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Evaluation of the Treatment Approaches and Complications of Calcium Channel Blocker Intoxications

Kalsiyum Kanal Blokörü Zehirlenmelerinin Tedavi Yaklaşımları ve Komplikasyonlarının Değerlendirilmesi

Emine Akıncı[1], Ramazan Köylü[2], Mehmet Yortanlı[2], Başar Cander[2]
[1]Department of Emergency Medicine, Keçiören Training and Research Hospital, Ankara, Turkey
[2]Department of Emergency Medicine, Konya Training and Research Hospital, Konya, Turkey

Abstract

Objective: Calcium channel blockers (CCBs) are used in the treatment of angina, hypertension, arrhythmias, and prevention of migraines. The incidence of accidental or intentional calcium channel blocker intoxication has increased in recent years, which is thought to be related to more frequent use. Calcium channel blockers intoxications may progress to mortality. In our study, we investigated the treatments of suicidal or accidental calcium channel blocker intoxications and the relationships between the complications and these therapies.

Material and Methods: The data of this retrospective study were obtained from the patient files. The patients who had been admitted to the Konya Training and Research Hospital with excessive intake of calcium channel blockers and been followed-up in the toxicology and emergency critical intensive care units between 2010 and 2012 were sequentially included in the study. No cases were excluded from the study.

Results: A total of 15 patients were included in the study. Eight patients had taken verapamil, 4 patients had taken amlodipine, and 3 patients had taken nifedipine. The treatment included 0.9% normal saline infusion for all patients. Ten patients were given calcium replacement and 4 were given renal replacement therapy. ILE infusion was begun in six patients. Six patients were given glucagon. Five patients had developed hyperglycemia, 4 of whom underwent high-dose insulin-glucose treatment. Various complications were observed in 10 of the 15 cases. Hyperglycemia and non-cardiogenic pulmonary oedema were observed in 33.3% of the patients, metabolic acidosis was observed in 40% and block was observed in 26.7%. Cardiac arrest was observed in two patients, one of whom died.

Conclusion: According to our results, none of the treatments had any priority over another. In order to prevent the possible complications, we suggest the application of multi-treatment strategies in the early period, particularly in high dose CCB intakes. *(JAEM 2013; 12: 189-94)*

Key words: Calcium channel blocker intoxications, treatment, complications

Özet

Amaç: Kalsiyum kanal blökörleri (KKB), anjina, hipertansiyon, aritmilerin tedavisinde ve migren profilaksisinde kullanılmaktadır. Kalsiyum kanal blökörleri zehirlenmelerinin sıklığı ilaçların kazara veya istemli olarak kullanılmasına bağlı olarak son yıllarda artmıştır. Biz bu çalışmamızda özkıyım amaçlı veya kazara değişen miktarlarda kalsiyum kanal blokörü alan hastaların tedavilerini ve verilen tedavilerin komplikasyonlarla ilişkilerini araştırdık.

Gereç ve Yöntemler: Çalışma retrospektif bir çalışma olup veriler hasta dosyalarından elde edilmiştir. Konya eğitim ve araştırma hastanesine kalsiyum kanal blokörü aşırı alımı ile başvuran, toksikoloji ve acil kritik yoğun bakımda takip edilen 2010-2012 yılları arasında hastalar ardışık olarak çalışmaya dâhil edildi. Çalışma dışı bırakılan hasta olmamıştır.

Bulgular: Çalışmaya 15 hasta dâhil edildi. Yedi hasta verapamil, 3 hasta amlodipin 2 hasta nifedipin almıştır. Tedavilere bakıldığında hastaların hepsine %0,9 SF infüzyonu yapılmıştır. On hastaya calsiyum replasmanı yapılmıştır. Dört hasta renal replasman tedavisi almıştır. Altı hastaya IV lipit infüzyonu başlanmıştır. Altı hastaya glukagon verilmiştir. Beş hastada hiperglisemi gelişmiş, bu beş hastanın dördüne yüksek doz insülin-glukoz tedavisi verilmiştir. On beş olgunun 10'unda değişik komplikasyonlar görülmüştür. Hastaların %33,3'de hiperglisemi ve non kardiyojenik akciğer ödemi, %40'ında metabolik asidoz, %26'sında blok gelişmiştir. 2 hasta kardiyak arrest olmuş ve bu hastaların sadece biri ölmüştür.

Sonuç: Bizim sonuçlarımıza göre KKB intoksikasyonlarında hiçbir tedavi birbirine üstün gözükmemektedir. Özellikle yüksek doz KKB alımlarında komplikasyonları önlemek için multi tedavi stratejilerini erken dönemde uygulanmasını önermekteyiz. *(JAEM 2013; 12: 189-94)*

Anahtar kelimeler: Kalsiyum kanal blokörü zehirlenmeleri, tedavi, komplikasyonlar

Correspondence to / Yazışma Adresi: Emine Akıncı, Şenlik Mahallesi, Baldıran Sokak, 40/18 Keçiören 06310 Ankara, Turkey
Phone: +90 312 355 22 19 e.mail: emineakinci@yahoo.com

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Introduction

Calcium channel blockers (CCBs) are used in the treatment of angina, hypertension, arrhythmias, and prevention of migraines. The incidence of accidental or intentional calcium channel blocker intoxication has increased in recent years, which is thought to be related to more their frequent use. The toxic effects of calcium channel blockers include dysrrhythmias, hypotension and bradycardia related to compression of the sinoatrial node. The reported complications include bowel infarction, stroke, hyperglycaemia, and non-cardiogenic pulmonary edema (1). The treatment options include decontamination, liquid replacement, vasopressor agents, glucagon, hyperinsulinemic euglycemia (HIE) therapy and intravenous lipid emulsions (ILE) (2).

In our study, we investigated the treatments of suicidal or accidental calcium channel blocker intoxications and the relationships between the complications and these therapies.

Material and Methods

The study was approved by the Konya Training and Research Hospital educational planning board. The data of this retrospective study were obtained from the patient files. There are two separate intensive care units in our emergency department. These include the third step emergency critical intensive care unit and the second step toxicology intensive care unit where the poisoning cases are evaluated and treated. All of the cases are examined and followed-up by emergency medicine physicians. The patients who had been admitted to the Konya Training and Research Hospital with excessive intake of calcium channel blockers and been followed-up in the toxicology and emergency critical intensive care units between 2010 and 2012 were sequentially included in the study. No cases were excluded from the study.

The age, gender and demographic data of the patients, their clinical parameters, treatments (decontamination treatments, intravenous (IV) fluid administration, positive inotropic support, glucagon, high dose insulin-glucose, IV lipid infusion, renal replacement treatments, and the treatments directed towards complications) were evaluated. The ingested dose of medication was learned from, patients or their relatives. Complications, mechanical ventilation support, duration of hospitalization and the mortality situation of the patients were recorded. For the clinical parameters, the medical records of the patients were scanned and the Glasgow Coma Score (GCS), cardiac findings, electrocardiography (ECG) findings, and kidney and liver functions at the time of admission were evaluated.

The intoxication severity was assessed according to the Poisoning Severity Score (PSS) of the European Association of Poison Centres and Clinical Toxicologists (3).

The patients were classified into 4 groups according to their PSS and were scored between 1 and 4.

1. The groups with no alteration related to the drug.
2. Minor symptoms; GCS: 14-15, tachycardia (100-140 ppm), hypotension (80-100 mmHg), moderate ECG changes,
3. Moderate group; coma (GCS: 9-13), tachycardia (>140 ppm), hypotension (<80 mmHg), and oxygen requirement (Saturation <90),
4. Severe group; coma (GCS<8), respiratory and cardiac arrest.

Statistical analysis

The analyses of the data were performed using the SPSS for Windows 11.5 program. The definitive quantitative data were expressed as median (minimum-maximum range), and the qualitative data were expressed as case numbers and percentages (%). The possible differences between the PSS scores on admission and discharge in the treatment groups were investigated using the Wilcoxon sign test. Statistical significance was accepted for p values of <0.05.

Results

A total of 15 patients were included in the study. The demographic data of the patients are presented in Table 1.

Various complications were observed in 10 of the 15 cases. Hyperglycemia and non-cardiogenic pulmonary oedema were observed in 33.3% of the patients, metabolic acidosis was observed

Table 1. The demographic data of the patients

Variables	**n=15**
Age(years)	22.47±14.61 (1-68)
Gender	
Male	3 (20%)
Female	12 (80%)
Drug type	
Verapamil	8 (53.3%)
Amlodipine	4 (26.7%)
Nifedipine	3 (20%)
Mean dose of intake (mg)	1728.0±1687.59 (10-4800)
PSS on admission	1.40±0.73 (1-3)
PSS at the 6th hour	2.07±0.28 (1-4)
Treatment	
IV Saline	15 (100%)
Calcium	10 (66.7%)
Inotropic agents (dopamine, noradrenaline)	11 (73.3%)
Glucagon	6 (40%)
RRT	4 (26.7%)
ILE	6 (40%)
HIE	4 (26.7%)
Intubation	2 (13.3%)
Complications	
Hyperglycemia	5 (33.3%)
Acidosis	6 (40%)
Pulmonary oedema	5 (33.3%)
AV block	4 (26.7%)
Cardiac arrest	2 (13.3%)
Intestinal ischemia	0 (0%)
Results	
Discharge	14 (93.3%)
Exitus	1 (6.7 %)
Duration of hospital stay (days)	3.5 (1-10)

HIE: Hyperinsulinemic euglycemia, ILE: Intra venous lipid emulsions, RRT: Renal replacement therapy, PSS: Poisoning severity score, IV: Intra venous, AV Block: Artioventricular block

in 40% and AV block was observed in 26.7%. Cardiac arrest was observed in two patients, one of whom died (Table 1).

The treatments and complications are presented in Figure 1. The blood pressure follow-up of patients with and without lipid infusion are presented in Figure 2.

The majority of the cases had been admitted in the early period, and their PSS scores were 1,4 on admission. The PSS scores of the patients are presented in Table 2.

No statistically significant finding was obtained at the 24th hour PSS scores of the patients with regard to the treatments received (Table 3).

Discussion

Although CCBs intoxications are infrequent, they may progress tofatality. They have no known antidotes. The treatments in the excessive intake of CCBs include gastrointestinal decontamination and intensive supportive treatments, including inotropic agents in order to maintain the ideal blood pressure (4, 5). Intravenous calcium infusion, glucagon, HIE, RRT and ILE are the other treatment options in intoxication.

The most frequent drug used in the patient group was verapamil. Verapamil is 94% bound to proteins metabolized through the liver, and 33% of it is excreted by the kidneys. Since it is bound to proteins at high rates and has a narrow range of distribution, its hemoperfusion efficacy is almost zero . However, in the literature, there are reports of cases resistant to intensive medical treatments who underwent cardiopulmonary by-pass, plasma exchange and continuous renal replacement therapy (CRRT) with hemodiafiltration in serious intoxications (6, 7). CRRT may be effective in hypotensive and unstable patients, such as our patient, who needed rapid and effective treatment. We applied RRT to only 4 of the 12 patients, since these patients had progressed to an unstable condition very rapidly. We performed RRT particularly in cases with resistant hypotension, metabolic acidosis and alterations of consciousness. These 4 patients had developed complications despite the RRT applications. Non-cardiogenic pulmonary edema was observed in 3 patients and complete AV block was observed in 1 patient. No pulmonary oedema has been reported in the therapeutic use of verapamil. However, 2 cases with pulmonary oedema have been reported in 2 case reports in 1994 and 1996 (8, 9). In our study, pulmonary oedema was observed in 5 patients. It is now known that pulmonary oedema may be observed in the follow-up of

Table 2. The PSS scores of the patients

	PSS on admission (n)	PSS at the 24th hour (n)
Normal (1)	11	6
Minor symptoms (2)	2	4
Moderate group (3)	2	3
Severe group (4)	0	2

PSS: Poisinig severity score

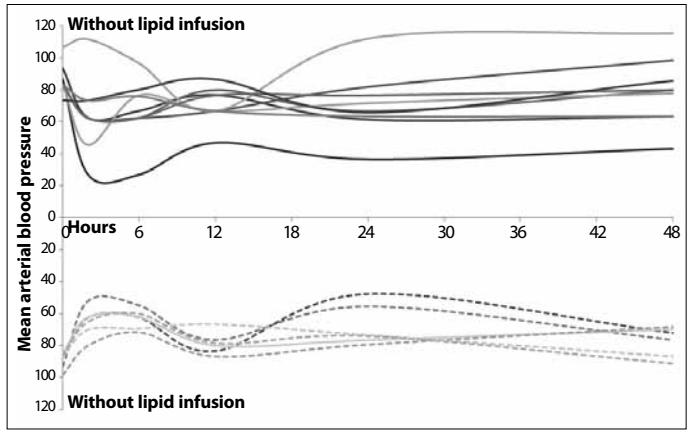

Figure 2. The tension follow up of patients with and without lipid infusion

	Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TREATMENT	ILE		X					X					X	X	X	X
	RRT		X			X		X	X							
	Glucagon		X		X			X					X		X	X
	Inotrops	X	X		X	X		X	X			X	X	X	X	X
	Calcium	X	X		X	X		X	X			X	X		X	X
	HIE		X		X			X	X							
	Normal saline	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Age	17	23	38	16	16	68	21	24	20	1	20	18	21	16	18
COMPLICATIONS	Hyperglycemia		X		X			X	X						X	
	AV Block		X		X	X			X							
	Acidosis		X		X	X		X	X						X	
	Pulmonary oedema	X	X		X	X			X							
	Cardiac arrest		X		X											
DRUGS	Verapamil		3600		3360	4320		2400	4800	800		480			2400	
	Amlodipine	300		100							10			50		
	Nifedipine						600						2400			300

Figure 1. Treatment and complications
HIE: Hyperinsulinemic euglycemia, ILE: Intra venous lipid emulsions, RRT: Renal replacement therapy

Table 3. The PSS scores of the patients on admission and at the 24th hour with regard to the treatments received

		PSS on admission		PSS at the 24th hour		p value
		Median	Mode	Median	Mode	
Fluid	Administered	1	1	2	1	0.14
	Not administered	´-	´-	´-	´-	
Calcium	Administered	1	1	2.5	2	0.14
	Not administered	1	1	1	1	
Inotropic agent	Administered	1	1	2	2	0.14
	Not administered	1	1	1	1	
Glucagon	Administered	1	1	2.5	2	0.39
	Not administered	1	1	1	1	
Dialysis	Performed	1.5	1	3	3	0.18
	Not performed	1	1	1	1	
ILE	Administered	1	1	2	1	0.66
	Not administered	1	1	1	1	
Intubation	Performed	2	1	4	4	0.18
	Not performed	1	1	2	1	
HIE	Administered	1.5	1	3.5	4	0.11
	Not administered	1	1	1	1	

PSS: Poisoning severity score, ILE: Intra venous lipid emulsions, HIE: Hyperinsulinemic euglycemia

patients with verapamil intoxications. The mechanism of action is not clearly understood; however, various theories have been put-forward. First, Leesar et al. (8) suggested that verapamil may lead to leaky capillary syndrome attributable to inhibition of prostacycline, a cellular membrane protector (10). Some mention that prolonged hypotension and a shock-like state may contribute to the development of pulmonary oedema (9-12). Secondly, calcium channel blockers cause precapillary vasodilatation and peripheral oedema, and a massive dose of verapamil may cause oedema in the lung through the same mechanism (9, 13). Finally, an interaction between verapamil and inflammatory cytokines may have a role in the acute respiratory distress-like syndrome that can be seen in the course of verapamil overdose. In addition to these underlying pathophysiological mechanisms, excessive hydration of the patients for the treatment of hypotension may be another important factor. However, pulmonary oedema was observed in only 5 of the patients in our study despite a similar type of hydration. The clinical picture of pulmonary oedema had developed particularly after the 2nd day. Four of these 5 patients had received verapamil and one had received amlodipine, and the drug doses received by the patients with pulmonary oedema were higher than that in patients without oedema. Pulmonary oedema should be considered carefully, particularly in patients with extreme doses verapamil intake, and in order to perform excessive hydration, inotropic therapies or other treatments may be started earlier to prevent peripheral vasodilatation or hypotension.

Intravenous calcium infusion is used for the prevention and treatment of verapamil-related intracellular hypocalcaemia. Calcium is commonly used in order to reduce the effect of CCBs on the cardiovascular system. However, the mechanism of action is not clearly understood (14). Hypocalcaemia was observed in 10 of the 12 patients, and these patients received IV calcium replacement. However, it had no effect on the complication.

Hyperinsulinemic euglycemia (HIE) therapy is another treatment option in CCB intoxications. HIE treatment and glucagon administrations have been recommended since they provide improvements in the cardiac inotrope function and glucose consumption (15). In the case-report of Patel regarding a patient with verapamil (5.8 gr) and Captopril (1.5 g) intake, it was reported that the 24 hour-HIE-therapy alone had been sufficient for stabilization of the patient (1). In our study, 4 patients had received HIE therapy. The patients' conditions included the development of serious hyperglycaemia and metabolic acidosis. However, HIE alone was not sufficient for the treatment of these patients, and other therapies were also included.

Intra venous lipid emulsions (ILE) infusion was administered to 6 patients. In hypotensive patients, an intravenous fluid bolus of 2 liters is warranted, especially in the absence of overt pulmonary edema. If hypotension persists, intravenous inotropes and vasopressors are warranted (16). A concomitant ILE infusion and inotropic treatment was begun particularly for patients with persistent hypotension despite IV fluid infusion. ILE infusion was applied in particular to patients who were followed-up in 2012. The reason for that was the recent case-reports that demonstrated the positive effects of ILE infusion on hypotension and patient management in CCB intoxication. In our clinics, we start lipid treatment in the early period, especially in patients with high-dose CCB intake. Montiel reported that the pace and vasopressor requirement of the patient had been eliminated by lipid solution and HIE in a 3.6 gr slow-release diltiazem intoxication (17). However, the optimal dosage, timing and treatment period of the lipid solutions are not clear. In general, there are case reports and animal studies in the literature. In the animal studies of verapamil intoxications, a single dose bolus lipid is administered as lipid infusion, whereas repeated infusions were applied following a loading dose in humans (18-20). Young was the first to report a successfully resuscitated case with lipid infusion in verapamil intoxication in humans (21). They had suc-

cessfully treated their patients with hypotensive shock resistant to standard resuscitation treatment, with 48-hour-ILE infusion. ILE treatment was applied as a 3-day therapy in the study by Liang (2). The dose suggestions are variable. The American Society of Regional Anaesthesia (ASRA) suggests a bolus dose of 1.5 mL/kg in local anaesthetic toxicity. The dose of 10 mL/kg should not be exceeded. The duration of the bolus may be 15-30 minutes. A subsequent 0.25 mL/kg/minute infusion has also been suggested. Similarly, a first bolus dose of 1.5 mL/kg, and a subsequent 0.5 mL kg/hour infusion have been recommended for CCB intoxications (22). We administered a bolus dose of 20% 1.5 cc/kg and a subsequent 0.5 cc/kg/hour for 48 hours as a standard. The follow-up of patient tensions demonstrated that the positive inotrope requirement of the patients receiving ILE infusion had gradually decreased throughout the infusion. The blood pressure follow-up of patients with and without lipid infusion is presented in Figure 2. The use of lipid has been reported in the intoxications of CCBs, beta-blockers, tricyclic antidepressants and various psychotropic drugs other than local anaesthetics (23, 24). The possible mechanisms of action of lipids on these drugs are decreasing the systemic toxicity by reducing the active drug amount in the target tissue (25). Lipids may reduce the systemic toxicity and the drug amount. French et al. (26) reported a case with a slight decrease in the amount of verapamil following the lipid administration.

The majority of the cases had been admitted in the early period of intoxication, and their PSS score on admission was 1.4. No pathological clinical or physical examination findings were present in 11 of the cases, whose PSS scores were normal. No statistically significant finding was observed at the 24th hour PSS scores of the cases with regard to the administered treatments.

Study Limitations

This study is retrospective and study data were obtained from patients' medical records. In addition, there are a small number of patients in our study.

Conclusion

According to our results, none of the treatments had any priority over one another. In order to prevent the possible complications, we suggest the application of multi-treatment strategies in the early period, particularly in high dose CCB intakes.

Conflict of Interest

No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Konya Training and Research Hospital.

Author Contributions

Concept - E.A.; Design - E.A., M.Y.; Supervision - B.C., E.A.; Funding - R.K., M.Y.; Materials - E.A.; Data Collection and/or Processing - E.A., R.K., M.Y.; Analysis and/or Interpretation - E.A.; Literature Review - E.A.; Writer - E.A.; Critical Review - E.A., R.K., B.C.; Other - B.C.

Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

Hakem değerlendirmesi: Dış bağımsız.

Etik Komite Onayı: Bu çalışma için etik komite onayı Konya Eğitim ve Araştırma Hastanesi'nden alınmıştır.

Yazar Katkıları

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