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Effects of Doxazosin Mesilate on Blood Pressure and Serum Lipids in Hypertensive Patients

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Summary. **In order to assess its effects on blood pressure and serum lipids, doxazosin was administered to patients with essential hypertension and a serum total cholesterol level above 220 mg/dl as part of a multicenter trial in which 7 institutions in Niigata Prefecture participated. Doxazosin was given either as monotherapy or in combination with some other antihypertensive agent. The systolic, diastolic, and mean blood pressures were all decreased significantly at weeks 4, 8 and 12 of treatment, while there was no change in the heart rate throughout the study. The antihypertensive effects in individual patients were rated according to the "Guideline for Clinical Evaluation of Antihypertensive Drugs." Moderate or improved reduction of blood pressure was attained in 29/39 patients (74%) after 12 weeks of treatment. Total cholesterol and low density lipoprotein (LDL) cholesterol levels decreased significantly after doxazosin treatment, while the cholesterol ratio (high density lipoprotein (HDL) cholesterol/total cholesterol) increased significantly. Although the apoprotein A_1 level remained unchanged, the apoprotein B level decreased significantly, and the apoprotein A_1/apoprotein B ratio increased significantly as a consequence. These results suggest that doxazosin is a useful antihypertensive drug which may be used as a first choice therapy in patients with essential hypertension and high serum cholesterol level.**

INTRODUCTION

Hypertension and the abnormality of serum lipids are considered to be the major risk factors for ischemic heart disease; they are thought to act synergistically when combined. Therefore, antihypertensive drugs should be selected based not only on their ability to reduce blood pressure but also on their effect on lipid metabolism. Accordingly, antihypertensive agents have been investigated for their effect on serum lipids in a number of studies, and the results have shown that both diuretics and β-blocking agents adversely effect serum lipids.[1,2]

On the other hand, α_1-blocking agents have been reported to have favorable results with respect to lipid metabolism. However, since fast-acting α_1-blockers such as prazosin hydrochloride have a short plasma half-life and rapidly reduce blood pressure, they are often associated with such adverse reactions as orthostatic hypotension, palpitation, and tachycardia at the commencement of treatment. Because of such adverse reactions, referred to as the "first dose" phenomenon, α_1-blockers have not been widely used as a drug of first choice in antihypertensive therapy.

Doxazosin mesilate (doxazosin) is a new α_1-blocking agent having a quinazolin nucleus, as dose prazosin. However, unlike prazosin hydrochloride, doxazosin has a longer plasma half-life (10-16 h),[3] allowing single daily administrations. Furthermore, since doxazosin exerts its antihypertensive more slowly than prazosin, a lower incidence of orthostatic hypotension has been reported when doxazosin is used for introductory therapy.[4] Also, since doxazosin shows favorable effects on lipid and glucose metabolism, α_1-blockers were recommended as drugs of first choice for antihypertensive monotherapy in the 5th American Joint Committee Report,[5] which was revised in 1992. We recently performed a study of doxazosin in patients with essential hypertension and hypercholesterol to assess its effects on blood pressure and serum lipid metabolism as well as its safety.

PATIENTS AND METHODS

A total of 39 outpatients with essential hypertension and a total serum cholesterol level above 220 mg/dl who were treated at any of the 7 participating institutions were enrolled in this study. As shown in Table 1, the patients were 43-75 years old, with a mean of 59.2±1.4 years. There were 11 men and 28 women. Patients with serious complications, including cerebral, cardiac, and renal complications, as well as those who were considered by the attending doctor to be unsuitable for participation in this study, were excluded. Doxazosin was started at a dosage of 0.5 mg/day once a day in general and was increased up to 2-4 mg/day at 1- to 2-week intervals when the effect was inadequate. If the effect was still inadequate, the dose was further increased to a maximum of 8 mg/day. In patients who were already taking antihypertensive agents, the drug was continued at the same dosage and doxazosin was given additionally. Patients receiving an anticholesterol agent were excluded from this study. The duration of doxazosin treatment was generally 12 weeks. The assessment parameters and investigation schedule were as follows:

1) Sitting blood pressure and heart rate were measured in the observation period and at weeks 4, 8 and 12 of treatment,

2) The following laboratory tests were performed in the observation period and at the completion of study; serum lipids (total cholesterol, HDL cholesterol, triglyceride, apoprotein A_1, and apoprotein B), blood biochemistry (glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), serum creatinine, uric acid, serum electrolytes, and blood glucose), blood cell count, and urinalysis. The LDL cholesterol level was determined using Friedewald's formula,

3) Adverse reactions that occurred during the study were recorded.

For the determination of serum lipid levels, blood was collected in the early morning after fasting for at least 10 h, with no particular instructions were given for diet during the study.

All the data represent the mean±SE. The statistical significance of differences was tested using paired t-test; those differences with a probability below 5% were defined as significant.

RESULTS

1. Patients' clinical profiles

The patients' clinical profiles are shown in Table 1. Doxazosin was given as monotherapy in 31 patients and as combination therapy in 8. The concomitant drugs were Ca antagonist in 4 patients, Ca antagonist + diuretic in 2, Ca antagonist +β-blocking agent in 1, and diuretic in 1. The severity of hypertension was WHO stage I (mild) in 31 patients and stage II (moderate) in 8. Seventeen patients were in their fifth decade, and this age group was the largest among all age groups. Six of the 39 patients had complications, including diabetes mellitus in 3 and liver dysfunction in 3.

The mean body weight was 58.0±1.8 kg and the body mass index was 24.75±0.44.

2. Antihypertensive and chronotropic effects

Hypertension was treated with doxazosin (1-8 mg/day, 1.9±1.2 mg/day). The systolic and diastolic blood pressures were 168.7±2.0 and 97.4±1.4 mmHg, respectively, in the observation period, and decreased to 146.9±2.9 and 85.2±1.5 mmHg after 4 weeks of doxazosin treatment. The reduction of both systolic and diastolic blood pressure was statistically significant ($p<0.001$) and the antihypertensive effect persisted throughout the 12-week period of treatment. The mean blood pressure was 121.1±1.2 mmHg in the observation period which decreased significantly to 105.8±1.8 mmHg, 102.8±1.6 mmHg, and 103.6±1.5 mmHg after 4, 8 and 12 weeks of treatment, respec-

Table 1. Patients' clinical profiles.

Sex	Man (11) Woman (28)
Body weight (body mass index)	58.0±1.8 kg (24.8±0.4)
Age (years)	43~49 (6) 50~59 (17) 60~69 (7) 70~75 (9) mean±SE 59.2±1.4
WHO stage	I (31) II (8)
Combination therapy	(−) (31) (+) (8)

( ): n Mean±SE

tively. No significant changes in heart rate were demonstrated throughout the study period (Fig. 1). The antihypertensive effects in the individual patients were rated according to the "Guideline for Clinical Evaluation of Antihypertensive Drugs."[6] "Moderate or improved reduction" occurred in 29/39 patients (74.4%).

3. Comparison of antihypertensive effect between the monotherapy and combination therapy groups

Thirty-one patients were treated with doxazosin alone and 8 patients were given doxazosin in combination with a Ca antagonist, diuretic, or other agents. As shown in Fig. 2, the observed reductions in systolic and diastolic blood pressures were comparable in both the doxazosin monotherapy and combination therapy groups.

4. Changes in serum lipid levels (Table 2)

The mean total cholesterol level was 234.8±3.2 mg/dl at the start of treatment, this decreasing significantly to 219.3±3.6 mm/dl after the 12-week doxazosin treatment period ($p<0.001$); the triglyceride level was 151.1±11.2 mg/dl at the start of treatment and decreased to 147.8±9.7 mg/dl, although this reduction was not significant. As for the cholesterol concentration in lipoprotein, the LDL cholesterol level was 158.3±3.7 mg/dl at the start of treatment but decreased significantly to 140.9±4.5 mg/dl after treatment; the HDL cholesterol level in lipoprotein increased from 46.6±2.1 mg/dl to 49.0±2.0 mg/dl after treatment. This change in HDL cholesterol represented an increase of about 5%, although the

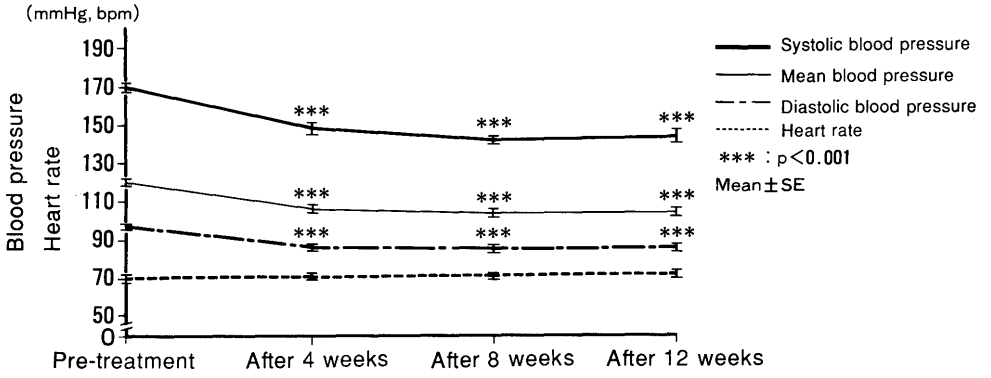

Fig. 1. Changes in blood pressure and heart rate.

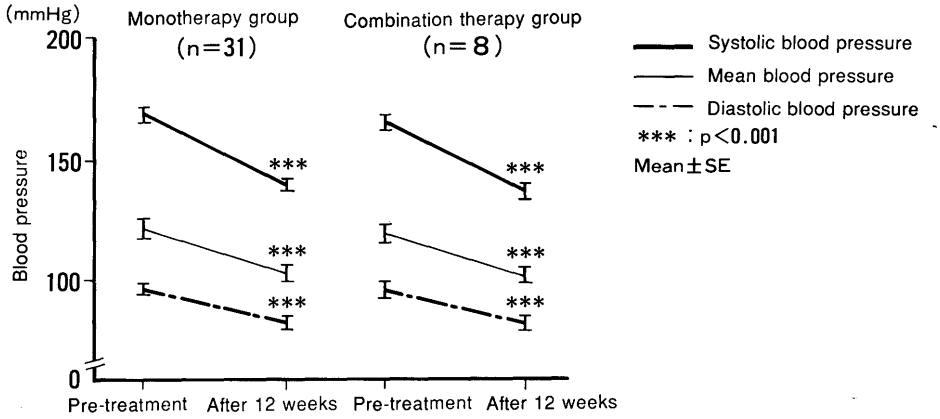

Fig. 2. Comparison of antihypertensive effect between the doxazosin monotherapy and combination therapy groups.

difference was not significant. The cholesterol ratio (HDL cholesterol/total cholesterol) was 0.20±0.01 at the start of treatment and increased significantly to 0.23±0.01 after treatment ($p<0.001$).

For apoprotein, serum apoprotein A_1 was virtually unaffected by doxazosin treatment, while the serum level of apoprotein B decreased significantly from 118.2±2.7 mg/dl to 111.2±2.9 mg/dl at the completion of treatment ($p<0.01$). As a result, the apoprotein A_1/apoprotein B ratio increased significantly. The mean body weight was identical before and after doxazosin treatment (58.0±1.8 kg).

The changes in the serum levels of total cholesterol, triglyceride, and HDL cholesterol were rated according to the criteria described by Goto et al.[7] For the total cholesterol level, slight or moderate improvement was achieved in 21/36 patients (58.3%). For HDL cholesterol level and triglyceride level, slight or moderate improvement was respectively achieved in 44.4% and 52.8% of the patients. Overall, the total cholesterol level increased only in 1 patient while it decreased in 21/36 patients, as compared with the start of treatment.

Table 2. Changes in serum lipid levels.

		Pre-treatment (n)	After 12 week (n)	
Total cholesterol	(mg/dl)	234.8±3.2 (39)	219.3±3.6 (36)	P<0.001
HDL cholesterol	(mg/dl)	46.6±2.1 (39)	49.0±2.0 (36)	NS
LDL cholesterol	(mg/dl)	158.3±3.7 (39)	140.9±4.5 (36)	P<0.001
HDL/total cholesterol		0.20±0.01 (39)	0.23±0.01 (36)	P<0.001
Triglyceride	(mg/dl)	151.1±11.2 (39)	147.8±9.7 (36)	NS
Apoprotein A_1	(mg/dl)	145.2±7.1 (37)	149.0±6.5 (34)	NS
Apoprotein B	(mg/dl)	118.2±2.7 (33)	111.2±2.9 (29)	P<0.01
Apoprotein A_1/B		1.187±0.06 (33)	1.289±0.02 (29)	P<0.01
Body weight	(kg)	58.0±1.8 (34)	58.0±1.8 (32)	NS

Mean±SE

Table 3. Changes in hematologic biochemistry tests.

		Pre-treatment (n)	After 12 week (n)	
RBC	($\times 10^4$/mm^3)	451.2±5.7 (39)	437.2±6.8 (35)	P<0.001
WBC	(/mm^3)	5,584.6±218.3 (39)	5,202.9±183.5 (35)	P<0.05
Hemoglobin	(g/dl)	13.9±0.2 (39)	13.5±0.2 (35)	P<0.001
Hematocrit	(%)	40.7±0.6 (36)	39.6±0.7 (32)	P<0.01
platelet	($\times 10^4$/mm^3)	24.2±0.9 (39)	23.2±0.9 (35)	NS
S-GOT	(IU/1)	19.4±0.7 (39)	18.5±0.7 (35)	NS
S-GPT	(IU/1)	16.8±1.5 (39)	15.7±1.2 (35)	NS
ALP	(IU/1)	118.0±7.7 (39)	107.9±7.7 (35)	P<0.01
LDH	(IU/1)	350.7±11.3 (39)	344.8±9.1 (35)	NS
BUN	(mg/dl)	14.2±0.6 (38)	14.6±0.5 (35)	NS
Creatinin	(mg/dl)	0.66±0.02 (37)	0.67±0.03 (35)	NS
Uric acid	(mg/dl)	4.6±0.2 (37)	4.8±0.3 (34)	NS
Na	(mEq/1)	140.7±0.4 (38)	141.0±0.3 (35)	NS
K	(mEq/1)	4.1±0.1 (38)	4.1±0.1 (35)	NS
Cl	(mEq/1)	104.2±0.3 (38)	104.3±0.4 (35)	NS
FBS	(mg/dl)	109.2±7.8 (24)	99.2±3.1 (23)	NS

Mean±SE

5. Effect on hematologic and urinary biochemistry tests (Table 3)

There were significant changes in red blood cells (RBC), white blood cells (WBC), hemoglobin, hematocrit, and ALP after treatment, compared with the pre-treatment values. However, these changes were within the normal ranges, and no abnormal changes were observed in the individual data.

6. Adverse reactions

No adverse reactions occurred in any patients, including orthostatic hypotension.

DISCUSSION

Doxazosin is the first α_1-blocking agent with an elimination half-life long enough to allow single daily administrations for antihypertensive therapy. In the present study, doxazosin was administered to patients with essential hypertension and a total cholesterol level above 220 mg/dl to assess its effects on blood pressure and serum lipids.

The antihypertensive efficacy of doxazosin has also been studied in many clinical trials in Japan. In a double-blind clinical trial[8] performed in Japan using prazosin hydrochloride as the control agent, doxazosin achieved an efficacy rate of as high as 70.8% in the 12-week monotherapy. In the present study, doxazosin significantly reduced blood pressure in both the monotherapy and combination therapy groups, and the extent of blood pressure reduction and clinical usefulness were consistent with those of the previous clinical studies of this drug. In the present study, blood pressure decreased significantly at week 4 of treatment and a stable antihypertensive effect was observed at the end of the 12-week treatment period. The systolic and diastolic blood pressures decreased respectively by 25.8 mmHg and 13.4 mmHg at the completion of treatment, as compared with pre-treatment levels.

Because abnormal serum lipid metabolism is a major risk factor of and often accompanies cardiovascular hypertensive disease, various agents have been studied for their effects on serum lipids. Some β-blocking agents and thiazide diuretics have been reported to adversely affect serum lipids, whereas angiotensin-converting enzyme inhibitors and Ca antagonists have been found to have little effect on serum lipids. On the other hand, various studies have demonstrated that α_1-blocking agents have favorable results with respect to lipid metabolism.[9,10]

Serum lipids are recognized as an indicator for the progression of arteriosclerosis. LDL is known as lipid-aggregated lipoprotein that transports cholesterol to the arterial wall, while HDL removes cholesterol from the peripheral vascular system and carries it back to the liver. Apoprotein A_1 and B are elements of lipoprotein, and thus changes in serum apoprotein A_1 and B levels are also considered to reflect the progression of arteriosclerosis.

Using atenolol as the control agent, Lehtonen et al.[11] performed a 20-week double-blind control study of doxazosin in patients with mild to moderate essential hypertension to assess the effects on blood pressure, serum lipids, and apoproteins. According to their report, the serum levels of total cholesterol and LDL cholesterol decreased significantly in patients given doxazosin, and the serum levels of HDL and the HDL cholesterol/total cholesterol ratio increased significantly in the doxazosin group following treatment. Also, they reported that the apoprotein A_1/apoprotein B ratio improved significantly with doxazosin as compared with atenolol.

Ferrara et al.[12] administered doxazosin or captopril for about 14 weeks in patients with essential hypertension and a fasting serum total cholesterol level of 200–300 mg/dl to assess the effects on blood pressure and serum lipids. In their study, both agents showed a similar antihypertensive effect and both significantly improved total cholesterol, although no change was observed in serum triglycerides. However, in the doxazosin group, the HDL cholesterol level increased significantly by 11% and the HDL cholesterol/total cholesterol ratio was also significantly improved by 23.1%.

In the present study, doxazosin was administered to hypertensive patients with a serum total cholesterol level above 220 mg/dl; after 12 weeks of treatment, the total cholesterol and LDL cholesterol levels decreased significantly by 15.5 and 17.4 mg/dl, respectively. The HDL/total cholesterol ratio increased significantly (by 15%) from the pre-treatment ratio. As for apoproteins, the apoprotein A_1 level increased but not significantly, while apoprotein B decreased significantly after treatment. Furthermore, there was a significant (8.1%) increase in the apoprotein A_1/apoprotein B ratio, which is recognized as an indicator for the development and progression of arteriosclerosis. This change in apoprotein levels also suggests that doxazosin has a protective activity against arteriosclerosis.

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