The Relationship in Hypertensive Patients Endothelin Levels, Echocardiographic Findings and Valsartan

Hipertansiyonda Endotelin Seviyeleri, Ekokardiyografi Bulguları ve Valsartan Tedavisiyle İlişkisi

Hipertansiyonda Endotelin Seviyeleri / Hypertensive Patients Endothelin Levels

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Özet

Amaç: Endotelin düzeylerini azaltan tedavi seçeneklerinin, hipertansiyon tedavisinde yeni bir yaklaşım olabileceği düşünülmüştür. Bu nedenle bu araştırmada Valsartan%u2019nın hipertansiyon tedavisindeki iyileştirici etkilerinin, endotelin düzeylerine de olan etkisinden kaynaklanıp kaynaklanmadığı araştırılmıştır. Aynı zamanda endotelin düzeyleri ile sol ventrikül hipertrofisi arasındaki ilişki değerlendirilmiştir. Gereç ve Yöntem: Çalışmaya toplam 14%u2019ü erkek, 9%u2019u kadın olmak üzere, 33-70 yaş aralığında, JNC VII ölçütlerine göre; evre I (n:3) ve evre II (n:20) birincil yüksek kan basınçlı 23 hasta dahil edilmiştir. Bulgular: Sağlıklı bireylerde leptin ve endotelin düzeyleri, literatürle uyumlu olarak hipertansiflere göre düşük bulunmuştur (p<0.05). Hipertansif grupta üç aylık valsartan ve/veya hidroklorotiyazid tedavisinden sonra endotelin düzeylerinde ve SVH azalma tespit edilmiştir (p<0.05) SVH veya hipertansif retinopatisi olan hastaların serum endotelin düzeyleri, SVH veya hipertansif retinopatisi olmayan hastalarınkine göre düşük olarak tespit edilmiş ancak; istatistiksel olarak anlamlı bulunmamıştır (p>0.05). Tartışma: Valsartan%u2019nın hipertansiyon üzerine faydalı etkilerinin yanında serum endotelin seviyelerini azaltıcı etkilerinin olduğu bulunmuştur.Ek olarak serum endotelin seviyelerinin hipertansiyon hastalarında yüksek olduğu gözlenmiştir. Bununla birlikte valsartan%u2019nın hipertansiyona bağlı komplikasyon gelişmesinde etkinliği görülmemiştir.

Anahtar Kelimeler

Hipertansiyon; Endotelin; Valsartan

Abstract

Aim: It is estimated that treatment options which lower endothelin (ET) levels may be a new treatment approach for hypertensive patients. For this purpose in this study, we investigated whether the antihypertensive effect of valsartan is due to its effect on serum ET levels or not. In addition to this, the relationship between serum ET evels and left ventricular hypertrophy (LVH) was also determined. Material and Method: Twenty-three patients (14 men, 9 women) with an age range of 33-70 years having Stage 1 (n=3) or Stage II (n=20) hypertension according to the criteria defined by the Joint National Committee Report VII (JNC VII) were included. Results: Compatible to previous studies, serum ET evels of the hypertensive patients were higher than of the healthy controls (p<0.05). In the hypertensive group, there were significant reductions in both ET levels and LVH after three months of valsartan and/or hydrochlorothiazide treatment (p<0.05). Serum ET levels of patients with LVH or hypertensive retinopathy were higher than patients without LVH or hypertensive retinopathy, however this finding was not statistically significant (p>0.05). Discussion: Valsartan was found to be effective in decreasing serum ET levels in addition to its beneficial effect on hypertension. In addition to this, serum ET levels were observed to be elevated in hypertensive patients. However, valsartan did not seem to be effective in the development of complications related to hypertension.

Keywords

Hypertension; Endothelin; Valsartan

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Introduction

It is known that angiotensin II (AT II) increases the sympathetic activity of the heart via direct and indirect pathways, stimulates protein synthesis and causes cardiac hypertrophy (1). AT II receptor blockers portray their effects via AT II-1 receptors. AT II-1 is responsible for the control of vasoconstriction, aldosteron release from the adrenal cortex and β–adrenergic blockade.

AT II receptor antagonists are potent, long acting non-peptide agents which block AT II-1 receptors selectively. Besides their effects to lower the activity of the renin-angiotensin-aldosteron system, they have sympatholytic and antiproliferative effects. They cause natriuresis via indirect effects on aldosteron (2).

Left ventricular hypertrophy (LVH) is an important predictor of cardiovascular morbidity and mortality (3). As an adaptive response to hypertension, patients with LVH have a high risk of arrhythmias, coronary heart disease and sudden death (4-6). A ten percent reduction in blood pressure levels during night was shown to cause significant decrease in left ventricular mass (7). Insulin has a proliferative feature in human body. In patients with hypertension, insulin levels are increasing because of insulin resistance. Increased levels of insulin causes structurel changings in arters and sodium retention.

A 21-amino acid peptide endothelin (ET-1, ET-2, ET-3 and ET-4) is the dominant isoform of the peptide family. Endothelin has various biological effects on both cardiovascular system and non-cardiovascular tissues including the stimulation of vasoconstriction and cell proliferation. Several studies have shown the relationship between the plasma ET-1 levels and the severity of cardiovascular diseases (8).

Elevated serum ET levels have been documented in ischemic heart diseases, acute myocardial infarction, pulmonary and essential hypertension, atherosclerosis, idiopathic cardiomyopathy, renal failure and heart failure..

In our study, we investigated the serum ET levels and ET response to AT II receptor blocker valsartan of patients with hypertension. In addition, we evaluated the relationship between serum ET levels and left ventricular hypertrophy. Thus, we investigated whether the antihypertensive effect of AT II receptor blocker is mediated via its effect on ET or not.

Material and Method

Twenty-three patients (14 men, 9 women) with a recent diagnoses of hypertension, who were not under treatment with antihypertensive drugs, had no other systemic disease, had Stage 1 (n=3) or Stage 2 (n=20) hypertension according to the criteria defined by the Joint National Committee Report VII (JNC VII) and were willing to participate in the study were included. Patients who did not meet these criteria or were using medicine which would possibly change the metabolic parameters were excluded. Compatible to the patient group in terms age and gender, we recruited 25 volunteers who were healthy and had no history of regular drug use as the control group

After a detailed physical examination, routine blood tests were performed to the participiants for the elimination of systemic illnesses. Additionally, serum insulin and ET levels were assessed and echocardiographic examination was performed for determination of the left ventricular mass. The patients were evaluated by the same opthalmologist for the presence of hypertensive retinopathy. The patient and control groups were comparable in terms of their body mass indices.

Venous blood samples were taken into tubes over a night of fasting and centrifuged at 5000 rpm/min for 15 min. Serum samples were kept at -70 oC. Serum ET levels were assessed using Human Acylated Endothelin Enzyme Immunoassay commercial kit.

Following these procedures, Stage I and Stage II hypertensive patients were treated with daily 80 mg and 160 mg valsartan, respectively. The patients were followed up monthly and all diagnostic tests which were performed at the beginning were repeated after three months of valsartan treatment. At monthly visits, valsartan dosages were adjusted or valsartan/ hydrochlorothiazide combination was given to patients according to their blood pressure levels. Transthoracic echocardiographic examination was performed by the same cardiologist at lateral decubitis position using Vivid 7 echocardiography (GE Medical Systems, Norway, 3.5 mHz probe). Left ventricular mass was determined using the criteria defined by Deverux et al. (25). Left ventricular mass value was divided to body surface area to calculate the left ventricular mass index (LVMI). LVMI of >131 gr/m2 for men, and >110 gr/m2 for women were accepted as a cut off value for left ventricular hypertrophy. All these procedures were repeated after three months of therapy with valsartan.

Insulin resistance was determined for all patients using the HOMA formule [fasting plasma insulin U/ml x fasting blood glucose mg/dl) / 22.5]. Values of >2.7 were accepted as insulin resistance.

All data were gathered in a common database and analyzed statistically using SPSS 15.0 software package. Normally distributed data were analyzed using parametric tests whereas those with non-normal distribution were analyzed using non-parametric tests. All data are expressed as mean ± SEM. The statistical significance was taken if $P < 0.05$ and the confidence interval was 95% for differences between the study groups.

Results

Twenty-three patients (14 men, 9 women) with an age range of 33-70 years having Stage 1 (n=3; mean blood pressure 146 ± 10.4 / 88 ± 2.8 mmHg) or Stage 2 (n=20; mean blood pressure 161 ± 15.5 / 102 ± 6.9 mmHg) hypertension according to the criteria defined by the Joint National Committee Report VII (JNC VII) were included. Table I shows the characteristics of the study population. The characteristics of the male and female participants are given in Table II.

Table I. The characteristics of the patient and control groups

	Patient (n=23)	Control (n=25)	p
Age (years)	49.26±9.3	48.2±7.7	>0.05
Height (m)	167.7±5.9	166.2±7.6	>0.05
Weight (kg)	75.7±10.8	76.8±10.4	>0.05
BMI (kg/m2)	26.9±4.3	27.2±4.8	>0.05
Systolic blood pressure (mmHg)	159.1±15.5	118.5±7.,5	<0.001
Diastolic blood pressure (mmHg)	100.2±8.0	70.8±6.7	<0.001
Endothelin (ng/ml)	0.92±1.1	0.25±0.32	<0.05
LVMI	129.8±26.1	122.4±55.7	>0.05

BMI: Body mass index; LVMI: Left ventricular mass index

Table II. General features of the patient and control groups in terms of gender

	Male controls	Female controls	p	Male patients	Female patients	p
Age (years)	43.6±11.0	42.4±3.9	>0.05	52±9.2	45±8.2	>0.05
Height (m)	166.6±7.7	164.8±8.6	>0.05	170.5±3.5	163.5±6.5	>0.05
Weight (kg)	78.0±12.1	78.1±15.3	>0.05	76.2±12.7	75±7.6	>0.05
BMI (kg/m2)	27.2±2.6	28.4±7.3	>0.05	26.3±5,0	28±3.03	>0.05
Systolic blood pressure (mmHg)	119.0±13.4	117.1±5.6	>0.05	157.8±14.6	161.1±17.6	>0.05
Endothelin (ng/ml)	0.24±0.34	0.35±0.38	>0.05	1.05±1.25	0.79±1.33	>0.05

Before the treatment, LVH was diagnosed in 7 (77.77%) of 9 female patients and 9 (64.28%) of 14 male patients. The serum ET levels of the patients with LVH (0.95 ± 1.32 ng/ml) and without LVH (0.80 ± 0.63 ng/ml) were not statistically significant (p >0.05).

The number of smokers among male patients (n=8, 57.14%) was higher than that of female patients (n=5, 55.55%). There was no statistically significant difference between smokers and non-smokers in terms of serum ET levels (p >0.05).

Hypertensive retinopathy (HTRP) was diagnosed in 10 patients. The systolic and diastolic blood pressure levels of these patients were higher than those of the patients without HTRP. However, these differences were not statistically significant (p >0.05) (Table III).

Table III. Relationships between hypertensive retinopathy and serum endothelin levels and blood pressure levels.

	HTRP (+)	HTRP (-)	p
SBP (mmHg)	160.6±14.7	158.3±16.4	>0.05
DBP (mmHg)	101.8±8.4	99.3±7.9	>0.05
Endothelin (ng/ml)	1.07±1.37	0.64±0.74	>0.05

HTRP: Hypertensive retinopathy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

The serum ET levels before and after the treatment were given in Table IV.

Table IV. Serum endothelin levels before and after treatment

	Endothelin (ng/ml)		p
	Before treatment	After treatment	
Total	0.92±1.1	0.38±0.48	<0.05
Gender			
Male	1.00±1.13	0.79±1.33	>0.05
Female	0.48±0.45	0.243±0.529	<0.05

The changes in systolic blood pressure and diastolic blood pressure levels and the changes in LVMI values before and after the treatment are shown in Tables V and VI, respectively.

Insulin resistance was diagnosed in all patients. HOMA indicis were not significantly different before and after valsartan treatment (45.92 ± 30.90 and 41.02 ± 18.33, respectively; p >0.05).

Discussion

The evaluation of all patients revealed that the mean systolic blood pressure levels were decreased after three months of treatment with valsartan and/or hydrochlorothiazide (from 158.9 ± 14.2 mmHg to 128.2 ± 9.1 mmHg; p<0.01). Similarly, the diastolic blood pressure levels were also decreased from 99.3 ± 7.6 mmHg to 83.5 ± 6.2 mmHg (p<0.01) at the end of the same treatment period (Table V). These findings are in aggreement with the previous studies reporting the antihypertensive effect of valsartan (15).

Table V. Blood pressure levels before and after treatment

	SBP (mmHg)			DBP (mmHg)		
	Before treatment	After treatment	p	Before treatment	After treatment	p
Total	158.9±14.2	128.2±9.1	<0.001	99.3±7.6	83.5±6.2	<0.001
Gender						
Male	156.8±14.3	127.1±9.6	<0.01	99.1±8.9	82.5±5.7	<0.001
Female	160.4±14.3	129.1±8.8	<0.01	99.5±6.6	84.2±6.5	<0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure

The mean serum ET levels were 0.25 ± 0.32 ng/ml and 0.92 ± 1.1 ng/ml in the control and hypertensive groups, respectively (Table I). This finding was also compatible with the previous findings that ET levels are higher in hypertensive patients than those in healthy individuals (11,13). There are other studies in the literature which support our findings (12-14).

In our study, we observed that mean serum leptin levels of the patients were 0.92 ± 1.1 ng/ml and 0.38 ± 0.48 ng/ml before and after three months of treatment with valsartan and/or hydrochlorothiazide, respectively (p<0.05) (Table IV). In 1999, Doumas et al. (24) evaluated the serum endothelin levels in hypertensive patients before and after four weeks of treatment with moxonidine or losartan. They reported reduced serum ET levels after four weeks of losartan or moxonidine treatment which was statistically significant in the former one. However, there is no study in the literatute demonstrating the effect of valsartan on serum ET levels. Thus, our results imply that valsartan has a beneficial effect in this regard.

Table VI. Changes in left ventricular mass index (LVMI) after the treatment

	LVMI (g/m2)		p
	Before treatment	After treatment	
Total	129.8±26.1	103.9±18.6	<0.001
Gender			
Male	139.8±24.4	112.4±14.3	<0.001
Female	122.1±25.2	97.4±19.1	<0.001

The smoking rate of male patients was higher than of females (57.14% vs. 55.55%) and the ET levels of the smokers were higher than those of the non-smokers. However, this finding was not statistically significant (p> 0.05). Further investigations are required to evaluate the effect of smoking on ET levels.

Besides their antihypertensive effects, the antihypertensive agents are expected to hinder the development of LVH. On the other hand, some antihypertansive agents have no such an effect as expected although they effectively reduce the blood pressure (16). In a study, LVH was shown to be revresed more than 10% in the first eigth weeks, 25% in the first year and more than 40% in the third year (19). In another study, left ventricular mass was demonstrated to decrease by 14% with captopril treatment, 30% with enalapril and 12% with lisinopril (20). Another study showed that valsartan reduced cardiac hypertrophy (19). We observed a 19.9% decrease in LVH with three months of valsartan and/or hydrochlorothiazide treatment. In 1999, Thurmann et al. (19) found a greater decrease in LVH with valsartan than with atenolol in patients with essential hipertension and this difference was statistically significant. Thus, our results are in accordance with other studies (19-23). Analysis of the reduction in LVH in terms of gender revealed that gender had no influence on valsartan's effect to reduce LVH.

We observed that all our patients had insulin resistance. After valsartan treatment, the ratio of decrease in insulin resistance was 10.7%. However, this result was not statistically significant (p>0.05).

In our investigation, serum ET levels were higher in patients with LVH or hypertensive retinopathy than in healthy controls. However, this finding which was not statistically significant implies that leptin is not so effective on the complications of hypertension as its effect on the development of hypertension. It is clear that further studies are required to evaluate this issue.

As a conclusion, valsartan seems to be a treatment option for restoration of serum ET levels in addition to its effects on blood pressure and SVH in the treatment of hypertension. Although our results demonstrate a role of valsartan on the development and treatment of hypertension, the drug does not seem to have a role in the development of complications related to hypertension.

Competing interests

The authors declare that they have no competing interests.

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