Original Article

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Evaluation of children poisoned with calcium channel blocker or beta blocker drugs

Çapan Konca[1], Rıza Dinçer Yıldızdaş[2], Mehmet Yusuf Sarı[2], Ufuk Yükselmiş[2], Özden Özgür Horoz[2], Hayri Levent Yılmaz[3]

[1]Adıyaman Medical Faculty, Department of Pediatrics, Adıyaman, Turkey

[2]Çukurova Medical Faculty, Division of Pediatric Intensive Care, Adana, Turkey

[2]Çukurova Medical Faculty, Division of Pediatric Emergency, Adana, Turkey

Summary

Aim: Calcium channel blockers (CCB) and beta blockers (BB) are primarily used to treat hypertension. Overdose of these medications can occur by accidental ingestion or ingestion for suicide attempt. Morbidity and mortality are higher in these poisonings compared to other poisonings. In this study, BB or CCB drug poisoning cases are discussed and the literature is reviewed.

Material and Method: Between January 2011 and July 2012, 590 cases of drug poisoning were admitted in the Pediatric Intensive Care Unit. In this study, 16 of these 590 subjects who were poisoned with calcium channel blockers or beta blockers were evaluated. 11 (68.8%) patients were female and 5 (31.2%) were male. Mean age of the patients was 11.8±5.94 (2.5-18) years.

Results: Hypotension was the most common clinical sign in CCB poisoning. Two patients were asymptomatic. On ECG, QT prolongation was found in four patients, AV block was found in two patients and ST depression was found in one patient. Nausea, vomiting, hypotension, lethargy and tremor were the most common clinical findings in patients with BB intoxication. Although seven patients had normal ECG, one patient had QT prolongation and one patient had Wolff–Parkinson–White syndrome. Only dopamine was given to two patients with CCB poisoning, dopamine and dobutamine were given to one patient and dopamine, dobutamine, epinephrine, norepinephrine, glucagon and insulin were given to another patient. Inotropic drugs were not given to any patient with BB poisoning. IV Ca-gluconate was given to all patients with CCB poisoning except two patients who were asymptomatic. 15 patients were discharged, while one patient with CCB poisoning was lost.

Conclusions: Because the prognosis of CCB or BB poisoning may be very severe, these patients should be followed up in a fully-equipped pediatric intensive care unit. *(Turk Arch Ped 2013; 48: 138-144)*

Key words: Beta blockers, calcium channel blockers, childhood, poisoning

Introduction

Intoxication with calcium channel blocker (CCB) and beta blocker (BB) drugs is responsible of 40% of intoxication cases and 65% of deaths due to cardiovascular drugs in USA (1). The effects of calcium channel blockers on the cardiovascular system include decrease in electromechanical contruction in the myocardium, slowing down of the “pacemaker” activity, decrease in the atrioventricular conduction and dilatation in vascular smooth muscles (2). In addition, CCB can lead to hyperglycemia and relative hypoinsulinsm by disrupting the function of the pancreatic beta cells (3). In intoxications with these drugs, these physiological responses may be exaggerated and lead to life-threatening conditions including bradicardia, metabolic acidosis, hypotension, conduction defects and shock. Beta blocker drugs competetively antagonize the binding sites of the catecholamines on beta receptors. The clinical findings in intoxications with these drugs depend on the receptor selectivity of the drug ingested, the lipid

Address for Correspondence: Çapan Konca MD, AAdıyaman Medical Faculty, Department of Pediatrics, Adıyaman, Turkey
E-mail: dr.capan@hotmail.com **Received:** 11.13.2012 **Accepted:** 12.07.2012
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solibility of the drug, its partial agonistic effect and the dose. Hypotension and bradicardia are the most common cardiac findings, but if the drug has partial agonistic effect, hypertension and tachycardia may be observed. The other clinical findings include varying degrees of cardiac block, pulmonary edema, hypoglycemia and central nervous system findings.

In this study, we discussed the characteristics and management plan of children with intoxication with calcium channel blocker or beta blocker drugs who were hospitalized and followed up in our pediatric intensive care unit under the ligth of literature information.

Material and Method

The recorded data of the cases of intoxication with CCB or BB drugs among 590 intoxication patients followed up in our pediatric intensive care unit between January 2011 and July 2012 were screened retrospectively. The files were screened in terms of age, gender, cause of intoxication, drug dose, clinical characteristics, electrocardiography (ECG) findings and biochemical and laboratory characteristics, treatment methods, responses to treatment and final status. The data were analysed using IBM SPSS 19 program (SPSS Inc, Chicago, IL) and the descriptive statistical characteristics of the patients were determined.

Results

16 patients with calcium channel blocker or beta blocker intoxication among 590 intoxication patients followed up in our pediatric intensive care unit between january 2011 and July 2012 were included in the study. 11 of the patients (68,8%) were female and 5 (31,2%) were male. The mean age of the patients was 11,8±5,94 (2,5-18) years. 11 of the patients (68,8%) ingested the drug with the aim of suicide. When the complaints at presentation were evaluated, it was found that the most common reasons for referring included nausea, vomiting and abdominal pain (Table 1). 12 patients presented from the provincial center and 4 patients presented from other provincial centers. 13 patients referred to a health institution in the first 2 hours, whereas the referal time prolonged up to 6 hours. Nine (56,25%) patients were followed up because of beta blocker intoxication and seven (43,75%) patients were followed up because of calcium channel blocker intoxication. A history of an additional drug ingestion was found in five patients (salicylate in two patients, neuronal serotonin (5-HT) reuptake inhibitor (SSRI) in two patients, antifungal in one patients and angiotensin receptor blocker in one patient).

In all patients who had signs, pediatric cardiology consultation was performed and treatments in accordance with the treatment management plan were administered. CK, CK-MB, Troponin-I and lactate levels were measured in these patients (values at presentation are given in Table 2). Patients who had cardiac findings were monitored by repeating these measurements.

While two of the calcium channel blocker intoxication patients were poisoned by accident, five patients ingested the drug for the aim of suicide. Five patients ingested only CCB, whereas one patient ingested angiotensin receptor blocker and one patient ingested flukonazole group-drug additionally. The doses of the drugs ingested by the patients are given in the table as mg/kg. The most common complaints at presentation included nausea, vomiting and abdominal pain. The most common clinical findings included hypotension in 5 patients and stupor and fainting in two patients. Two patients had no clinical finding. The laboratory findings in four patients with CCB intoxication were normal, but one patient had hypocalcemia, one patient had hypoglycemia and metabolic acidosis and one patient had increased ALT-AST level and metabolic acidosis. While ECG findings were found to be normal in two CCB intoxication patients, pathological findings were observed in five patients. QT prolongation was found in four patients, AV block was found in two patients (first degree in one patient and second degree in the other patient) and ST depression was found in one patient. Hyperglycemia was not observed in any of our patients (Table 3).

While three of beta blocker intoxication patients were poisoned by accident, six patients ingested the drug for the aim of suicide. While six patients ingested only BB drug, one patient ingested SSRI+salicylate, one patient ingested SSRI and one patient ingested salicylate group drug additionally. The doses of the drugs ingested by the patients are given as mg/kg in the table. Five BB intoxication patients had nausea and vomiting, two had stupor, two had tremor in the hands and one had dizziness as presenting complaints. Clinical findings included hypotension in two patients and bradicardia in one patient. Three patients had no clinical finding. The laboratory tests in the majority of our beta blocker intoxication patients were found to be

Table 1. Complaints of the patients at presentation to the emergency department

Presenting complaint	Number	%
Nausea	8	50.0
Vomiting	8	50.0
Abdominal pain	2	12.5
Tremor	2	12.5
Stupor	2	12.5
Dizziness	1	6.25
Fainting	1	6.25

normal, but one patient had hypoglycemia and one patient had hypocalcemia and hypopotacemia. While ECG was found to be normal in 7 of 9 patients, one patient had QT prolongation and one patient had Wolff–Parkinson–White syndrome (Table 4).

The treatment management plan applied in CCB and BB intoxication cases is given below (11) (Figure 1).

In six of the 7 patients with CCB intoxication who presented to the emergency department in the first 2 hours, gastric lavage and active charcoal administration were performed. In two asymtomatic patients, additional treatment was not given and vital signs were monitored. In five patients who had hypotension, primarily repeated serum physiologic loading was performed in the intensive care unit; the blood pressure was normalized in one patient, whereas repeated Ca-gluconate loadings at a dose of 0,6 ml/kg were administered in four patients who did not respond. In these patients who did not respond to calcium treatment, inotrpic drugs were needed. The blood pressure values normalized with only dopamine administration in two patients and with combined use of dopamin and dobutamine in one patient. The mean hospitalization time of the patients was 57.14±43 (20-127) hours. Six patients were discharged and one patient was lost. The lost patient was a 16-year old girl who ingested 20 libradin® (Barnidipin) and 10 olmetec plus® (Olmesertan). She presented with

Table 2. Cardiac enzymes of the patients at presentation

Patient	Intoxication type	CK (U/L)	CK-MB (U/L)	Troponin I (ng/ml)	Lactate (mmol/L)
F.Y.	BB	87	1.1	0.01	non-existent
E.G.	CCB	52	1.1	0.13	non-existent
N.D.İ.	CCB	112	1.2	0	1
M.D.	BB	104	1.8	0	2
S.Ö.	CCB	263	8.2	0	non-existent
M.C.	CCB	104	1.8	0	1
Ş.Ş.	CCB	611	19.2	0.15	1
B.U.	BB	128	1.7	0.01	1
G.G.	CCB	654	36.4	1.09	2.4

BB: Beta blocker, CCB: calcium channel blocker

Table 3. Recorded data of the patients with calcium channel blocker intoxication

Patient	Gender/ Age	Drug /dose (mg/kg)	PIM II (%)	PRISM II	PELOD	Clinical findings	Laboratory findings	ECG findings	Treatment
M.C.	E/15	Amlodipine / (1)	7.8	4	10	Hypotension.	Hypocalcemia	Normal	Dopamin.calcium
T.P.	K/4	Lerkanidipine / (3)	0.4	0	0	Asymptomatic	Normal	Normal	Supportive
N.D.İ	K/16	Verapamil / (8) + fluconazole	14.9	2	10	Hypotension	Normal	AV block. QT prolongation	Calcium
S.Ö.	E/3	Nifedipine / (3)	1.6	0	0	Asymptomatic	Normal	Normal	Supportive
S.Ş.	K/14	Verapamil / (30)	25.3	10	10	Hypotension. stupor	Metabolic acidosis. hypoglycemia	QT prolongation	Dopamin. dobutamin calcium
G.G.	K/16	Barnidipine/ (8) + Olmesertan/ (2)	91.1	27	31	Anuria. hypotension. stupor	Metabolic acidosis. increased AST-ALT	QT prolongation. AV block. ST depression	Dopamin. kalsiyum. insülin. glükagon plazmaferez. adrenalin noradrenalin
E.G.	K/15	Verapamil / (44)	8.8	13	10	Fainting. hypotension	Normal	QT prolongation	Dopamin. calcium

complaints including vomiting, numbness in the hands and feet, respiratory distress, headache and dizziness two hours after ingestion of drug to the emergency department and she was referred after gastric lavage and active charcoal administration. When the patient was taken to the intensive care unit her consciousness was blurred and she had marked hypotension. According to the treatment management plan isotonic loadings, ca-gluconate, dopamin infusion, adrenalin and noradrenalin, hyperinsulinemia-eglycemia treatment and glucagon treatment were administered respectively. Plasmapheresis was administered, when clinical response was not obtained. Repeated ventricular fibrillation (VF) attacks started in the 19th hour in the patient who did not respond to the treatment methods administered (Picture 1). Defibrillation was performed three times and cardioversion was performed once for these VF attacks. However, the patient who did not respond to the treatment methods administered and in whom implantable cardioverter-defibrillators could not be used because there was no sufficient time was lost in the 20th hour of hospitalization.

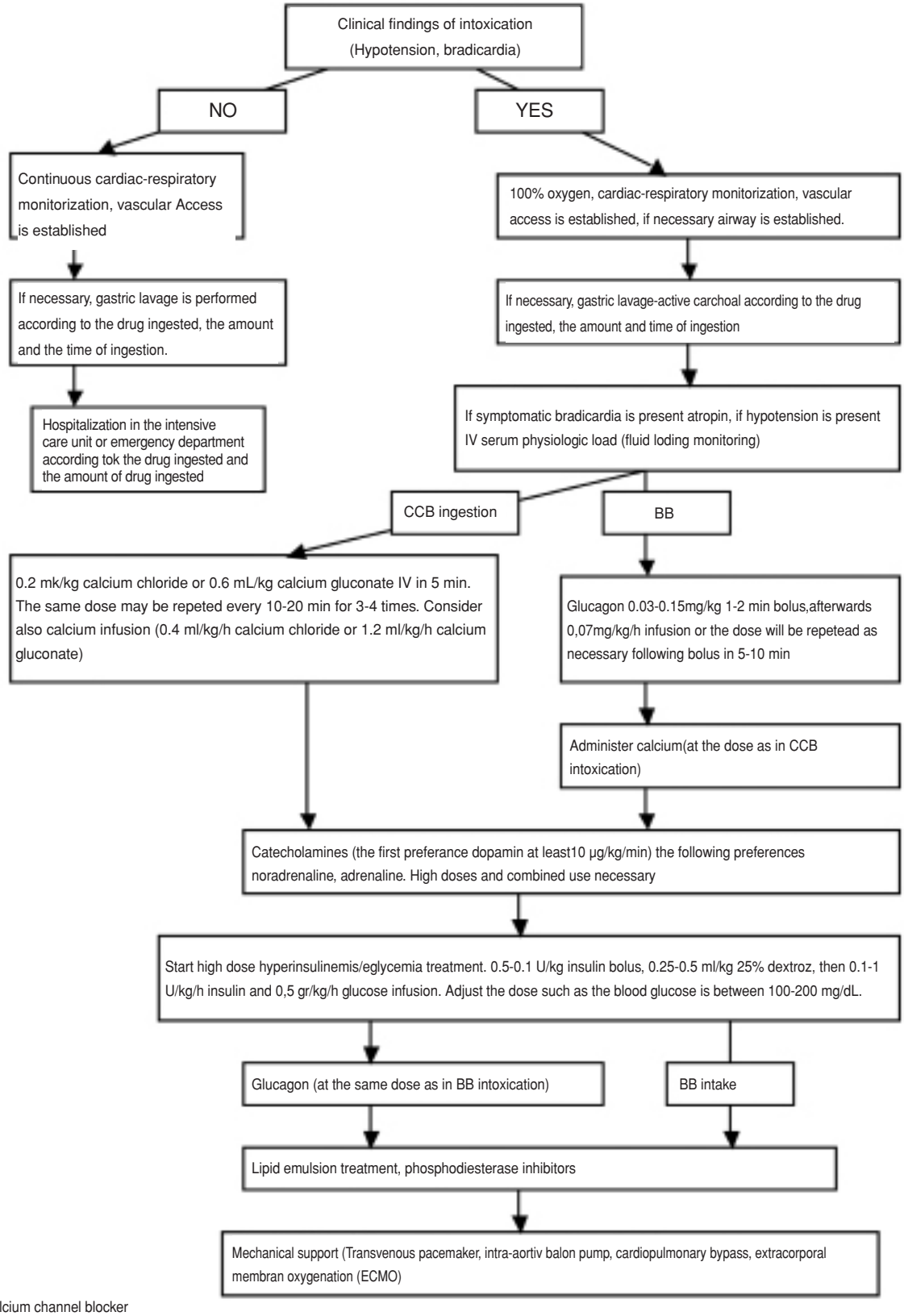
Gastric lavage and active charcoal administration were performed in 7 patients who presented to emergency departments in the first two hours among 9 beta blocker intoxication patients in the emergency departments they were referred. Atropin was administered in one patient who had bradicardia. Repeated isotonic loadings were performed primarily in two patients who had hypotension in the follow-up and the blood pressure values normalized. No additional treatment was needed in any BB intoxication patient. Intravenous calcium-gluconate was given to one patient who had hypocalcemia. The mean hospitalization time of the patients was 44±32.5 (23-120) hours and all patients were discharged after full recovery.

Discussion

Intoxications with calcium channel blockers may be lethal, if not diagnosed and treated in time. Symptoms appear in the first 6 hours after ingestion. Dizziness, lethargy, agitation, confusion, seizures and hemiplegia may be observed. Sinus bradicardia may be observed in mild intoxication and varying degrees of conduction blocks may be observed in severe intoxication. Urinary output may be decreased as a result of decreased renal perfusion (4). In calcium channel blocker intoxications, clinical pictures may differ according to the type of drug ingested. Diltiazem and verapamil may lead to a severe clinical picture characterized with bradicardia, conduction disorders (sinus arrest, asystole, AV block), vasodilatation and hypotension (5). Since dihydropyridin derivatives (nifedipinei amlodipine) are selective for vascular structures, they do not lead to conduction defects and marked myocardial dysfunction while casuing vasodilatation (6). Since impairement in insulin release and increase in peripheral insulin resistance ocur in calcium channel blocker intoxication, hyperglycemia is observed ferequently (7). Only two of our

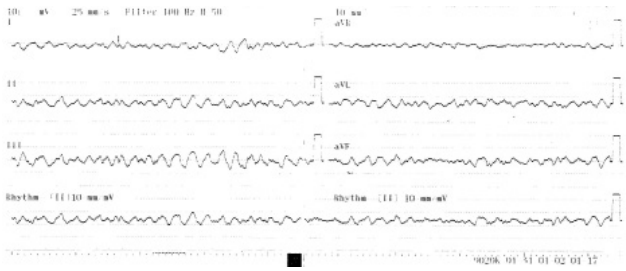
Table 4. Data of the patients with beta blocker intoxication

Patient	Gender /Age	Drug /dose (mg/kg)	PIM II (%)	PRISM II	PELOD	Clinical findings	Laboratory findings	ECG findings	Treatment
B.U.	E/15	Metoprolol / 7.27 Calicylate / 18.1 sertraline / 9	6.4	5	10	Hypotension	Hypocalcemia hypopotassemia	Normal	Calcium
M.D.	E/2.5	Propranolol / 6.6	1.4	0	0	Asymptomatic	Normal	Normal	Supportive
I.D.	K/5	Propranolol / 10	1.2	0	0	Asymptomatic	Hypoglycemia	Normal	Supportive
G.Y.	K/16	Propranolol / 5.3 citalopram / 2.3	1.4	0	0	Stupor. tremor	Normal	Normal	Supportive
S.Ö.	K/18	Metoprolol / 3 calicylate / 15.3	1.4	0	0	Stupor	Normal	Normal	Supportive
Ö.K.	E/2.5	Carvedilol / 3	0.9	0	0	Asymptomatic	Normal	Normal	Supportive
A.U.	K/16	Metoprolol / 12.5	1.7	13	10	Dizziness	Normal	QT prolongation	Supportive
F.Y.	E/15	Propranolol / 11	6.2	11	10	Bradycardia. tremor	Normal	WPW finding	Calcium adrenaline bicarbonate glucagon atropin
Ü.Ö.	K/16	Carvedilol / 2	2	5	10	Hypotension	Normal	Normal	Supportive



CCB: Calcium channel blocker
BB: Beta blocker

Figure 1: Management of calcium channel blocker and beta blocker intoxication[11]



Picture 1. Ventricular fibrillation on ECG in the patient who was lost

patients with calcium channel blocker intoxication were asymptomatic. In symptomatic patients, the most common complaints at presentation included nausea, vomiting and abdominal pain, while the most common clinical findings included hypotension and somnolence in turn. Pathological laboratory findings included hypocalcemia in one patient, hypoglycemia and metabolic acidosis in one patient and increased AST-ALT and metabolic acidosis in one patient. Electrocardiographic findings included QT prolongation in four patients, AV block in two patients and ST depression in one patient. Hyperglycemia was not found in any of our patients.

Clinical findings may vary according to the drug type also in beta blocker intoxication. “Torsade de pointes” may be observed in addition to hypotension and bradicardia in sotalol intoxication (8). Since the blood-brain barrier is crossed more easily in lopophylic BB intoxication, delirium, convulsion and coma may be observed (9). Prolongation in QRS interval may be observed in intoxication with BBs which have membrane-protecting effect (10). In symptomatic patients, the most common complaints included nausea and or vomiting and the most common findings included hypotension, somnolence and tremor in the hands. Laboratory findings included hypoglycemia in one patients and hypocalcemia and hypopotassemia in one patient. Electrocardiographic findings included QT prolongation in one patient and WPW syndrome in another patient.

For treatment of beta blocker intoxication gastic lavage should be performed in patients who are brought in the first two hours to decrease the absorption of the drug and increase excretion and active charcoal should be given. Repeated active charcoal administration may be beneficial. Stepwise treatment is recommended for hypotension and shock (11). As the fisrt step intravenous fluid should be given. If there is no response, the first-line treatment is administration of glucagon in the second step (12). If there is no response, calcium is given in the third step. If there is still no response, catecolamines, high dose insulin treatment, lipid emulsion treatment and mechanical support (pacemaker, ECMO, intraaortic balloon pump) may be administered. In an animal study, it was shown that glucagon was superior to isoproterenol and amrinone treatment (13). Reith et al. (14) showed that propranolol or other BB drugs could lead to quinidine-like arhyhtmias (QRS prolongation) and these arhythmias could response to intravenous bolus NaHCO3 treatment. High dose insulin treatment is recommended in presence of unresponsiveness to treatment or hyperglycemia (12). Gastric lavage and active charcoal administration had been performed in 7 patients who presented to an emergency department in the first two hours among the patients with beta blocker intoxication. Atropin was administered to a patients who had bradicardia. Repeated isotonic loadings were performed primarily in two patients who had hypotension in the follow-up and their blood pressure values returned to normal. Additional treatment was not needed in any patient with BB intoxication.

Gastric lavage should be performed and active charcoal should be given to decrease the absorption of the drug and increase excretion for treatment of calcium channel blocker intoxication. Repeated active charcoal administration may be beneficial. Stepwise treatment is recommended for hypotension and shock. Intravenous fluid should be administered initially. Of there is no response, calcium should be given. If there is no response to calcium treatment, catecolamines should be given and if there is no response to high dose insulin, glucagon, lipid emulsion and mechanical supportive treatment (pacemaker, ECMO, intraaortic balloon pump) may be administered. Use of glucagon is recommended for its positive inotropic and chronotropic effects in BB and verapamil intoxication (15). A study supported use of high dose insulin and fluid with dextrose for treatment in CCB intoxication (16). Combined use of calcium and adrenalin is recommend, if there are cardiotoxicity findings (12). Jacek et al (17) argued that life-supportive therapies including plasmapheresis were beneficial in fatal cardiotoxic drug intoxications. Gastric lavage and active charcoal administration were performed in six of the 7 patients with CCB intoxication who presented to the emergency department in the first 2 hours. While five patients who had hypotension in the follow-up were administered the necessary interventions in accordance with the treatment management plan and recovered, one patient did not respond to any treatment method and was lost in the 20th hour of hospitalization because of VF attacks. If there were enough time for implantation of ICD, he could probably survive.

Scoring systems have been developed to determine the mortality risk in patients hospitalized in intensive care units and the quality of intensive care. For this purpose pediatric risk of mortality (PRISM 1, PRISM 2 and PRISM 3) (18,19) and pediatric index of mortality (PIM ve PIM 2) (20,21) have been developed. It has been reported that these scoring

systems can be used in evaluation of disease severity of pediatric intensive care patients, in prediction of the mortality risk and in comparison of care levels of different pediatric intensive care units (22,23,24). The most widely known and used ones among these systems include PRISM 2 and PIM 2 (25). Only the "Pediatric Logistic Organ Dysfunction'' score (PELOD) has been reported to be beneficial in predicting disease severity in patients with multiple organ dysfunction in pediatric intensive care units (26). In our patients, there was a marked compatibility between disease severity and scorings performed. Therefore, these scoring systems can be used in patients with calcium channel blocker and beta blocker intoxications.

Calcium channel blocker and beta blocker intoxications can lead to increased morbidity and mortality rates, though they ocur rarely in children. To decrease the morbidity and mortality rates patients should be monitored in pediatric intensive care units with an early and appropriate treatment approach.

Conflict of interest: None declared.

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