

Intravenous Lipid Emulsion Treatment and High-Dose Amlodipine Intoxication: A Case Report

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Abstract

Background: Calcium channel blockers (CCBs) are widely used for various indications such as hypertension, coronary artery disease, and certain cardiac arrhythmias. As they are frequently prescribed, overdoses are common. Our aim in this paper was to present a case of intoxication with amlodipine, captopril, and doxazosin where ILE treatment proved unsuccessful and to review literature for effectiveness of ILE therapy in amlodipine poisonings.

Case Presentation: A 54-year-old female patient presented to the emergency department after taking 300 mg of amlodipine, 1000 mg of captopril, and 120 mg of doxazosin with suicidal intention. The patient was treated with gastric lavage, activated charcoal, calcium gluconate, hydration, vasopressor, inotrope, insulin and glucose, and intravenous lipid emulsion and transferred to intensive care unit at the 8th hour. Hemodynamics did not improve and the patient underwent plasmapheresis at the 10th hour. Patient was extubated and discharged without sequelae. Considering the pharmacokinetics of captopril and doxazosin, worsening of hemodynamics after 8 hours was related to amlodipine.

Conclusion: While verapamil and diltiazem poisonings were generally reported to be successfully treated with intravenous lipid emulsion, salvage treatment with intravenous lipid emulsion was reported to be unsuccessful in the literature for amlodipine intakes of 280 mg or more.

Keywords: Amlodipine; Intoxication; Lipid Emulsion; Plasmapheresis

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INTRODUCTION

Calcium channel blockers (CCBs) are widely used for various indications such as hypertension, coronary artery disease, and certain cardiac arrhythmias. As they are frequently prescribed, overdoses are common. CCBs bind to L-type calcium channels in cardiac and vascular smooth muscles and cause shock by vasodilatation, negative inotropy, and chronotropy in intoxications. They can also inhibit the effect of vasopressor drugs such as epinephrine, norepinephrine, and phenylephrine. Therefore, the morbidity and mortality rates are high due to toxicities with CCBs (1-6).

Current consensus reports for CCB intoxications recommend airway control, adequate oxygenation, gastrointestinal decontamination, fluid management, intravenous calcium, atropine, inotropes, vasopressors, and high-dose insulin therapy (HDIT) as first-line treatment options (1, 7). Salvage treatments for refractory patients are high-dose insulin, intravenous lipid emulsion (ILE), pacemaker use, and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) (8).

Amlodipine, a dihydropyridine CCB, has a pharmacokinetic profile of 10 mg daily maximum oral therapeutic dose with an elimination half-life of 30-55 hours (2, 9). Peak plasma concentrations are reached within 6-12 hours. Sustained release forms of amlodipine are available with delayed absorption from the gastrointestinal tract. Amlodipine is highly bound to proteins and has a large distribution volume. The onset of CCB intoxication symptoms with amlodipine may be delayed up to 24 hours (1).

ILE treatment was initially used for toxicities of local anesthetics while it is also used as a salvage therapy for intoxications with lipophilic drugs, even though the exact mechanism of action is not fully clarified (10). Serious adverse effects of ILE treatment are reported including lipemia, pancreatitis, deep vein thrombosis, neurological disorders, and acute lung and kidney injury (11, 12). ILE treatment is not found to be effective for improving hemodynamics in animal studies of dihydropyridine poisoning (13, 14). Both successful (12, 15, 16) and unsuccessful (6, 17, 18) outcomes of improved hemodynamics are reported with ILE treatment in patients presenting with dihydropyridine poisoning.

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Our aim in this paper was to present a case of intoxication with amlodipine, captopril, and doxazosin where ILE treatment proved unsuccessful and to review literature for effectiveness of ILE therapy in amlodipine poisonings.

CASE REPORT

A 54-year-old woman with comorbidities of hypertension, asthma, and gout was brought to the emergency department after ingesting 300 mg of amlodipine (immediate release form), 1000 mg of captopril, and 120 mg of doxazosin two hours earlier with suicidal intentions. The patient had a blood pressure of 90/40 mmHg, heart rate (HR) of 110 bpm and Glasgow Coma Scale of 13. Treatments of activated charcoal, calcium gluconate, hydration, vasopressor, inotrope, and HDIT with glucose were administered. Despite initial treatment, hemodynamics further deteriorated and ILE treatment was performed with 20% lipid emulsion injected with a bolus dose of 1.5 mL/kg followed by a maintenance dose of 0.25 mL/kg over 30 minutes. The patient was transferred to the intensive care unit 8 hours after ingestion.

The patient was tachycardic and hypotensive with bilateral rhonchi heard on respiratory examination. Arterial blood gas analysis showed pH of 7.32, PCO₂ of 26 mmHg, PaO₂ of 61 mmHg, lactate of 3 mmol/L, base deficit of minus 10, and bicarbonate of 13 mEq/L while patient was breathing oxygen (15 L/min) with a diffusion mask. The patient was intubated. Despite dopamine (30 µg/kg/min) and norepinephrine (2 µg/kg/min) infusions, mean arterial pressure (MAP) was 55 mmHg and adrenaline infusion was started with a dose of 0.01 µg/kg/min. HDIT was continued and 10 mL of 10% CaCl₂ solution was given in two intravenous boluses along with a repeated ILE treatment (1.5 mL/kg bolus dose of 20% lipid emulsion, followed by 0.25 mL/kg/min infusion). Hemodynamics continued to worsen and adrenaline dose was increased. Therapeutic plasma exchange (TPE) with albumin was performed at the 10th hour of ingestion. Following TPE, MAP was 60 mmHg, HR was 100 bpm and adrenaline dose was decreased to 0.01 µg/kg/min with noradrenaline and dopamine infusions continuing on the same doses. The liquid balance of the first day was positive 3,900 mL. Second TPE was performed 12 hours after the first TPE and subsequently adrenaline infusion was discontinued while dopamine and noradrenaline were reduced to half-dose. Following a third TPE, dopamine and noradrenaline infusions were discontinued and the patient was extubated. The patient, who was hemodynamically stable, was discharged without sequelae.

DISCUSSION

As with other intoxications, prospective, randomized, and controlled trials of CCB intoxication are lacking. Therefore, the efficacy of treatments is evaluated based upon animal studies and case reports. In an animal experiment investigating the efficacy of ILE treatment on vasodilation and cardiovascular depression associated with CCB toxicity, ILE treatment was found most effective for inhibiting vasodilation related to bepridil, verapamil, nifedipine, and diltiazem toxicities (19). ILE treatment was also found effective in animal studies of verapamil poisoning (20-22). However, ILE treatment failed to improve hemodynamics

and provide survival benefit in swine and mouse models of severe shock induced with nifedipine (13, 14).

Case reports and case series generally report successful ILE treatment in verapamil and diltiazem intoxications (12, 17, 23-26). Six cases of amlodipine overdose were reported previously where ILE treatment was employed similar to our case. In three of these cases, amlodipine intake was 100 mg or unknown and ILE treatment was found to be beneficial. Other three cases were reported with amlodipine intakes of 280 mg or more with unsuccessful ILE salvage therapy (Table 1).

The most common recommended ILE treatment dosing in CCB intoxication is 1.5 mL/kg bolus injection of 20% lipid emulsion (bolus dose can be repeated twice until clinical stability is reached) and a maintenance dose of 0.25 mL/kg/min continued for 30-60 minutes (8). The doses of ILE administered in our case were similar to these recommended doses.

It is not known whether ILE treatment paradoxically increases the absorption of lipophilic toxins by GI tract (27). A case presentation of a patient with an intake of 280 mg of amlodipine with other medications reports that ILE treatment was not found to be effective whereas endoscopic removal of a drug bezoar resulted in improvement of hemodynamics and discontinuation of inotropes after 12 hours (28). We did not perform endoscopy in our case and ILE treatment might have increased the absorption of residual amlodipine from the gastrointestinal tract.

Our patient ingested short-acting medications of captopril (peak plasma concentration time 0.5-1.5 hours, half-life 1.9 hours) and doxazosin (peak plasma concentration time 2-5 hours, half-life 8-22 hours) along with the long-acting amlodipine (peak plasma concentration time 6-9 hours, half-life 30-50 hours). Considering the pharmacokinetics of these medications, we consider that worsening of hemodynamics after 8 hours was related to amlodipine. Due to technical limitations, we were not able to measure plasma drug levels of amlodipine.

The use of TPE in drug intoxications is based solely on case reports and case series (29). It is recommended as an adjunctive therapy for cleansing of drugs with a low volume of distribution (<0.2 L/kg) and/or a high binding affinity to plasma proteins (30). Amlodipine is bound to plasma proteins with a high degree and its half-life is long. Thus, we decided to perform TPE in our case as a salvage therapy. Three patients with an overdose of amlodipine were also reported to be successfully treated with TPE (Table 1) (6, 31, 32).

As a conclusion, although not recommended in consensus reports, we consider that TPE could be applied with ease as a salvage therapy for amlodipine intoxications if ILE treatment is not of benefit and VA-ECMO is not available.

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Table 1. Characteristics of patients with amlodipine intoxications reported in literature

	Case 1 Reuter-Rice et al., 2016	Case 2 Ezidigwu et al., 2008	Case 3 Koschny et al., 2014	Case 4 KarbekAkarca et al., 2017	Case 5 Cumpston et al., 2017	Case 6 Hopkins et al., 2017	Cases 7,8 Geib AJ et al., 2009
Age, gender	16, Female	22, Female	21, Female	25, Female	55, Male	21, Female	34, Female 18, Female
Ingested drug	Amlodipine 400 mg	Amlodipine besylate 425 mg	Amlodipine 300 mg, Carvedilol 1750mg, Amipriptyline 6000mg, Torsemide 500 mg, Ketoprofen 1500mg, Gabapentine 16g, Nicotinic acid 28.000mg	Amlodipine 100 mg	Amlodipine unknown, Labetal unknown	Amlodipine 280 mg, Propranolol6.4 g,Olanzapine 560 mg	Amlodipine (Case 7), Amlodipine Lisinopril (Case 8)
Comorbidities	None	None	None	Unknown	Unknown	Unknown	Unknown
Treatment	Epinephrine Phenylephrine hydrochloride Norepinephrine Dopamin Calcium chloride Intralipid HIET Plasmapheresis PASG CVVH	Catecholamines Calcium gluconate, Charcoal hemoperfusion CVVH TPE	Catecholamines Therapeutic hypothermia ECMO Plasma exchange	Calcium gluconate Catecholamines Glucagone ILE	Glucagone calcium gluconate calcium chloride HDIT ILE	Glucagon HDIT Catecholamines ILE oesophago- gastro- duodenoscopy	ILE
ILE dose	Unknown	None	None	20% ILE 2 ml/kg bolus and 0.25 ml/kg infusion over 60 minutes.	20% ILE 0.004-0.25 ml/kg/min infusions up to 30 hours.	20% ILE 1.5 ml/kg bolus (twice) and 0.25 ml/kg/min infusion for 48 hours (425 ml of 20% ILE was infused in total).	Unknown
ILE treatment outcome	Not beneficial	Not applicable	Not applicable	Beneficial	Beneficial	Beneficial	Not beneficial for Case 7, beneficial for Case 8
Intensive care admission	4 hours	Unknown	Unknown	None	Unknown	Unknown	Unknown
Outcome	Survived	Survived	Survived	Survived	Survived	Unknown	Case 7 deceased, Case 8 survived

Abbreviations: HDIT: High-dose insulin treatment, TPE: therapeutic plasma exchange, ILE: intravenous lipid emulsion, ECMO: extracorporeal membrane oxygenation, CVVH: continuous venovenous hemodialysis, PASG: pneumatic antishock garment.

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