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Severe Cardiac and Renal Findings in an Adolescent Girl: Trandolapril/Verapamil Hydrochloride Overdose

Bir Adolesan Kızda Trandolapril/Verapamil Hidroklorür Kombinasyon Toksisitesi İle Ciddi Kardiyak ve Renal Bulgular

Olgu Sunumu
Case Report

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ABSTRACT

Trandolapril/verapamil hydrochloride combination is an antihypertensive drug. A 15-year-old female patient was brought to our hospital with the findings of fatigue and somnolence. It was learnt that 12 hours before her admittance, she had taken tablets each containing 180 mg verapamil and 2 ml trandolapril. Temporary pacemaker was implanted to the patient for monitorization who had clinical picture of bradycardia, hypotension and acute renal failure and appropriate fluid treatment was administered. Pacemaker was removed after 12 hours because normal heart rhythm was restored. Acute renal failure was resolved with fluid replacement. This case was reported in order to present findings of cardiac and renal toxicity which may develop due to the use of fixed-dose combination drugs such as trandolapril/verapamil hydrochloride that are rarely prescribed in childhood and adolescent age group.

Keywords: *Trandolapril, overdose, calcium channel blocker, angiotensin-converting enzyme inhibitor, adolescent, verapamil*

ÖZ

Trandolapril/Verapamil Hidroklorid kombinasyonu bir antihipertansif ilaçtır. 15 yaşında kız hasta hastanemize halsizlik ve somnolans bulguları ile getirildi. Başvurusundan 12 saat önce her bir tabletinde 180 mg verapamil ve 2 mg trandolapril bulunan tabletlerden içtiği öğrenildi. Bradikardi, hipotansiyon ve akut böbrek hasarı tablosunda olan hastaya izlem amaçlı geçici pacemaker takılarak uygun sıvı replasmanı sağlandı. Normal kalp ritminin sağlanmasından 12 saat sonra pacemaker çıkarıldı. Akut böbrek hasarı sıvı tedavisi ile düzeldi.Bu vaka çocukluk ve adolesan çağda Trandalopril/Verapamil gibi sabit doz da ilaç kombinasyonları içeren ve çocukluk çağında kullanımı nadir olan ilaçların toksisitesi ile ilgili gelişebilecek kardiyak ve renal toksisite bulgularını sunmak için yazılmıştır.

Anahtar kelimeler: *Trandolapril, yüksek doz, kalsiyum kanal blokeri, anjiotensin konveting enzim, adolesan, verapamil*

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INTRODUCTION

Fixed-dose combination treatments in hypertension therapy are very frequently used. These drug combinations enable use of a single drug and single dose per day [1]. Tarka R is a combination drug consisting of verapamil hydrochloride and trandolapril and it has various dosage combinations such as 180-240 mg verapamil and 1-4 mg trandolapril [1]. INVEST (International Verapamil-trandolapril Study) study has shown that verapamil and trandolapril combination is useful on 22576 individuals having hypertensive and coronary artery disease in terms of both mortality and morbidity which has increased the chance of prescribing the drug especially for adults [2]. Tarka may cause some adverse effects such as overdose lethargy, fatigue,

sensory loss, bradycardia, hypotension, hyperglycemia, metabolic acidosis and shock [3]. Toxic dose of Tarka is not definitely known in the literature. However in some case reports; it is notified that lethal dose may occur with intake of 4-7 tablets, thus this may correspond to 720-1680 mg verapamil and 8-14 mg trandolapril intake [3]. This paper represents a 15-year-old female patient who applied with complaints of fatigue and somnolence 12 hours after drug intake.

CASE REPORT

A 15-year-old female patient was admitted to our hospital due to somnolence and fatigue 12 hours after suicidal ingestion of six tablets of Tarka®, each tablet of which contained 180 mg verapamil and 2 mg trandolapril.

Activated charcoal was given to the patient who was referred from another hospital. Hypocalcemia (5,8 mg/dl) was also detected and she was given calcium gluconate intravenously. On physical examination, her body weight and height were 46 kg (10-25 percentile) and 163 cm (50 percentile) respectively. She was hypotensive (80/50 mmHg) bradycardic (68/min) and had tachycardia (28/min). Otherwise her physical examination findings were within normal limits except for somnolence. During laboratory analyses, her complete blood count and liver function tests were normal except for leucocytosis and mild elevation of C-reactive protein. She had acute renal failure, hypocalcemia and hypopotassemia with normal arterial blood gas analysis results, prothrombin time, and activated partial thromboplastin time values. (Hemoglobin 12,7 g/dl, white blood cell 22.000/mm^3, C-reactive protein 18 mg/dl, BUN 38 mg/dl, creatinine 2.28 mg/dl, AST 23 IU/L, ALT 32 U/L, LDH 176 U/L, albumin 4.0 mg/dl, phosphorus 4.38 mg/dl, calcium 7.8 mg/dl, sodium 138 mmol/l, potassium 3.3 mmol/l, pH :7.45 PCO_2: 22 mmHg, HCO_3 20 mmol/l). Hydration was provided with NaCl %0.9 and an echocardiography was performed (Figure 1). Temporary transvenous pacemaker was implanted because of bradycardia and hypotension and after the pacemaker placement, the vital findings began to return within normal limits (pulse rate: 80/min, respiratory rate:18/min, arterial pres-

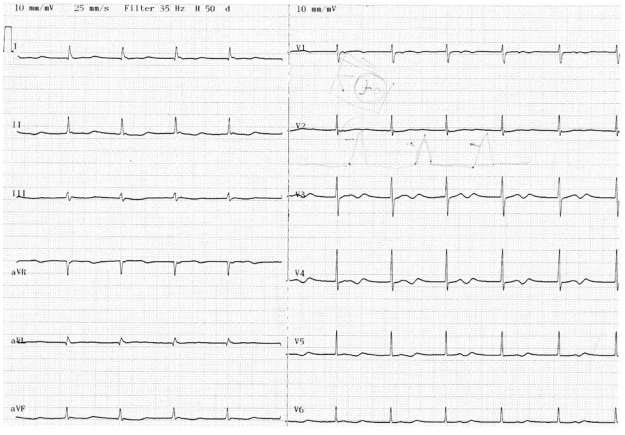

Figure 1. Bradycardia due to depression of the sinoatrial node, apperent U waves in lead V3-5, early repolarization in V2 and long QT intervals (QTc ~610 msec) of our patient before pacemaker insertion.

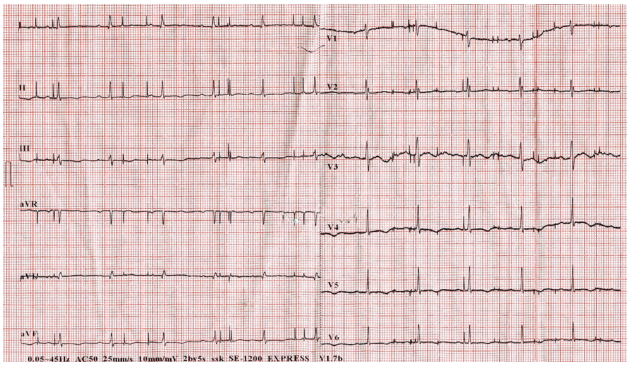

Figure 2. 1. degree AV block rhythm competing with pacemakers and long QT intervals (QTc: ~480 msec).

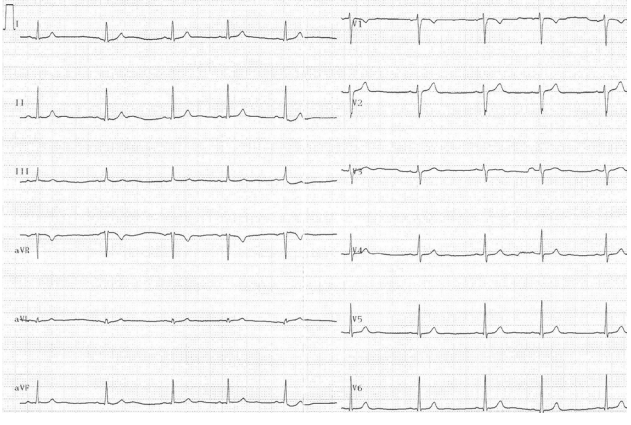

Figure 3. Normal sinus rhythm after pulling out of pacemaker.

sure 100/80 mmHg) (Figure 2). Twelve hours after pacemaker implantation, the pacemaker was removed because normal heart rhythm was restored. Figure 3 illustrates ECG after removal of the pacemaker. Renal function started to recover after 24 hours. She was discharged with complete remission on day 3 of her hospitalization.

DISCUSSION

Tarka® is an antihypertensive drug that is approved by US Food and Drug Administration and contains combination of verapamil SR and trandolapril [4]. Verapamil is a calcium channel blocker (CCB). It is used in the treatment of hypertension, cardiac arrhythmias and angina. Sustained-release form of verapamil is also marketed (verapamil (SR) and one dose per day is sufficient due to its sustained release [5]. Its significant part passes through the portal system and gets metabolized and it is converted to norverapamil that is its primary bioactive metabolite. Norverapamil has approximately 20% activity of verapamil [5]. In healthy individuals, peak verapamil and norverapamil concentrations are reached within 4-15 hours and 5-15 hours respectively. Besides, these periods may be prolonged with sustained release tablets [5]. A significant part, and metabolites of verapamil (70%) are excreted through kidneys. Due to the wide usage area of verapamil and verapamil SR, numerous intoxication cases are reported in the literature [4]. Trandolapril is an angiotensin-converting enzyme inhibitor (ACE-I) and it reduces the angiotensin II level which is a potent vasoconstructor and decreases systemic blood pressure [6]. Furthermore, it can provide benefit for the type 2 diabetes mellitus patients whose renal functions deteriorated. Indeed, trandolapril and some other ACE inhibitors keep the blood pressure under control [6]. In human body, trandolapril is deesterified and converted into trandolaprilate which is 8-times more potent bioactive metabolite. Trandolaprilate reaches to the peak plasma concentration within 2-12 hours independent from simultaneous food intake. Urinary, and fecal Clearance rates of trandolapril and its metabolites are 33% and 66% respectively [3].

In trandolapril toxicity; patients are typically presented with hypotension and relative bradycardia. Non-cardiac symptoms consist of lethargy, fatigue and changes in consciousness [5]. Severe angioedema and hypotension are the most serious adverse effects that distinguish trandolapril from the other ACE inhibitors. All of the reported trandolapril toxicities are associated with Tarka preparation. In CCB poisonings clinical manifestations of bradycardia, hypotension, hyperglycemia, metabolic acidosis and shock can be seen. Also the stroke is also reported in verapamil toxicity [7,8]. Toxicity with standard verapamil formulas occur normally within 2-4 hours after drug intake. However in cases with sustained-release verapamil toxicity symptoms appear 12 hours after drug intake and they may persist for 48-72 hours [9,10]. In verapamil toxicity myocardial toxicity or the development of heart failure related to complete heart block are responsible for mortalities [11]. The symptoms of this case started 12 hours after intake of 6 Tarka tablets, each tablet containing 180 mg verapamil and 2 mg trandolapril and the first adverse symptom was fatigue. The patient ingested totally 1080 mg (23 mg/kg) verapamil and 12 mg trandolapril (0.26 mg/kg). It was thought that symptoms of fatigue were related to trandolapril toxicity. Additionally, bradycardia and hypotension during the admittance may be observed in both trandolapril and verapamil toxicities. Even though other adverse effects such as hyperglycemia, complete AV block, flushing have been reported in the literature as manifestations of verapamil toxicity, we did not observe these side effects and leukocytosis and hypocalcemia were detected at admission.

Minimal toxic dose of verapamil has not been established clearly. Both in fetal and non-fetal cases doses of 800 mg and 24000 mg values have been indicated [11,12]. The average non-toxic dose of verapamil is 320 mg and its average toxic dose is 3.2 g [13]. Additionally,

use of fixed-dose combinations, especially Tarka should be limited in children. Intoxication case reported by Doğan M et al. on a 3.5-year-old child is an examplary case for the early childhood period. The patient was brought with somnolence 7 hours after drug intake and pacemaker had been implanted because of hypotension and bradycardia that developed during follow-up. Gokel et al. reported two adult cases with thrombotic microangiopathy which developed after taking 180 mg verapamil and 2 mg trandolapril and also acute renal failure with rhabdomyolysis had developed [14,15]. Additionally, our case had acute renal failure; and any laboratory finding did not suggest the presence of rhabdomyolysis and thrombotic microangiopathy. Renal failure was treated with appropriate fluid replacement and alkalinization of urine.

Batalis et al. [16] reported a case who was found in an unconscious state 12 hours after taking Tarka and died within a short period of time. Cohen et al. [11] reported a 60-year-old male patient admitted with complaint of dizziness after taking 5 tablets of Tarka and he had been found in a hypotensive and bradycardic state 8 hours later.

In Tarka poisonings; lethargy and fatigue may be the first symptoms which should be definitely considered by the clinicians. The patients should be hospitalized for at least 24-48 hours if their clinical state worsens.

As in all other intoxication cases; primarily airways, respiration and circulation should be assessed in Tarka poisonings and crystalloid fluids should be given in the presence of hypotension [3]. Activated charcoal can be given orally within up to 1 hour after drug intake. However in cases of toxicity with sustained-release verapamil; use of active charcoal after 2 hours may decrease absorption of the drug [17]. In our case, activated charcoal was given about 12 hours after drug ingestion. Activated charcoal was not given again because the patient was not expected to gain benefit from its application.

Due to the highly protein-bound state of verapamil, hemofiltration and hemodialysis treatment do not provide any benefit in verapamil intoxication, trandolapril overdose may be used [18]. Calcium treatment can be used in verapamil intoxication in order to provide the blockage of calcium channels [19]. We gave 1 mg/kg 10% calcium gluconate bolus treatment to our patient for a single day at 12-hour intervals.

Various sympathomimetic drugs (dopamine, dobutamine, norepinephrine etc) can be used against hypotensive effect in CCB overdose [3]. However in this patient, immediate pacemaker implantation was performed without the need of such sympathomimetics and then her clinical picture improved.

Consequently, we did not find any suicidal intoxication cases related to Tarka in the literature. In such patients; especially in the development of cardiac side effects, immediate pacemaker implantation and in case of acute renal failure appropriate fluid replacement are critically important.

Conflict of Interest: None.
Informed Consent: Taken from family.

Çıkar Çatışması: Yoktur.
Hasta Onamı: Aileden alınmıştır.

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