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Effects of Valsartan/ Hydrochlorothiazide and Amlodipine on Ambulatory Blood Pressure and Plasma Norepinephrine Levels in High-Risk Hypertensive Patients

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ABSTRACT

The efficacy and tolerability of the combination of valsartan and hydrochlorothiazide (HCTZ) were compared with that of amlodipine in reducing ambulatory blood pressure and plasma norepinephrine levels in patients with mild to moderate hypertension and at least 1 cardiovascular risk factor. At the end of a 2-week washout period, 92 outpatients with a sitting diastolic blood pressure ≥95 and <110 mm Hg, associated with at least 1 additional risk factor, were randomly assigned to receive either valsartan 160 mg and HCTZ 12.5 mg once daily (n=46) or amlodipine 10 mg alone once daily (n=46) for 12 weeks, according to a prospective, randomized, open-label, blinded end point, parallel-group design. At the end of the washout period and after 6 and 12 weeks of active treatment, 24-hour ambulatory blood pressure monitoring was performed, and clinical blood pressure and heart rate and plasma norepinephrine levels were assessed (by high-performance liquid chromatography). Both the valsartan/HCTZ combination and amlodipine had a demonstrable antihypertensive effect, but the combination showed an antihypertensive effect significantly greater than that of amlodipine, as demonstrated by the 24-hour ($P<.001$), daytime ($P<.001$), and nighttime ambulatory blood pressure values ($P<.01$) and by the clinical blood pressure values at trough, which were all significantly lower. Although the trough-to-peak ratios were similar in both groups, the smoothness indexes pertaining to both systolic and

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diastolic pressures were significantly higher ($P<.05$ and $P<.001$, respectively) in patients receiving valsartan/HCTZ, suggesting the combination produces a more homogeneous antihypertensive effect. A significant increase in plasma norepinephrine levels was associated with amlodipine (+9% at 6 weeks, +15% at 12 weeks) but not with the valsartan/HCTZ combination. The valsartan/HCTZ combination was better tolerated than amlodipine, which was associated with a higher frequency of ankle edema. These results indicate that the combination of valsartan 160 mg and HCTZ 12.5 mg provides more sustained and homogeneous control of blood pressure than does amlodipine 10 mg in high-risk hypertensive patients, without producing reflex sympathetic activation.

Keywords: valsartan/HCTZ combination, amlodipine, norepinephrine

INTRODUCTION

Current treatment guidelines for the treatment of hypertension recommend that hypertensive patients reduce their blood pressure to <140/90 mm Hg.[1,2] Even lower blood pressure goals are suggested for hypertensive patients who have concomitant diabetes mellitus, renal insufficiency, or evidence of other target organ damage.[1-4] Monotherapy with any class of antihypertensive drugs, even at high doses, is likely to provide effective blood pressure control in only 40% to 50% of hypertensive patients.[5] Multidrug therapy, which offers the advantage of the additive, if not synergistic, effects of its individual components, has therefore been advocated to achieve the newly recommended blood pressure goals. In addition, by carefully balancing the dose ratio of a 2-drug combination, not only is the antihypertensive action enhanced but the risk of adverse effects is minimized.[6,7]

Hydrochlorothiazide (HCTZ) is a thiazide diuretic that is often used in multidrug antihypertensive therapy.[6-8] Since the drug's pharmacologic effects include the activation of the renin-angiotensin system, the association of HCTZ with an angiotensin-converting enzyme inhibitor or an angiotensin II AT_1-receptor antagonist (ARB) is a rational and useful approach.[6-8] Valsartan is an ARB that has demonstrated efficacy in lowering blood pressure values,[9] and when combined with HCTZ, its antihypertensive effect is significantly enhanced.[10] At the optimal dosage of 160 mg once daily, valsartan blocks angiotensin II AT_1-receptors more completely and longer than the 80-mg dose and may counteract completely the renin-angiotensin system activation elicited by HCTZ. Amlodipine is a long-acting dihydropyridine calcium-antagonist widely used in the treatment of hypertension, and it is particularly effective at high dosages.[11] Long-term amlodipine therapy, however, has been reported to produce an activation of the sympathetic nervous system,[12-14] and sympathetic nervous system hyperactivity is closely related to both the progression of hypertensive disease and a reduced survival rate among cardiac patients with cardiovascular disease.[15-17]

The aim of this study was to compare the efficacy and tolerability of the combination of valsartan 160 mg and HCTZ 12.5 mg with that of amlodipine 10 mg in lowering blood pressure and plasma norepinephrine levels in patients with increased risk due to the concomitance of mild to moderate essential hypertension and at least 1 additional cardiovascular risk factor.

MATERIALS AND METHODS

Study Population

Eligible patients had a sitting diastolic blood pressure (DBP) ≥95 mm Hg and at least 1 of the following cardiovascular risk factors: family history of ischemic disease, current history of smoking, type 1 or 2 diabetes mellitus, high-density lipoprotein (HDL)-cholesterol <40 mg/dL, total cholesterol >200 mg/dL, low-density lipoprotein (LDL)-cholesterol >160 mg/dL or treatment with hypocholesterolemic drugs, electrocardiographic evidence of left ventricular hypertrophy, or known microalbuminuria (urinary albumin excretion >30 mg/day). Patients who had a sitting DBP >120 mm Hg or sitting systolic blood pressure (SBP) >200 mm Hg at the end of an initial 2-week washout period were excluded from the study, as were those with secondary or malignant hypertension, myocardial infarction or cerebrovascular accident within the preceding 6 months, heart failure, clinically significant valvular heart disease, renal or hepatic insufficiency, or known hypersensitivity to the drugs used in the study.

Patients eligible for the study were informed of its design and purpose and provided written consent before their inclusion. The study was conducted in accordance with good clinical practice and the principles of the Helsinki declaration and was approved by the local ethical committee.

Protocol

This was a prospective, randomized, open-label, blinded (masked) end point (PROBE),[18] parallel-group study with 2 treatment arms. At the end of an initial 2-week washout period, during which any antihypertensive drug was discontinued, patients were randomly assigned to receive either valsartan 160 mg combined with HCTZ 12.5 mg or amlodipine 10 mg alone, taken once a day at approximately 8:00 AM, irrespective of meals, except on the morning of the scheduled visits, for 12 weeks. Office visits were scheduled at the end of the washout period and after 6 and 12 weeks of treatment. On the day of each visit, patients were administered their trial medication just before undergoing noninvasive ambulatory blood pressure monitoring (ABPM).

Ambulatory Blood Pressure Monitoring

At each visit, 24-hour ABPM was performed with a portable, fully automatic blood pressure recorder (ICR 90207, Spacelabs Inc, Bellevue, Calif), and the results were validated against intra-arterial blood pressure measurements.[19] The recorder was set to take readings at 15-minute intervals throughout a 24-hour period. Recordings were started at the same hour in the morning and were performed throughout a 24-hour period, during which patients were allowed to follow their normal daily routine after they left the laboratory.

Data Analysis

For each patient, the following data relating to SBP, DBP, and heart rate were provided by the analysis of the recordings: 24-hour mean values, daytime (7 AM to 11 PM) mean values, nighttime (11 PM to 7 AM) mean values, and hourly mean values. Record-

ings were excluded from the analysis when more than 10% of all readings or more than 1 reading/hour was missing or incorrect.

Calculation of Trough-to-Peak Ratio and Smoothness Index

In accordance with the recommendations of the US Food and Drug Administration,[20] the trough-to-peak (T/P) ratio, defined as the ratio between the effect of an antihypertensive agent at the end of the interval between doses (trough) and at the time of the agent's maximum effect (peak), was evaluated in each treatment group. For each ABPM recording, the trough SBP and DPB levels were calculated as the average of the blood pressure readings taken 22 to 24 hours after the dose. The peak values were calculated as the average during the hour that showed the maximal average decrease in blood pressure (within 2 to 8 hours after the dose, inclusive of the preceding or following hour, depending on which showed the greater decrease in blood pressure).[21,22] The data were averaged (mean) for all patients. The smoothness index (SI), used to quantify the homogeneity of the antihypertensive effect during the previous 24 hours, was computed by dividing the average of the 24-hour blood pressure changes after treatment by the corresponding standard deviation.[23,24] This measurement reveals whether treatment reduces blood pressure smoothly throughout a 24-hour period, and it appears to provide a better assessment than the T/P ratio.[23,24]

Clinical Blood Pressure and Heart Rate

Casual blood pressure and heart rate were also taken before patients began ABPM. Casual blood pressure (Korotkoff's sounds phases I and V) was measured with a standard mercury sphygmomanometer after each patient had rested for 10 minutes in a sitting position. Three measurements, taken at 2-minute intervals, were averaged and used as the clinical blood pressure. The heart rate was measured by pulse palpation at the radial artery.

Norepinephrine Levels

At the end of the placebo washout period and after 6 and 12 weeks of treatment, plasma norepinephrine levels were assessed as a parameter of sympathetic nervous activity.[25] Blood samples were taken 20 minutes after an intravenous line was inserted in the antecubital vein. Venous blood was drawn into prechilled tubes containing sodium heparin (143 USP/10 mL). The 2-mL samples were vortexed and centrifuged immediately at 4°C for 20 minutes at 300 rpm and stored at –80°C until assayed in the tubes containing 40 µL preservative solution composed of 95 mg EDTA and 60 mg glutathione in 10 mL water adjusted to pH 7.0. The norepinephrine levels were determined by high-performance liquid chromatography, based on a modification of the method of Remie and Zaagsma[26] and described by Hjemdahl.[27] The detection limit was 10 pg/mL, the recovery in plasma was 98%, and the interassay variability was 4%.

Statistical Analysis

A total of 88 patients were necessary, assuming a 10% drop-out rate, to evaluate the changes in the main variable, represented by the 24-hour DBP at the end of

the 12 weeks of treatment. When the sample size in each group is 44, a 2-sided 90.0% confidence interval for the difference of 2 means will extend 1500 from the observed difference in means, assuming that the common standard deviation is know to be 4000 and the confidence interval is based on the large sample z statistic. The calculations have been performed according to the nQuery Advisor program (version 4) (Statistical Solutions, Saugus, Mass). All analyses were conducted using the SAS system, version 6.12 (SAS Institute, Inc, Cary, NC). Analysis of covariance (ANCOVA) was used to compare the changes in the clinical variables in the 3 groups. In addition, 95% confidence intervals for pairwise differences between treatment means were calculated. The nonparametric Wilcoxon signed-rank test (proc univariate) was used to evaluate differences in T/P ratios between treatments, whereas the paired Student's *t* test was used to assess the differences in SI. The Pearson correlation coefficient was calculated to evaluate the relationship between plasma norepinephrine levels and blood pressure changes. The level of clinical significance was set at $P<.05$.

RESULTS

A total of 92 patients (43 men and 49 women; mean±SD age, 57.4±5.2 years) entered the randomization phase: 46 received valsartan 160 mg and HCTZ 12.5 mg and 46 were given amlodipine 10 mg. Seven patients withdrew after randomization, 4 in response to adverse events, 2 after achieving insufficient blood pressure control, and 1 for poor compliance. Eighty-five patients completed the study, 45 in the group receiving the valsartan/HCTZ combination and 40 in the amlodipine group. The 2 treatment groups demonstrated similar baseline characteristics pertaining to sex, age, blood pressure, and norepinephrine levels.

Blood Pressure Lowering Effect According to Drug Regimen

Both treatments significantly decreased mean ambulatory blood pressure values below those of baseline (Table 1 and Fig 1). The mean decrease in 24-hour SBP and DBP obtained with the valsartan/HCTZ combination, however, was greater than that obtained with amlodipine at both 6 and 12 weeks (Table 2). The difference between the valsartan/HCTZ regimen and amlodipine was already evident after 6 weeks, becoming more marked after 12 weeks of treatment. The hourly mean SBP (Fig 2) and DBP (Fig 3) after 6 and 12 weeks showed that both the valsartan/HCTZ combination and amlodipine maintained their antihypertensive effect throughout the 24-hour period, including the end of the interval between doses.

In both treatment groups, the T/P ratios for SBP and DBP at 12 weeks were greater than 0.5 and did not differ significantly (Table 3). On the contrary, the average SI pertaining to SBP and to DBP was significantly higher at 6 and 12 weeks in the group receiving the valsartan/HCTZ combination than in the group given amlodipine (Table 3). The ambulatory heart rate tended to decrease slightly in patients given the valsartan/HCTZ combination and to increase slightly in those given amlodipine; this increase was statistically significant for the 24-hour and daytime evaluations but not for the nighttime value assessment (Table 1).

Table 1. Mean (±SD) Ambulatory Blood Pressure Obtained During 24-hour Monitoring, Daytime, and Nighttime in Patients Receiving Amlodipine or Valsartan/HCTZ

	24-hour		Daytime		Nighttime	
	Amlodipine	V+$H_{12.5}$	Amlodipine	V+$H_{12.5}$	Amlodipine	V+$H_{12.5}$
SBP, mm Hg						
Baseline	146.5±7.0	145.7±5.0	150.6±7.0	150.3±5.1	134.3±8.7	132.2±7.0
6 weeks	134.7±6.8*	132.9±5.4*	138.3±6.6*	137.1±5.5*	123.7±8.6*	120.6±6.8*
12 weeks	133.3±6.4*	130.5±5.1*	136.9±6.4*	134.7±5.1*	122.3±7.8*	118.0±6.9*
DBP, mm Hg						
Baseline	91.7±4.3	91.6±3.6	95.2±4.7	95.0±3.8	81.2±5.1	81.6±5.3
6 weeks	81.7±4.1*	80.9±3.6*	84.5±4.2*	83.8±3.7*	73.3±5.3*	71.7±5.2*
12 weeks	80.7±3.8*	78.5±3.7*	83.6±3.9*	81.5±3.5*	71.8±4.8*	69.8±5.2*
Heart Rate, beats/min						
Baseline	69.5±5.8	70.8±6.6	71.7±6.5	73.2±7.1	62.9±5.4	63.6±6.0
6 weeks	70.0±5.4	70.8±6.4	72.3±5.9	73.3±6.9	62.9±5.2	63.4±6.0
12 weeks	71.1±5.4†	70.0±6.3	73.5±6.0†	72.1±6.9	63.2±5.1	63.1±5.6

DBP=diastolic blood pressure; HCTZ=hydrochlorothiazide; SBP=systolic blood pressure; V+$H_{12.5}$=valsartan 160 mg/HCTZ 12.5 mg

*P<.001 vs baseline.
†P<.05 vs baseline.

Table 2. Adjusted Mean (95% Confidence Interval) Ambulatory Blood Pressure at 6 and 12 Weeks in Patients Receiving Amlodipine or Valsartan/HCTZ

	24-hour		Daytime		Nighttime	
	6 Weeks	12 Weeks	6 Weeks	12 Weeks	6 Weeks	12 Weeks
SBP, mm Hg						
Amlodipine	134.7 (133.8–135.5)	133.2 (132.4–134.1)	138.5 (137.6–139.5)	137.1 (136.2–138.0)	123.1 (122.1–124.1)	121.7 (120.7–22.8)
V+$H_{12.5}$	132.9* (132.1–133.7)	130.5† (129.7–131.3)	137.1* (136.2–137.9)	134.7† (133.8–135.5)	120.6* (119.6–121.5)	118.0‡ (116.9–119.1)
DBP, mm Hg						
Amlodipine	81.7 (81.0–82.4)	80.6 (79.9–81.3)	84.6 (83.8–85.4)	83.7 (83.0–84.4)	73.0 (72.0–74.0)	71.5 (70.6–72.5)
V+$H_{12.5}$	80.8 (80.1–81.4)	78.5† (77.9–79.2)	83.8 (83.1–84.5)	81.5† (80.8–82.1)	71.7 (70.8–72.7)	69.8* (68.9–70.7)

*P<.05, amlodipine vs V+$H_{12.5}$.
†P<.001, amlodipine vs V+$H_{12.5}$.
‡P<.01, amlodipine vs V+$H_{12.5}$.

Fig 1. Mean (±SD) differences from baseline in 24-hour, daytime, and nighttime ambulatory blood pressure after 6 and 12 weeks of treatment with amlodipine or valsartan/HCTZ.

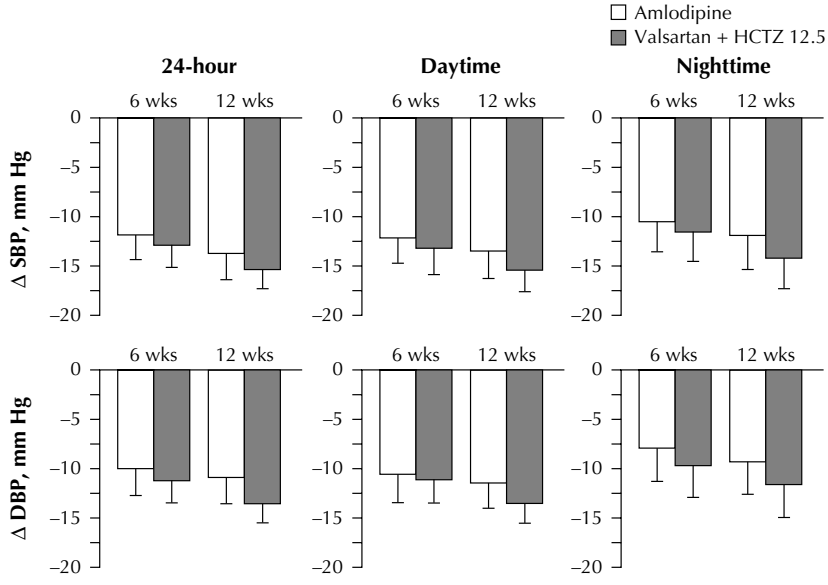

Fig 2. Twenty-four-hour SBP at baseline and after treatment with amlodipine or valsartan/HCTZ.

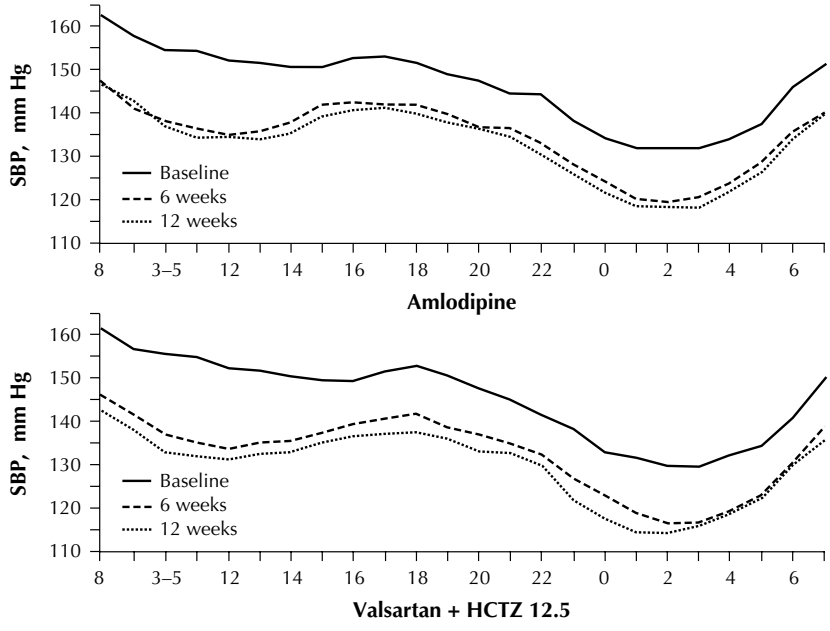

Fig 3. Twenty-four-hour DBP at baseline and after treatment with amlodipine or valsartan/HCTZ.

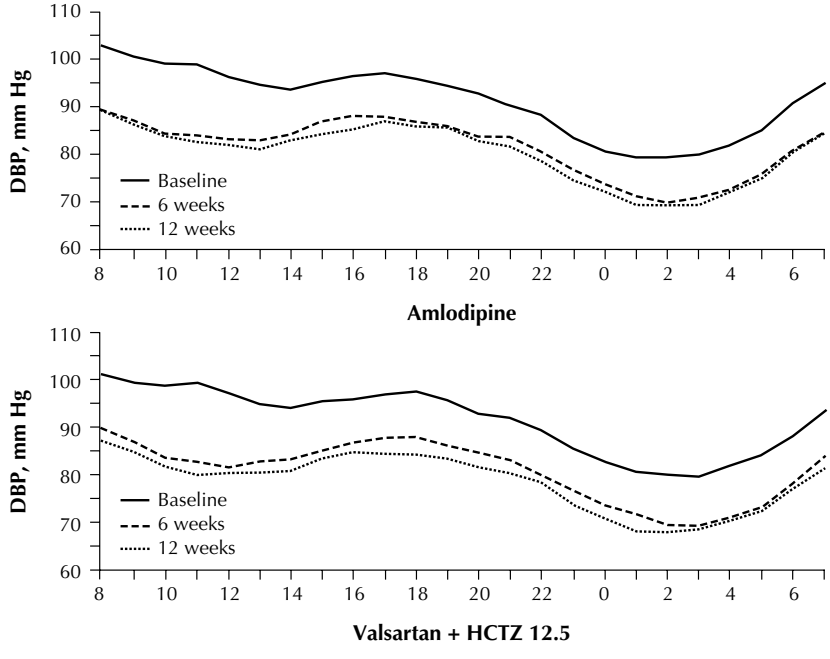

Table 3. Trough/Peak and Smoothness Index (±SD) at 6 and 12 Weeks in Patients Given Amlodipine or Valsartan/HCTZ

	Trough/Peak Ratio		Smoothness Index	
	6 Weeks	12 Weeks	6 Weeks	12 Weeks
SBP, mm Hg				
Amlodipine	0.62±0.47	0.62±0.38	1.47±0.41	1.85±0.87
$V+H_{12.5}$	0.52±0.43	0.59±0.41	1.69±0.55*	1.97±0.41*
DBP, mm Hg				
Amlodipine	0.61±0.29	0.59±0.32	1.53±0.52	1.84±0.73
$V+H_{12.5}$	0.56±0.5	0.58±0.51	1.79±0.5*	2.11±0.47†

*$P<.05$ vs amlodipine.
†$P<.01$ vs amlodipine.

Both treatments significantly reduced clinical blood pressure (Table 4), but at 12 weeks, the mean reductions in SBP and DBP obtained with the valsartan/HCTZ combination were significantly greater than the corresponding reductions obtained with amlodipine. The clinical heart rate did not change in patients given amlodipine, but it decreased slightly in those given the valsartan/HCTZ combination. This decrease was statistically significant after 12 weeks of treatment.

The valsartan/HCTZ combination did not change plasma norepinephrine levels significantly, although a decreasing trend was observed. Conversly, amlodipine therapy increased norepinephrine levels (+9% at 6 weeks, +15% at 12 weeks) (Table 4); the difference between groups was statistically significant at 12 weeks. A correlation analysis showed no relationship between absolute blood pressure and norepinephrine values, nor between SBP/DBP and norepinephrine changes in both treatment groups.

Table 4. Mean (±SD) Clinical Blood Pressure, Heart Rate, and Plasma Noradrenaline Levels at Baseline and 6 and 12 Weeks in Patients Given Amlodipine or Valsartan/HCTZ

	Baseline	6 Weeks	12 Weeks
Amlodipine			
SBP, mm Hg	162.38±8.2	149.5±6.7	147.25±6.1
DBP, mm Hg	103.4±3.7	91.9±3.3	89.8±3.6
Heart rate, beats/min	74.1±7.2	76.7±7.2	76.4±7.3
Noradrenaline, pg/mL	303.2±106.5	329.8±119.2	349.3±117.2
$V+H_{12.5}$			
SBP, mm Hg	163.9±6.6	148.8±5.3	145.3±4.5*
DBP, mm Hg	103.1±3.7	91.3±3.3	87.9±3.4†
Heart rate, beats/min	75.2±6.8	74.5±6.9	74.2±7.2†
Noradrenaline, pg/mL	304.0±101.4	297.4±114.4	283.8±111.5†

*$P<.01$.
†$P<.05$ vs amlodipine.

Tolerability

The rate of adverse events among patients given amlodipine was 31.8%, versus 4.4% among those given the valsartan/HCTZ combination (Table 5). The incidence of ankle edema was especially elevated among the amlodipine group.

Table 5. Adverse Events Observed in Patients Given Amlodipine or Valsartan/HCTZ

	V+H$_{12.5}$ (n=44) n (%)	Amlodipine (n=44) n (%)
Ankle edema	1 (2.2)	7 (15.9)
Headache	–	2 (4.4)
Dizziness	–	1 (2.2)
Polyuria	–	1 (2.2)
Nausea	1 (2.2)	1 (2.2)
Fatigue	–	-
Rash erythematosus	–	1 (2.2)
Flushing	–	1 (2.2)
Palpitation	–	1 (2.2)
Pruritus	–	–

DISCUSSION

The results of this study indicate that in high-risk hypertensive patients, the once-daily administration of the combination of valsartan 160 mg and HCTZ 12.5 mg or of amlodipine 10 mg alone led to a clinically relevant decrease in ambulatory blood pressure, without affecting the normal blood pressure circadian profile. The antihypertensive effect after 12 weeks of treatment, however, was significantly greater with the valsartan/HCTZ combination, which decreased not only the mean 24-hour SBP and DBP values but also the daytime and nighttime values.

The clinical blood pressure results confirmed that the antihypertensive efficacy of valsartan/HCTZ combination was superior to that of amlodipine at the end of the dosing interval after 6 and 12 weeks of treatment.

The duration and homogeneity of the antihypertensive action during the 24-hour evaluation, as measured by the T/P ratios, indicated that both treatments administered once a day fulfilled the FDA guidelines (T/P ratio >50%) at 6 and 12 weeks and that their effects were not significantly different. By contrast, when the duration and homogeneity of the antihypertensive action of these treatments were measured by the SI, the valsartan/HCTZ combination demonstrated greater values than did amlodipine, and this difference was more marked after 12 weeks. These observations suggest that the antihypertensive effect of both regimens was sustained through the 24-hour period with once-daily dosing, but a more homogeneous antihypertensive action was provided by the combination. This result may be linked to the more complete and prolonged blocking of angiotensin AT_1 receptors provided by the higher, 160-mg dose used in this study; this dose may counteract completely the renin-angiotensin system activation elicited by HCTZ during the whole 24-hour interval between doses. Indeed, in a previous study,[28] when valsartan 80 mg was

combined with HCTZ 12.5 mg, the SI obtained with the combination did not exceed that of amlodipine 10 mg once daily; therefore, when valsartan is combined with the diuretic, 160 mg may be the optimal daily dosage.

The capability of valsartan 160 mg/HCTZ 12.5 mg to reduce blood pressure fluctuations more effectively than amlodipine, as indicated by the more favorable SI, may be of clinical relevance, given the reported correlation between blood pressure variability and target organ damage.[29,30]

The mean ambulatory and clinical heart rates among patients given valsartan/HCTZ were lower than those among patients given amlodipine, which may be clinically relevant: a lower heart rate leads to reduced cardiac work load and oxygen consumption and, as epidemiologic studies show, has been associated with reduced cardiovascular mortality and morbidity.[31-33]

Amlodipine therapy increased plasma norepinephrine levels, an effect which was already evident after 6 weeks and statistically significant after 12 weeks. By contrast, the valsartan/HCTZ combination did not significantly affect norepinephrine levels at any time. The results of amlodipine therapy confirm previous observations[12-14] and suggest that reflex sympathetic activation may occur during long-term treatment. Regarding the effects of the valsartan/HCTZ combination on plasma norepinephrine levels, it is well known that angiotensin II can modulate the sympathetic nervous system with an enhanced release of catecholamines.[34-36] Consequently, the blockade of the specific AT_1 receptors by ARBs should lead to decreased norepinephrine release. Actually, although definite data are still lacking, some experimental and clinical evidence suggests these agents can reduce sympathetic activation.[37-39] In this study, the hypothetical norepinephrine-lowering action of valsartan might have been counteracted by the opposite effect of HCTZ, which is known to activate the sympathetic nervous system,[40,41] with a consequently neutral effect on plasma norepinephrine levels.

CONCLUSION

Findings from this study indicate the combination of valsartan 160 mg and HCTZ 12.5 mg provided more effective and homogeneous blood pressure control and, generally, a lower heart rate than did amlodipine monotherapy. A significant increase in norepinephrine levels occurred during long-term amlodipine therapy but not during valsartan/HCTZ therapy. In view of the negative effect of sympathetic activation in hypertension, a pharmacologic approach that allows better blood pressure control without eliciting sympathetic activation should be advantageous in the treatment of hypertension in high-risk patients.

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