Intrapleural and Intraperitoneal Free Fluid in Calcium Channel Blocker Overdose

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Abstract

Aim: Toxicity findings affecting many systems, particularly the cardiovascular system, are observed in calcium channel blocker (CCB) overdose. Here, we aimed to present the incidence of CCB overdose patients with intraperitoneal and intrapleural free fluids detected by abdominal ultrasonography (USG).

Materials and Methods: CCB overdose patients admitted to the emergency room in a 2-year period were prospectively included. All patients with CCB overdose were evaluated by bedside abdominal USG in terms of the presence of pleural and peritoneal fluid.

Results: A total of 14 patients with CCB poisoning were included in our study. Six (42.8%) patients had taken verapamil, 7 (50%) patients amlodipine, and 1 (7.2%) patient nifedipine. The mean age of the patients was 27.2±15.9 years (range: 18–65 years). The median time from drug intake to arrival at the hospital was 3.0 h (IQR: 1.75–5). Nine (64.28%) of these patients were detected to have intraperitoneal and intrapleural free fluid by bedside USG. The mean arterial pressure of patients with intraabdominal and intrapleural fluid was lower than that of patients without the detected fluid, i.e., 56.8 (IQR: 54.8–61.8) vs. 65.6 (IQR: 64.2–66.8), respectively ($p<0.001$).

Conclusion: Besides the cardiovascular findings, intraperitoneal and intrapleural free fluid is also a common feature in CCB overdose. Bedside USG may help to identify these patients. *(Eurasian J Emerg Med 2016; 15: 82-5)*

Keywords: Hypotension, calcium channel blocker, overdose, peritoneal free fluid, pleural free fluid

Introduction

Calcium channel blockers (CCBs) are used in the treatment of hypertension, angina pectoris, Reynaud's phenomenon, arrhythmia, and for the prophylaxis of migraine. All CCBs show their physiological effects by blocking voltage-sensitive calcium channels (L-type). The cardiac effects of excessive intake are myocardial depression, cardiovascular collapse, heart block, bradycardia, vasodilatation (relative volume deficit), and hypotension. These effects emerge in the first few hours after ingesting standard pills, while it can take up to 18–24 h with slow-release medications. Nausea and vomiting are common and occur because of ileus or even ischemia in the intestine (1, 2). In addition, hyperglycemia, lactic acidosis, seizures, coma, and non-cardiogenic pulmonary edema have been reported in CCB overdose (1, 3).

Intestinal tract complications such as mesenteric ischemia, paralytic ileus, colonic ischemia, pseudo-obstruction, gangrene, and perforation in the terminal ileum and cecum have been reported as case reports with CCB overdose in previous studies (2, 4-7).

In this study, we aimed to present the incidence of CCB overdose patients with intraperitoneal and intrapleural free fluids detected via abdominal ultrasonography (USG).

Materials and Methods

Calcium channel blockers overdose cases admitted to the emergency room in a 2-year period were studied prospectively. The local ethics committee approved the study. Patients under 18 years of age and who were poisoned with multiple drugs were

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excluded. The diagnosis of CCB drug poisoning was confirmed with information obtained from the patients or their relatives, presentation of the drug boxes, and the presenting clinical findings of the patient. Determining an exact toxic dose for a given individual was difficult because of the variability in patient-specific factors, such as age, weight, genetics, health status, and other recently ingested substances. The minimum toxic doses were determined to be 0.03 g for amlodipine, 0.16 g for verapamil, and 0.2 g for nifedipine by considering the lowest reported toxic doses for adults (8). The demographic characteristics of the patients (age, gender), time of arrival at the hospital, type of suspected drug intake, stated amount of drug taken (g), vital signs (pulse rate per minute, blood pressure), physical examination findings, laboratory values, given treatment, results of bedside USG, and situation regarding patient survival were recorded in the standard data form. USG examinations of patients were conducted by a radiologist. Patients whose mean arterial pressure (MAP) was under <65 mmHg were considered to be hypotensive. Patients with pleural and peritoneal fluids detected with USG were called back for control 10 days after hospital discharge and USG was performed again.

Statistical analysis

The Statistical Package for the Social Sciences version 21 (IBM SPSS Statistics, New York, USA) statistical software was used for the analysis of data. Numerical variables were given as the mean, median, and interquartile ratio (IQR), whereas categorical variables were given as frequencies (n) and percentages. Because the data were not normally distributed, two group comparisons of the numeric variables were performed by Mann–Whitney U test. All the hypotheses were constructed as two tailed, and an alpha critical value of 0.05 was accepted as significant.

Results

During the study period, there were 33 patients with CCB overdose, 19 (58%) of whom were excluded because of other multiple drug ingestions. A total of 14 patients, 11 (78.5%) female and 3 (21.5%) male, with CCB poisoning were included in our study. The characteristics of the patients with CCB poisoning are shown in Table 1. The mean age of the patients was 27.2±15.9 years (range 18–65 years). The median time from drug intake to arrival at the hospital was 3.0 (IQR: 1.75–5) h. All of the patients were taking the drugs in an attempt to commit suicide. Six (42.8%) patients had taken verapamil, 7 (50%) patients amlodipine, and 1 (7.2%) patient nifedipine. A 65-year-old patient with known hypertension and coronary artery disease was found to have attempted suicide with his own CCB drugs, whereas the other patients had no previous history of cardiovascular diseases or chronic medication use. The aforementioned 65-year-old patient had AV complete block just after entering ED. The block failed to respond to atropine and external cardiac pacemaker treatment. He died 3 h after hospital admission. Among the surviving patients, none of them were on medication, except a woman who was using oral contraception.

The MAP of patients was 61.8 mmHg (IQR: 56.4–65.3). The MAP of patients with detected intraabdominal and intrapleural fluid and without detected fluid was 56.8 (IQR: 54.8–61.8) and 65.6 (IQR: 64.2–66.8), respectively ($p<0.001$). Patients with hypotension were treated with an intravenous infusion of calcium and inotropic treatment.

Nine (64.8%) of 14 patients were found to have free fluid in the peritoneum and pleura. None of the other patients had abdominal pain or constipation. Physical examination findings of the acute abdomen (defense, rebound) were not present. The mean laboratory values of the patients are shown in Table 2, except for the mortality case, whose laboratory values were unavailable. Table 3 shows the

Table 1. Characteristics of the study patients with CCB poisoning

Age (years)/ gender	Pulse rate (/minute)	MAP (mmHg)	Time of arrival at hospital after drug intake (h)	Type of suspected drug	Stated amount of drug taken (g)	Intrapleural fluid	Intraperitoneal fluid	Dead
18/F	45	53.8	1	V	2.8	+	+	-
29/F	58	63.3	3	N	0.3	+	+	-
18/F	51	61.7	5	V	4.8	+	+	-
19/F	47	53.2	2	A	0.2	+	+	-
65/M	59	55.9	5	A	0.2	+	+	+
20/F	56	56.8	5	A	0.3	+	+	-
23/F	47	56.6	2	V	4.8	+	+	-
18/F	62	59.4	1	A	0.3	+	+	-
19/M	60	62.0	3	A	0.15	+	+	-
38/M	59	63.1	5	V	1.44	-	-	-
32/F	60	65.3	4	A	0.08	-	-	-
19/F	68	66.4	1	A	0.1	-	-	-
18/F	57	65.6	5	V	2.4	-	-	-
48/F	71	67.2	3	V	1.2	-	-	-

CCB: calcium channel blocker; F: female; M: male; MAP: mean arterial pressure; V: verapamil; A: amlodipine; N: nifedipine

Table 2. Laboratory values of patients

Laboratory data	Mean values of patients	Normal value
White blood cell	15.7±4.9	4.5–11 µL
Hemoglobin	11.7±2.0	13.6–17.2 g/dL
Hematocrit	35.3±5.0	39.5%–50.3%
Platelet count	225.8±95.5	156–373 µL
Glucose	170.5±71.4	70–105 mg/dL
Aspartate aminotransferase	20.4±9.8	<30 U/L
Alanine aminotransferase	13.8±13.6	<30 U/L
Blood urea nitrogen	13.4±5.6	8–25 mg/dL
Creatinine	1.1±0.6	0.9–1.3 mg/dL
Sodium	139.3±3.2	135–145 mmol/L
Potassium	3.8±0.6	3.5–5.1 mmol/L
Ionized calcium	1.25±0.07	1.1–1.3 mmol/L
INR	1.27±0.21	1
pH	7.31±0.03	7.35–7.45
Bicarbonate	18.8±2.6	22–28 mmol/L

Table 3. ECG changes of the patients during observation

ECG findings	n (%)
Severe Sinus Bradycardia (<50/min)	5 (35.7)
Complete AV block	1 (7.1)
Prolonged PR	4 (28.6)
QRS widening	2 (14.2)
Ventricular early beat	3 (21.4)
ST-T wave changes	1 (7.1)
Premature atrial contractions	0

ECG: Electrocardiography; PR: PR interval; QRS: QRS duration; ST: ST segment; T: T wave

electrocardiography (ECG) changes of all 14 patients under observation. Except for the dead patient, none of them had complete AV block. There was prolonged PR detected in four patients (Table 3). The Glasgow Coma Scale score of the patients, excluding the mortality case, was 15. Only one patient had a seizure, but the patient was back to normal after the seizure and there were no pathological findings in his brain CT.

The median duration of hospital stay for the hypotensive and non-hypotensive patients was 9 (IQR: 3.5–15.2) days and 1.5 (IQR: 1–12) days, respectively. Control ultrasounds of the patients with free fluid 10 days after discharge revealed no evidence of intraperitoneal and intrapleural fluid.

Discussion

Although frequently used for treatment, CCB overdose may be fatal if prompt treatment is not administered with early diagnosis. In CCB overdose, cardiovascular collapse, heart block, bradyarrhythmia and hypotension, hyperglycemia, lactic acidosis, seizures, coma, and non-cardiogenic pulmonary edema and intestinal ischemia may occur (1, 3, 9). In our case series, there was just one complete AV block.

Hypotension may occur because of peripheral vasodilation, decreased cardiac contractility, bradycardia, or a combination thereof. Although hypotension occurs in the first few hours, it can also appear as late as 18–24 h with modified slow-release preparations (3, 10). Our patients had no slow-release preparations intake, and the mean time from the intake of drugs to arrival at the hospital was approximately 3 h.

The differential diagnosis of the signs and symptoms occurring in patients with undiagnosed CCB poisoning should be clear and patients should be treated. The most commonly occurring and life-threatening symptoms of CCB poisoning are AV block and hypotension. Here, the use of bedside USG in the emergency department as part of the examination to investigate the cause is suggested because of the ease of use, lack of radiation risks, and rapid diagnosis (11, 12). USG provides information, particularly about intraabdominal organs, intrapleural fluid, pericardial effusion, and cardiac functions. We believe ultrasonographic free fluid in patients with hypotension and the lack of clearly identified CCB poisoning from information received from patients and/or their relatives can guide the physicians in their diagnosis.

Establishing fluid support in the treatment of hypotension in CCB poisoning is the first step. However, in patients with severe hypotension, IV calcium, glucagon, inotropic therapy, high-dose insulin therapy, lipid emulsion, and aortic balloon pump application are other treatments (10, 13, 14). In our study, IV calcium, hydration with normal saline, and inotropic therapy were administered to the patients with hypotension and with USG-detected peritoneal and pleural free fluid. Despite the given treatment, complete AV block developed in one patient. The patient did not respond to atropine and external pacemaker treatment and died at the 3rd hour. The other patients were completely treated and discharged.

Different clinical findings can occur in patients because of extensive tissue hypoperfusion due to hypotension. The presence of variable amounts of collaterals makes the colon susceptible to ischemia (15). Depending on the CCB overdose, although complicated and surgery-requiring complications such as submucosal edema, ischemia, necrotic ulceration, bleeding, and even gangrene have been observed in case reports in the literature, clinical situations, such as pseudo-obstruction, that can be treated without surgical treatments have also been shown (2, 10). In a patient who developed non-occlusive colonic ischemia due to verapamil overdose, Perbet et al. (5) found a gangrenous segment in the left column with exploratory laparotomy, and a histopathological examination revealed submucosal edema, necrotic patchy ulceration areas, and intramural hemorrhage due to submucosal vessel dilatation. Gutierrez et al. (6) reported gangrene segments in the ileum and cecum with exploratory laparotomy in a verapamil-overdose patient who had a blood pressure of 73/30 mmHg, a pulse rate of 75 beats/min, and who had developed abdominal pain and abdominal distension during treatment. We believe that there was peritoneal and pleural fluid leakage because of tissue perfusion defects and vasodilation due to CCB overdose in our patients and that hypotension had aggravated this. Hypotension being the common characteristic of the published papers on intestinal ischemia supports our thoughts. In previous publications, patients had abdominal complaints, such as abdominal pain and distention, and intestinal symptoms had emerged as a consequence. However, in our patients, intrapleural and peritoneal

fluids were detected despite the lack of abdominal pain, constipation, or distension complaints.

Study limitations

There are limitations to this study. First, the sample size was small. Second, intestinal examinations using abdominal computed tomography or magnetic resonance imaging would better define the etiology of the fluid by showing the intestinal pathologies better. Third, we considered CCB overdose based on history and clinical findings. Finally, laboratory drug levels would be a more logical approach but were unavailable in our study setting.

Conclusion

Calcium channel blockers overdose patients with hypotension but without abdominal pain and constipation complaints, peritoneal and intrapleural free fluid is common and may be detected using bedside USG. Further extensive multicenter controlled trials are needed for determining the relationship between the presence of intrapleural and intraperitoneal free fluid and hypotension and the prognosis of patients with CCB overdose.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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