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# Our Treatment Experience in Poisoning With Calcium Channel Blockers: A Series of Twelve Cases

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## Abstract

**Background:** Intoxications with cardiovascular system drugs constitute a small percentage of all poisoning cases. Calcium Channel Blockers (CCBs) are the most common drug poisoning in this group.
**Objectives:** We aimed to evaluate the effectiveness of treatments for CCB poisoning and add to the current body of literature by outlining the clinical treatments we employ for bradyarrhythmia, hypotension, and resistant vasodilation resulting from CCB poisoning, as well as sharing our clinical insights in this field.
**Methods:** Twelve patients, ranging in age from 1 month to 18 years, were admitted to the Tertiary Paediatric Intensive Care Unit (PICU) for treatment of medication poisoning related to the CCB group. Patients who ingested several drugs that caused CCB were not allowed to participate in the trial.
**Results:** Twelve patients were followed up in the PICU due to poisoning with CCB group drugs. Of the patients, 7 were male and 5 were female. Five of the patients had taken CCB medication with the purpose of committing suicide, and 7 of them accidentally. All of the patients who received CCB to commit suicide had taken verapamil. Five patients whose hypotension and bradycardia continued were administered inotropes. In addition to PI, calcium gluconate, intravenous lipid, glucagon, insulin, bicarbonate, and methylene blue were given as therapy to our symptomatic patients. Plasmapheresis was applied to a patient who was hospitalized in the PICU due to a sudden loss of consciousness.
**Conclusions:** In the management of patients with CCB poisoning, the use of hyperinsulinemia euglycemia, intravenous lipid emulsion treatment, glucagon treatments, and treatments including methylene blue and extracorporeal life support should be considered in cases of resistant hypotension, bradycardia, and coma in the early period.

*Keywords:* Calcium Channel Blockers, Poisoning, Children

## 1. Background

Poisoning with Calcium Channel Blockers (CCBs) should be considered in every patient admitted to the emergency department with bradycardia, hypotension, and shock. Intoxications with Cardiovascular System (CVS) drugs such as ENTs and/or beta-receptor antagonists (BB) constitute a small percentage of all poisoning cases (1). However, the most frequently observed drug intoxication among CVS agents encompasses CCBs (2).

Calcium channel blockers inhibit voltage-gated L-type calcium channels. As a result of the inhibition of these channels, the flow of calcium into the cells is directly inhibited, and the amount of calcium in the cytoplasm decreases. This results in muscle relaxation and arterial dilatation (3, 4). Besides, CCBs reduce systemic vascular resistance and almost always present with low blood pressure and resistant shock (5). Signs of lethargy or agitation, confusion, coma, convulsions, and multiple organ failure may occur due to insufficient organ perfusion as a result of hypotension or bradycardia (5, 6). Also, CCBs inhibit calcium channels in pancreatic islet cells, reducing insulin secretion and resulting in hyperglycemia and reduced cardiac glucose utilization (7).

Calcium channel blockers are mainly excreted by hepatic biotransformation, with around 5% excreted by the kidneys. In life-threatening poisonings, determining

the pharmacokinetics of the drug taken, current approaches, and choosing the extracorporeal method are as important as knowing the drug taken (8). In the management of CCB poisonings, decontamination, hyperinsulinemia euglycemia (HIE), intravenous lipid emulsion (ILE) therapy, glucagon, IV calcium, positive inotropes (PI) such as dopamine and norepinephrine, pacemakers, levosimendan, and extracorporeal treatments such as plasmapheresis and dialysis are used (4).

Recently, ILE treatment has been used as an effective antidote in all lipophilic drug poisonings, especially those with local anesthetic drugs (9, 10). Lipids not only act with systemic toxicity but can also reduce drug levels. In one of their cases, French et al. reported a decrease in verapamil levels after lipid administration (11).

Methylene Blue (MB) has been used for treating CCB poisoning, post-cardiac surgery, septicemia, anaphylaxis, and drug-induced vasodilator shock. Also, MB cleans Nitric Oxide (NO) and inhibits NO synthesis (12).

## 2. Objectives

We aimed to evaluate the effectiveness of treatments for CCB poisoning and add to the current body of literature by outlining the clinical treatments we employ for bradyarrhythmia, hypotension, and resistant vasodilation resulting from CCB poisoning, as well as sharing our clinical insights in this field.

## 3. Methods

We enrolled 12 patients aged one month to 18 years who were followed up in the Tertiary Paediatric Intensive Care Unit (PICU) for poisoning with CCB group drugs between 01/01/2019 and 01/11/2022. Patients with CCB intake through multiple drug intake were excluded from the study. Patient files were obtained from the archives of Diyarbakır Gazi Yaşargil Training and Research Hospital. The patients' daily treatment charts, nurse observations with recorded vital signs, laboratory results, and clinical course were scanned retrospectively from the data in the patient files. Patient age, gender, and length of hospital stay were recorded as demographic data. The patients' arrival times at the hospital and the procedures performed in the emergency department were examined. The clinical course of the patients since their hospitalization was retrospectively scanned from the hospital data. The patients' age, first positive physical examination findings on admission to the PICU, GCS, PRISM scores, medical treatments, and inotropes they received were checked, and their Vasoactive Inotrope Scores (VIS) were calculated based on the highest doses.

VIS score = Dopamine dose (mcg/kg/min) (mcg/kg/min) + 100x Adrenaline dose (mcg/kg/min) + 10x Milrinone dose (mcg/kg/min) + 10000x Vasopressin dose (units/kg/min) + 100x Noradrenaline dose (mcg/kg/min) + Dobutamine dose (13).

### 3.1. Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used as descriptive statistics. The distribution of variables was analyzed with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data, and the chi-square test was used in the analysis of qualitative independent data. The effect level was analyzed by univariate and multivariate logistic regression. Also, the SPSS 15.0 (IBM Corp. Armonk NY) program was used in the analysis. The P values $<0.05$ were considered significant.

### 3.2. Ethics Committee Approval

The approval dated 09/12/2022 and numbered 272 for the study was taken from the Good Clinical Practices Ethics Committee of Diyarbakır Gazi Yaşargil Training and Research Hospital. Consent was obtained from the families for the use of data in patient hospitalization files in academic studies.

## 4. Results

Twelve patients were followed up in the PICU between 01/01/2019 and 01/11/2022 due to poisoning with CCB drugs. The patients had a median of 52.5 (min: 21; max: 213) months old; 7 were male, and 5 were female. Five of the patients had taken CCB medication with the purpose of committing suicide, and 7 of them accidentally. The median age of 5 patients who took CCB with the purpose of committing suicide was 198 (min: 192; max: 213) months, and four of them were girls. Six of the patients received a CCB named verapamil, five received amlodipine, and one received benipin. All of the patients who received a CCB to commit suicide had taken verapamil.

The median time to hospital arrival was 120 minutes (min: 120; max: 210). Gastric lavage and activated charcoal were administered to seven patients in the emergency departments. On admission, 7 of the patients were asymptomatic. The median Glasgow Coma Scale (GCS) of the symptomatic patients was 10 (min: 10; max: 12), and the median PRISM Score was 18 (min: 9; max: 20) (Table 1). The most common findings of the patients

on admission were hypotension, nausea and vomiting, dizziness, hypotension, and bradycardia in 5 patients, followed by confusion in 4 patients, hyperglycemia in 2 patients, and tachycardia in 1 patient, in order of frequency (Table 2).

**Table 1.** Demographic Data of Patients

| Parameters | Patient Data |
|---|---|
| **Age** | 104.08 ± 87.92 |
| **Male/female** | 5/7 |
| **Glasgow Coma Score** | 13.25 ± 2.26 |
| **PRISM Score** | 11.83 ± 4.43 |
| **Hospital arrival time, min** | 120 + 42.3 |
| **Intensive care stay, h** | 62.17 + 56.13 |
| **Hospitalization time, h** | 93.67 + 58.48 |

Abbreviation: PRISM, Pediatric Risk of Mortality.

**Table 2.** Symptoms of Patients

| Variables | No. (%) |
|---|---|
| **Asymptomatic** | 7 (41.6) |
| **Nausea-vomiting** | 5 (41.6) |
| **Dizziness** | 5 (41.6) |
| **Hypotension** | 5 (41.6) |
| **Bradycardia** | 5 (41.6) |
| **Confusion** | 4 (33.3) |
| **Hyperglycemia** | 2 (16.7) |
| **Tachycardia** | 1 (8.3) |

Normal Saline (NS) loading was applied to 6 patients with a capillary refill time of >3 seconds, and the symptoms of one of our patients improved after NS loading. In five patients whose hypotension and bradycardia continued, PI was started. Adrenaline, noradrenaline, and dopamine were administered as inotropes. The median Vasoactive Inotrope Score (VIS) in patients who took PI was 40 (min: 20; max: 70) (Table 1).

In addition to PI, calcium gluconate, intravenous lipid, glucagon, insulin, bicarbonate, and methylene blue were given as single or multiple therapy to our symptomatic patients. The patient, who experienced a sudden loss of consciousness, underwent plasmapheresis after being admitted to the Pediatric Intensive Care Unit (PICU). Initially, the family did not report any drug intoxication. However, after obtaining a detailed medical history, it was discovered that the patient had ingested 4560 mg of verapamil. After 14 hours of intensive care monitoring, the patient regained consciousness, and bradycardia resolved after 36 hours (Table 3).

The median length of PICU stay was 72 (min: 40; max: 232) hours. The median duration of hospitalization was 120 (min: 120; max: 210) hours (Table 1). The patients were taken from the PICU to the pediatric ward 24 hours after their symptoms improved. None of our patients developed complications or died due to the treatment administered.

## 5. Discussion

In our study, six of the 12 patients followed up for CCB intoxication did not need any medical treatment. Since symptoms improved in one of our patients after NS loading, no additional treatment was required. The remaining five patients underwent medical treatments such as PI and calcium gluconate, and plasmapheresis was applied to one. None of our patients died.

In CCB poisonings, the mortality rate is high; cardiac conduction disorders, severe hypotension, cardiogenic shock, and pleural effusion may also occur (14). In patients with severe bradycardia, dopamine (10 - 20 $\mu$g/kg/min), which has a prominent tachycardic effect, can be used as the first choice as PI. It can be used in combination with norepinephrine and dobutamine in patients with acute pulmonary edema or severe ventricular dysfunction (14). There are also publications recommending adrenaline infusion (1 - 10 $\mu$g/min) for patients whose hypotension persists despite PI treatment (15). In our study, we administered dopamine, adrenaline, and noradrenaline as PI to 5 patients with severe bradycardia and hypotension. In patients who received PI, our median VIS value was 40.

Calcium gluconate was started as an antidote in all patients (Table 3). Calcium salts are recommended as antidotes as the first step in the treatment of CCB poisoning. Calcium chloride is preferred to calcium gluconate since it provides a higher concentration of ionized calcium. If the patient's hypotension persists despite calcium infusion and if the clinical response is inadequate, glucagon should be added to the treatment. Glucagon was added to the treatment of all of our patients who received PI and calcium gluconate, as none presented adequate response in the follow-up. Insulin was started in two of these patients since they did not present adequate clinical response. Another treatment applied is HIE. As known, HIE and glucagon therapy are recommended because they create positive chronotropic and inotropic effects on the heart and improve glucose utilization (16).

Akinci and Koylu published a case in which a patient whose hypotension continued despite maximum therapy was successfully resuscitated with ILE treatment (17). Montiel et al. reported that in a case of slow-release diltiazem poisoning with 3.6 g, the patient's need for pace

**Table 3.** Treatments Given to Symptomatic Patients

| | VIS Score | PI | IV Calciumgluconate | ILE | Glucagon | Insülin | Metilen Blue | Sodiumbicarbonate | Plasmapheresis |
|---|---|---|---|---|---|---|---|---|---|
| **Case 1** | 70 | + | + | + | + | + | - | - | + |
| **Case 2** | 40 | + | + | + | + | - | - | - | - |
| **Case 3** | 20 | + | + | + | + | - | + | + | - |
| **Case 4** | 30 | + | + | - | + | - | - | - | - |
| **Case 5** | 40 | + | + | + | + | + | + | - | - |

Abbreviations: VIS, Vasoactive Inotrope Score; PI, positive inotrope; IV, intravenous; ILE, intravenous lipid emulsion.

and vasopressor disappeared with ILE treatment and HIE (18). For ILE treatment in CCB poisoning, the first bolus dose of 1.5 ml/kg, followed by an infusion of 0.25 - 0.5 ml/kg/hour, is recommended (19). A significant decrease in the need for positive inotrope was observed within an average of 2 - 4 hours after ILE treatment. The results regarding ILE treatment were observed to be similar to other studies.

Almost all CCB drugs are high in plasma protein binding and are also fat-soluble drugs. Since they are primarily metabolized in the liver, total plasma exchange (TPD) should always be considered in the treatment of patients unresponsive to medical therapy (20, 21). For one of our patients who presented with sudden loss of consciousness but no history of intoxication, plasmapheresis was performed at the fourth hour due to presenting hypotension and bradycardia unresponsive to PI. The patient regained consciousness at the 14th hour of follow-up, and the patient's bradycardia regressed after approximately 36 hours. As seen in our case, plasmapheresis should be considered as an option in CCB intoxication.

Aggarwal et al. reported clinical improvement after the administration of MB in hypotension caused by vasodilator shock in cases of CCB poisoning resistant to inotropes (22). The recommended MB dose is 2 mg/kg/dose (13). Also, MB was administered to two of our patients who had loss of consciousness in addition to hypotension and bradycardia, were resistant to vasopressors, and did not respond to any other treatment; as a result, their bradycardia improved in 4 - 6 hours after MB administration.

In the management of patients with critical findings in CCB poisoning, decontamination, IV calcium, PI treatments, and other treatments should be applied by making quick decisions when necessary. In the management of patients with CCB poisoning, the use of HIE, ILE treatment, glucagon treatments, as well as treatments including methylene blue and extracorporeal life support should be considered in cases of resistant hypotension, bradycardia and coma in the early period. Studies in the literature are generally case reports (3, 7, 10, 18, 21, 22). We believe that the data presented regarding these 12 cases will provide an approach for physicians when encountering CCB intoxication.

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## Footnotes

**Authors' Contribution:** M.N.T., M.N.Ö., Ö.O. conceived and designed the evaluation and drafted the manuscript. M.N.T. and M.K. E.E.T. participated in designing the evaluation, performed parts of the statistical analysis, and helped draft the manuscript. M.N.T., M.N.Ö., and Ö.O. re-evaluated the clinical data, revised the manuscript, performed the statistical analysis, and revised the manuscript. M.N.T. and M.K. E.E.T. collected the clinical data, interpreted them, and revised the manuscript. M.N.T., M.N.Ö., and Ö.O. re-analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

**Conflict of Interests:** As the corresponding author, I declare that there is no conflict of interest.

**Data Availability:** The dataset presented in the study is available on request from the corresponding author during submission or after publication.

**Ethical Approval:** The approval dated 09/12/2022 and numbered 272 for the study was taken from the Good Clinical Practices Ethics Committee of Diyarbakır Gazi Yaşargil Training and Research Hospital and uploaded to the system as an additional file.

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**Informed Consent:** Consent was obtained from the families for the use of data in patient hospitalization files in academic studies.

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