Intravenous Lipid Emulsion Therapy: A Crucial Approach for Treating Lipophilic Drug Poisoning- A Case Study from Nepal

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ABSTRACT

Intravenous lipid emulsion (ILE) therapy has emerged as a promising treatment for lipophilic drug poisoning, particularly in cases where conventional therapies fail. This case study from Nepal highlights the successful use of ILE therapy in treating a severe calcium channel blocker (CCB) overdose. A 37-year-old female patient with an intentional amlodipine overdose presented with bradycardia, hypotension, and metabolic acidosis. Despite initial treatment with high-dose insulin, calcium gluconate, and inotropic support, her condition remained critical. The initiation of ILE therapy led to rapid hemodynamic stabilization, allowing the discontinuation of vasopressors and normalization of metabolic parameters within 24 hours. The patient recovered without adverse effects and was discharged in stable condition. This case underscores the potential of ILE therapy as a life-saving intervention in severe CCB toxicity and highlights the need for further research to optimize its use in clinical practice.

Keywords: Intravenous Lipid Emulsion Therapy, lipophilic drug poisoning, calcium channel blockers, Intensive Care Unit.

INTRODUCTION

Calcium channel blockers (CCBs) are widely prescribed and are essential in treating conditions such as hypertension, angina, atrial fibrillation/flutter, pulmonary arterial hypertension, and supraventricular tachycardia. They are also effective for various non-cardiac conditions, including Raynaud's phenomenon, subarachnoid hemorrhage, and variceal hemorrhage[1]. However, the incidence of CCB overdoses is rising due to medication errors or suicidal tendencies.

There are several treatment options for CCB poisoning. Beyond first-line therapies, ILE therapy and venoarterial extracorporeal membrane oxygenation (VA-ECMO) have gained attention as unconventional interventions. In recent years, ILE therapy has shown promise as a treatment option in toxicology, initially being used for local anesthetic toxicity and now increasingly applied as an antidote for various lipophilic drug poisonings[2]. However, despite its growing popularity, there are still uncertainties about the indications, timing, and dosage for ILE treatment[3].

ILE therapy is recommended for treating patients with cardiac arrest secondary to lipophilic drugs, such as beta-blockers (BBs) and CCBs[4]. It is increasingly used by clinicians in patients suffering drug- or poison-related cardiovascular collapse.

In Nepal, there has been an increase in cases of suicidal poisoning from CCBs among young adults. While various treatment approaches have been tried, ILE therapy has not yet been used. Here, we present the case of a 37-year-old female patient with amlodipine poisoning who was successfully treated with ILE therapy alongside high-dose insulin, calcium gluconate, inotropes, and hydration.

CASE PRESENTATION

A 37-year-old female was brought to our emergency department with complaints of difficulty in breathing, headache, and dizziness. These symptoms followed the intentional ingestion of multiple drugs, particularly antihypertensives. Her medication history included the ingestion of 50 tablets (total 250 mg) of Amlodipine and undetermined amounts of other tablets. She had a medical history of hypertension.

Initial vital signs on presentation: heart rate (HR) of 112 beats per minute, blood pressure (BP) of 70/40 mmHg, respiratory rate (RR) of 20 breaths per minute, oxygen saturation (SpO2)

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of 98% in room air, and a temperature of 36.4°C. She was confused with a Glasgow Coma Scale (GCS) of 12/15. Sinus bradycardia with first-degree AV block was evident on the ECG (Figure 1).

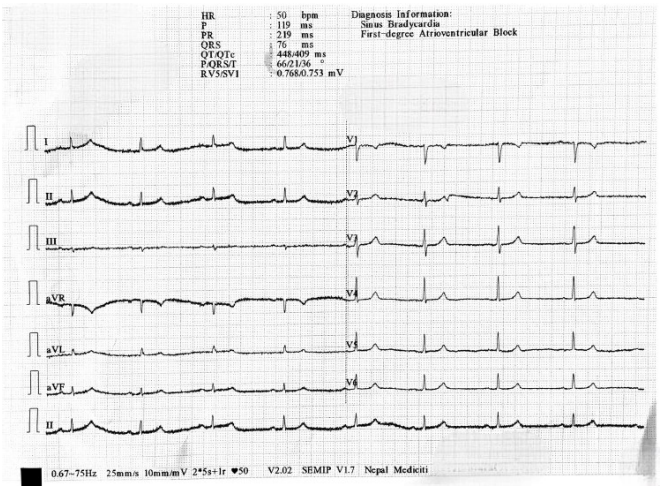

Figure 1. 12-lead ECG on presentation.

LABORATORY FINDINGS

Her laboratory examination showed a serum creatinine level of 5.2 mg/dl, sodium of 127 mmol/L, potassium of 3.2 mmol/L, urea of 53 mg/dl, total leukocyte count (TLC) of 10,970 cells/cumm, hemoglobin of 12.1 g/dl, platelets of 330,000 cells/cumm, creatinine kinase-MB (CK-MB) of 4 U/L, troponin-I of 6.21 ng/l, and a random blood glucose of 208 mg/dl. Liver function tests were mildly elevated at twice the upper limits (AST 75 U/L, ALT 60 U/L, bilirubin 1.2 mg/dl). Urine output was 10-20 ml/hr. A urine toxicology screen was negative. Serum acetaminophen and salicylate levels were negative. Serum amlodipine concentration was not obtained. Arterial blood gas (ABG) analysis indicated severe metabolic acidosis with lactic acidosis (pH: 7.22, PCO2: 36.6, HCO3: 10 mmol/L, and lactate: 4.2 mmol/l). Ionized serum calcium (4 mg/dl; normal range: 4.6-5.6 mg/dl).

TREATMENT

At ED, gastric lavage was performed with activated charcoal through a nasogastric tube. A total of 2 L of fluid (0.9% normal saline) was administered along with a bolus of 2 gm of IV calcium gluconate due to hypotension (70/40 mmHg). The patient was shifted to the ICU for hemodynamic monitoring, inotropic support, and possible mechanical circulatory support. Upon arrival in the ICU, a central venous catheter (CVP) and an arterial line were placed, and treatment was started with hydration using balanced crystalloids (1000 ml intravenous bolus followed by 100 ml/hr over 24 hours). However, there was no improvement in blood pressure (80/60 mmHg). In response to the continued drop in blood pressure, inotropic support with intravenous noradrenaline was started. Despite this, the patient remained hypotensive. Subsequently, a dopamine infusion was also initiated to maintain a mean arterial pressure (MAP) above 65 mmHg. In addition to that, high doses of insulin (short-acting) along with 50% dextrose, IV 10% calcium gluconate, and IV potassium chloride were also started. We also considered intravenous sodium bicarbonate for the patient due to QRS prolongation and underlying metabolic acidosis (Table 1 and Figure 2). VA-ECMO and glucagon were unavailable, and therapeutic plasma exchange was impractical due to delayed presentation.

On the second day, her consciousness returned to normal, but she remained hypotensive and bradycardic despite the continuation of inotropes. Given the suspected severe overdose of lipophilic drugs, the ILE therapy was started (SMOFKABIVEN-FRESENIUS KABI). After 4 hours of ILE therapy, her hemodynamics were stable. BP was 100/60 mmHg, the pulse was 65-70 beats per minute, and the respiratory rate was 20 breaths per minute. Intravenous sodium bicarbonate infusion was stopped with the improvement in metabolic acidosis. Her bedside echocardiogram findings were normal. Urine output was adequate.

On the third day, and 24 hours after the initiation of ILE therapy, all vasopressors were weaned off. Regular insulin with dextrose and calcium supplements were also stopped. Her ECG and echocardiography findings were normal. The patient was kept under observation. Repeated laboratory analysis 12 hours after discontinuation of ILE infusion revealed that serum chemistries and lactate normalized, liver function tests and prothrombin time/international normalized ratio (PT/INR) were within normal limits, and complete blood counts were normal. The patient remained afebrile, and repeated ECG showed a normal sinus rhythm.

Table 1: Treatment algorithm for CCB poisoning

TREATMENT ALGORITHM FOR CCB POISONING	
INTRALIPID EMULSION 20% (ILE)	A loading dose of 1.5 mL/kg (SMOFKABIVEN 20%) over 2-3 minutes, followed by an infusion of 0.25 mL/kg/min for 24 hours.
REGULAR INSULIN	1 unit/kg IV bolus followed by infusion of 0.5 unit/kg/hour.
DEXTROSE	Dextrose 50% is strongly preferred at 1 ml/kg/hour. Target glucose level above 100 mg/dl.
CALCIUM GLUCONATE	A high dose of calcium gluconate (0.6-1.2 ml/kg/hour of 10%).
SODIUM BICARBONATE	A loading dose of 100 mEq of 7.5% or 8.4%, followed by 50 mEq/hour for severe metabolic acidosis or if QRS widening is noted on an ECG.
POTASSIUM CHLORIDE	As per the hospital ICU protocol.
CATECHOLAMINES	Norepinephrine and dopamine are preferred in CCB poisoning.

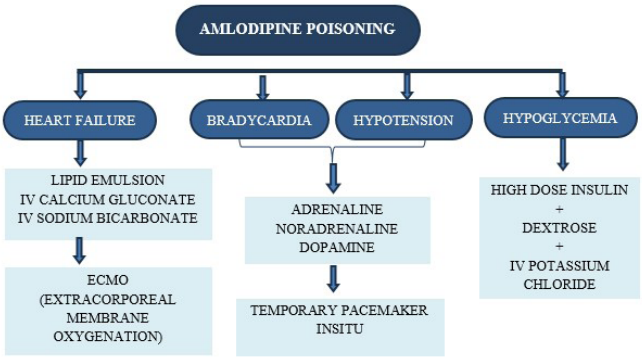

*Figure 2: Treatment modalities of Amlodipine Poisoning.

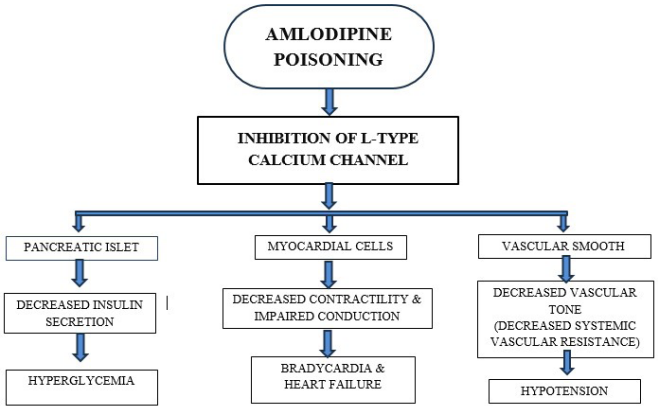

*Figure 3: Pathophysiology of Amlodipine Poisoning

OUTCOME

After a total of four days in the ICU, the patient was transferred to a ward with advice for a 12-lead ECG during transfer. Psychiatric consultation was recommended before discharge from the hospital.

This case study demonstrates the successful use of ILE therapy in treating severe CCB overdose, particularly in a patient unresponsive to conventional treatments. The administration of ILE therapy led to rapid hemodynamic stabilization and the normalization of vital signs, laboratory parameters, and renal function. This case suggests that ILE therapy is a viable and effective treatment option for CCB poisoning, especially in cases of life-threatening cardiovascular collapse. The successful outcome, with no adverse effects in this patient, further supports considering ILE therapy in similar cases, particularly in regions like Nepal, where its use has not been widespread.

Further randomized controlled trials (RCTs) are needed to standardize the dosing and timing of ILE therapy to optimize patient outcomes.

DISCUSSION

CCBs are rapidly absorbed via the oral route and undergo extensive first-pass hepatic metabolism, predominantly by the CYP3A subgroup of cytochrome P450 enzymes[5]. These drugs act through L-type calcium channels present in cardiac and smooth muscle cells. By controlling cardiac conduction systems, myocardial and vascular smooth muscle contractility, and pacemaker cells, CCBs have significant effects on cardiovascular function[6]. Additionally, CCBs inhibit L-type calcium channels in pancreatic islet cells, reducing insulin secretion, which results in hyperglycemia and reduced cardiac glucose utilization[2] (Figure 3).

In cases of overdose, several severe symptoms can occur. Hypotension, atrioventricular conduction abnormalities, idioventricular rhythms, and complete heart block may be seen due to impaired myocardial inotropy and chronotropy as well as peripheral vasodilation[7]. The negative chronotropic and inotropic effects can lead to tissue ischemia and lactic acidosis. Common symptoms include dizziness, fatigue, and lightheadedness, while more severe poisoning can manifest as altered mental status, coma, and even death[8]. At toxic levels, extreme channel blockade can cause significant cardiac dysfunction and harmful peripheral vasodilation[9]. Toxicity is seen in doses up to 5-10 times the therapeutic dose and becomes evident within 20 to 60 minutes following ingestion. Most CCBs are more than 90% protein-bound with large volumes of distribution (21 L/kg). They usually have a long half-life (30-58 hours) and are not cleared by hemodialysis[10].

Initial management: The initial treatment modality for the management of CCB poisoning includes supportive care with airway, breathing, and circulation (ABCs)[11]. Gastric lavage with water or polyethylene glycol and activated charcoal (1 g/kg initially and to be continued for 24 hours through the nasogastric tube) can be a useful modality, especially in long-acting preparations. Gastric lavage can remove unabsorbed drugs from the stomach for an extended time, as CCB reduces gastric motility[12].

Intravenous calcium gluconate: A high dose of calcium gluconate (0.6-1.2 ml/kg/hour of 10%) has been used anecdotally with success[13]. Intravenous calcium gluconate can increase the transmembrane flow of calcium, so cardiac contractility and vascular tone are increased[14].

High-dose insulin: A high dose of insulin improves the inotropic effect. A loading dose of 1 unit per kilogram (U/kg) of regular insulin is given, followed by an infusion of 0.5 units per kilogram per hour (U/kg/hr). If the response is unsatisfactory, insulin may be up-titrated every 10-15 minutes within a range of 1-10 units/kg/hour. Dextrose (50% D5W) infusion may be started at a rate of 1 ml/kg/hr

to maintain euglycemia[13,14]. Notably, hypokalemia is the main adverse effect of insulin therapy. Baseline serum potassium level should be checked before the initiation of insulin therapy, and potassium level should be corrected as needed.

Sodium Bicarbonate: This is another potentially valuable treatment for CCB overdose. At high doses, CCBs inhibit fast sodium channels, causing QRS prolongation similar to the effect of tricyclic antidepressants. If the QRS duration exceeds 120 milliseconds, administering a 1-2 mEq/kg bolus of sodium bicarbonate may be necessary[15].

Vasoactive agents: CCB intoxication has a negative chronotropic and dromotropic effect, which may result in bradycardia and heart block and may require a pacemaker. Various literatures have suggested epinephrine and norepinephrine as the initial choice of catecholamines in patients with substantial vasodilation intoxicated by both CCBs due to their vasoconstrictive and inotropic effects, which make them the preferred first-line agent in amlodipine overdoses. Dopamine can be used for patients with persistent bradycardia and hypotension[16, 17, 18].

Intravenous lipid emulsion (ILE): This therapy has become a crucial approach in recent years for CCB Poisoning [19]. It is often used as part of total parenteral nutrition and has now shown success in treating local anesthetic toxicity. First described by Weinberg et al. in 2003 for bupivacaine toxicity, ILE therapy has three proposed mechanisms of action[20]. The most supported theory is the "lipid sink" hypothesis, which suggests that the toxic drug concentration in the plasma decreases as the lipophilic drug dissolves in the lipid pool created by IV lipid administration[21]. Another theory posits that lipids improve cardiac function by providing metabolic energy for myocytes, offering fatty acids as fuel for the mitochondria of heart cells[22, 23]. The third theory suggests that ILE therapy achieves a positive inotropic effect by increasing cytosolic calcium, with long-chain fatty acids directly activating voltage-gated calcium channels in cardiac myocytes[23].

Regarding the dosing consideration, numerous literature suggest that a 20% intralipid is used, with 1 mL/kg given as a bolus followed by a continuous infusion of 0.25 to 0.5 mL/kg/min for 60 minutes. This treatment can be repeated up to three times if there is no improvement, particularly if the patient experiences asystole, pulseless electrical activity, or hemodynamic dysfunction. The maximum dose is 10–12 ml/kg[13, 24, 25].

Lam SHF et al. suggested a maximum of 12.5 mL/kg of 20% ILE over 24 hours in adults and 15 mL/kg over 24 hours in children, as recommended by the United States Food and Drug Administration[3]. Bucklin MH et al. reported a case of the administration of 46 mL/kg over 12 hours in a pediatric mixed drug overdose patient with successful treatment and only mild adverse effects[26]. However, most reports of successful administration of lipid emulsion therapy were within the upper limits of 10 mL/kg total dose[27]. In the study by Sebe et al., a loading dose of 1.5 mL/kg in 5 minutes was given. If the patients remained unstable within 15 minutes of this treatment, the loading dose was repeated (maximum three times, maximum loading dose of 8 mL/kg). Then, a maintenance dose of 0.25 mL/kg/h lasting 1 hour was started when a sufficient response was detected[28]. Though the maximum duration of ILE therapy is not specified in the literature, treatment generally lasts 30-60 minutes. Following the bolus administration, an infusion is started at 0.25-0.5 mL/kg/minute until hemodynamic variables normalize. The infusion rate should be adjusted to avoid hypotension[29, 30].

Our case aligns with Lam et al.[3], where ILE achieved hemodynamic stability in 80% of CCB overdoses. Unlike Meaney et al[16], our patient did not develop lipemia, likely due to adherence to dose limits (<10 mL/kg total). The rapid response (4 hours) mirrors Sebe et al[28], supporting early ILE use in refractory cases.

The commonly encountered adverse effects following ILE therapy include allergic reactions, pancreatitis, respiratory distress syndrome, interference with vasopressors, fat overload syndrome, hepatosplenomegaly, jaundice, seizures, fat embolism, hypertriglyceridemia, and coagulopathy[27]. In the case reported by Meaney et al., a 47-year-old female with amlodipine poisoning in the presence of ethanol developed shock unresponsive to first-line therapies. After administration of 2300 mL of 20% ILE over 4.5 hours (20.9 mL/kg infusion total), lipemia and hypoxia were experienced, but they quickly resolved[16]. A systematic review by Hayes BD et.al. pointed out untoward effects include kidney injury, cardiac arrest, ventilation-perfusion mismatch, acute lung injury, venous thromboembolism, extracorporeal circulation machine circuit obstruction, and increased susceptibility to infections[31], but in our case, acute kidney injury, attributed to hypoperfusion, resolved with ILE-guided hemodynamic improvement.

Despite many untoward effects being attributed to ILE therapy, more in-depth data are necessary to identify the risk of complications from ILE therapy in patients with acute toxicity.

CONCLUSION

In our case, the treatment was effective with no adverse events noted, and the patient was transferred from the ICU to the ward with psychiatry consultation and was discharged with no sequelae after completing the treatment.

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AUTHOR CONTRIBUTIONS

Saroj Poudel: Conceptualization; data curation; methodology; validation; visualization; writing – original draft; writing – review and editing, **Kishor Khanal**: Supervision; writing – original draft; writing – review and editing. **Anup Ghimire**: Supervision; writing – original draft; writing – review and editing. **Pallawi Shrestha**: Data curation; writing – original draft. **Bishakha Rijal**: Data curation; writing – original draft. **Aastha Shrestha**: Data curation; writing – original draft. **Selika Shyaka**: Data curation; writing – original draft. **Akchhyeta Shrestha**: Data curation; writing – original draft. **Yogesh Bikram**: Data curation; writing – original draft.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

The authors received no financial support for the research.

ETHICS CONSIDERATIONS

This case report did not require the approval of any ethical committee. Written informed consent was obtained from the patient.

DISCLOSURE

A preprint has previously been published [Poudel S, Khanal K, Ghimire A, et al., September 11, 2024, doi: 10.22541/au.172605636.62857784/v1. It has not been peer-reviewed[32].

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