Case Report

Intravenous Lipid Emulsion in the Management of Amlodipine Overdose

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Abstract

Objective: To report a case of amlodipine overdose successfully treated with intravenous lipid emulsion (ILE).

Case Summary: A 47-year-old, 110 kg female ingested at least 350 mg of amlodipine with an unknown amount of ethanol. Initial blood pressure was 103/57 mm Hg, mean arterial pressure (MAP) 72 mm Hg, and heart rate 113 beats per minute. In the early clinical course, activated charcoal, intravenous fluid, and calcium boluses were administered. Worsening hypotension prompted a 100 mL bolus of 20% ILE. Stable hemodynamics were maintained for 2 hours. Subsequently, profound hypotension and shock developed (MAP 38 mm Hg), which failed to fully respond to 3 vasopressor agents, calcium, and glucagon. With continuing shock despite optimized vasopressors, an infusion of 2,300 mL 20% ILE was administered over 4.5 hours (20.9 mL/kg infusion total). By completion of the infusion, 2 vasopressors were tapered off and MAP remained above 70 mm Hg; within 12 hours, no further interventions were required. Possible adverse events of ILE, lipemia and hypoxia, were experienced but quickly resolved. The patient survived to hospital discharge within 8 days.

Discussion: Toxicity of amlodipine presents similar to distributive shock as both are due to marked peripheral vasodilation. There are numerous interventions in the management of amlodipine overdose, despite which many patients continue to suffer life-threatening shock as observed with this patient. ILE has been used with promising preliminary results as salvage therapy in case reports of other lipophilic molecules. This is the first report of lone amlodipine overdose treated with ILE.

Conclusion: ILE is a novel antidote for overdoses of lipophilic substances and demonstrated efficacy in this case of amlodipine overdose without the use of hyperinsulinemic euglycemia.

Key Words—amlodipine, calcium channel blocker, lipid emulsion, overdose, toxicology

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Cardiovascular medications were the second leading cause of death from medication overdose in 2010, with amlodipine contributing to 24 of those fatalities.¹ Calcium channel blocker (CCB) toxicity presents a particular clinical challenge due to the negative cardiac conduction and contractility properties, along with potent peripheral vasodilatory effects. All CCBs act through blockade of voltage

gated L-type calcium channels.²⁻⁴ At therapeutic doses, dihydropyridine CCBs (amlodipine, nifedipine, felodipine, nimodipine, and nicardipine) act by relaxation of smooth muscle surrounding blood vessels in the periphery and heart.³ Non-dihydropyridine CCBs (diltiazem and verapamil) work in the cardiac nodal tissue to slow conduction and demonstrate negative chronotropic, dromotropic, and inotropic

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effects.³ However, at toxic levels this difference in site of effect between classes is less pronounced,^{2,5} thus all dihydropyridine and non-dihydropyridine CCBs may cause hypotension, bradycardia, heart block, and shock.

There are a number of therapeutic modalities used in the management of CCB overdose, including fluid resuscitation, intravenous calcium, glucagon, atropine, hyperinsulinemic euglycemia, and vasopressor agents. Despite these interventions, CCB toxicity continues to cause significant mortality. We report the successful use of an emerging treatment strategy, intravenous lipid emulsion (ILE), in the management of amlodipine toxicity, despite hyperinsulinemic euglycemia not being provided.

CASE REPORT

A 47-year-old, 110 kg, 168 cm, African American woman with a history of alcohol abuse, psychiatric disorder, and hypertension presented to the emergency department (ED) via emergency medical services after she reported ingesting at least 70 tablets of amlodipine 5 mg along with an undetermined amount of ethanol. The patient presented to the ED approximately 1 hour after exposure and denied other co-ingestants. Past medical history included delirium tremens, post-traumatic stress disorder, and mitral valve prolapse. Home medication regimen included ziprasidone 60 mg by mouth once daily, pregabalin 150 mg by mouth once daily, and amlodipine 5 mg by mouth once daily. The patient consumed ethanol daily and denied other illegal substance use.

The patient arrived to the ED at 14:08 (2:08 p.m.) and was found to be mildly intoxicated, but in no acute distress. Initial vital signs revealed a blood pressure (BP) of 103/57 mm Hg with a mean arterial pressure (MAP) of 72 mm Hg. The patient was tachycardic with a heart rate (HR) of 113 beats per minute (bpm). The patient was afebrile. Her respiratory rate was 18 breaths per minute, and oxyhemoglobin saturation was 96% on room air. Electrocardiogram (ECG) revealed an accelerated junctional rhythm with a QTc interval of 429 ms and QRS interval of 92 ms. Pertinent findings on physical examination included mild tongue fasciculation and warm extremities. Initial laboratory data revealed a serum ethanol of 189 mg/dL, aspartate aminotransferase (AST) 33 units/mL, alanine aminotransferase (ALT) 18 units/mL, and bilirubin 0.6 mg/dL. Initial complete blood count and chemistries were without significant abnormalities, and serum glucose was 108 mg/dL. A urine toxicology screen was negative. Serum levels of acetaminophen

and salicylates were negative. Serum amlodipine concentration was not obtained.

In the ED, a total of 75 g of activated charcoal was administered orally within 30 minutes of presentation. A central venous catheter and an arterial line were placed. A total of 3 L of 0.9% sodium chloride (normal saline; NS) was administered sequentially between 14:20 (2:20 p.m.) and 15:20 (3:20 p.m.) due to hypotension (BP 95/56 mm Hg). In response to continued drop in blood pressure (89/57 mm Hg at 16:13 [4:13 p.m.]), intravenous (IV) calcium gluconate 2 g bolus and 20% ILE (*Intralipid*; Fresenius Kabi, Uppsala, Sweden) 100 mL bolus (0.91 mL/kg) were also administered. This was followed by stable hemodynamics for 2 hours. The patient was transferred to the medical intensive care unit (MICU) at 18:50 (6:50 p.m.). Upon arrival to the MICU, vital signs were BP 75/46 mm Hg, MAP 56 mm Hg, heart rate 118 bpm, and respiratory rate 20 breaths per minute. The patient appeared mildly anxious, but otherwise there were no significant interval changes in her examination. However, between 19:00 and 20:00 (7:00 p.m. and 8:00 p.m.), the patient's clinical status deteriorated significantly, marked by overwhelming hemodynamic instability and shock (MAP 38-52 mm Hg), which required prompt critical care management.

Vasopressors (norepinephrine, vasopressin, and phenylephrine) were immediately initiated and doses were augmented rapidly to maintain a MAP above 65 mm Hg. Vasopressor doses were increased to 200 mcg/min, 0.06 units/h, and 300 mcg/min for norepinephrine, vasopressin, and phenylephrine, respectively. Additionally, a total of 6 L of NS boluses were administered along with calcium chloride at 40 mg/kg/h, glucagon at a maximum dose of 10 mg/h, and a regular insulin infusion at an initial rate of 5 units/h titrated to 15 units/h per MICU blood glucose control protocol. Hyperinsulinemic euglycemia was not initiated due to logistics regarding insulin dosing. Bedside echocardiogram revealed a hyperdynamic left ventricle, and systemic vascular resistance was estimated as severely reduced. New laboratory data at 22:00 (10:00 p.m.) revealed a compensated severe anion gap metabolic acidosis with pH of 7.13, serum bicarbonate 8 mmol/L, and a serum lactate of 8.2 mmol/L. Serum glucose was 560 mg/dL. Two ampules of sodium bicarbonate containing 50 mEq each were administered, followed by a 15 mEq/h infusion. By 22:15 (10:15 p.m.), the MAP was 70 mm Hg on vasopressor therapy, but again it began to decline rapidly. This prompted an infusion of 20% ILE at 100 mL/h, which was quickly increased to 500 mL/h

after toleration of the infusion was noted. A total of 2,300 mL (20.9 mL/kg infusion total) was administered over 4.5 hours. Following the initiation of ILE therapy, all vasopressors were weaned to off within 12 hours. Other infusions of glucagon and calcium were discontinued soon thereafter. Additional laboratory analysis shortly after discontinuation of ILE infusion was unable to be performed due to lipemia. **Figure 1** displays the clinical course during the patient's first 24 hours of care.

Throughout the remainder of her MICU stay, the patient remained hemodynamically stable without

further vasopressor requirement. On hospital day 2, oxyhemoglobin saturation declined to 88% and chest radiograph showed mild bilateral pleural effusions with increased basilar density, but the episode quickly resolved with 3 L of supplemental oxygen therapy that was successfully weaned off within 24 hours. The patient was never intubated and remained alert and oriented during the clinical course. Repeated laboratory analysis 8 hours after discontinuation of ILE infusion revealed that serum chemistries and lactate normalized, liver function tests did not change significantly from their initial values, prothrombin

Figure 1. Clinical course during the first 24 hours in amlodipine overdose patient treated with intravenous lipid emulsion (ILE). The *dotted black line* indicates administration of ILE. The first administration was a 100 mL bolus of 20% ILE (0.91 mL/kg), and the second was an infusion totaling 2,300 mL over 4.5 hours of 20% ILE (20.9 mL/kg infusion total). After the first administration, there was a transient increase in mean arterial pressure with stable hemodynamics for 2 hours. Following the infusion, all vasopressors and other infusions were quickly discontinued with stabilization of hemodynamics. Mean arterial pressure was directly measured with an arterial line. Other infusions not shown in the figure include vasopressin (0.04 units/h started at 21:50 [9:50 p.m.], titrated to 0.06 units/h at 22:30 [10:30 p.m.] and discontinued at 03:30 [3:30 a.m.]), glucagon (5 mg/h started at 19:50 [7:50 p.m.], titrated to 10 mg/h at 22:20 [10:20 p.m.], discontinued at 23:50 [11:50 p.m.]), insulin (5 units/h started at 21:11 [9:11 p.m.], titrated to 15 units/h at 23:00 [11:00 p.m.], discontinued at 16:00 [4:00 p.m.]), and sodium bicarbonate (15 mEq/h started at 23:42 [11:42 p.m.] and discontinued at 16:00 [4:00 p.m.]).

time/international normalized ratio (PT/INR) were within normal limits, and white blood cell count was elevated at 22,700 cells/mm³. The patient remained afebrile, and repeat ECG showed normal sinus rhythm. Four days later, the patient was transferred to the medical ward with close psychiatric monitoring and was discharged to home 8 days after admission.

DISCUSSION

General Management

The initial management of amlodipine overdose involves usual standards of care for an overdose patient. The ABCs (airway, breathing, and circulation) should be immediately assessed and stabilized. Gastrointestinal decontamination with activated charcoal is effective if administered within 2 hours of ingestion,⁶ as was possible with this patient. This is particularly important in cases of amlodipine overdose, given its long half-life of 30 to 50 hours⁴ and the potential for prolonged refractory hypotension.

Intravenous calcium can be administered via boluses or continuous infusion to achieve a mass effect on any remaining available L-type calcium channels. Systemic calcium administration has demonstrated positive inotropic and increased blood pressure effects.^{2,7,8}

Given the underlying pathophysiology of severe peripheral vasodilation, vasopressors may be required to maintain systemic perfusion. Norepinephrine has potent vasoconstrictive effects through agonism of the alpha-1 receptor and positive inotropic effects through agonism of the beta-1 receptor and is the recommended first-line vasopressor.^{2,9} The patient described in this case required 3 vasopressor agents to maintain adequate tissue perfusion (goal MAP of 65 mm Hg). Vasopressin is not a preferred agent, because it may exacerbate negative inotropic effects seen in CCB toxicity. An alternative to vasopressin in this case could have been to further increase the dose of norepinephrine or add another vasoactive agent such as epinephrine. This case and others⁹ highlight the profound depressive effects that amlodipine overdose can have on the cardiovascular system and the large vasopressor requirement necessary to maintain perfusion.

Glucagon therapy is considered a first-line intervention in beta-blocker toxicity. However, its use in CCB overdose has conflicting evidence and is not universally recommended.¹⁰ In this case, glucagon was utilized due to rapid clinical deterioration in the MICU with multiple interventions being initiated simultaneously in an effort to reverse the toxicity. The

patient received two 5 mg boluses followed by a 5 mg/h infusion that was titrated to 10 mg/h without notable improvement in hemodynamics.

Hyperinsulinemic euglycemia therapy has been described in numerous CCB toxicity case reports.¹¹⁻¹⁵ The release of insulin from pancreatic beta cells is dependent on calcium influx, thus CCB toxicity causes a state of hypoinsulinemia that predisposes the patient to decreased cardiac function by preventing glucose utilization and aerobic metabolism in the cardiac myocyte. By providing high-dose insulin therapy (1 unit/kg bolus followed by an infusion initiated at 0.5 to 1 units/kg/h and titrated to effect), the myocardium is able to utilize glucose for cellular energy. Due to high-dose insulin infusion, supplemental dextrose and potassium may be required to prevent hypoglycemia and hypokalemia, respectively. The insulin infusion should be titrated to hemodynamic response until 2 units/kg/h is reached, although up to 10 units/kg/h has been reported.¹⁶ Hyperinsulinemic euglycemia was not able to be provided in this case due to difficult logistics with the large doses of insulin. Logistical challenges included the transfer of the patient from ED to MICU; miscommunication between transferring teams; poor familiarity with high-dose insulin therapy among physicians, pharmacists, and nurses; and no guideline or protocol in place to aid in dosing and supplemental requirements. This highlights the ongoing challenge of administering non-traditional doses of insulin in a critically ill patient. Practitioners should be aware of these pitfalls and proactively prepare in an effort to avoid them when hyperinsulinemic euglycemia is indicated.

Intravenous Lipid Emulsion Therapy

The therapeutic use of ILE was first described in the management of local anesthetic toxicity.¹⁷ The proposed mechanism of action is that the emulsion forms a lipid sink that traps the molecule in a lipid partition of the plasma, preventing molecule-effector interaction and subsequent downstream effects.^{17,18} Also, ILE is proposed to provide direct energy substrate to cardiac myocytes during CCB toxicity.^{19,20} Under normal physiologic conditions, cardiac myocytes utilize beta-oxidation of fatty acids for cellular energy.¹⁹ However, during a state of stress, the cardiac myocyte depends on glucose utilization. As CCB overdose decreases the release of insulin from pancreatic beta cells, the cardiac myocyte cellular metabolism is impaired. Thus, ILE may provide direct energy substrate to the myocardium in the form of free fatty acids.^{19,20} Additionally, the direct

stimulation of L-type calcium channels by ILE has been described in small animal and in vitro studies^{16,18,20,21} and is a third proposed mechanism for its beneficial effect in CCB toxicity. Despite these and other postulated mechanisms of ILE effect in acute poisonings,¹⁸ its benefit is widely believed to be a result of the lipid sink. Based on this theory, ILE would be most effective for molecules with a large lipid-aqueous partition coefficient (log P value) as it will preferentially attract the molecule toward the lipid sink. The log P value is a measure of lipophilicity, with larger values representing increased lipophilicity. Although there is no definition of a log P value above which ILE is considered useful, the use of ILE in the management of bupivacaine (log P value of 3.64²²) toxicity is well established.¹⁷ Amlodipine has a log P value of 3.72,²² demonstrating a theoretical benefit from ILE in amlodipine toxicity given the lipid sink theory of action.

A recent review examined 74 animal and human studies of ILE in the treatment of acute poisonings.²³ The authors concluded that ILE should be used in the management of local anesthetic toxicity with neurologic or cardiovascular symptoms and may be utilized in other toxicities of lipid soluble substances if standards of care have not resulted in hemodynamic stability. The dosing recommended by the authors consists of a 20% lipid emulsion given as a 1.5 mL/kg bolus, followed by a 0.25 to 0.5 mL/kg/min infusion for 30 to 60 minutes (7.5 mL/kg to 30 mL/kg infusion total), with a repeat of the bolus in cases of cardiac arrest. These recommendations are consistent among other consensus statements.^{10,24} The dosing strategy used in this case consisted of an initial bolus of 100 mL (0.91 mL/kg) given in the ED followed by an infusion not started until 7 hours later in the MICU of 2,300 mL over 4.5 hours (20.9 mL/kg infusion total). The initial bolus was given at a target dose of 1 mL/kg in the ED because the patient was beginning to clinically decline and other interventions were being prepared, but the ILE was readily available in an automated dispensing cabinet with ease of dosing at 100 mL. The infusion was started in the MICU again after a precipitous decline in hemodynamics at a target infusion dose of 20 mL/kg. For both the ED and the MICU, ILE dosing guidance was provided by local poison control center. The infusion was prolonged to assess for patient tolerability and due to limited vascular access with a number of other infusions running. Another bolus was not provided, however the infusion rate was rapidly titrated to 500 mL/h. This dosing strategy varied from the consensus

statement recommendations in that the dose was administered over a more prolonged period, but it proved effective without sustained adverse events. Also, the use of ILE in this case report was not consistent with recommendations as all standards of care (hyperinsulinemic euglycemia) had not been exhausted and ILE was used early in the clinical course. The various dosing regimens documented in this and other case reports highlight the need for a standardized dose to be used and the importance of consultation with poison control centers or a toxicologist when using ILE.

There are few reports of ILE in the management of CCB overdoses, specifically amlodipine. The case of a 34-year-old male with a mixed overdose including an unknown amount of amlodipine described the use of 20% ILE at a total dose of 12 mL/kg.²⁵ After ILE administration, the patient's vasopressor requirements declined, acidosis improved, and hemodynamics stabilized. The authors concluded that ILE may have bound the lipid soluble medications of the mixed overdose and contributed to the survival of this patient.

West and colleagues described an overdose of ILE in the treatment of amlodipine toxicity.²⁶ A 71-year-old female ingested 135 mg of amlodipine and was initially treated with fluid resuscitation, intravenous calcium gluconate, dopamine, phenylephrine, vasopressin, and hyperinsulinemic euglycemia. Despite this aggressive management, the patient continued to deteriorate. ILE was initiated at a target dose of 75 mL bolus and 312.5 mL infusion over 30 minutes, but the patient inadvertently received 2,000 mL of 20% lipid emulsion over 4.5 hours. Although improvements in hemodynamics were seen after ILE, the patient expired on hospital day 6 after withdrawal of care. The extreme lipemia of the patient's blood complicated laboratory analysis.

A recent series described 9 cases of shock and/or cardiac arrest from medication overdoses treated with ILE.²⁷ Of the 9 cases, 6 involved a CCB and 6 were a mixed overdose. Five patients (55%) survived without any difference noted in hemodynamics among patients treated with bolus or bolus and infusion therapy. Adverse events were monitored and rated on a Naranjo scale.²⁸ Lipemia was the only adverse event considered to be "probably" related to ILE. This series was the first to closely examine adverse events associated with ILE when used for treatment of medication overdose. As noted, lipemia occurs consistently among these patients as has been reported in other experiences,^{21,23,25-27,29} including this

case report. The patient described in this case developed lipemia after infusion of ILE that prevented the analysis of laboratory studies, scoring a 6 on the Naranjo scale (probable). Practitioners should be aware that laboratory analysis may be delayed after administration of ILE and plan accordingly by pre-emptively drawing blood samples prior to ILE therapy.

The patient in this report experienced an acute hypoxic episode on hospital day 2 requiring supplemental oxygen that quickly resolved. Acute lung injury and acute respiratory distress syndrome have been described in other reports of ILE use for toxic ingestions.^{23,27} The development of hypoxia in this patient was possibly due to administration of ILE (score of 2 on Naranjo scale; possible) but may have also been idiopathic in nature.

The manufacturer's labeling for ILE states the following as possible adverse events: liver damage, pulmonary disease, anemia, blood coagulation disorders, fat embolism, aluminum toxicity, thrombophlebitis, infection, and sepsis.³⁰ It should be noted that these listed adverse events are in the setting of ILE use for total parenteral nutrition. Dosing of ILE for the treatment of medication overdoses is more aggressive and may theoretically present exaggerated or additional adverse events. The incidence of adverse events during the use of ILE for medication overdose needs to be further studied.

CONCLUSION

To our knowledge, this is the first case describing the successful use of ILE in the management of lone amlodipine overdose, without administration of hyperinsulinemic euglycemia. Use of ILE in the management of CCB toxicity is a rational therapeutic intervention as it has been demonstrated to be effective in a number of case reports, including this one. However, the lack of robust evidence and the potential for significant adverse events limit the use of ILE to salvage therapy in patients with medication overdoses not responding to standard of care. As there is more definitive evidence to support hyperinsulinemic euglycemia in CCB overdose, ILE should not supersede this therapy. With the increasing use of ILE in the management of overdoses involving lipophilic molecules, further research is necessary to determine optimal dosing strategies, adverse events, and place in therapy.

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