnet* 30 g, *Ramulus Cinnamomi* 15 g, and predecocting *Concha Ostreae* 30 g. After taking two decoctions, the patient's symptoms of dizziness, cold, and clammy were relieved. But she still had complaints of palpitation, shortness of breath, and bilateral pedal edema, which indicated deficiency of yang-qi and stagnancy of dampness. Hence *Rhizoma Alismatis Orientalitis* 15 g and of *Poria Peels* 30 g were added into the decoction for the next 3 days to eliminate dampness.

On day 5, the patient showed gradual improvement in her clinical condition allowing gradual discontinuation of vasopressors and ventilator support. Results of repeat bedside CXR scans showed gradual improvement in the pulmonary infiltrates (Figures 1C and 1D). She received Dushen Decoction (独参汤) to tonify yang-qi as she still had symptoms of fatigue and spontaneous perspiration. On day 8, hemodynamic stability of the patient improved and the result of the CXR scan showed nearly complete clearance (Figures 1E and 1F). Results of repeat serum calcium level, serum lactate level, ABG, and hemogram were normal. Vasopressors were stopped. Calcium infusions were tapered off. She was successfully weaned off from the ventilator on the following day. Her condition continued to improve clinically and she was discharged on day 12 of admission after a psychiatric consultation without long-term complications.

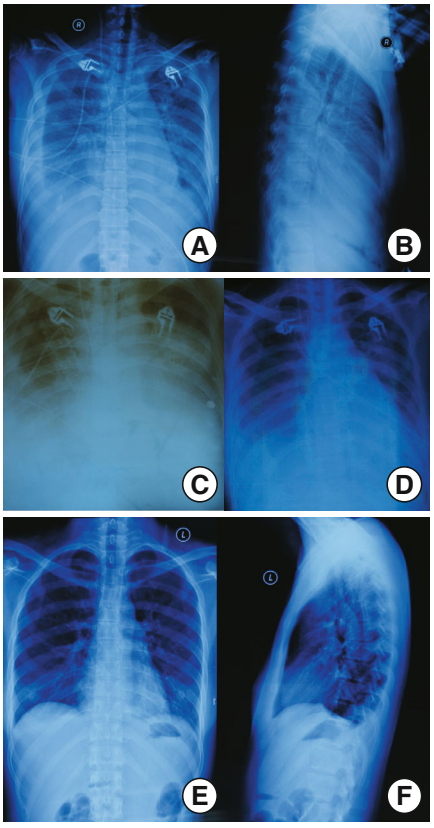

Figure 1. Paient's CXR Scans during the Treatment

Note: A, B: on day 2, CXR scan showed signs of bilateral pulmonary infiltrates without cardiomegaly; C,D: on day 5 and 6, CXR scan showed gradual improvement in the pulmonary infiltrates; E, F: on day 8, CXR scan showed nearly complete clearance

Discussion

Amlodipine is absorbed slowly, with peak plasma concentrations observed after 6 to 9 h. The mean peak plasma concentration of amlodipine is correlated with the ingested dose.[7] But the severity of symptom is not necessarily correlated with the plasma concentration, as it is described in the literature.[4,5] Some of the previously reported cases in which amlodipine in plasma was quantitatively determined are summarized in Table 1.

In case 3, the patient's peak serum concentration of amlodipine was 20–30 times higher than the peak serum concentration after single intake of 10 mg amlodipine, however, no severe symptom was detected.[5] In case 1, the patient needed no more treatment with catecholamines when the amlodipine plasma concentration was 132 ng/mL, which was still 10-fold higher than the therapeutic (5–18 ng/mL) concentration and therefore was still above the assumed

Table 1. Comparison of Cases Involving Amlodipine Overdoses

Case	1[4]	2[13]	3[5]	4[14]	5[15]	6[16]
Age (Year)	42	63	43	37	42	76
Gender	Male	Female	Male	Male	Female	Male
Dose of amlodipine	1000 mg	70 mg	350 mg	6.7 mg/kg	50-100 mg	100 mg
Plasma concentration of amlodipine	393 ng/mL, after 8.5 h	185 ng/mL, after 11 h	Peak concentration 143 ng/mL, after 64.5 h	Peak concentration 130 ng/mL, after 12 h	88 ng/mL, after 2.5 h	67 ng/mL, day 1
Other drug involved	Mefenamic acid, chlorthalidone	Oxazepam, 5.5 mg/L (toxic level)	None	Alprazolam 1 mg/kg, atenolol 33.3 mg/kg, peak serum atenolol 3.6 mg/mL	Blood ethanol concentration 263 mmol/L	None
Signs and symptoms	Shock, pulmonary edema	Shock, cardiac arrest 26 h after ingestion	Sinus tachycardia	Hypotension, bradycardia, acidosis	Hypotension, mild metabolic acidosis, mild hypocalcemia, mild pulmonary edema	Shock, jaundice, acute renal failure, pulmonary edema
Medical history	Mild hypertension and a splenectomy due to an accident several years earlier	NA	Gout	Coronary artery disease, hypertension, depression	Hypertension	Coronary artery disease, mild congestive heart failure, hypertension, etc.*
Outcome	Survived	Fatal	Survived	Survived	Survived	Suvived**

Notes: *Moderate mitral regurgitation with severe mitral annular calcification, intermittent ventricular bigeminy and right bundle branch block, coronary artery bypass graft and prosthetic aortic valve replacement 7 years earlier. **Survival of overdose, but death after 112 days because of sequential complications. NA: not available

toxic level of 88 ng/mL.[4] Unfortunately, amlodipine concentrations of the patient in our case were not determined as there was lack of detection technology at that time. However it should not be a deterrent in judging the amlodipine intoxication.

Management guidelines for amlodipine overdose are limited and treatment remains challenging. It is important to be aware of the potentially life-threatening complications. Because of the lack of specific efficacious antidote, sufficient early gastrointestinal decontamination is advocated. It is suggested that decontamination should be aggressive with use of activated charcoal for the first hour after ingestion of overdose, whole bowel irrigation may be performed in case of massive overdose, and multiple doses of charcoal may be given every 4 h if whole bowel irrigation cannot be performed.[7] Because of high protein binding and extensive tissue distribution, hemofiltration and dialysis cannot be of help in amlodipine overdose except for acute kidney injury induced by poisoning and severe fluid overload after aggressive fluid resuscitation. Several case reports described beneficial effect of treatment with plasma exchange of amlodipine overdose.[8] However, the optimum timing and dosage of plasma exchange remain unclear. Supportive treatment with intravenous fluid resuscitation is important as profound hypotension is common but lethal symptom in amlodipine poisoning. Meanwhile, non-cardiogenic pulmonary edema could be a life-threatening complication. A rapid assessment and detailed management of the haemodynamics could challenge even the most experienced physician. Calcium infusion is often utilized in the overdose of amlodipine in an attempt to increase circulating calcium and overcome blockade of calcium channels. However, the optimum dosage of calcium remains unclear. And there is a concern about flooding of excessive calcium due to calcium infusion.[7] Utilization with monitoring of serum calcium would be preferable. As a calcium sensitizer, levosimendan can improve cardiac function and acidosis without the risk of acutely high serum concentrations of calcium. It has been reported that the administration of levosimendan is useful in treating of calcium channel blocker overdose.[9] Other experimental therapies such as the administration of lipid emulsion infusion, glucagon, and insulin have also been reported. Further research is required to define their roles in the treatment of overdose of amlodipine.[10,11]

In this case, XPJD was provided to the patient when her health condition deteriorated. It was derived from Poge Jiuxin Decoction (破格救心汤, PJD), which was created by LI Ke. PJD is composed of high dose of *Radix Aconiti lateralis*, *Rhizoma Zingiberis*, *Radix Glycyrrhizae Preparata*, *Korean Ginseng*, *Fructus Corni*, *Os Draconis*, *Concha Ostreae*, *Magnetitum*, and *Moschus*. *Radix Aconiti lateralis* is used for removing yin and restoring yang for its pungent and hot properties; *Radix Glycyrrhizae Preparata* can reduce toxicity of *Radix Aconiti lateralis* and replenish the vital qi; *Fructus Corni* is used to hold qi and resuscitate the collapse; *Os Draconis* and *Concha Ostreae* can reinforce the Kidney and resuscitate essence and qi; *Magnetitum* is used to restrain yang, replenish vital essence, and equilibrate yin and yang; *Moschus* is used for awakening consciousness and opening cardiac orifice, promoting circulation and removing blood stasis. The whole PJD aims at reviving the yang for resuscitation, replenishing qi, promoting circulation, awakening consciousness, and opening cardiac orifice.[12] Given the fact that the patient became conscious already and she was going to have her menses, *Moschus* was removed from PJD. And the patient and her parents were really concerned about the possible adverse reaction of high-dose of *Radix Aconiti lateralis*, *Rhizoma Zingiberis*, etc. Hence the dose of these herbs was reduced and was finally transformed into XPJD, which also showed satisfactory effect, meeting the need of clinical practice. This might be due to some prescription medicines having the pharmacological effects of improving myocardial contractility, resisting arrhythmia, and enhancing the function of the adrenal cortex system, as indicated in the literature.[17,18]

In the present case, treatments with plasma exchange and levosimendan were not performed because they were too expensive for the family to afford. However, the patient fully recovered from the life-threatening complications of persistent profound hypotension, noncardiogenic pulmonary edema, acute respiratory failure, metabolic acidosis, and hypocalcemia after the administration of integrated Chinese and Western medicine. However, the patient's young age and no severe comorbidity definitely contributed to the satisfactory clinical outcome. Further study is necessary for assessing the curative effect of the integrated treatment for severe overdose of amlodipine.

REFERENCES

1. Sklerov JH, Levine B, Ingwersen KM, Aronica-Pollack PA, Fowler D. Two cases of fatal amlodipine overdose. J Anal Toxicol 2006;30:346-351.
2. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev 2004;23:223-238.
3. Persad EA, Raman L, Thompson MT, Sheeran PW. The use of extracorporeal life support in adolescent amlodipine overdose. Indian J Crit Care Med 2012;16:204-206.
4. Vogt S, Mehlig A, Hunziker P, Scholer A, Jung J, Gonzalez AB, et al. Survival of severe amlodipine intoxication due to medical intensive care. Forensic Sci Int 2006;161:216-220.
5. Poggenborg RP, Videbaek L,Jacobsen IA. A case of amlodipine overdose. Basic Clin Pharmacol Toxicol 2006;99:209-212.
6. Blankfield RP, Iftikhar I, Glickman E, Harris S. Temperature and blood pressure following amlodipine overdose. Wilderness Environ Med 2008;19:39-41.
7. Hasson R, Mulcahy V, Tahir H. Amlodipine poisioning complicated with acute non-cardiogenic pulmonary oedema. BMJ Case Reports 2011;10.1136/bcr.07.2011.4467.
8. Ezidiegwu C, Spektor Z, Nasr MR, Kelly KC, Rosales LG. A case report on the role of plasma exchange in the management of a massive amlodipine besylate intoxication. Ther Apher Dial 2008;12:180-184.
9. Varpula T, Rapola J, Sallisalmi M, Kurola J. Treatment of serious calcium channel blocker overdose with Levosimendan, a calcium sensitizer. Anesth Analg 2009;108:790-792.
10. Ghosh S, Sircar M. Calcium channel blocker overdose: experience with amlodipine. Indian J Crit Care Med 2008;12:190-193.
11. Kute VB, Shah PR, Goplani KR, Gumber MR, Vanikar AV, Trivedi HL. Successful treatment of refractory hypotension, noncardiogenic pulmonary edema and acute kidney injury after an overdose of amlodipine. Indian J Crit Care Med 2011;15:182-184.
12. Li K, ed. Clinical experience of the veteran practioner of traditional Chinese medicine LI Ke for emergency, critical and intractable diseases. 1st ed. Taiyuan: Shanxi Sciences Publishing House; 2006:1-17.
13. Koch AR, Vogelaers DP, Decruyenaere JM, Callens B, Verstraete A, Buylaert WA. Fatal intoxication with amlodipine. J Toxicol Clin Toxicol 1995;33:253-256.
14. Yuan TH, Kems WP 2nd, Tomaszewski CA, Ford MD, Kline JA. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol Clin Toxicol 1999;37:463-474.
15. Stanek EJ, Nelson CE, DeNofrio D. Amlodipine overdose. Ann Pharmacother 1997;31:853-856.
16. Adams BD, Browne WT. Amlodipine overdose causes prolonged calcium channel blocker toxicity. Am Emerg Med 1998;16:527-528.
17. Ding T. Modern pharmacology theory research and clinical new-application of *Aconitum Carmichaeli* Debx. China J Chin Med (Chin) 2012;27:1630-1631.
18. Liu P, Ge YC, Ma TS. Pharmacological research advance in Sini Tang serial decoctions. Liaoning J Tradit Chin Med (Chin) 2007;34:248-251.

(Received 25 March, 2014)
Edited by YUAN Lin