

The effect of doxazosin on arterial distensibility in hypertensive patients with type II diabetes mellitus

Hipertansif tip II diyabetes mellituslu hastalarda doksazosinin arteriyel distansibiliteye etkileri

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Background: The aim of the present study was to investigate the effect of doxazosin, an alpha-1 adrenergic receptor blocker, on arterial distensibility in hypertensive patients with type II diabetes mellitus.

Methods: The study included 46 outpatients (31 females, 15 males; mean age 58.4±8.3 years; range 37 to 70 years) with type II diabetes mellitus and stage 1 or 2 hypertension according to the JNC 7 report. In addition to antidiabetic and antilipidemic drugs, the patients were given doxazosin 2 mg daily for eight weeks, during which measurements of blood pressure and pulse were made every two weeks. To regulate blood pressure, the dose of doxazosin was increased to 4 mg in the second week in three patients (6.5%), and in the fourth week in four patients (8.7%). Arterial distensibility was assessed by measuring carotid-femoral pulse wave velocity with an automatic device (Complior Colson, Createch Industrie, France).

Results: Compared to pretreatment values, significant decreases occurred at the end of eight weeks in the following parameters: systolic blood pressure (p<0.001), diastolic blood pressure (p=0.002), mean blood pressure (p<0.001), pulse pressure (p<0.001), heart rate (p<0.001), and pulse wave velocity (p=0.004). The only adverse effect was headache seen in four patients (8.7%).

Conclusion: Both blood pressures and carotid-femoral pulse wave velocity decreased after doxazosin therapy. Being an indicator of increased arterial elasticity, decreased pulse wave velocity with doxazosin treatment shows that doxazosin is a good option in hypertensive patients with type II diabetes mellitus.

Key words: Antihypertensive agents; aorta; blood pressure; carotid arteries; cholesterol; coronary disease; diabetes mellitus, type 2; diastole; doxazosin; hypertension; pulse.

Amaç: Bu çalışmada, hipertansif tip II diyabetes mellituslu hastalarda, alfa-1 adrenerjik reseptör blokleri olan doksazosinin arteriyel distansibilite üzerine olan etkileri incelendi.

Çalışma planı: Çalışmaya, JNC 7. raporuna göre tip 1 veya 2 hipertansiyonu ve tip II diyabeti olan 46 poliklinik hastası (31 kadın, 15 erkek; ort. yaş 58.4±8.3; dağılım 37-70) alındı. Hastaların kullanmakta olduğu antidiyabetik ve antilipidemic ilaçlara ek olarak, sekiz hafta süreyle günde 2 mg dozda doksazosin verildi. Bu süre içinde kan basınçları ve nabızlar iki haftada bir ölçüldü. Kan basıncını düzenlemek için, doksazosin dozu üç hastada (%6.5) ikinci haftada, dört hastada (%8.7) dördüncü haftada 4 mg'ye çıkarıldı. Arteriyel distansibilitenin değerlendirilmesi için, karotis-femoral nabız dalga hızı Complior Colson cihazı (Createch Industrie, Fransa) kullanılarak hesaplandı.

Bulgular: Tedavi süresi sonunda, tedavi öncesine göre, sistolik kan basıncı (p<0.001), diyastolik kan basıncı (p=0.002), ortalama kan basıncı (p<0.001), nabız basıncı (p<0.001), kalp hızı (p<0.001) ve nabız dalga hızı (p=0.004) değerlerinin anlamlı derecede düştüğü görüldü. Tedaviyle ilgili tek yan etki, dört hastada (%8.7) görülen baş ağrısı idi.

Sonuç: Doksazosin tedavisi sonucunda kan basıncı ve karotis-femoral nabız dalga hızı azaldı. Artmış arteriyel elastisitenin göstergesi olan nabız dalga hızının azalması, hipertansif tip II diyabetes mellituslu hastaların tedavisinde doksazosinin iyi bir seçenek olabileceğini göstermektedir.

Anahtar sözcükler: Antihipertansive ilaç; aort; kan basıncı; karotis arter; kolesterol; koroner hastalık; diyabetes mellitus, tip 2; diyastol; doksazosin; hipertansiyon; nabız.

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Atherosclerosis is one of the complications of diabetes mellitus due to partial or complete failure in insulin secretion. The association between hypertension and atherosclerosis is complicated involving endothelial dysfunction, disturbances of insulin and lipid metabolisms, vascular biological disorders, and impaired arterial adaptation. For this reason, antihypertensive treatment must be performed through a careful selection among specific medications, aiming to decrease blood pressure, produce a positive effect on various components of the disease, and prevent or reduce atherosclerosis. Angiotensin converting enzyme inhibitors, calcium channel blockers, and alpha-blockers seem to be the most promising medicines in this field.^[1-4] Alpha-1 blockers improve left ventricular hypertrophy and atherogenic lipid profile and reduce the risk of thrombotic complications and formation of fatty lining which are the starters of advanced atherosclerosis.^[5]

The pulse wave velocity, which is defined as the velocity of arterial pulse waves moving along the vessel wall, is an indicator of arterial rigidity and plays an important clinical role in defining patients at high cardiovascular risk.^[6] Pulse wave velocity is higher in rigid vessels and lower in vessels with high distensibility and compliance. In this study, we investigated the effect of doxazosin, an alpha-1 adrenergic receptor blocker, on distensibility of the arterial wall in hypertensive patients with type II diabetes mellitus.

PATIENTS AND METHODS

Patients. The study included 46 outpatients (31 females, 15 males; mean age 58.4±8.3 years; range 37 to 70 years) diagnosed as having type II diabetes mellitus^[7] and hypertension of high-normal, stage 1 or stage 2 according to the JNC 7 report.^[8] All the patients gave informed consent for inclusion in the study.

Following an irrigation (washout) period of two weeks, doxazosin tablets of 2 mg were given daily to the patients in addition to antidiabetic and antilipidemic drugs for eight weeks. During treatment, the patients were called to hospital every two weeks to have their blood pressures and pulses measured. The doses were increased to 4 mg in patients whose blood pressures could not be regulated.

Exclusion criteria included the presence of at least one of the following: stage 3 hypertension, type I diabetes mellitus, diabetic autonomic neuropathy, peripheral arterial disease (>70% stenosis), severe aortic valve disease, cerebrovascular disease, anamnesis of myocardial infarction, atrial fibrillation on 12-channel surface electrocardiography, second or third degree atrioventricular block or postmyocardial infarction, congestive heart

failure, renal failure (plasma creatinine >1.8 mg/dl), anemia (hematocrit <35%), body mass index (>35 kg/m²), and waist-hip ratio >1.

Measurements. Measurements of weight and height were made with patients in light clothes and without shoes. Body mass index (kg/m²) was calculated dividing the body weight in kilograms by square of the body height in meters. Waist circumference was measured between the last rib and the iliac crest on the midline while the patient was standing. Hip circumference was measured by using the line between the right and left major trochanter of the femur. Waist-hip ratio was found by dividing waist circumference by hip circumference.

Pulse wave velocity and blood pressure measurements. Clinic blood pressure was measured at each visit after 20 min rest in compliance with the World Health Organization guidelines, using a mercury sphygmomanometer with a cuff appropriate to arm circumference. The first and the fifth Korotkoff phases were taken as the systolic and diastolic pressures, respectively. The pulse pressure and the mean blood pressure were calculated using the following formulas:

Pulse pressure =

Systolic blood pressure - Diastolic blood pressure

Mean blood pressure =

[Systolic blood pressure + 2 x Diastolic blood pressure] / 3

Arterial distensibility was assessed by measuring carotid-femoral pulse wave velocity with an automatic device (Complior Colson, Createch Industrie, France). Technical characteristics and the use of this device were described in detail by Asmar et al.,^[9] with inter- and intraobserver repeatability coefficient values >0.9. Pulse wave velocity along the aorta was measured using two TY-306 pressure-sensitive transducers (Fukuda, Tokyo, Japan) fixed transcutaneously over the course of the femoral and right common carotid arteries. Measurements were repeated over 10 different cardiac cycles, and the mean value was used for the final analysis. Pulse wave velocity was calculated from the measurements of pulse transit time and the distance between the two recording sites using the following formula (Fig. 1):

Pulse wave velocity (m/s) =

Distance (m) / Transit time (ms)

Statistical analysis. Statistical analyses were made using the ready-to-use program of SPSS version 8.0. Pre- and posttreatment values were compared by the paired Student's t-test. All the values were expressed as mean ± standard deviation. The level of statistical significance was set to a p value of <0.05.

Table 1. Comparison of pre-and posttreatment findings

	Pretreatment	Posttreatment	<i>p</i>
Systolic blood pressure (mmHg)	148.3±11.6	131.1±14.2	<0.001
Diastolic blood pressure (mmHg)	80.2±12.2	73.5±9.2	=0.002
Mean blood pressure (mmHg)	103.2±10.2	92.6±9.3	<0.001
Pulse pressure (mmHg)	67.6±12.1	57.4±13.2	<0.001
Heart rate (beat/min)	81.4±5.8	76.8±5.5	<0.001
Pulse wave velocity (m/s)	12.2±1.6	11.8±1.5	=0.004

RESULTS

Thirteen patients (28.3%) and 33 patients (71.7%) were taking insulin and oral antidiabetic drugs, respectively, and all the patients were receiving lipid-lowering treatment with a statin (10 to 40 mg daily).

Compared to pretreatment values, significant decreases occurred at the end of eight weeks in the following parameters: systolic blood pressure ($p<0.001$), diastolic blood pressure ($p=0.002$), mean blood pressure ($p<0.001$), pulse pressure ($p<0.001$), heart rate ($p<0.001$), and pulse wave velocity ($p=0.004$) (Table 1). The dose of doxazosin was increased to 4 mg in the second week in three patients (6.5%), and in the fourth week in four patients (8.7%).

Four patients (8.7%) experienced headache, which did not require discontinuation of doxazosin administration. No dizziness of orthostatic character, palpitation or syncope developed in any of the patients.

DISCUSSION

In our study, we investigated the effect of doxazosin, an alpha-blocker, on arterial distensibility using a noninvasive method in hypertensive patients with type II diabetes mellitus. We preferred to measure carotid-femoral pulse wave velocity because of the easy recording of the pressure wave forms in both areas, adequacy of the distance between the two recording sites, and adequate

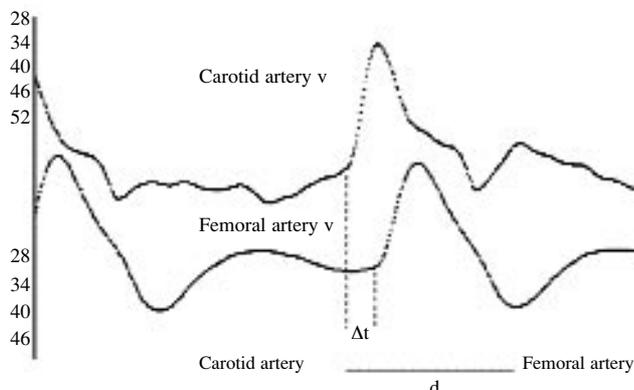


Fig. 1. Measurement of carotid-femoral (C-F) pulse wave velocity (PWV). [d: distance (m) between two recording sites (C-F) is measured on the surface of body in meters, Δt : transit time (ms), $PWV=d/\Delta t$].

illustration of the elasticity of the arterial wall including the aorta.

Arteries transmit pressure on one hand and perform a braking function on the other. Pressure transmitting function is related to the mean blood pressure and dependent on the volume of the heart beat and resistance of the vessel. Braking function is characterized by pulsatile flow and pulsatile pressure and decreases with fluctuations in pressure due to ventricular ejection. During systolic ejection, the aorta and its branches are loaded with a significant volume of blood due to pressure, but during diastole, accumulated pressure energy pushes the blood forward. This Windkessel function enables the pulsatile blood flow to turn to a smoother flow. For this reason, pulse pressure is essentially formed by blood volume (pulsation volume) ejected in each beat and compliance of the aorta and large vessels. Reduction of this compliance by age, hypertension, and diabetes results in dilatation and increased rigidity of vessels.^[10,11] In hypertension and atherosclerosis, wave amplitude of the aortic pulse rises, tidal wave becomes clearer, and diastolic wave diminishes.^[12] At the same time, depending on the increase in arterial stiffness, peripheral arterial reflection occurs earlier, resulting in augmentation of pressure in late systole instead of in diastole. This influence is added to the reflection from upper parts, increasing the length of the tidal wave and, in the end, the pulse pressure is increased by the contribution of the systolic pressure.

Increased resting heart rate may increase arterial rigidity (decrease arterial distensibility) and cardiovascular mortality.^[12,13] Mangoni et al.^[14] showed that arterial distensibility reduced in parallel with increased heart rate in rats. Increased heart rate shortens the time available for recoil, resulting in increased arterial stiffness.^[14] Contrary to a previous report,^[15] in our study, doxazosin significantly reduced the heart rate. This may account for the decrease in pulse wave velocity.

On the other hand, oral antidiabetic and lipid-lowering drugs taken by the patients might have contributed to the decreases in blood pressure and pulse wave velocity. Data on the arterial efficiency of antidiabetic treatment

in type I or type II diabetic patients are limited. A few studies reported a correlation between improved glucose control and decreased rigidity of carotid arteries.^[16,17] Moreover, statins play a role, independent of their effect on lipid profile, in the regulation of blood pressure in hypertensive patients.^[18] However, Kool et al.^[19] reported that no significant change occurred in carotid, femoral, and brachial distensibility after short-term lowering of plasma cholesterol with pravastatin treatment in patients with primary hypercholesterolemia.

Earlier studies demonstrated that decrease in pressure was not the only factor acting on wall tension, compliance, and distensibility. Various drugs, in spite of analogous falls in pressure levels, were associated with different responses in vessel wall tension and diameters of arteries. Hydralazine causes constriction in the diameter of an artery, whereas angiotensin converting enzyme inhibitors and nitrates act *vice versa*.^[20,21] Despite changing values of pressure with autonomic nervous system blockers, no changes were observed in artery diameters.^[22] Decrease in the mean blood pressure with doxazosin treatment, without a change in the diameter of the vessel, may indicate an increase in compliance. A change in wall tension may be due to changes in the structure of the artery wall, hypertrophy of smooth muscle cells, and decreases in contents of extracellular matrix.^[23] Pannier et al.^[24] demonstrated that arterial diameter did not change despite significant improvement in arterial wall tension with antihypertensive treatment with rilmenidine, suggesting the presence of other vasomotor effects. In another study, vasoconstrictor effect of angiotensin II and noradrenaline was examined in the brachial artery and the latter was associated with a more severe vasoconstriction.^[25] In our study, doxazosin-induced alpha-receptor blockage might have caused a decrease in the vasomotor tonus, which then contributed to the improvement in distensibility.^[26]

Our results show that doxazosin treatment in hypertensive patients with type II diabetes mellitus is associated with decreases in the carotid-femoral pulse wave velocity, blood pressure, and resting heart rate. However, it is not clear whether the mechanism of the decrease in pulse wave velocity is via changes in mechanical properties of the arterial wall or changes in cardiac hemodynamics. The role of doxazosin in these changes warrants further studies.

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