Turk J Intensive Care
DOI: 10.4274/tybd.galenos.2022.68442

CASE REPORT / *OLGU SUNUMU*

Hatice Feray Arı,
Fatih Eren,
Dorukhan Besin,
İbrahim Altun

The Cardiogenic Shock with Antihypertensive Drugs Intoxication in a Child

Antihipertansif İlaç Zehirlenmesi Olan Bir Çocuktaki Kardiyojenik Şok

Received/Geliş Tarihi : 28.02.2022
Accepted/Kabul Tarihi : 07.04.2022

Hatice Feray Arı
Şanlıurfa Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Intensive Care, Şanlıurfa, Turkey

Fatih Eren, Dorukhan Besin, İbrahim Altun
Şanlıurfa Training and Research Hospital, Clinic of Pediatrics, Şanlıurfa, Turkey

Hatice Feray Arı MD, (✉),
Şanlıurfa Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Intensive Care, Şanlıurfa, Turkey

E-mail : dr.hferayyavas@gmail.com
Phone : +90 505 685 49 23
ORCID ID : orcid.org/0000-0002-2208-2524

ABSTRACT Combination antihypertensive treatments are usually used in everyday life, which has a life-threatening risk of using an overdose accidentally or suicidally. The effects of calcium channel blockers on the cardiovascular system are negative chronotropic, myocardial depression, decreasing atrioventricular signals, and vasodilatation. Beta blocker drugs are affected to beta receptors of catecholamines with competitively inhibition. Hypotension and bradycardia are the most common cardiac manifestations, and the others are arrhythmias, pulmonary edema, depression of the central nervous system. A previously healthy 4-year-old boy used accidentally 240mg verapamil/4mg trandolapril two pieces and 5mg nebivolol one, at the time of admission his clinical condition was in cardiogenic shock. We successfully treated him with insulin-euglycemia/glucagon treatment, calcium, and lipit infusion therapy, plasmapheresis, and continuous venovenous hemodiafiltration without any sequels. The intoxication of calcium channel blockers and beta blocker drugs are rare but severe cases because of life-threatening.
Keywords: Antihypertensive treatments, calcium channel blocker, beta blocker, cardiogenic shock, intoxication

ÖZ Günlük yaşamda genellikle kombine antihipertansif ilaçlar kullanılmaktadır ve kazara veya intihar amaçlı olarak aşırı dozda kullanılması hayati tehlike taşıyabilir. Kalsiyum kanal blokerinin kardiyovasküler sistemler üzerindeki etkileri; negatif kronotropi, miyokardiyal depresyon, atriyoventriküler sinyallerde azalma ve vazodilatasyondur. Beta bloker ilaçlar ise katekolaminlerin beta reseptörlerine yarışmalı inhibisyonu ile etki eder. Hipotansiyon ve bradikardi en sık görülen kardiyak belirtiler olup aritmiler, pulmoner ödem, merkezi sinir sisteminin depresyonu da görülür. Daha önce sağlıklı olan 4 yaşında erkek çocuk, kazara iki adet 240 mg verapamil/4 mg trandolapril ve bir adet 5 mg nebivolol kullanmıştı. Başvuru anında hastanın klinik durumu kardiyojenik şok idi. İnsülin-öglisemi/glukagon tedavisi, kalsiyum ve lipit infüzyon tedavisi, plazmaferez ve sürekli venovenöz hemodiyafiltrasyon tedavileri ile başarılı bir şekilde herhangi bir sekel gelişmeden hastayı tedavi ettik. Kalsiyum kanal blokeri ve beta bloker ilaç intoksikasyonu nadir fakat hayatı tehdit edici olması nedeniyle ciddi vakalardır.
Anahtar Kelimeler: Antihipertansif tedavi, kalsiyum kanal blokeri, beta bloker, kardiyojenik şok, zehirlenme

Introduction

The combination antihypertensive treatments are usually used in everyday life for being easy (1, 2). However, these drugs have a life-threatening risk for using an overdose. Intoxication is rare and can be caused serious problems. Severe hypotension, cardiac failure, multiple organ failure, arrhythmias can be developed, and then the patient may be die (3). In this case report, we presented a 4-year-old boy who used combined antihypertensive drugs accidentally. These two drugs contained combined verapamil/trandolapril and nebivolol. When the patient was admitted to the hospital, he had a severe cardiogenic shock. We successfully treated him with insulin-euglycemia/glucagon treatment, calcium, and lipid infusion therapy, plasmapheresis, and continuous venovenous hemodiafiltration (CVVHDF) without any sequels.

Case Report

A previously healthy 4-year-old boy was admitted to the pediatric emergency department for suddenly developed weakness and conscious. After questions about his medical history, it has learned that he used accidentally 240mg verapamil/4mg trandolapril two pieces and 5mg nebivolol one, they were antihypertensive drugs of his grandfather.

At the time of admission, his heart rate was 62/min, respiratory rate 18/min, blood pressure 53/22(39) mmHg. Glasgow coma scale (GCS) was 12, he was conscious. His body temperatures were 36.5 ^{0}C, oxygen saturation 100% in room air, capillary refill time was normal. The physical examination revealed, there was no obvious physical examination finding other than weakness. Arterial blood gas examination, pH:7.20 pCO_2:57 mmHg HCO_3:18 mmol/L Laktat:4.8 mmol/L was consistent with metabolic acidosis. Additional blood test results were as follows: his complete blood count (CBC) white blood cell (WBC) was 32.210x10^3/mm^3, his haemoglobin (Hb) was 10.4 g/dl, total platelet (Plt) count was 306x10^3/mm^3; serum urea/creatinine was 44/0.8mg/dl, serum sodium/potassium (Na/ K) was 139/3.9mEq/L, aspartate transaminase/alanine aminotransferase (AST/ALT) was 19/26U/L, glucose was 160mg/dl, International Normalized Ratio (INR):1, prothrombin time (PT):12.8seconds (sec), activated plasma thromboplastin time (APTT):25.7sec, Troponin-T:6.6pg/ml.

The patient was admitted to pediatric intensive care unit (PICU) for close monitoring and treatment. Rapid intravenous fluid boluses (20 cc/kg IV bolus three times) were given and inotropic agents were initiated for severe hypotension. Gastric lavage and activated charcoal treatment were not applied because of six hours before being admitted to the hospital he used 27mg/kg verapamil, 0.45mg/kg trandolapril, and 0.28mg/kg nebivolol.

His GCS score was below 8 and then intubated to protect his airway and required mechanical ventilation. Although inotropic drugs (noradrenaline 1mcg/kg/min, adrenalin 1mcg/kg/min and dopamin 20mcg/kg/min) and hydrocortisone 4mg/kg/day intravenous were given, his blood pressure was 47/12(29) mmHg. Therefore insülin/glucagon, lipid and calcium (Ca) infusion treatment was initiated. Intravenous fluid was given 2000cc/m^2 and insulin infusion 0.5U/kg/h, glucagon 1mg/dosage twice times, lipid 0.25ml/kg/min and 10% Ca gluconate infusion 0.1cc/kg/h were initiated. In the 6th hour of being transferred to PICU, his resistance hypotension was continued, then developed oligo/anuria and renal failure. Supporting to decrease blood drug levels, we began high volüme (1.5 times plasma volume) plasmapheresis centrifugally with femoral venovenous hemodialysis catheter and then CVVHDF extracorporeal treatment at the time of the 8th hour of being transferred to PICU. Only hemodiafiltration treatment was begun at the beginning, after that by following closely his blood pressure ultrafiltration (UF) was done and slowly increased. The aim volume of UF was determined to 1-2 cc/kg/h negative balance.

After these extracorporeal treatments, his blood pressure increased hour by hour, consequently, his inotropic doses were decreased gradually. The urine output of the patient increased due to the improvement of renal perfusion, accordingly, we stopped CVVHDF at the 30th hour of treatment. In the 32th hour of admitted to PICU, his insülin/glucagon, lipid and Ca infusion treatment was terminated, he extubated. In the 50th hour of admitted to PICU, he transferred to the general ward without any sequels.

Discussion

The intoxication of calcium channel blocker (CCB) and beta-blocker (BB) drugs are rare but severe cases because of life-threatening. The reason of drug intoxication deaths was reported to CCB 40% and BB 65% in America (4). The effects of CCB on cardiovascular systems are negative chronotropic, myocardial depression, decreasing atrioventricular signals, and vasodilatation. In addition to that

the effects of CCB drugs in pancreas are dysfunctional beta cell, and hyperinsulinemia and hyperglycemia. Beta-blocker drugs are effected to beta receptors of catecholamines with competetively inhibition. Clinical findings in poisoning with these drugs are dependent on the receptor selectivity, lipit solubility, partial agonist effect and dose. Hypotension and bradycardia are the most common cardiac manifestations, and others are arrhythmias, pulmonary edema, depression of the central nervous system (5).

The combination drug which contains 240mg verapamil hydrochloride and 4mg trandolapril is generally using for antihypertensive treatment in adults in Turkey. Also, Nebivolol 5mg is a BB drug to protect from arrhythmias and hypertension. The toxic dose of verapamil, trandolapril and nebivolol has not been known yet in childhood. The case of verapamil/trandolapril combination drug's intoxication is reported on a 3.5 year-old is an remarkable. Seven hours after ingestion, the patient was detected hypotension and bradycardia then implanted pacemaker, was reported (6).

Supportive care is important which contains airway, breathing, and circulation firstly. CCB and BB poisonings have the same principles of treatment mainly. Gastrointestinal decontamination can be applied if suitable for ingestion time. In the treatment of hypotension and cardiovascular collapse fluid, inotropic, vasopressor and chronotropic agents are used. If these treatments are insufficient, glucagon, insulin-euglysemia, calcium and lipid infusion treatment should be applied. Mortality is decreased when insulin-euglycemia treatment is added in addition to adrenaline or glucagon (7). In our case, although inotropic drugs were given, there was no adequate response. Therefore insülin/glucagon, lipid and Ca infusion treatment was initiated. In cardiogenic shock, insulin 0.5-1U/kg loading dose followed by 0.5-2U/kg/hour infusion therapy is recommended (7).

Lipid infusion is recommended as salvage therapy, especially in severe poisoning with lipophilic anesthetic drugs. It was reported that a 13-year-old girl was responded to lipid treatment after suicidal use of drugs containing carvedilol and verapamil (8). The lipid infusion dose is either 1.5mL/kg bolus or 0.25-0.5mL/kg/min of 20% lipid emulsion infusion. We were initiated lipid 0.25ml/kg/min and 10% Ca gluconate infusion 0.1cc/kg/h. After all these treatments were initiated, he has been observed close monitored for vital signs and the changing of biochemical parameters. Three hours later his blood pressure was begun to increase. Associated with increased renal perfusion his diuresis was begun and accordingly, his edema was decreased.

In calcium channel blocker and beta-blocker overdose, extracorporeal treatment strategy has limited usefulness because of drugs' lipid-soluble (4,9). These drugs verapamil (90%), trandolapril (80%) and nebivolol (98%) which our patient ingested accidentally bound to plasma proteins highly (2, 4). In plasmapheresis treatments are 100-150% of plasma volume (1-1.5 times plasma volume) rate of change. When plasmapheresis is applied at this rate, 50-70% of pathological proteins are removed in a single session. In severe cases like intoxication with 2-3 plasma exchange rates can be treated (10). In our case, we thought that the plasmapheresis could have an active role, because of drugs that cause intoxication are highly protein bound. In addition, our patient is 4 years old and could not give a history because of unconsciousness. His family was socioculturally poor, so no clear communication could be established. Therefore, it could not be clarified whether he also took other drugs. Although the efficacy is known to be low, it can be applied in selected cases. In our local tertiary hospital limited opportunities and having no extracorporeal membrane oxygenation support (ECMO), for decreasing blood drug levels, we began plasmapheresis and CVVHDF treatment at the time of the 8th hour of being transferred to PICU. Thanks to all the treatments we were able to provide, our patient was transferred to the service without sequelae.

The intoxication of calcium channel blocker and beta-blocker drugs are rare but severe cases because of life-threatening. Especially in children these drugs are ingested accidentally. In clinically, hypotension and bradycardia are the most common cardiac manifestations. Developing subsequently sustained hypotension and cardiac failure are related to mortality. If treatments are not started early and managed well, it causes to hypotension-induced multiple organ failure syndrome and the patient may be die.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.F.A., F.E., D.B., İ.A., Concept: H.F.A., Design: H.F.A., Data Collection and/or Processing: F.E., D.B., İ.A., Analysis and/or Interpretation: F.E., Literature Search: D.B., İ.A., Writing: H.F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Steven G. Chrysant using fixed-dose combination therapies to achieve blood pressure goals. Clin Drug Invest 2008;28(11):713-34. PMID: 18840014, DOI: 10.2165/00044011-200828110-00005.
2. Alaygut D, Orbatu D, Oflaz MB. Severe cardiac and renal findings in adolescent girls: Trandolapril/verapamil hydrochloride overdose. Tepecik Eğit ve Araşt Hast Dergisi 2019;29(3):302-6. DOI: 10.5222/terh.2019.60352.
3. Kolcz J, Pietrzyk J, Januszewska K, Procelewska M, Mroczek T, Malec E. Extracorporeal Life Support in Severe Propranolol and Verapamil Intoxication. J Intensive Care Med 2007; 22(6): 381-5. PMID: 18062140, DOI: 10.1177/0885066607307528.
4. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev 2004; 23(4): 223-38. PMID: 15898828, DOI: 10.2165/00139709-200423040-00003.
5. Konca Ç, Yıldızdaş RD, Sarı MY, Yükselmiş U, Horoz ÖÖ, Yılmaz HL. Evaluation of poisoned children with calcium channel blockers or beta blockers drugs. Turk Arch Ped 2013; 138-44. DOI: 10.4274/tpa.133.
6. Doğan M, Basaranoglu M, Peker E, Akbayram S, Sahin M, Uner A, et al. Tarka overdose in a young child. Hum Exp Toxicol 2011;30(9):1392-1398. PMID: 21148598, DOI: 10.1177/0960327110389834.
7. Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol 2016; 81: 453-61. PMID: 26344579, DOI: 10.1111/bcp.12763.
8. Durak F, Can FK, Zengin N, Durak İ, Yıldız K, Anıl AB. Successful intravenous lipid infusion therapy in a case with life-threatening calcium channel and beta blockers overdose. J Pediatr Emerg Intensive Care Med 2016; 3: 151-4. DOI: 10.4274/cayd.40427.
9. Kerns W. Management of b-adrenergic blocker and calcium channel antagonist toxicity. Emerg Med Clin North Am 2007; 25(2): 309-31. PMID: 17482022, DOI: 10.1016/j.emc.2007.02.001.
10. Özen E, Ekemen S, Şen E, Akcan A, Büyükkıdan B. Evaluation of the effectiveness of plasmapheresis in intoxicated patients followed up in intensive care unit. Tepecik Eğit. ve Araşt. Hast. Dergisi. 2018; 28(2): 111-115.