Effect of 8-Week Combination Therapy with an Extended-Release α_1-Blocker (Bunazosin or Doxazosin) in Inadequate Responders to an Angiotensin II Antagonist (Valsartan) in Patients with Stage 1 or 2 Essential Hypertension

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Background: Given the favorable impact of α_1-blockers on lipid and glucose metabolism, this study was designed to compare the efficacy of two extended-release α_1-blockers (bunazosin and doxazosin) as an add-on treatment in subjects with stage 1 or 2 essential hypertension which was inadequately controlled by valsartan 80 mg/day.

Methods: After a 5-week treatment of valsartan monotherapy, subjects with inadequately controlled hypertension were randomized to receive either extended-release bunazosin (n = 47) or doxazosin (n = 46) after breakfast for 8 weeks. Office sitting blood pressure (BP), 24-hour ambulatory BP, and metabolic profiles were measured at baseline, start of study drug, and study end.

Results: In the intention-to-treat population (n = 93), the average daily doses of bunazosin and doxazosinwere 2.8 mg and 3.6 mg, respectively. The two add-on treatments achieved significant and similar BP reductions from monotherapy (bunazosin, 13.2/9.3 mmHg; doxazosin, 9.2/8.5 mmHg, all $p < 0.001$). However, in patients with stage 2 hypertension, patients randomized to the bunazosin group, compared to those in the doxazosin group, achieved a significantly greater reduction in sitting systolic BP (14.4 ± 8.1 vs. 6.6 ± 13.8 mmHg, $p = 0.015$). In addition, patients who received bunazosin had significant changes in night-day systolic and diastolic BP ratios compared with those who received doxazosin (-0.02 vs. 0.02, $p = 0.04$ and 0 vs. 0.04, $p = 0.04$). No significant changes in metabolic profiles were observed in both add-on groups. Both drugs were well-tolerated, but adverse events related to the study drugs were marginally more frequent in the doxazosin group than in the bunazosin group (20% vs. 6%, $p = 0.058$).

Conclusions: Both extended-release bunazosin and doxazosinwerewell-tolerated and similarly effective as add-on therapy in hypertensive patients uncontrolled by valsartan monotherapy. However, add-on treatment with bunazosin seemed to be associated with favorable night-day BP ratio and greater sitting systolic BP reductions in stage 2 hypertensive patients.

Key Words: Combination therapy • Hypertension • α_1-blocker

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INTRODUCTION

Most clinical studies and large-scale trials have shown the importance of reducing blood pressure (BP) to help prevent cardiovascular events in hypertensive patients.[1,2] However, only a limited number of hypertensive patients achieve their target BP by monotherapy.[3] To obtain optimal control of BP, it has been reported

that the combined use of multiple anti-hypertensive drugs might be necessary, particularly in diabetic, renal and high-risk patients.[4,5]

Based on the findings of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), α_1-blockers are not considered as first-line anti-hypertensive drugs in most hypertension treatment guidelines.[3,6,7] Nevertheless, it has been shown that α_1-blockers are effective in reducing BP as second- or third-line anti-hypertensive agents.[8-11] In addition to their anti-hypertensive property, α_1-blockers also exert a favorable impact on both glucose and lipid metabolism.[12-15] Even more, α_1-blockers can alleviate urinary symptoms associated with benign prostatic hypertrophy. They are therefore indicated, when co-administered with other anti-hypertensive agents, in hypertensive patients with clinical features indicating metabolic syndrome and/or benign prostatic hypertrophy.[16]

Drugs in the class of α_1-blockers include bunazosin, doxazosin, terazosin and prazosin. Among these, doxazosin has been the most studied. Bunazosin, a quinazoline derivative α_1-blocker structurally analogous to prazosin, also exerts a good BP-lowering effect as well as having positive impacts on lipid and glucose profiles.[13,17,18] In this study, we aimed to evaluate the efficacy of these two extended-release formulations of α_1-blockers, bunazosin and doxazosin, as second-line anti-hypertensive agents, in stages 1 and 2 Taiwanese hypertensive patients who were inadequately controlled by an angiotensin II antagonist, valsartan. This study was registered with ClinicalTrials.gov, number NCT 00130156.

METHODS

Patients

We enrolled patients with stage 1 or 2 essential hypertension [systolic BP (SBP) $\geq$ 140 mmHg but < 180 mmHg and/or diastolic BP (DBP) $\geq$ 90 mmHg but < 110 mmHg] who were 20 to 80 years of age. Patients were excluded if they had heart failure, atrial fibrillation, a history of myocardial infarction, prior cerebrovascular accident, poorly controlled diabetes mellitus (HbA1c > 10%), severe obesity (body mass index > 30 kg/m^2), malignancy, and significant hepatic or renal disease. During the study period, patients were not allowed to take non-study anti-hypertensive and lipid-lowering drugs.

Study design

This was a single-center, randomized, open-label, parallel group, active-controlled study. Every subject started with a 2-week placebo run-in phase. Eligible subjects were treated with 80 mg valsartan once daily after breakfast for 5 weeks. Patients who showed adequate responses, i.e. SBP < 140 mmHg and DBP < 90 mmHg or BP reduction > 10%, were excluded from this study. The remaining patients then received an extended-release formulation of α_1-blocker, either bunazosin or doxazosin once daily after breakfast for 8 weeks. The initial dose of bunazosin and doxazosin was 3 mg and 4 mg respectively; 4 weeks later, there was a titration accompanied by a double dose of bunazosin or doxazosin if patients had inadequate BP control (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg).

The primary efficacy outcome was to compare the reduction of sitting SBP and DBP as well as 24-hour ambulatory BP. Blood pressure was measured by mercurial sphygmomanometer after a 15-minute rest. Measurements were repeated 3 times, and taken at 2-minute intervals. The 24-hour ambulatory BP measurements were performed after a 5-week valsartan monotherapy (start of add-on therapy) and after an 8-week α_1-blocker add-on therapy. The secondary outcome included changes of waist circumference, body weight, lipid profiles and fasting glucose level. Safety was evaluated by assessing adverse events and routine physical and laboratory examinations in each visit.

This study was approved by the Ethics Committee of National Taiwan University Hospital. The study protocol was conducted in accordance with the Declaration of Helsinki and regulations of the Taiwan Department of Health. All study patients provided written informed consent.

Statistical analysis

Our target sample size was approximately 70 patients. This assumption was made based on previous studies on α_1-blockers, to detect a difference in SBP change of 4 mmHg with a standard deviation of 6 mmHg between both groups. Because an exclusion rate of 40% (ineligible to reach the add-on therapy stage) was ex-

pected, more than 117 patients should be enrolled. Statistical comparisons for baseline demographic variables were carried out (two-tailed), with an associated 5% level of significance. The Wilcoxon rank sum test was used for continuous variables and the Fisher's exact test was used for categorical variables.

The efficacy analyses were performed in the intention-to-treat population, which included all patients who were randomized to an add-on treatment and received at least one dose of study medication. The last-observation-carried-forward method was used for the last visit analyses. The primary statistical analysis was comparison of BP changes within and between two treatment groups, which were analyzed by Wilcoxon signed-rank test and Wilcoxon rank sum test, respectively. Pre-specified subgroup analyses in patients stratified by the stages of baseline BP and the presence or absence of the metabolic syndrome were also performed.

RESULTS

Patient disposition

One hundred and thirty-three patients were enrolled in our study, and the disposition of study patients is shown in Figure 1. Forty (30%) of them had adequate responses to the 5-week valsartan monotherapy and were ineligible for the subsequent add-on α_1-blocker treatment. Thus, 93 patients (51 men, 42 women) were randomized to receive bunazosin (n = 47) or doxazosin (n = 46). Thereafter, all of them formed the intention-to-treat population. The baseline characteristics of the two add-on treatment groups were similar (Table 1). Based on data obtained after the 2-week run-in period, forty-six patients had stage 1 hypertension (bunazosin, n = 25; doxazosin, n = 21), and the rest 47 patients had stage 2 hypertension (bunazosin, n = 22; doxazosin, n = 25).

Four patients did not complete the study. Two patients in the doxazosin group discontinued due to adverse events, and two patients in the bunazosin group withdrew their consent.

Efficacy

Both add-on treatment groups achieved significant reductions in sitting SBP and DBP after 8-week α_1-blocker add-on therapy ($p < 0.001$), but the difference

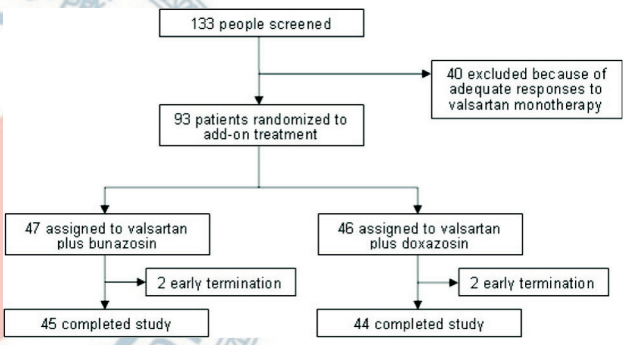

Figure 1. *Disposition of study patients.*

Table 1. Baseline demographic and clinical characteristics of patients

	Bunazosin group (N = 47)	Doxazosin group (N = 46)	p value
Age, years	54.0 ± 10.8	55.0 ± 9.6	0.546
Male, n (%)	26 (55.3)	25 (54.4)	0.999
Body weight, kg	70.8 ± 11.2	66.8 ± 10.3	0.060
Waist circumference, cm	89.5 ± 8.5	87.5 ± 6.5	0.459
Current smoker, n (%)	4 (8.5)	1 (2.2)	0.361
Treated hypertension	30 (63.8)	26 (56.5)	0.528
Systolic BP, mmHg	143.1 ± 8.4	139.3 ± 11.7	0.211
Diastolic BP, mmHg	93.0 ± 7.0	91.5 ± 7.1	0.412
Total cholesterol (mg/dl)	206.4 ± 34.9	203.2 ± 45.9	0.403
Triglycerides (mg/dl)	138.7 ± 77.9	152.9 ± 97.6	0.634
HDL-C (mg/dl)	45.9 ± 11.8	43.9 ± 11.8	0.365
LDL-C (mg/dl)	133.5 ± 30.2	128.4 ± 39.3	0.308
Fasting glucose (mg/dl)	96.2 ± 15.9	100.2 ± 26.1	0.845

Values are number (%) or mean ± SD. BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

between the two groups did not reach statistical significance (bunazosin, 13.2/9.3 mmHg; doxazosin, 9.2/8.5 mmHg) (Table 2). However, there was a trend (p = 0.052) towards a greater reduction in sitting SBP in the bunazosin group. The response rate was similar between both groups (bunazosin, 80.9% vs. doxazosin, 78.3%, p = 0.802). The average daily doses of bunazosin and doxazosin were 2.8 mg and 3.6 mg (p = 0.087), respectively, in the intention-to-treat population.

In patients with stage 2 hypertension, treatment with bunazosin caused greater SBP reduction than with doxazosin (14.4 ± 8,1 vs. 6.6 ± 13.8 mmHg, p = 0.015, Table 3). However, in patients with stage 1 hypertension, the two add-on treatments achieved a similar drop in SBP and DBP. Patients with or without the metabolic syndrome did not result in significant differences in treatment-related BP changes between them (data not shown).

The changes of day-time, night-time, and mean 24-hour ambulatory SBP and DBP were similar between both groups. Nevertheless, treatment with bunazosin was associated with significant changes of night-day ratios of SBP and DBP compared with doxazosin (-0.02 vs. 0.02, p = 0.04; 0 vs. 0.04, p = 0.04) (Table 4). Both add-on treatments did not result in significant changes in waist circumference, serum levels of triglycerides, high-density lipoprotein, total cholesterol or fasting glucose (Table 5).

Safety

The two combination treatments were well-tolerated, and only two patients discontinued the study drug due to adverse events. A total of 91 adverse events occurred in fifty-three (53%) patients and most of them (96%) were mild in intensity. The incidence of adverse events was similar in the two groups (59.5% in bunazosin vs. 54.4% in doxazosin, p = 0.677). The most commonly reported adverse events were dizziness (10 events), headache (4 events) and palpitation (4 events). No event of heart failure was reported during the entire study period. As judged by the investigators, 3 (6%) patients in the bunazosin group and 9 (20%) in the doxazosin group experienced adverse events related to the study drugs (p = 0.058).

DISCUSSION

The current study was the first head-to-head comparison to assess the clinical efficacy of two different long-acting α_1-blockers as second-line anti-hypertensive agents in patients with stage 1 or 2 hypertension whose BP could not be controlled by valsartan monotherapy. Although the two study drugs produced similar extents of BP reductions in the whole intention-to-treat population, bunazosin achieved a greater reduction in sitting SBP in patients with stage 2 hypertension at baseline. Moreover, patients treated with bunazosin had a lower night-day BP ratio, which might imply bunazosin had a relatively steadier BP-lowering effect than doxazosin. In contrast to previous studies, both α_1-blockers seemed to be metabolically neutral in this study. Both combina-

Table 2. Changes in sitting systolic and diastolic BP after add-on treatment with α_1-blockers

	Valsartan + Bunazosin (N = 47)	Valsartan + Doxazosin (N = 46)	p value (between groups)
Systolic BP (mmHg)			
Start of add-on therapy	143.1 ± 8.4	139.3 ± 11.7	0.211
Study end	129.9 ± 10.2	130.1 ± 16.6	0.533
Change	-13.2 ± 8.7	-9.2 ± 15.0	0.052
Percentage change	-9.2 ± 6.0%	-6.5 ± 9.6%	0.077
p value (within group)	< 0.001	< 0.001	
Diastolic BP (mmHg)			
Start of add-on therapy	93.0 ± 7.0	91.5 ± 7.1	0.412
Study end	83.8 ± 7.0	82.9 ± 10.2	0.460
Change	-9.3 ± 5.0	-8.5 ± 6.6	0.746
Percentage change	-9.9 ± 5.2%	-9.5 ± 7.4%	0.842
p value (within group)	< 0.001	< 0.001	

BP, blood pressure.

Table 3. Changes in sitting systolic and diastolic BP after add-on treatment with α_1-blockers in stage 1 and stage 2 hypertensive patients

Stage 1 hypertension at baseline	Valsartan + Bunazosin (N = 25)	Valsartan + Doxazosin (N = 21)	p value (between groups)
Systolic BP (mmHg)			
Start of add-on therapy	140.6 ± 5.3	138.6 ± 11.1	0.894
Study end	128.4 ± 12.0	126.3 ± 13.8	0.433
Change	-12.2 ± 9.2	-12.3 ± 13.8	0.825
Percentage change	-9.0 ± 6.0%	-6.8 ± 9.5%	0.368
p value (within group)	< 0.001	< 0.001	
Diastolic BP (mmHg)			
Start of add-on therapy	91.7 ± 4.8	89.2 ± 6.8	0.204
Study end	82.3 ± 7.0	79.5 ± 8.6	0.255
Change	-9.4 ± 5.2	-9.7 ± 5.6	0.947
Percentage change	-10.1 ± 5.6%	-10.1 ± 5.9%	0.802
p value (within group)	< 0.001	< 0.001	
Stage 2 hypertension at baseline	**Valsartan + Bunazosin (N = 22)**	**Valsartan + Doxazosin (N = 25)**	**p value (between groups)**
Systolic BP (mmHg)			
Start of add-on therapy	145.9 ± 10.4	139.9 ± 12.3	0.098
Study end	131.6 ± 9.3	133.3 ± 18.2	0.693
Change	-14.4 ± 8.1	-6.6 ± 13.8	0.015
Percentage change	-9.7 ± 5.3%	-4.7 ± 9.5%	0.020
p value (within group)	< 0.001	< 0.001	
Diastolic BP (mmHg)			
Start of add-on therapy	94.6 ± 8.8	93.4 ± 6.9	0.536
Study end	85.5 ± 7.8	85.8 ± 10.7	0.796
Change	-9.9 ± 5.0	-7.6 ± 7.4	0.798
Percentage change	-9.5 ± 4.9%	-8.2 ± 8.0%	0.840
p value (within group)	< 0.001	< 0.001	

BP, blood pressure.

Table 4. Changes of night-day ratio of 24-hour ambulatory pressure after add-on treatment with α_1-blockers

	Valsartan + Bunazosin (N = 47)	Valsartan + Doxazosin (N = 46)	p value (between groups)
Night-Day SBP ratio			
Start of add-on therapy	0.93 ± 0.06	0.91 ± 0.07	0.208
Study end	0.91 ± 0.08	0.93 ± 0.09	0.262
Change	-0.02 ± 0.08	0.02 ± 0.08	0.040
p value (within group)	0.115	0.375	
Night-Day DBP ratio			
Start of add-on therapy	0.93 ± 0.08	0.91 ± 0.08	0.260
Study end	0.93 ± 0.09	0.95 ± 0.11	0.242
Change	0.00 ± 0.09	0.04 ± 0.09	0.038
p value (within group)	0.859	0.020	
Night-Day mean BP ratio			
Start of add-on therapy	0.93 ± 0.07	0.91 ± 0.08	0.215
Study end	0.92 ± 0.08	0.94 ± 0.19	0.237
Change	-0.01 ± 0.08	0.03 ± 0.08	0.032
p value (within group)	0.494	0.070	

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 5. Changes in metabolic profiles after add-on treatment with α_1-blockers

	Valsartan + Bunazosin (N = 47)	Valsartan + Doxazosin (N = 46)	p value (between groups)
Waist circumference (cm)			
Start of add-on therapy	89.5 ± 8.5	87.5 ± 6.5	0.459
Study end	89.5 ± 8.0	87.9 ± 7.0	0.381
p value (within group)	0.779	0.832	
Triglycerides (mg/dl)			
Start of add-on therapy	138.7 ± 77.9	152.9 ± 97.6	0.634
Study end	162.4 ± 117.9	143.3 ± 87.7	0.529
p value (within group)	0.210	0.632	
High-density lipoprotein cholesterol (mg/dl)			
Start of add-on therapy	45.9 ± 11.8	43.9 ± 11.8	0.365
Study end	44.1 ± 10.6	43.4 ± 10.4	0.902
p value (within group)	0.082	0.685	
Fasting glucose (mg/dl)			
Start of add-on therapy	96.2 ± 15.9	100.2 ± 26.1	0.845
Study end	96.9 ± 15.0	98.0 ± 18.0	0.767
p value (within group)	0.377	0.636	

tion treatments were generally well-tolerated, despite a marginally higher treatment-related adverse event rate that was reported in patients receiving doxazosin.

The observation that bunazosin exerted a stronger BP-lowering potency, compared to doxazosin, in patients with stage 2 hypertension was of clinical significance. The differences observed in the BP-lowering effect between agents of variable BP-lowering potency would be more apparent in patients with higher baseline BP than in patients with lower BP. It might explain why bunazosin only showed its relative superior potency in patients with higher baseline BP. Criticism could be forthcoming that the relatively weak potency of doxazosin observed in our study might be due to inadequate dosage. However, based on previous reports, the doses we chose were just the lowest effective dose of bunazosin and doxazosin.[18,19] Besides, the extent of BP reduction in our study was similar to that observed in previous studies.[9,20]

Twenty-four hour BP control is of equal importance in assessing the efficacy of antihypertensive agents as well as sitting BP. It has been speculated that the higher rates of stroke and congestive heart failure in the doxazosin limb of the ALLHAT trial might be partially due to the use of a short-acting formulation of doxazosin. In another study, the Hypertension and Lipid Trial (HALT), it has been shown that the mean night-day SBP ratio increased significantly from 0.89 to 0.91 after treatment with doxazosin.[21] Despite an improved pharmacokinetic profile, an extended-release formulation of doxazosin, compared with extended-release bunazosin, was still less effective in reducing night-time BP in our study. Therefore, doxazosin treatment resulted in a higher night-day BP ratio. There is a growing body of evidence showing that night-day BP ratio not only predicts hypertension-related end-organ damage but also cardiovascular mortality.[22,23] Although we are not certain whether the relatively lower night-day BP ratio in the bunazosin group will result in better cardiovascular outcomes, it is evident that extended-release bunazosin as an add-on treatment did provide a more sustained and steady BP-lowering effect than extended-release doxazosin.

Previous studies have shown that both bunazosin and doxazosin can improve plasma lipid profiles, insulin sensitivity, and glucose metabolism.[9,12,15,17,24] However, in this study, we could not demonstrate the metabolically beneficial effects in patients treated with either α_1-blocker on top of background valsartan therapy. It is still uncertain whether background valsartan therapy can influence the metabolic effects of both α_1-blockers. In addition, the study period was only 8 weeks long, which might be too short to show the changes of metabolic profiles.

The present study has several limitations. First, the long-term cardiovascular impact could not be assessed for both combination antihypertensive treatments due to the small sample size. Second, in our study, the drug

was administered after breakfast. However, in most daily practices, due to the potential side effect of orthostatic hypotension, α_1-blocker is suggested to be taken at bedtime. Night-time dosing of doxazosin has been associated with better BP control over a 24 hour period.[25] Hence, the superiority of bunazosin on the night-day BP ratio in our study becomes uncertain once both study drugs are administered at bedtime.

Both α_1-blockers were generally well-tolerated and there was no apparent difference in the incidence of adverse events. Besides, no event of heart failure was reported with either agent. The satisfactory tolerance of our study drugs further supports the clinical use of α_1-blockers in combination therapy.

CONCLUSION

The study results suggested that the extended-release formulation of bunazosin and doxazosin are similarly effective in reducing blood pressures in hypertensive patients uncontrolled by valsartan monotherapy. However, add-on treatment with bunazosin seemed to be associated with favorable night-day BP ratio and greater reduction in sitting SBP in patients of stage 2 hypertension. These findings need to be verified in larger-scale trials.

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