Original Article

Usefulness of the α_1-Blocker Doxazosin as a Third-Line Antihypertensive Drug

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It has been reported that a substantial majority of hypertensives receive insufficient blood pressure (BP) control. As combination therapy for the treatment of hypertension, Ca channel blockers (CCBs), angiotensin II (AII) receptor blockers (ARBs), and/or AII-converting enzyme (ACE) inhibitors are mainly prescribed, while the efficacy of α_1-blockers in such combination therapy remains unknown. The aim of this study was to investigate the efficacy of a low dose of an α_1-blocker added to combination therapy with CCBs and either ARBs or ACE inhibitors for the treatment of hypertension. Subjects were 41 hypertensive patients (23 women and 18 men, mean age 66±12 years) who had been followed at the National Kyushu Medical Center. All patients showed poor BP control despite haven taken a combination of CCBs and ARBs or ACE inhibitors for more than 3 months. Doxazosin at a dose of 1 to 2 mg was added to each treatment regimen. The changes in various clinical parameters, including BP and blood chemistry, following the addition of doxazosin were then evaluated. The mean follow-up period was 170 days. BP decreased from 152±14/81±12 mmHg to 135±14/70±11 mmHg after the addition of doxazosin at a mean dose of 1.5 mg/day ($p<0.001$). When good systolic blood pressure (SBP) control was defined as <140 mmHg, the prevalence of patients with good SBP control increased from 24% to 61% ($p<0.01$). Similarly, the prevalence of patients with good diastolic blood pressure (DBP) control (<90 mmHg) increased from 78% to 98% ($p<0.01$). Patients whose SBP decreased more than 10 mmHg ($n=25$) showed significantly higher baseline SBP, serum total cholesterol and low-density lipoprotein (LDL) cholesterol levels compared to those who showed less SBP reduction (<10 mmHg) ($n=16$, $p<0.01$). Comparable BP reductions were obtained between obese (body mass index [BMI] ≥25, ΔBP at 3 months: −15 ± 15/−12 ± 9 mmHg, $n=18$) and non-obese (BMI<25, ΔBP: −14 ± 19/−7 ± 8 mmHg, $n=23$) patients. The results suggest that addition of a low dose of the α_1-blocker doxazosin effectively reduces BP in patients taking CCBs and ARBs or ACE inhibitors. Thus, doxazosin seems to be useful as a third-line antihypertensive drug. (*Hypertens Res* 2007; 30: 301–306)

***Key Words*: α_1-blocker, antihypertensive drug, combination therapy**

Introduction

Although the guidelines for the treatment of hypertension emphasize strict blood pressure (BP) control, it has been reported that a substantial majority of hypertensives receive insufficient BP control (*1–3*). Thus, aggressive combination therapy is recommended to achieve the target BP levels (*1–5*). Ca channel blockers (CCBs) and either angiotensin II (AII) receptor blockers (ARBs) and/or AII-converting enzyme (ACE) inhibitors are widely used as a combination therapy. As to α_1-blockers, many studies have suggested that α_1-blockers reduce coronary heart disease by lowering BP and favorably affecting serum lipid profiles (*6–9*). However, the ALLHAT trial has advised against the use of α_1-blockers as first-line antihypertensive drugs (*10*). On the other hand, α_1-

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blockers have been reported to be effective in combination with other antihypertensive drugs, such as CCBs, ACE inhibitors, diuretics and β-blockers (*11–16*). However, there are insufficient data regarding the efficacy of α_1-blockers as third-line antihypertensive drugs. Thus, the aim of this study was to investigate the usefulness of a low dose of the α_1-blocker doxazosin in combination therapy with CCBs and either ARBs or ACE inhibitors.

Methods

Participants were hypertensive outpatients who visited the National Kyushu Medical Center. Patients who were newly prescribed the α_1-blocker doxazosin were retrospectively investigated. Subjects consisted of 41 hypertensive outpatients (23 men and 18 women; mean age, 66±12 years) of the National Kyushu Medical Center who had taken the combination of a CCB and either an ARB or ACE inhibitor for more than 3 months, but had failed to achieve the target BP recommended by the Japanese guideline (JSH 2004) (*1*). Doxazosin at a dose of 1 to 2 mg was added to each treatment regimen; 6 patients received doxazosin once daily in the morning, 19 patients received doxazosin once daily at bedtime, and 16 patients received doxazosin twice daily. Then, the patients were followed for at least 3 months (average 170 days). The changes in various clinical parameters, including BP and blood chemistry, following the addition of doxazosin were then evaluated. Clinic BP was measured during the morning hours with subjects in a seated position by physicians using a mercury sphygmomanometer. Diabetes mellitus (DM) was defined as fasting plasma glucose ≥126 mg/dl, plasma glucose ≥200 mg/dl at any time, HbA1c ≥6.5%, or the current use of hypoglycemic agents. Hyperlipidemia was defined as serum total cholesterol ≥220 mg/dl, serum triglyceride ≥300 mg/dl at any time, or the current use of lipid-lowering drugs. Body mass index (BMI) was calculated as BMI = weight/height^2 (kg/m^2). "Good control" was defined as a systolic blood pressure (SBP) of <140 mmHg and diastolic blood pressure (DBP) of <90 mmHg. "Satisfactory control" was defined as SBP of <130 mmHg and DBP of <85 mmHg. The protocol was explained to each patient in detail, and informed consent was obtained from each patient. This study was conducted following the guidelines of the National Kyushu Medical Center.

Statistical Analysis

Values are presented as the mean±SD. The differences in the variables were compared by one-way ANOVA. A χ^2 test was also utilized when appropriate. p values less than 0.05 were considered significant.

Results

The patient characteristics are shown in Table 1. The mean age was 67±12 years, and 56% of the patients were women. The average BP decreased from 152±14/81±12 mmHg to 135±14/70±11 mmHg after the addition of doxazosin at a mean dose of 1.5 mg/day ($p<0.01$, Fig. 1). Baseline BP, ΔBP and the mean dose of doxazosin were not significantly different among the three groups, although baseline BP tended to be lower in the patients taking doxazosin at bedtime and ΔBP tended to be higher in the patients taking doxazosin twice daily (once daily in the morning, 152±11/85±11 mmHg, −13±5/−9±8 mmHg, 1.3±0.5 mg; once daily at bedtime, 144±10/75±11 mmHg, −13±17/−9±10 mmHg, 1.4±0.5 mg; twice daily, 163±12/87±11 mmHg, −23±19/−14±14 mmHg, 1.9±0.3 mg, n.s., respectively). In addition, total cholesterol and low-density lipoprotein (LDL) cholesterol levels decreased during this period (Table 1). The prevalence of patients with good SBP control (<140 mmHg) increased from 24% to 61% ($p<0.01$, Fig. 2). The prevalence of patients with satisfactory SBP control (<130 mmHg) also increased, from 0% to 32% ($p<0.01$, Fig. 2). Similarly, the prevalence of patients with good (<90 mmHg) and satisfactory (<85 mmHg) DBP control increased from 78% to 98% ($p<0.01$) and from 68% to 90% ($p<0.05$, Fig. 2).

Patients whose SBP decreased more than 10 mmHg ($n=25$) showed significantly higher baseline SBP, serum total cholesterol and LDL cholesterol levels compared to those who showed less SBP reduction (<10 mmHg) ($n=16$) ($p<0.01$, Table 2). Patients with small SBP reduction tended to have higher serum creatinine levels. In addition, patients whose DBP decreased more than 10 mmHg ($n=18$) showed significantly higher baseline DBP and LDL cholesterol levels compared to those who showed less DBP reduction (<10 mmHg) ($n=23$) ($p<0.01$ and $p<0.05$, respectively, Table 3). Patients

Table 1. Characteristics of the Patients

	Baseline	After
Number of patients	41	—
Sex (men/women)	18/23	—
Age (years)	67±12	—
Body mass index (kg/m^2)	25±4	—
SBP (mmHg)	152±14	135±14**
DBP (mmHg)	81±12	70±11**
Pulse rate (/min)	72±9	70±9
Serum creatinine (mg/dl)	0.8±0.4	0.9±0.4
Serum total cholesterol (mg/dl)	199±27	192±32**
Serum triglyceride (mg/dl)	144±82	143±108
Serum HDL cholesterol (mg/dl)	54±15	55±14
Serum LDL cholesterol (mg/dl)	116±29	107±29*
Plasma glucose (mg/dl)	119±37	112±23
Diabetes mellitus (%)	25	—
Hyperlipidemia (%)	39	—

Values are means±SD. *$p<0.05$, **$p<0.01$ *vs*. Baseline. LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diasolic blood pressure.

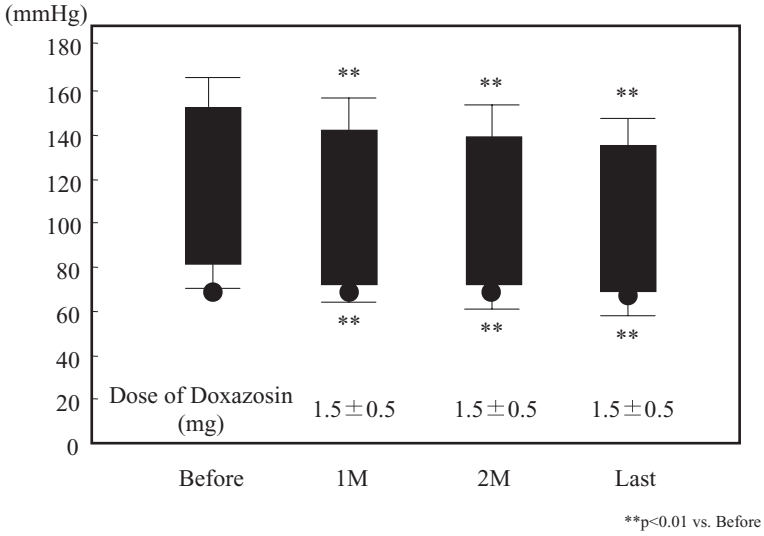

Fig. 1. *Changes in blood pressure (closed bars) and pulse rate (closed circles) by doxazosin.*

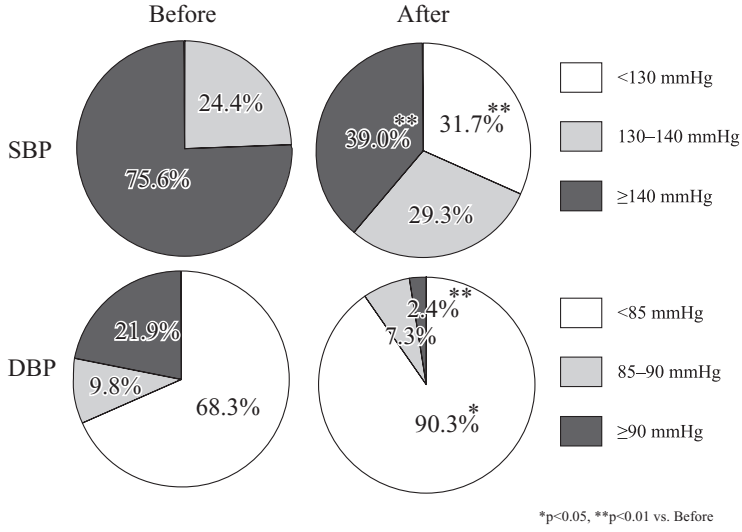

Fig. 2. *Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) by doxazosin.*

with large DBP reduction tended to have higher BMI, and a higher dose of doxazosin was used for these patients. Comparable BP reductions were obtained between obese (BMI≥25, ΔBP: −17±18/−13±13 mmHg, n=18) and non-obese (BMI<25, ΔBP: −10±10/−3±11 mmHg, n=23) patients. In the multivariate analysis, ΔSBP was independently associated with baseline SBP. On the other hand, ΔDBP was independently associated with baseline DBP and the dose of doxazosin (Table 4).

Discussion

The results of the present study demonstrate the usefulness of a low dose of the α_1-blocker doxazosin in combination therapy.

Recent hypertension guidelines emphasize that drugs with an additive or synergistic hypotensive effect should be added to the treatment regimen if the target BP levels are not achieved (*1–3*). Combination therapy using CCBs, ARBs, and/or ACE inhibitors is quite common in Japan, but the BP control still seems to be insufficient.

Both the guidelines of the Japanese Society of Hypertension and the JNC 7 guidelines recommend the use of diuretics when more than three antihypertensive drugs are required (*1*, *2*). We have previously reported that salt intake in Japanese hypertensive patients remains high despite the increasing

Table 2. Comparison of the Characteristics between Patients with Large ΔSBP and Small ΔSBP

	ΔSBP	
	Large (≥10 mmHg)	Small (<10 mmHg)
Number of patients	25	16
Sex (men/women)	11/14	7/9
Age (years)	66±10	65±14
Body mass index (kg/m^2)	26±4	24±4
Baseline SBP (mmHg)	157±15**	145±9
Baseline DBP (mmHg)	82±12	80±13
Serum creatinine (mg/dl)	0.7±0.2$^{\#}$	0.9±0.5
Serum total cholesterol (mg/dl)	210±21**	180±27
Serum triglyceride (mg/dl)	146±86	142±78
Serum HDL cholesterol (mg/dl)	56±15	51±15
Serum LDL cholesterol (mg/dl)	127±24**	99±30
Serum glucose (mg/dl)	116±39	123±36
Dose of doxazosin (mg)	1.7±0.7	1.6±0.5

Values are means±SD. $^{\#}p<0.1$, $^{**}p<0.01$ *vs*. Small. LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diasolic blood pressure.

Table 3. Comparison of the Characteristics between Patients with Large ΔDBP and Small ΔDBP

	ΔDBP	
	Large (≥10 mmHg)	Small (<10 mmHg)
Number of patients	18	23
Sex (men/women)	7/11	11/12
Age (years)	67±10	65±13
Body mass index (kg/m^2)	26±5$^{\#}$	24±3
Baseline SBP (mmHg)	154±16	151±13
Baseline DBP (mmHg)	87±10**	77±12
Serum creatinine (mg/dl)	0.9±0.5	0.8±0.2
Serum total cholesterol (mg/dl)	203±27	195±28
Serum triglyceride (mg/dl)	112±38*	171±99
Serum HDL cholesterol (mg/dl)	52±13	55±17
Serum LDL cholesterol (mg/dl)	129±28*	105±27
Serum glucose (mg/dl)	125±47	115±29
Dose of doxazosin (mg)	1.8±0.7$^{\#}$	1.5±0.5

Values are means±SD. $^{\#}p<0.1$, $^{*}p<0.05$, $^{**}p<0.01$ *vs*. Small. LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diasolic blood pressure.

emphasis on dietary modification, and that very few patients achieve the salt restriction recommended by the guidelines (*17*, *18*). Thus, the use of diuretics seems to be reasonable. However, diuretics have a number of side effects, including potassium depletion, hyperuricemia, hyperlipidemia and impaired glucose tolerance that may limit their use. Indeed, the ASCOT and ALLHAT studies have shown that diuretics, particularly when used as a combination therapy with β-blockers, may increase the risk of new-onset diabetes and may not improve the long-term prognosis (*10*, *19*).

In contrast to the disadvantages of diuretics, many studies have reported that α_1-blockers are well tolerated not only as first-line, but also as second-line drugs (*6–9*, *11–16*, *20*). In the previous studies, potent antihypertensive effects were observed when doxazosin was added to β-blockers, ACE inhibitors and/or CCBs (*11–16*). Furthermore, the low dose range of doxazosin used as monotherapy as well as combination therapy has been reported to be free of side effects (*5*). Despite the disappointing results of the ALLHAT study, which indicated that α_1-blockers increase the risk of combined cardiovascular disease events (*21*), there are some justifications for the use of α_1-blockers. In addition to their BP-lowering action, α_1-blockers have favorable effects on glucose and lipid metabolism. Shieh *et al*. have indicated that doxazosin improves glucose and insulin metabolism (*8*). Beneficial effects of doxazosin on lipid profiles have also been reported in other studies (*6–9*). Consistent with these reports, our study demonstrated that doxazosin decreased total cholesterol and LDL cholesterol levels. On the other hand, serum triglyceride and plasma glucose levels remained unchanged, although we did not evaluate insulin resistance. Thus the positive effects of doxazosin were less pronounced than expected, especially in light of another clinical trial that demonstrated a positive effect of doxazosin (*9*). In some reports, the change in triglyceride level was of lesser magnitude than that in cholesterol level (*6*, *8*). In addition, another study reported that cholesterol and triglyceride levels were significantly decreased by doxazosin monotherapy, although there was no change in the glucose level. In contrast, the cholesterol, triglyceride and glucose levels remained unchanged in patients receiving doxazosin combination therapy (*7*). Although the mechanism by which α_1-blockers effect serum lipid profiles is unclear, several hypotheses have been put forward. These include 1) stimulation of lipoprotein lipase activity, 2) reduction in very low density lipoprotein synthesis and secretion, 3) increase in LDL receptor number, and 4) decrease in cholesterol synthesis. Considering recent evidence that the management of diabetes and dyslipidemia in hypertensive patients is important for the prevention of cardiovascular diseases, the use of α_1-blockers as part of a combination therapy should be preferentially considered.

α_1-Blockers can also be used to suppress morning surge in BP. The HALT study suggested that nighttime dosing of doxazosin suppressed the BP morning surge that was associated with an increase in α_1-adrenergic activity (*22*, *23*). The peak effect of doxazosin might be determined not only by the pharmacokinetics of the drug, but also by the level of vascular tone (*21*). It is expected that an α_1-adrenergic antagonist would have its greatest effect when α_1-adrenergic tone is at its greatest. Morning surge could be a new therapeutic target for preventing target organ damage and subsequent cardiovascular events in hypertensive patients (*24*, *25*). Thus, addition of

Table 4. Clinical Factors Affecting ΔSBP and ΔDBP: Multivariate Analysis

	ΔSBP			ΔDBP		
	β	Partial r^2	p	β	Partial r^2	p
Baseline SBP (mmHg)	−0.784	0.392	<0.001	—	—	—
Baseline DBP (mmHg)	—	—	—	−0.365	0.272	<0.001
Dose of doxazosin (mg)	—	—	—	−5.090	0.120	0.013

Independent variables: age, sex, body mass index, baseline SBP/DBP, serum total cholesterol, plasma glucose. SBP, systolic blood pressure; DBP, diasolic blood pressure.

doxazosin seems to be reasonable, when the combination therapy with CCBs and ARBs or ACE inhibitors is insufficient to suppress α_1-adrenergic activity.

Finally, it is noteworthy that comparable BP reductions were obtained between obese and non-obese patients in the present study. This result might have attributable to the fact that we used a higher dose of doxazosin in the obese patients. In fact, Toyonaga *et al*. reported that doxazosin was dose-dependently effective in patients with obesity-associated hypertension (*26*). It has been suggested that the mechanism underlying the association between obesity and hypertension is the activation of the sympathetic nervous system caused by insulin resistance or hyperleptinemia. α_1-Blockers exert their antihypertensive effect by inhibiting the α_1-receptors of the sympathetic nervous system, causing relaxation of the vascular smooth muscles and lowering vascular resistance. Since α_1-blockers have a beneficial effect on insulin resistance and lipid metabolism, they may be suitable for patients with obesity-associated hypertension.

In conclusion, the addition of a low dose of doxazosin to the treatment regimen of patients taking CCBs and either ARBs or ACE inhibitors improved BP control and had beneficial effects on glucose and lipid metabolism. Thus, doxazosin seems to be useful as a third-line antihypertensive drug.

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