Postprint: Clinical Features of Acute Calcium Channel Blocker Poisoning

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Abstract

Background: Calcium channel blockers (CCBs) are the most commonly used class of antihypertensive drugs in China. Severe CCBs poisoning is associated with high mortality, yet there are currently few reports on its clinical characteristics.

Objective: To analyze the clinical features of acute CCBs poisoning and the value of blood purification therapy by summarizing the clinical manifestations, diagnosis, and treatment outcomes of 11 patients with acute CCBs poisoning.

Methods: This study retrospectively analyzed the clinical manifestations, scores, treatment course, and prognosis of 11 patients with acute CCBs poisoning who presented to the Emergency Department of Peking University Third Hospital between January 2019 and June 2022.

Results: Among the 11 patients with acute CCBs poisoning, there were 3 females and 8 males; the mean age was (39.82$±$18.01) years; the median interval from drug ingestion to medical consultation was 2.25 (6.58) hours. The main clinical manifestations at presentation included shock in 9 cases (81.8%), nausea and vomiting in 5 cases (45.5%), dizziness in 4 cases (36.4%), fatigue in 3 cases (27.3%), increased heart rate in 3 cases (27.3%), decreased heart rate in 2 cases (18.2%), syncope in 1 case (9.1%), and lethargy in 1 case (9.1%). The vast majority (91%) of patients were conscious upon arrival at the emergency department (GCS 15 points). In addition to conventional treatment, 6 patients received blood purification therapy, including 2 cases of hemoperfusion combined with plasma exchange and CVVH, 2 cases of hemoperfusion combined with CVVH, and 2 cases of hemoperfusion alone. Among these 6 patients, 4 received extracorporeal membrane oxygenation (ECMO) therapy. Re-examination after the first blood purification treatment revealed decreases in all CCBs blood drug concentrations, with the nifedipine decrease rate (40.00%-63.64%) being higher than that of amlodipine and verapamil (9.09%-26.67%). The survival rate of the 11 patients at discharge was 81.8%. The median APACHE II score at 24

hours after admission was 10 (25) points. The median PSS score at admission was 3 (1) points. Among the 8 patients with an admission PSS score of 3, 2 died (2/8, 25%), while among the 5 patients with an admission APACHE II score $ $15, 2 died (2/5, 40%).

Conclusion: Early shock with preserved consciousness is a relatively common manifestation of acute CCBs poisoning. In terms of reducing blood drug concentration, hemoperfusion may be more effective in acute nifedipine poisoning than in acute amlodipine and verapamil poisoning. The APACHE II score may be superior to the PSS score in predicting mortality prognosis in acute CCBs poisoning.

Full Text

Preamble

Clinical Study of Characteristics of Acute Poisoning Caused by Calcium Channel Blockers

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Abstract

Background: Calcium channel blockers (CCBs) are the most commonly used antihypertensive drugs in China. Severe CCBs poisoning carries a high mortality rate, yet there are few reports on its clinical characteristics at present. **Objective:** To analyze the clinical features of acute CCBs poisoning and the value of blood purification treatment by summarizing the clinical manifestations, diagnosis, and treatment outcomes of 11 patients with acute CCBs poisoning. **Methods:** We retrospectively analyzed the clinical manifestations, scores, treatment processes, and prognoses of 11 patients admitted to the Emergency Department of Peking University Third Hospital for acute CCBs poisoning between January 2019 and June 2022. **Results:** Among the 11 patients, 3 were female and 8 were male, with a mean age of (39.82$±$18.01) years. The median interval between drug ingestion and presentation was 2.25 (6.58) hours. The main clinical manifestations upon arrival were shock in 9 cases (81.8%), nausea and vomiting in 5 cases (45.5%), dizziness in 4 cases (36.4%), fatigue in 3 cases (27.3%), tachycardia in 3 cases (27.3%), bradycardia in 2 cases (18.2%), syncope in 1 case (9.1%), and lethargy in 1 case (9.1%). The vast majority (91%) of patients

were conscious (GCS 15) upon arrival at the emergency department. In addition to conventional treatment, 6 patients received blood purification therapy, including 2 who received hemoperfusion combined with plasma exchange and CVVH, 2 who received hemoperfusion combined with CVVH, and 2 who received hemoperfusion alone. Among these 6 patients, 4 received extracorporeal membrane oxygenation (ECMO) treatment. After the first blood purification treatment, blood CCBs concentrations decreased in all cases, with the reduction rate for nifedipine (40.00%-63.64%) being higher than that for amlodipine and verapamil (9.09%-26.67%). The survival rate at discharge was 81.8%. The median APACHE II score at 24 hours after admission was 10 (25), and the median PSS score at admission was 3 (1). Among the 8 patients with an admission PSS score of 3, 2 died (2/8, 25%), while among the 5 patients with an admission APACHE II score $ $15, 2 died (2/5, 40%). **Conclusion:** Maintaining consciousness in the early stage of shock is a relatively common manifestation of acute CCBs poisoning. Hemoperfusion may be more effective in reducing blood drug concentrations in acute nifedipine poisoning than in acute amlodipine or verapamil poisoning. The APACHE II score may be superior to the PSS score in predicting mortality prognosis in acute CCBs poisoning.

Keywords: Calcium channel blockers; Poisoning; Blood concentration; Blood purification; Clinical score

Introduction

Calcium channel blockers (CCBs), also known as calcium antagonists, are drugs that primarily block calcium channels on the cell membranes of cardiac and vascular smooth muscle cells, inhibiting extracellular calcium influx and reducing intracellular calcium levels to alter cardiovascular and other organ functions. They represent the most commonly used class of antihypertensive medications clinically. CCBs are divided into dihydropyridines and non-dihydropyridines, with typical dihydropyridine representatives including nifedipine and amlodipine, and non-dihydropyridine representatives including diltiazem and verapamil. According to surveys, the crude prevalence of hypertension among Chinese adults aged 18 and above is 27.9%, with a weighted prevalence of 23.2% [1], suggesting that approximately one in four adults has hypertension, with a total of 244 million hypertensive patients [2]. CCBs have the highest prescription frequency among antihypertensive drugs used in primary healthcare institutions in China [3]. Additionally, CCBs are used for coronary artery disease and certain arrhythmias. Severe CCBs poisoning carries a high mortality rate; CCBs poisoning accounted for 4.62% of poisoning-related deaths reported by American poison control centers in 2019 [4], increasing to 6.4% in 2020 [5], showing an upward trend. However, there are currently few clinical reports on acute CCBs poisoning internationally and domestically, mostly consisting of case reports. This study retrospectively analyzed 11 consecutive cases of acute calcium channel blocker poisoning admitted to Peking University Third Hospital from

January 2019 to June 2022 to explore the clinical manifestations, treatment measures, and prognosis of acute CCBs poisoning, providing references for clinicians in managing such patients.

Methods

1.1 Study Subjects

We selected patients with acute calcium channel blocker poisoning consecutively admitted to the Emergency Department of Peking University Third Hospital from January 2019 to June 2022 as study subjects. **Inclusion criteria:** (1) Age $ $16 years; (2) Clear history of excessive CCBs ingestion within a short period (48 hours) or blood drug concentration indicating CCBs exceeding the normal therapeutic range; (3) Clinical manifestations of CCBs poisoning. **Exclusion criteria:** (1) Suspected CCBs overdose but negative blood drug concentration test; (2) Patients with hypotension, bradycardia, or similar clinical manifestations but negative blood drug concentration test.

1.2 Data Collection

Using the electronic medical record system of Peking University Third Hospital, we collected relevant patient data including gender, age, past medical history, poisoning cause and dose, and clinical manifestations. We gathered clinical vital signs and laboratory indicators including blood routine, liver function, kidney function, cardiac enzymes, electrolytes, glucose, coagulation function, NT-pro BNP, troponin I, procalcitonin, blood gas analysis, and initial and post-blood-purification blood drug concentrations. We collected examination results including echocardiography, head CT, chest X-ray, and electrocardiogram. We documented main treatment methods such as gastric lavage, vasoactive drugs, cardiopulmonary resuscitation, blood purification therapy, and organ function support treatments including mechanical ventilation and extracorporeal membrane oxygenation (ECMO). We also recorded hospitalization duration and survival rate at discharge. The Glasgow Coma Scale (GCS) was used to assess patient consciousness status, the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Poisoning Severity Score (PSS) were used for condition assessment, and the Cerebral Performance Category (CPC) was used to evaluate neurological prognosis in patients after cardiopulmonary resuscitation.

1.3 Statistical Methods

SPSS 23.0 statistical software was used for data processing. Normally distributed measurement data were expressed as mean ± standard deviation, non-normally distributed measurement data were expressed as median (interquartile range), and count data were expressed as frequency and percentage.

Results

2.1 Patient Demographics

A total of 11 patients with acute calcium channel blocker poisoning were included, numbered 1-11 (corresponding relationships in each table below are consistent). Among them, 8 were male and 3 were female, aged 19-74 years with a mean age of (39.82$±$18.01) years. Six patients had a history of hypertension and regularly took CCBs, 5 had psychiatric disorders, 3 had diabetes, 2 had old cerebral infarction, 1 had nephrotic syndrome, 1 had coronary heart disease, and 1 had iron deficiency anemia. Details are shown in Table 1 .

Table 1 Demographic Characteristics of Patients
Note: + indicates present, - indicates absent

2.2.1 Medication and Drug Concentrations

Among the 11 cases, 9 involved intentional overdose, 1 was accidental ingestion, and 1 developed poisoning during normal medication use. Eight cases involved concurrent ingestion of multiple drugs. Except for 1 case where the overdose time could not be determined due to normal medication use, the interval between overdose and presentation ranged from 0.5-10 hours, with a median of 2.25 (6.58) hours. All patients completed blood drug concentration testing at presentation. Specific results are shown in Table 2 .

Table 2 The Oral Dose and Maximum Plasma Concentration of Patients

2.2.2 Clinical Manifestations

The main clinical manifestations upon arrival were shock in 9 cases (81.8%), nausea and vomiting in 5 cases (45.5%), dizziness in 4 cases (36.4%), fatigue in 3 cases (27.3%), tachycardia in 3 cases (27.3%), bradycardia in 2 cases (18.2%), syncope in 1 case (9.1%), and lethargy in 1 case (9.1%). Shock was defined as: systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, or requiring $ $2 vasopressors [6]. The 2 patients (No. 4 and No. 6) with normal blood pressure at presentation subsequently developed hypotension during observation, with systolic pressure dropping by more than 30%. Specific clinical manifestations are shown in Table 3 .

Table 3 Clinical Manifestations of Patients on Arrival
Note: + indicates present, - indicates absent

2.3 Laboratory Findings

Initial laboratory tests upon arrival showed elevated white blood cells in 8 cases, primarily neutrophilia; elevated lactate levels in 8 cases; hyperglycemia in 5 cases; acute renal insufficiency in 3 cases; metabolic acidosis in 2 cases; and elevated troponin in 2 cases. Details are shown in Table 4 . Two patients with

refractory shock (No. 1 and No. 10) and two more critically ill patients with cardiac arrest (No. 7 and No. 9) developed multiple organ dysfunction during hospitalization, including leukocytosis, thrombocytopenia, renal insufficiency, hepatic insufficiency, myocardial injury, markedly elevated creatine kinase levels, hyperglycemia, metabolic acidosis, pancreatic injury, and coagulation dysfunction. Details are shown in Table 5 .

Table 4 The Abnormal Results of Patient' s First Test
Note: + indicates present, - indicates absent

Table 5 Main Laboratory Results of Patients with Multiple Organ Dysfunction

2.4.1 Main Treatment Measures

Except for patient No. 3, all 11 patients received gastric lavage; patients No. 1 and No. 5 initially presented to external hospitals, received gastric lavage, and were then transferred. Although patient No. 7 presented more than 6 hours after ingestion, gastric lavage was still performed due to the massive overdose. Three patients received activated charcoal, and 2 received cathartics. All patients received fluid resuscitation, with 8 requiring vasoactive drugs for blood pressure support, 8 receiving calcium agents, 8 receiving high-dose insulin-glucose therapy, and 6 receiving lipid emulsion. Two patients with bradycardia received atropine, and 1 received temporary pacing. Three patients underwent cardiopulmonary resuscitation (patient No. 1 developed CA after ECMO and received CPR; patient No. 7 had asystole during CA, underwent extracorporeal cardiopulmonary resuscitation (ECPR) and regained spontaneous circulation; patient No. 9 had ventricular fibrillation during CA, and regained spontaneous circulation after ECPR and blood purification therapy). Four patients received ECMO (patients No. 1 and No. 10 for refractory shock; patients No. 7 and No. 9 for ECPR), 5 received endotracheal intubation and mechanical ventilation, and 6 received blood purification therapy. Details are shown in Table 6 .

Table 6 Therapeutic Measures of Patients
Note: + indicates used, - indicates not used. , outside hospital.*

2.4.2 Blood Purification Treatment and Drug Concentration Changes

Among the 6 patients who received blood purification therapy, all received hemoperfusion (treatment duration 2-3 hours each session, heparin anticoagulation, interval between sessions 8, 12, or 24 hours based on condition). Patients No. 1 and No. 10 also received plasma exchange (treatment dose 2000 ml each session). Patients No. 1, 7, 9, and 10 received continuous veno-venous hemofiltration (CVVH) for acute renal insufficiency (treatment duration 5-17 hours each session). Details are shown in Table 7 . After the first hemoperfusion and plasma exchange, blood CCBs concentrations decreased in all patients, as shown in Table 8 .

Table 7 Methods and Times of Blood Purification
Note: - indicates not used. Hemoperfusion+CVVH indicates hemoperfusion filter connected in series with hemofiltration filter, starting simultaneously; CVVH continued after hemoperfusion ended.

Table 8 The Plasma Concentration of Patients Before and After the First Blood Purification
Note: The first hemoperfusion or plasma exchange was not performed simultaneously with CVVH.

2.5 Prognosis

After treatment, 9 of the 11 patients survived, with a discharge survival rate of 81.8%. All 9 survivors had a GCS score of 15 at discharge. Among the 3 patients who received CPR, 2 died (patients No. 1 and No. 7) with CPC grade 5, while 1 survived (patient No. 9) with CPC grade 1 at discharge, having only peripheral nerve injury as a sequela of ECMO treatment. The APACHE II scores at 24 hours after admission ranged from 5-43, with a median of 10 (25). Admission PSS scores ranged from 1-3, with a median of 3 (1). Hospitalization duration was 1-32 days, with a median of 4 (4) days. Details are shown in Table 9 .

Table 9 The Clinical Score, Hospitalization Days and Prognosis of Patients

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Discussion

Our results show that acute CCBs poisoning in adults primarily affects middle-aged individuals and is more common in males. The route of exposure was exclusively oral ingestion (11/11, 100%), with most cases (8/11, 73%) being intentional self-poisoning. European reports indicate that adults (18-65 years) account for 48% of CCBs poisoning exposures, with 50% being intentional [7], proportions that are lower than those observed in our study. Due to their widespread use and easy availability, poisoning events can occur not only in patients with psychiatric histories or those taking these drugs for hypertension, but also in previously healthy young individuals.

The majority of cases in this study involved mixed poisoning with multiple drugs (8/11, 73%), with cardiovascular drugs being the most common co-ingestants, making the condition more complex and severe. The most common CCBs in acute poisoning cases were amlodipine, followed by nifedipine. Among the 2 deceased patients, 1 had amlodipine poisoning and 1 had mixed amlodipine and nifedipine poisoning. Data from American poison control centers in 2020 showed that CCBs ranked 6th among substances causing fatal poisoning, with amlodipine being the most common, followed by verapamil, diltiazem, and nifedipine [5].

The main clinical manifestation upon presentation was shock (8/11, 73%), with the vast majority requiring vasoactive drugs, and even refractory shock requiring ECMO support. Notably, although most patients presented in shock, except for 1 patient with verapamil plus metoprolol poisoning who had impaired consciousness (GCS 9), the majority of CCBs poisoning patients (10/11, 91%) remained conscious (GCS 15). This relatively "stable" early consciousness status may mislead clinicians regarding disease severity, particularly in busy clinical settings, and warrants attention. We also observed that most patients (8/11, 73%) had elevated blood lactate levels at admission, reflecting inadequate tissue and cellular perfusion and oxygen metabolism disorders.

The cardiovascular toxicity manifestations of CCBs poisoning are determined by their pharmacological effects. At therapeutic doses, dihydropyridines preferentially block calcium channels in vascular smooth muscle, potentially causing reflex sympathetic activation and tachycardia, while non-dihydropyridines block calcium channels in cardiac cells, inhibiting sinoatrial and atrioventricular node function. Generally, non-dihydropyridine CCBs poisoning can cause severe hypotension and bradycardia, leading to conduction system disturbances [8-9]. Dihydropyridine CCBs overdose typically produces marked hypotension with reflex tachycardia [10]. Cases of bradycardia secondary to loss of selectivity in dihydropyridine poisoning have also been reported [11].

The relatively "stable" early consciousness status in CCBs poisoning is hypothesized to be related to the neuroprotective effects of calcium channel antagonists on the central nervous system, though the mechanism remains unclear. Research has found that cerebral infarction due to local cerebral circulation impairment involves multiple pathophysiological cascades, including calcium overload, excitatory amino acid toxicity, free radical damage, nitric oxide (NO), and inflammatory responses, ultimately leading to activation of apoptosis-regulating genes and neuronal death [12]. Throughout this process, calcium influx through various calcium channels into nerve cells is particularly important in causing neural tissue injury. When intracellular calcium overload occurs, various degradative enzymes are activated, leading to disintegration of important structures such as cell membranes, cytoskeletal proteins, and nucleic acids. Additionally, increased free radical production and accelerated Ca2+-dependent ATPase decomposition can cause neuronal death and aggravate ischemic brain damage [13-14]. Calcium channel blockers can serve as a therapeutic measure to protect nerve cells by preventing pathological calcium overload. Animal experiments and clinical studies have confirmed that dihydropyridine calcium channel blockers such as lercanidipine and nicardipine can protect brain cells [15,16]. Animal experiments have also shown that in a rat model of acute cerebral ischemia-reperfusion injury, amlodipine can cross the blood-brain barrier to protect brain cells by reducing free radical generation and alleviating cerebral edema during ischemia-reperfusion [17]. In a mouse model of focal cerebral ischemia, levamlodipine may help reduce ischemic infarct volume [18].

Consensus recommendations for treating CCBs poisoning include first-line treat-

ments of fluid resuscitation, calcium agents, vasoactive drugs, and high-dose insulin, with intravenous lipid emulsion recommended for refractory patients. For refractory shock and periarrest resuscitation, high-dose insulin, intravenous lipid emulsion, and V-A ECMO are emphasized, with atropine recommended for bradycardia and conduction block, and pacing for refractory cases [19]. Based on disease severity, our study cases utilized all treatment methods mentioned in the consensus. Among them, 1 patient received temporary pacing, 3 received CPR, 4 received ECMO, 5 received endotracheal intubation and mechanical ventilation, and 6 received blood purification therapy.

Blood purification therapy for acute severe poisoning is a safe and effective treatment modality [20]. Both domestic and international case reports have documented good clinical outcomes using plasma exchange in massive CCBs poisoning [21,22]. However, due to the large apparent volume of distribution and high intrinsic clearance of CCBs (amlodipine protein binding 98%, apparent volume of distribution 20-25 L/kg, intrinsic clearance 300-450 ml/min; nifedipine protein binding 90-95%, apparent volume of distribution 1-2 L/kg, intrinsic clearance 400-600 ml/min; diltiazem protein binding 80%, apparent volume of distribution 3-6 L/kg, intrinsic clearance 600-800 ml/min; verapamil protein binding 85-90%, apparent volume of distribution 2.5-5 L/kg, intrinsic clearance 600-1000 ml/min), the EXTRIP workgroup currently does not recommend extracorporeal methods to enhance elimination of amlodipine, diltiazem, and verapamil in severe poisoning [23]. It must be noted, however, that these parameters were obtained under normal physiological conditions and differ significantly under pathological conditions of poisoning, particularly with circulatory failure, organ hypoperfusion, and hepatic/renal insufficiency, where intrinsic clearance decreases substantially, making exogenous clearance methods more important.

Our observations showed that nifedipine blood concentration decreased more than amlodipine and verapamil after hemoperfusion (40%-63.64%), suggesting that hemoperfusion may be considered as a clearance method in acute severe nifedipine poisoning. Domestic reports have also documented good recovery in massive nifedipine poisoning after active hemoperfusion treatment [24]. Our study also found that acute poisoning with these drugs mostly involved mixed drug ingestion, with multiple drugs potentially having synergistic effects that enhance toxicity. Compared with CCBs, other drugs showed higher reduction rates after blood purification; for example, in patient No. 2, valsartan decreased by 43.7% after hemoperfusion, difenidol by 58.06%; in patient No. 7, metformin decreased by 51.85% and metoprolol by 50%; in patient No. 9, captopril decreased by 78.57%, digoxin by 62.07%; and in patient No. 10, metoprolol decreased by 52% after hemoperfusion and 66.67% after plasma exchange. This suggests that when CCBs are mixed with other drugs, particularly with large doses, blood purification methods such as hemoperfusion or plasma exchange are worth attempting. We also observed that hemoperfusion and plasma exchange had similar effects on blood drug concentrations, but hemoperfusion is more clinically accessible, requires no large amounts of plasma, and is relatively simpler to perform, offering undeniable advantages.

Our evaluation of PSS and APACHE II scores in early CCBs poisoning admission found that the APACHE II score may be superior to the PSS score in predicting mortality. Among 8 patients with admission PSS score of 3 (severe), 2 died (2/8, 25%), while among 5 patients with admission APACHE II score $ $15, 2 died (2/5, 40%). Studies comparing PSS, APACHE II, SAPS II, and SOFA scoring systems in acute poisoning prognosis assessment have concluded that APACHE II has better predictive ability and accuracy than the other three systems [25]. Other research has shown that APACHE II is superior to PSS in predicting mortality in acute organophosphate poisoning [26], consistent with our observations. The predictive value of different scoring systems for CCBs poisoning prognosis requires confirmation through larger prospective clinical studies.

In conclusion, shock is the most prominent clinical manifestation of CCBs poisoning. CCBs suppress the cardiovascular system and circulation, with severe cases at risk of refractory cardiogenic shock, circulatory collapse, and even cardiac arrest. Maintaining consciousness in the early stage of poisoning is a relatively common manifestation of CCBs poisoning that deserves particular clinical attention and enhanced recognition of shock. The reduction rate of nifedipine blood concentration after hemoperfusion is higher than that of amlodipine and verapamil, suggesting that hemoperfusion may be considered as a clearance method in acute severe nifedipine poisoning. The APACHE II score may be superior to the PSS score in predicting mortality prognosis in acute CCBs poisoning.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.