



Successful Intravenous Lipid Infusion Therapy in a Case with Life-Threatening Calcium Channel and Beta Blockers Overdose

Hayatı Tehdit Eden Kalsiyum Kanal Blokeri ve Beta Bloker Zehirlenme Olgusunda Başarılı İntravenöz Lipit İnfüzyon Tedavisi

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Abstract

Life-threatening cardiovascular collapse symptoms can develop due to calcium channel and beta-receptor blocker poisoning and there are no specific antidotes for treatment.

A 13-year-old girl was admitted with severe hypotension and bradycardia after the ingestion of a large quantity of carvedilol and verapamil. Cardiovascular collapse was resistant to fluid therapy, calcium gluconate and high-dose vasopressor infusion. Intravenous lipid infusion was administered in the patient who had resistant hypotension with hyperinsulinemic euglycemia on the first hour of hospitalization. Hemodynamic stability of the patient was achieved 30 minutes after lipid administration. Calcium channel and beta-receptor blocker overdose may result in life-threatening intoxication. Classical therapies that are suggested for these intoxications can be insufficient. Favorable results can be obtained after intravenous lipid infusion. With this report, we aimed to draw attention to those intoxications that can be life-threatening and to emphasize that intravenous lipid infusion therapy can be successful in patients refractory to other treatments.

Keywords: Intoxication, calcium channel blocker, beta receptor blocker, hyperinsulinemic euglycemia, intravenous lipid infusion

Öz

Kalsiyum kanal ve beta reseptör blokerleri ile olan zehirlenmelerde hayatı tehdit edici kardiyovasküler kollaps bulguları gelişebilmekte ve tedavi için özgül bir antidot bulunmamaktadır.

On üç yaşında kız olgu, aşırı doz karvedilol ve verapamil alımını takiben ciddi hipotansiyon ve bradikardi bulguları ile getirildi. Kardiyovasküler kollaps tablosu sıvı tedavisi, kalsiyum glukonat ve yüksek doz vasopressör infüzyonuna dirençli idi. Hiperinsülinemik öglisemi tedavisi ile de dirençli hipotansiyonu devam eden olguya intravenöz lipit infüzyonu izleminin 1. saatinde uygulandı. Olgunun hemodinamik stabilitesi lipit uygulamasından yarım saat sonra sağlandı. Kalsiyum kanal ve beta reseptör blokerleri ile olan zehirlenmeler, hayatı tehdit edebilen zehirlenmelerdir. Bu zehirlenmelerde önerilen klasik destek tedavileri yetersiz kalabilmekte, intravenöz lipit infüzyonu ile başarılı sonuçlar alınabilmektedir. Biz de bu olgu ile hayatı tehlike yaratabilen bu zehirlenmelere tekrar dikkat çekmek ve diğer tedavilere yanıtız olgularda intravenöz lipit infüzyonu tedavisinin başarılı olabileceğini vurgulamak istedik.

Anahtar Kelimeler: Zehirlenme, kalsiyum kanal blokeri, beta reseptör blokeri, hiperinsülinemik öglisemi, intravenöz lipit infüzyonu

Introduction

Calcium channel blocker (CCB) and β receptor blocker (BB) overdoses constitute a small percentage among all intoxications.¹ According to the 2014 Annual Report of the American Association of Poison Control Center's National Poison Data System, 0.6% of all overdoses occur with CCB and 0.9% take place with BB.² However, these overdoses lead to severe toxicity and their mortality rates are quite high.³ BB drugs cause hypotension and bradycardia by attaching to the beta adrenoceptors.⁴ In some BB overdoses, however,

since the drug has lipid resolution, central nervous system findings (such as seizure, respiratory depression, coma) can be observed.⁴ Following the excessive intake of CCB and BB drugs, treatments, such as glucagon, calcium gluconate, and hyperinsulinemic euglycemia therapy (HIET) as well as vasopressor drugs and intravenous fluid therapy are used in cases with cardiovascular collapse.⁵ Lately, in CCB and BB poisonings unresponsive to standard therapy, Recently, intravenous lipid infusion (ILI) therapy, which is used for poisoning with lipophilic local anesthetics and chemical

agents, is a new therapy option when the standard therapy is ineffective for poisoning with CCB and BB intoxications.⁵ A variety of theories have been suggested on the mechanism of action of ILI. According to the "lipid-sink theory"; ILI holds the lipophilic drugs where by forming a separate compartment in plasma and reduces the unwanted side effects of these drugs. Meanwhile, it also decreases toxic effects by drawing drugs that entered into cells to the extracellular field; namely, plasma. Free fatty acids contribute to inotropic effect by providing energy substrate to depressed myocardium.⁶ In addition, in myocardium with poor contractility, ILI administration has been claimed to cause positive inotropic and chronotropic effects by ameliorating functions of ion channels (like sodium and calcium) located on cell membranes.⁷

In this paper, we aimed to emphasize the effectiveness of ILI therapy in a pediatric patient who developed severe cardiovascular toxicity following high-dose BB and CCB drugs resistant to standard therapies.

Case

A 13-year-old girl was brought to our hospital due to intake of unknown amount of carvedilol and verapamil in a suicide attempt. Gastric lavage was performed in the primary care center after two hours of drug intake. At the same center she was conscious and she was given 1 g/kg of oral activated coal. The patient, who had developed cardiac arrest during transport to our hospital and had been intubated after cardiopulmonary resuscitation for 5 minutes, was admitted to the emergency department on the 3rd hour of her overdose drug intake. On the first physical examination, her general condition was poor, Glasgow coma scale score was 6, heart rate was 40 beats per minute. She was intubated with 6.5 mm cuffed tube and respired with bag-valve-mask at a rate of 20 breaths/minute; oxygen saturation was 100%; blood oxygen saturation level (SpO₂) was 90%, the skin was cold, peripheral

pulse could not be taken, capillary refill time was 5 seconds and blood pressure could not be measured. Her body weight was measured as 50 kg (50p). Blood gas analysis revealed the following results: pH: 7.29, PCO₂: 40 mmHg, PO₂: 100 mmHg, HCO₃: 19 mmol/L, and lactate: 3 mmol/L. The results of complete blood count were as follows: leukocyte: 22800/mm³, hemoglobin: 12 g/dL, hematocrit: 37%, and platelet count: 383000/mm³. On biochemical examination, the blood glucose level was 320 mg/dL, creatinine - 1.1 mg/dL, aspartate aminotransferase - 191 U/L, and the alanine aminotransferase level was 115 U/L. Other results were within the normal range. Electrocardiography (ECG) showed first-degree atrioventricular block, PR interval was 0.21 second, QTc interval was 0.40 second. On bedside cardiac ultrasound, it was observed that cardiac contraction was poor and there was no pericardial or pleural fluid. Two 1000 mL boluses of isotonic saline were administered intravenously. 1 mg intravenous atropine was given three times. The patient was admitted to the pediatric intensive care unit and then was followed up on mechanical ventilatory support. Right femoral central venous catheter and right radial artery catheter were placed. Calcium gluconate (10%) was administered at 0.6 mL/kg intravenously and also glucagon (5 mg) was given subcutaneously (intravenous form was not available). Adrenalin (0.1 mcg/kg/min) and noradrenalin (0.1 mcg/kg/min) infusions were initiated for the patient with hypotension. The rates of these infusions were gradually increased up to 2 mcg/kg/min to provide normal blood pressure. Insulin bolus of 1 U/kg was administered intravenously for severe hypotension; infusion was started as 0.5 U/kg/hour. Intravenous bolus of Calcium gluconate (10%) was administered given at 0.6 mL/kg for hemodynamic instability. At the 60th minute of the follow-up, despite intravenous fluid, calcium, insulin (2 U/kg/hour) and high-dose vasopressors (2 mcg/kg/min), 1.5 mL/kg infusion of 20% lipid solution was given in 15 minutes due to resistant hypotension (Table 1).⁸ The infusion rates of

Table 1. Timeline of the patient's clinical course and treatment

Time	Pulse/min	Blood pressure mmHg	Blood glucose mg/dL	Atropine mg	Calcium mL/kg/hour	Glucagon Mg	Insulin U/kg/hour	Adrenalin/ Noradrenalin mcg/kg/minute	Lipid mL/kg
0. minute	40	-	320	3x1	0.6*	5	-	0.1/0.1	
40. minute	60	65/33	273	-	0.6*	-	1*	1/1	
60. minute	80	78/53	110	-	0.5	-	0.5		
2. hours	82	92/58	75	-	0.5	-	1.5	0.5/0.5	
6. hours	60	94/56	92	-	0.5	5	1.5	0.1/0.2	
24. hours	92	105/56	90	-	0.5	-	1	-/0.1	
48. hours	102	99/60	88	-	0.1	-	0.5	-/-	
72. hours	88	110/72	90	-	-	-	-	-	

*Bolus dose

adrenalin and noradrenalin were reduced rapidly due to good response to lipid therapy. The treatments and follow-up are given in Table 1. At the 48th hour of the follow-up, as the vital signs, the results of blood gas and biochemistry tests, and ECG were normal, the patient was extubated. At the end of the 72th hour, the heart rate was 88/min (normal sinus rhythm), respiratory rate - 18/min, blood pressure - 110/72 mmHg, and SpO₂ was 99%. Intravenous insulin infusion was discontinued. The patient was transferred to the ward on the 4th day of the follow-up. She was discharged without sequelae on the 7th day.

Discussion

CCB and BB intoxications can cause life-threatening conditions and they are treated with similar treatment principles. In the treatment of hypotension and cardiovascular collapse developed in overdoses of these drugs; fluid, vasopressor, inotrope and chronotrope agents are used. In the treatment of cardiovascular collapse, glucagon, calcium, and ILI treatment can be applied in cases refractory to intravenous fluid and catecholamines.⁵ In our case, cardiopulmonary resuscitation was necessary following CCB and BB overdose; resistant hypotension did not ameliorate despite fluid, catecholamine, calcium, glucagon, and high-dose insulin treatment; the patient was discharged from the hospital without any sequelae after ILI treatment.

HIET has numerous positive effects in cardiogenic shock developed in CCB and BB intoxication. In animal models of propranolol and verapamil toxicity; it has been shown that survival rate increased and they ensured good hemodynamic stability when HIET was added compared to adrenalin and glucagon application alone.⁵ Following HIET, the effect of the treatment begins between 15 and 60 minutes.⁵ It is recommended that HIET should be commenced in cardiogenic shock and 0.5-2 U/ kg/hour maintenance infusion treatment is suggested following 0.5-1 U/kg load dose.⁵ In our case, after a loading dose of 1 U/kg intravenous insulin, the infusion of 0.5 U/kg/hour was started and finally was increased up to 2 U/kg/hour. Some amount of dose could be reduced in vasopressors with insulin bolus administration for a short time. However, permanent hemodynamic stability could not be enabled with insulin administration.

ILI treatment is recommended as a rescue therapy in cases of severe overdose of lipophilic anesthetics largely and other drugs.⁹ Most studies carried out regarding ILI treatment were performed in CCB overdoses due to high lipophilicity. Five minutes after applying verapamil to 30 rats at toxic dose, Tebbutt et al.¹⁰ administered serum physiologic infusion to rats in control group over a five-minute period, and 12 mL/kg of 20% lipid infusion to those in study group. They showed

that survival rate increased in the lipid-administered group. In addition, lipid therapy doubled the average lethal dose of verapamil. The first lipid treatment was successfully applied in a case with intravenous bupivacaine toxicity in 2006.¹¹ One hundred and three cases with single or multiple drug overdoses including local anesthetics with lipid and water solubility, antidepressant, antipsychotic, and cardiovascular drugs were retrospectively evaluated and it was reported that the positive effects of the treatment were not observed in only 16 cases (15.5%). In 10 cases out of 12 with verapamil overdose and two cases with carvedilol overdose, the positive effects of lipid therapy were reported.¹² Graudins et al.⁵ have reported that the positive effects of ILI applied as a rescue therapy in CCB and BB multiple drug overdoses were seen in some cases in an hour and a few hours in some patients. While the efficiency of ILI application was shown in BB and CCB overdoses, the recommended dose range is still controversial. The ILI dose according to the proposal of the American Regional Anesthesia Association in 2012 was intravenous bolus of 20% lipid emulsion, 1.5 mL/kg of lean body mass, (can be repeated in persistent cardiovascular collapse) or it was in a continuous infusion way as 0.25-0.5 mL/kg/min.⁸ In a retrospective study of nine adult patients, bolus application was compared with continuous infusion application. No significant difference was determined on the average arterial pressures.¹³ Despite 2 U/kg/hour insulin infusion in our case poisoned with carvedilol and verapamil in lipophilic characteristic^{14,15}, bolus ILE application was given at a dose of 1.5 mL/kg in the 1st hour of follow-up (20% intralipid®) and hemodynamic stability was ensured in half an hour. Vasopressor drugs could be decreased rapidly, ILI therapy was not required again. Potential side effects of ILI therapy were reported to be lipemic plasma, biochemistry laboratory abnormalities, hyperviscosity, pancreatitis, and noncardiogenic pulmonary edema.⁵ No side effect was observed in our case following ILI therapy.

Poisonings of CCB and BB can be life-threatening. Recommended standard therapies can be inadequate in these poisonings. ILI treatment can be a life-saving treatment option in patients with CCB and BB intoxication who do not respond to classical supportive therapy and can develop life-threatening cardiovascular collapse.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Fulya Kamit Can, Concept: Fatih Durak, İkbal Durak, Design: Ayşe Berna Anıl, Data

Collection or Processing: Neslihan Zengin, Kerem Yıldız, Analysis or Interpretation: Ayşe Berna Anıl, Fulya Kamit Can, Literature Search: İkbal Durak, Neslihan Zengin, Kerem Yıldız, Writing: Fatih Durak, Ayşe Berna Anıl.

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