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Original Article

Effect of intravenous lipid therapy in critically ill pediatric patients with calcium channel blocker toxicity

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ABSTRACT

Background. Overdose with calcium-channel blockers (CCBs) still maintain their importance with a high lethality rate after exposure. We report the intravenous lipid emulsion therapy (ILE) therapy in our CCB overdose patients.

Methods. We retrospectively analyzed the records of 6 patients with CCB intoxication from Batman Training and Research Hospital PICU between March 2021 and September 2022. Patients aged 0-18 years who received ILE treatment for CCB poisoning were included.

Results. All six patients ingested CCB with the intention of committing suicide and were followed up in the pediatric intensive care unit (PICU). All patients received ILE therapy due to hemodynamic instability despite intravenous fluid boluses, calcium, glucagon, insulin-dextrose, and vasoactive agents. Vasoactive-Inotropic Score (VIS) decreased after ILE treatment. All patients were transferred from the PICU after recovery.

Conclusions. ILE therapy should be kept in mind as a salvage therapy in hemodynamically unstable CCB poisoning cases that do not respond to initial and advanced options.

Key words: calcium channel blockers, lipid emulsion, pediatrics, intoxication.

Calcium-channel blockers (CCBs) are a widely accepted class of drugs for the treatment of cardiovascular diseases. They have inhibitory effects on arterial smooth muscle and have an important potential for use in diseases other than the cardiovascular system.[1,2] It has been reported that a single tablet can be lethal, even though there are no symptoms at low levels in cases of poisoning.[3] Cardiovascular instability, bradycardia, hypotension, metabolic acidosis, hyperglycemia and seizures may be observed in poisoning.[3] CCBs still maintain their importance despite their high fatality rate following exposure.[2] intravenous lipid emulsion (ILE), which is used as a rescue therapy in lipophilic drug poisoning, has also become an option in severe cases of CCB poisoning.[4] In this case series, we report the efficacy of ILE in cases of CCB poisoning unresponsive to initial and advanced therapies.

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Material and Methods

The hospital data of 6 pediatric patients with CCB intoxication in the Pediatric Intensive Care Unit (PICU) of the Batman Training and Research Hospital between March 2021 and September 2022 was retrospectively analyzed. Inclusion criteria comprised patients aged 0-18 years who were administered ILE treatment for CCB poisoning. Patients presenting with hypotension and circulatory system disorders received fluid bolus, intravenous (IV) calcium, hyperinsulinemia-euglycemia treatment (HIET), and glucagon. In cases where stabilization was not achieved, ILE treatment was administered. ILE was given to six out of 11

patients with CCB poisoning during this period; the remaining five patients were excluded from the study as they did not receive ILE. Recorded data included age, sex, drug dosage, symptoms, vital signs, Vasoactive Inotrope Score (VIS), Pediatric Risk of Mortality III Score (PRISM III), ejection fraction percentage (EF), and laboratory data such as blood sugar and kidney function tests. All patients were consulted with cardiology before and after ILE and hemodynamic findings were recorded (Table I). A recommended dosing regimen for lipid emulsion is an infusion of 20% solution, 1 mL/kg over 1 minute, repeated every 3 to 5 minutes for a maximum of 3 mL/kg followed by 0.25 mL/kg/min.[5]

VIS was calculated as follows: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × dose of vasopressin (U/kg/min). The study adhered to the principles of the Declaration of Helsinki. The Institutional Ethics Committee of the Batman Training and Research Hospital approved the study protocol (Date: 18.09.2022/No: 319).

Results

Case 1

A 13-year-old girl was brought to the emergency department 6 hours after ingestion of 27 tablets of amlodipine (270 mg) and valsartan for suicidal purposes (Table I). She was conscious, with a pulse of 100 beats/min, blood pressure of 90/40 mm Hg, respiratory rate of 24 breaths/min, temperature of 36.5°C, and 98% pulse oxygen saturation at the arrival at the PICU. IV calcium, hyperinsulinemia euglycemia treatment (HIET; 0.1 IU/kg/h+ 0.25 gr/kg/h) was administered while closely monitoring blood glucose levels and targeting euglycemia (Table II). IV noradrenaline (up to 0.20 mcg/kg/min) and IV adrenaline (up to 0.1 mcg/kg/min) were started (Table I). ILE treatment was started during the third hour of the supportive therapy. Four hours after ILE, blood pressure increased to 110 /59 mm Hg.

Case 2

A 16-year-old girl was brought to the emergency department after receiving 20 tablets of nitrendipine (400 mg) and enalapril maleate for suicidal purposes after 1 hour. She was agitated with a pulse of 120 beats/min, blood pressure of 85/39 mm Hg, respiratory rate of 26 breaths/min, temperature of 36.5°C, and 98% pulse oxygen saturation under supplemental oxygen. IV calcium, hyperinsulinemia euglycemia treatment and IV glucagon (0.15 mg/kg bolus) were administered while closely monitoring blood glucose levels and targeting euglycemia. IV noradrenaline (up to 0.30 mcg/kg/min) and IV adrenaline (up to 0.20 mcg/kg/min) were started. ILE treatment was started during the second hour of the supportive therapy. Four hours after ILE her blood pressure increased to 110 /59 mm Hg.

Table I. Hemodynamic findings before and after ILE.

Case	Pre-ILE EF %	Post-ILE EF%*	Pre- ILE VIS	Post- ILE VIS**	Intubated	Outcome	LOS – PICU (day)
1	45	60	30	10	-	survived	8
2	40	65	50	20	-	survived	9
3	50	55	15	5	-	survived	6
4	40	55	30	10	-	survived	5
5	45	50	30	15	-	survived	6
6	35	65	40	20	+	survived	10

*72 hours after ILE treatment., **24 hours after ILE treatment.
EF: Ejection fraction, ILE: Intravenous lipid emulsion, LOS: Length of stay, VIS: Vasoactive inotrope score

Table II. Summary of patient characteristics and medical treatments applied before intravenous lipid emulsion therapy.

Case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age/sex	13/F	16/F	14/F	17/F	16/M	15/M
Drug	Amlodipine	Nitrendipine	Amlodipine	Verapamil	Verapamil	Verapamil
Dose(mg)	270	400	20	680	800	1600
Number of tablets	27	20	4	17	20	40
Gastric lavage	-	+	-	-	+	-
Active charcoal	-	+	-	+	+	-
Fluid bolus	+	+	+	+	+	+
Bicarbonate deficit	-	-	+	+	-	+
Noradrenaline	+	+	+	+	+	+
Adrenaline	+	+	-	-	-	+
Glucagon	-	+	-	-	-	-
HIET	+	+	+	+	+	+
Time to PICU	6 hours	1 hour	24 hours	4 hours	2 hours	8 hours

HIET: Hyperinsulinemia euglycemia treatment, PICU: Pediatric intensive care unit

Case 3

A 14-year-old girl was admitted to the emergency services of another hospital 24 hours after ingesting 4 tablets of amlodipine (20 mg) and hydrochlorothiazide (14 tablets) for a suicide attempt. The patient was admitted to the PICU for further treatment after developing acute kidney injury and hypotension during an examination at the external center. She was agitated with pulse of 105 beats/min, blood pressure of 86/42 mm Hg, respiratory rate of 25 breaths/min, temperature of 36.6°C, and 99% pulse oxygen saturation under supplemental oxygen. IV calcium, hyperinsulinemia euglycemia treatment was started while closely monitoring blood glucose levels and targeting euglycemia. IV noradrenaline (up to 0.15 mcg/kg/min) was started. ILE treatment was started during the second hour of the supportive therapy. In the follow-up after the ILE her blood pressure increased to a normal level within 4 hours. Renal function tests were impaired at admission, and they regressed to normal values at the 24th hour after ILE treatment.

Case 4

A 17-year-old female patient was brought to the emergency department with nausea, 4 hours after ingesting 17 tablets of verapamil (680 mg) for a suicide attempt. The heart rate was 71 beats per minute, the blood pressure was 73/33 mm Hg, pulse oxygen saturation was 96%, the respiratory rate was 22 breaths per minute, and the body temperature was 36.9°C. IVcalcium (4x 0.5 cc/kg 10% calcium gluconate), hyperinsulinemia euglycemia treatment and bicarbonate deficit were given for refractory acidosis. IV noradrenaline as a vasopressor was started (up to 0.30 mcg/kg/min). ILE treatment was started during the first hour of the supportive therapy. During follow-up, his blood pressure increased up to 110/61 mm Hg within 4 hours after the ILE.

Case 5

A 16-year-old male patient was brought to the emergency department with nausea 1 hour after ingesting 20 tablets of verapamil (800 mg) for a suicide attempt. His heart rate was 55 beats per minute, the blood pressure was

75/35 mm Hg, pulse oxygen saturation 96% under supplemental oxygen, the respiratory rate was 20 breaths per minute, and the body temperature was 36.6°C. IV calcium (4x 0.5 cc/kg 10% calcium) and hyperinsulinemia euglycemia treatment was started while closely monitoring blood glucose levels and targeting euglycemia. IV noradrenaline as a vasopressor was started (up to 0.30 mcg/kg/min). ILE treatment was started during the third hour of the supportive therapy. In the follow-up, blood pressure increased up to 105/56 mm Hg within 4 hours after the initiation of ILE.

Case 6

A 15-year-old male patient was brought to the emergency department of another hospital with unconsciousness and respiratory distress 8 hours after ingesting 40 tablets of verapamil (1600 mg) for suicide. His heart rate was 55 beats per minute, the blood pressure was 75/35 mm Hg, pulse oxygen saturation 80% under supplemental oxygen, the respiratory rate was 40 breaths per minute, and the body temperature was 36.9°C. The patient was intubated because of the signs of respiratory failure. IV calcium (4x 0.5 cc/kg 10% calcium gluconate) and hyperinsulinemia euglycemia treatment were started while closely monitoring blood glucose levels and targeting euglycemia. IV noradrenaline (up to 0.30 mcg/kg/min) and IV adrenaline (up to 0.10 mcg/kg/min) infusion were started. ILE treatment was started during the first hour of the supportive therapy. Blood pressure increased up to 110/60 mm Hg within 4 hours after the initiation of ILE. On the third day, the patient was extubated.

Discussion

CCBs are used in the treatment of hypertension, angina pectoris and arrhythmias.[1] CCBs reduce extracellular calcium through ion-channels that span the cell wall. Several types of such channels have been identified and existing CCBs inhibit L-type channels in humans.[6] CCBs can be physiologically divided into two main categories: dihydropyridines, which block L-type calcium channels in vessels; and non-dihydropyridines such as verapamil and diltiazem, which block L-type calcium channels in the myocardium.[1] When calcium channels are blocked, vascular smooth muscle cells relax, causing vasodilation and lowering of blood pressure. Cardiac contraction decreases and atrioventricular conduction slows down.[6] Dihydropyridines only have a mild effect on decreasing myocardial contraction, while verapamil causes profound inhibition of the sinoatrial and atrioventricular nodes.[7] Non-dihydropyridine poisonings like diltiazem and verapamil may present with bradycardia or cardiogenic shock. In cases of overdose, the selectivity of calcium channel blockers may be lost.[8]

Although CCBs have a limited number of FDA-approved pediatric indications, very high CCB exposures are reported to the US Poison Control Centers. According to the 2019 report of the American Association of Poison Control Centers, calcium antagonist poisoning is prominent after antipsychotics and analgesics.[2] Although small ingestions pose little risk, deaths have been reported even after exposure to 1 or 2 tablets, and symptomatic cases can be suddenly fatal.[3]

Cardiovascular imbalance may present with hypotension, bradycardia, conduction abnormalities, and arrhythmias. Patients may present with hyperglycemia, metabolic acidosis, seizures, mental status changes, and respiratory depression.[9] Our patients exhibited symptoms such as nausea, vomiting, mental status abnormalities, and respiratory distress either alone or in combination.

There is no effective antidote and the mainstay of treatment is hemodynamic support.[10] With careful clinical evaluation, dysregulation of cardiac activity can be prevented, and symptoms can be improved with advanced life support.[8] More specifically, IV calcium, glucagon and insulin-glucose medical treatments are also used.[4] Our patients were given IV calcium,

glucagon, insulin-dextrose treatments after fluid boluses. Bicarbonate infusion was started in patients with resistant acidosis.

The fact that CCBs have a wide distribution in volume in the body and are highly bound to proteins makes it difficult to remove them by extracorporeal methods.[10] Hemodialysis and hemoperfusion can be applied to hemodynamically unstable patients despite initial treatments.[11] There are also case reports in which extracorporeal membrane oxygenation (ECMO) is activated and advanced life support is given to patients who do not respond to other extracorporeal life support.[12] Vasoactive agents, which are one of the main supports in providing hemodynamics, were titrated by frequent blood pressure monitoring in 6 of our patients. With the initiation of ILE treatment in the early period, extracorporeal methods were not needed in any of our patients.

Lipid emulsion has been used as a nutritional supplement as a component of total parenteral nutrition.[13] It has been reported that the use of ILE, known as lipid rescue, is beneficial for local anesthetic toxicity in animal models and human case.[14] Although there is no definitive mechanism of action for the treatment of ILE, there are possible mechanisms. It is thought that the main mechanism in local anesthesia poisoning because of the binding property of the lipid emulsion.[15] ILE can reduce the amount of free drug by keeping the lipophilic medicine in a separate compartment. ILE can promote drug clearance by hepatic administration of compound-laden chylomicrons and can also transition from lipid to glucose metabolism in cardiac myocytes by increasing nitric oxide and α-ketoacids.[16] These compounds increase the calcium influx from blocked cells.

ILE therapy is generally recommended for use in life-threatening poisonings due to its balance of benefits and negative effects, despite a neutral agreement on its general usage regions.[17] It is also recommended to be used for life-threatening bupivacaine and other local anesthetics, amitriptyline, bupropion poisoning where other treatments are ineffective.

Pediatric case series are not commonly found in medical literature. However, Katlan et al.[18] published a pediatric case series and literature review which demonstrated that ILE treatment can be an effective rescue treatment option for patients who do not show cardiovascular improvement despite receiving supportive treatments.

A recommended dosing regimen for lipid emulsion is an infusion of 20% solution, 1 mL/kg over 1 minute, repeated every 3 to 5 minutes for a maximum of 3 mL/kg followed by 0.25 mL/kg/min.[5]

Although further studies are needed, potential adverse events with ILE therapy include allergy, anaphylaxis, fat embolism, thrombophlebitis, and seizures.[13] After ILE treatment, none of our patients had any side effects during their stay in the PICU.

When patients with cardiovascular hemodynamic instability do not respond to initial and advanced supportive treatments, ILE treatment can be considered a rescue therapy. This treatment can help reduce VIS and avoid the need for extracorporeal life support. Therefore, it is important for clinicians to use ILE treatment without prejudice during the early period.

Ethical approval

Batman Training and Research Hospital Scientific Research Ethics Committee approved this study (approval date/no: 22.09.2022 / 319).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AA; data collection: RGS; analysis: MMK; methodology: DA; software; SY; writing – original draft and writing review & editing. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Xiao L, Chen XJ, Feng JK, Li WN, Yuan S, Hu Y. Natural products as the calcium channel blockers for the treatment of arrhythmia: Advance and prospect. Fitoterapia 2023; 169: 105600. https://doi.org/10.1016/j.fitote.2023.105600
2. Gummin DD, Mowry JB, Beuhler MC, et al. 2019 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th annual report. Clin Toxicol (Phila) 2020; 58: 1360-1541. https://doi.org/10.1080/15563650.2020.1834219
3. Ranniger C, Roche C. Are one or two dangerous? Calcium channel blocker exposure in toddlers. J Emerg Med 2007; 33: 145-154. https://doi.org/10.1016/j.jemermed.2007.02.010
4. Walter E, McKinlay J, Corbett J, Kirk-Bayley J. Review of management in cardiotoxic overdose and efficacy of delayed intralipid use. J Intensive Care Soc 2018; 19: 50-55. https://doi.org/10.1177/1751143717705802
5. Weinberg G. Reply to Drs. Goor, Groban, and Butterworth-Lipid Rescue: Caveats and Recommendations for the "Silver Bullet". Regional Anesthesia & Pain Medicine 2004; 29: 74-75. https://doi.org/10.1016/j.rapm.2003.11.009
6. Abernethy DR, Schwartz JB. Calcium-antagonist drugs. N Engl J Med 1999; 341: 1447-1457. https://doi.org/10.1056/nejm199911043411907
7. Hao K, Yasuda S. Calcium-channel blockers: an alternative therapy to beta-blockers for myocardial infarction? JACC Asia 2023; 3: 455-456. https://doi.org/10.1016/j.jacasi.2023.04.002
8. Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol 2016; 81: 453-461. https://doi.org/10.1111/bcp.12763
9. Bathinapatla A, Kanchi S, Chokkareddy R, Puthalapattu RP, Kumar MR. Recent trends in the electrochemical sensors on β- and calcium channel blockers for hypertension and angina pectoris: a comprehensive review. Microchemical Journal 2023; 192: 108930. https://doi.org/10.1016/j.microc.2023.108930
10. Stephen VS, Pluymers NA, Gauton SJ. Emergency management of calcium channel blocker overdose. S Afr Med J 2019; 109: 635-638. https://doi.org/10.7196/SAMJ.2019.v109i9.13704
11. Li H, Ren Z, Guo ZG. Clinical study of characteristics of acute poisoning caused by calcium channel blockers. Chinese General Practice 2023; 26: 1758-1765. https://doi.org/10.12114/j.issn.1007-9572.2022.0798
12. Finn DJ, Stevens J, Tolkacz M, Robinson J, Simpson E, Iacco A. P3: ECMO and calcium channel blocker overdose: a systematic review. ASAIO J 2023; 69(Suppl. 2): 107. https://doi.org/10.1097/01.mat.0000943836.12954.47
13. Krohn K, Koletzko B. Parenteral lipid emulsions in paediatrics. Curr Opin Clin Nutr Metab Care 2006; 9: 319-323. https://doi.org/10.1097/01.mco.0000222118.76536.ad
14. Assiry MM, Aldayini IAA, Howsawi AA. Lipid emulsion treatment for drug toxicity in pediatric patients. Saudi J Med Pharm Sci 2023; 9: 203-213. https://doi.org/10.36348/sjmps.2023.v09i03.010
15. Mazoit JX, Le Guen R, Beloeil H, Benhamou D. Binding of long-lasting local anesthetics to lipid emulsions. Anesthesiology 2009; 110: 380-386. https://doi.org/10.1097/ALN.0b013e318194b252
16. Lee SH, Sohn JT. Mechanisms underlying lipid emulsion resuscitation for drug toxicity: a narrative review. Korean J Anesthesiol 2023; 76: 171-182. https://doi.org/10.4097/kja.23031
17. Gosselin S, Hoegberg LCG, Hoffman RS, et al. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. Clin Toxicol (Phila) 2016; 54: 899-923. https://doi.org/10.1080/15563650.2016.1214275
18. Katlan B, Kesici S, Bayrakci B. Intravenous lipid emulsion treatment for calcium-channel blocker intoxication: pediatric case series and review of the literature. Pediatr Emerg Care 2023; 39: 120-124. https://doi.org/10.1097/PEC.0000000000002703