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CLINICAL TRIALS

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Trough:peak ratio and smoothness index in the evaluation of 24-h blood pressure control in hypertension: a comparative study between valsartan/hydrochlorothiazide combination and amlodipine

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Abstract *Objective*: The aim of this study was to measure the time-effect profiles of a once-daily administered valsartan/hydrochlorothiazide combination and amlodipine on blood pressure using various indices derived from 24-h ambulatory blood pressure (BP) monitoring.
Methods: Of the 310 randomized outpatients with uncomplicated mild-to-moderate primary hypertension, 259 (133 on valsartan/hydrochlorothiazide, 126 on amlodipine) were eligible for analysis. After a 2-week placebo wash-out period, the patients were randomly allocated to treatment with either valsartan 80 mg once daily (o.d.) or amlodipine 5 mg o.d. for 4 weeks; in the case of an unsatisfactory blood pressure response, the treatments could be respectively changed to the fixed combination of valsartan 80 mg plus hydrochlorothiazide 12.5 mg o.d. or amlodipine 10 mg o.d. for a further 8 weeks. The trough:peak ratio (global and individualized approaches) and smoothness index (i.e., the ratio between the average of the 24-hourly BP changes after treatment and the corresponding standard deviation) were calculated from 24-h ambulatory blood pressure recordings made after the placebo period and after 4 weeks and 12 weeks of active treatment.
Results: Both regimens effectively lowered systolic and diastolic ambulatory pressures after 4 weeks and 12 weeks (all $P < 0.001$) but, among the responders, the valsartan/hydrochlorothiazide combination had a greater antihypertensive effect during the night-time hours after 12 weeks ($P = 0.03/0.02$). In the responders, the placebo-adjusted, mean trough:peak ratios were 0.76/0.74 in the valsartan/hydrochlorothiazide group ($n = 111$) and 0.66/0.62 in the amlodipine group ($n = 101$). The corresponding global trough:peak ratios were 0.61/0.57 for the valsartan/hydrochlorothiazide combination and 0.56/0.56 for amlodipine. However, the between-group differences in individual or global trough:peak ratios were not significant. The smoothness index was slightly, but insignificantly, greater for valsartan/hydrochlorothiazide than for amlodipine in the responders and the groups as a whole.
Conclusion: Valsartan/hydrochlorothiazide and amlodipine were equally effective in reducing ambulatory BP, but the valsartan/hydrochlorothiazide combination led to more homogeneous BP control during the inter-dosing interval. Trough:peak ratio and smoothness index did not reflect this finding accurately.

Keywords Fixed combination · Ambulatory blood pressure · Trough:peak

The authors have written this paper on behalf of investigators of the Italian Collaborative Study Group.

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Introduction

There is a convincing volume of evidence to support the contention that optimal control of blood pressure should be based upon therapeutic strategies that reduce blood pressure in a smooth and consistent fashion [1, 2], but this is difficult to assess using traditional clinic blood pressure measurements. Ambulatory blood pressure monitoring is therefore increasingly being used to eval-

uate new antihypertensive drugs and to assess the adequacy of treatment [3]. Ambulatory measurements may provide a number of advantages in the development of antihypertensive therapies by permitting better identification of trough and peak effects [4, 5]. In the last few years attention has been focused on calculation of trough:peak (T/P) ratio and smoothness index for defining the duration of action of an antihypertensive drug and for discriminating among alternative treatments, but the clinical value of these two indices is still a subject for debate [6, 7, 8]. To achieve sustained blood pressure control, the use of fixed-dose combinations of two drugs has been advocated [9] on the grounds that their individual components given at low doses can produce a homogeneous blood pressure-lowering effect during the 24 h and minimize dose-dependent side effects.

Valsartan is a selective antagonist of the angiotensin II subtype 1 receptor and has been reported to be highly effective in lowering blood pressure when given alone [10] or in combination with hydrochlorothiazide (HCTZ) [11]. Amlodipine is known to exert a good blood pressure control over 24 h, but a significant incidence of dose-dependent, lower-extremity edema may limit its usefulness [12, 13, 14].

This double-blind randomized trial used data acquired by means of ambulatory blood pressure monitoring to compare the efficacy and 24-h blood pressure control of the valsartan/HCTZ combination and amlodipine in subjects with mild to moderate hypertension. The aim of the study was to ascertain whether the average decrease in 24-h blood pressure, the 24-h blood pressure profile, and the T/P ratio and smoothness index differed between the two treatments and whether these indices of homogeneous blood pressure control actually reflect changes in the blood pressure profile caused by therapy.

Subjects and methods

Patient selection

This prospective, multicenter trial was performed in Italy between 3 June 1999 and 5 June 2000 as a side project of a larger study involving 690 patients [15]. In 19 of the 52 centers participating in the larger trial, the patients were also assessed by means of ambulatory blood pressure monitoring. Outpatients with mild to moderate essential hypertension [sitting diastolic blood pressure (DBP)≥95 mmHg and a sitting systolic blood pressure (SBP)≥ 160 mmHg] aged 21–70 years were eligible for enrollment. The subjects with a sitting SBP of at least 220 mmHg or sitting DBP of at least 130 mmHg at the end of the wash-out period were excluded, as were those with a history of myocardial infarction, transient ischemic attack, or cerebrovascular accident within the preceding 6 months; the other exclusion criteria were secondary hypertension, clinically significant valvular heart disease, insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus with poor glucose control (defined as persistent fasting blood sugar levels of >200 mg/dl), clinically significant cardiac, pulmonary, renal, neurologic, hepatic, hematologic or metabolic diseases, and hypersensitivity to angiotensin II antagonists or dihydropyridine calcium-entry blockers. Women of childbearing potential were also excluded. The study was approved by the ethics committee of each participating institution, and written informed consent was obtained from all patients before enrollment.

Study design

This was a randomized, double-blind, controlled, parallel-group study that was conducted in accordance with Good Clinical Practices and the principles of the Declaration of Helsinki and its amendments. After a 2-week, single-blind, placebo wash-out period during which any previous antihypertensive drug treatment was discontinued, the 310 patients satisfying the inclusion criteria were randomly allocated to receive valsartan 80 mg once daily (o.d.) or amlodipine 5 mg o.d. between 0700 hours and 1000 hours for 4 weeks (treatment level 1). The patients underwent 24-h ambulatory blood pressure monitoring immediately before randomization and a second period of ambulatory monitoring after 28 ± 4 days. The patients who responded to treatment continued their randomized treatments at an unchanged dose for a further 8 weeks (treatment level 1). Treatment response was defined on the basis of clinical blood pressure measurements if: (1) sitting SBP was less than 150 mmHg, (2) there was a decrease in sitting SBP greater than 20 mmHg in comparison with the end of the placebo period if this value was less than 180 mmHg, (3) there was a decrease in sitting SBP greater than 30 mmHg in comparison with the end of the placebo period if this value was greater than 180 mmHg, or (4) sitting DBP was less than 90 mmHg. The patients who did not reach any of these pressure target values were treated for a further 8 weeks with valsartan 80 mg plus HCTZ 12.5 mg o.d. if randomized to valsartan or amlodipine 10 mg o.d. if randomized to amlodipine (treatment level 2). At the end of this period, the patients underwent a third period of 24-h ambulatory monitoring.

Efficacy

Antihypertensive efficacy was assessed by means of conventional pressure measurements (trough) and 24-h ambulatory blood pressure monitoring. All clinical decisions were based on the casual (clinic) readings made using a mercury sphygmomanometer and the first (for systolic) and fifth (for diastolic) Korotkoff sounds. Each evaluated patient underwent three 24-h ambulatory monitoring periods (at baseline, after 4 weeks, and at the end of the study) on working days of average activity. Ambulatory monitorings were performed using the A&D TM-2420 model 7 (A&D Company, Tokyo, Japan), which uses a microphone to detect Korotkoff sounds, or the ICR Spacelabs 90207 (Spacelabs, Inc., Redmond, Wash.), which uses an oscillometric method. Both devices were previously validated [16, 17]. The recorders were applied between 0800 hours and 0900 hours, and patients were asked to perform their usual activities but to keep their arms still at the time of each measurement. Readings were obtained every 15 min from 0600 hours to 2400 hours and every 30 min from 0001 hours to 0559 hours. Thirty-minute intervals were chosen during night time in order to increase patients' compliance and to minimize sleep disturbance [18]. All of the ambulatory recordings were truncated so that their total duration did not exceed 24 h. In each patient, the performance of the device was validated by the agreement (± 5 mmHg) of three systolic and diastolic values with those obtained simultaneously using a sphygmomanometer. The active treatment was started at the end of the first 24-h monitoring period and, during treatment, the drug was given just before starting the 24-h recording.

Data analysis

The data provided by the centers were read, edited, and analyzed at the University of Padova's Department of Clinical and Experimental Medicine. The recordings were edited by computer using the modified Casadei method in order to ensure a uniform procedure [19]. Each 24-h report was reduced to 24 consecutive 1-h averages as previously described [20]. An ambulatory study was considered adequate for evaluation when the number of valid readings was greater than 75% of those programmed; if two or more consecutive hours contained non-valid readings, the

ambulatory study was considered inadequate. The measurements made during each hour were averaged to provide the individual hourly values used for the calculation of 24-h and daytime (0700 hours to 2259 hours) and night-time blood pressures (1100 hours to 0659 hours) [14, 15].

Calculation of T/P ratio and smoothness index

The peak effect was assessed by concentrating on the interval from 2 h to 8 h after dose administration, with the largest mean difference from placebo in the change from baseline over a 2-h period being used for the estimate. This is considered to be a reasonable minimum for most agents prescribed on a once-daily basis [21]. The trough blood pressure for each treatment was the difference from placebo between 22 h and 24 h after dose administration [21].The T/P ratio was calculated from the mean peak and trough values of each group as a whole and the individual values of the subset of responders, i.e., those with lower peak and average 24-h blood pressure on treatment than at baseline [22]. The smoothness index was calculated on the basis of the standard deviation of all hourly blood pressure measurements during the 24-h period and normalized for the mean blood pressure decrease during this period [8].

Statistical methods

It was calculated that a sample of 165 patients was needed to provide at least a 90% power of detecting a 2.7 mmHg difference in 24-h blood pressure between the two treatment groups – assuming a 15% dropout rate, a standard deviation of 7 mmHg, and two-sided testing at a significance level of $\alpha = 0.05$. Demographic characteristics of the two treatment groups were compared with Student's *t*-tests and Chi-squared tests. Analysis of covariance was used to compare drug-induced changes from baseline for the ambulatory variables. Differences in the adjusted between-group means were calculated and expressed as mean values (±SD). A *P* value of 0.05 or less (two-sided) was considered statistically significant for all tests.

Table 1 Clinical characteristics and baseline blood pressure in the two study groups. Values are expressed as mean (±SD). All differences are not significant, *BP* blood pressure

	Valsartan-based treatment ($n = 133$)	Amlodipine-based treatment ($n = 126$)
Males/females	79/65	76/58
Age (years)	51.9 ± 9.4	51.8 ± 9.2
Clinic systolic BP	166.2 ± 9.1	164.9 ± 7.8
Clinic diastolic BP	101.9 ± 5.3	101.8 ± 5.7
Clinic heart rate (bpm)	72.9 ± 8.4	72.9 ± 7.2
24-h systolic BP	141.4 ± 11.4	140.8 ± 13.1
24-h diastolic BP	88.3 ± 7.6	88.0 ± 8.1
24-h heart rate (bpm)	73.5 ± 9.5	74.0 ± 7.2

Results

A total of 310 patients entered the double-blind phase of the study but, as 51 had one or two missing or inadequate ambulatory blood pressure monitoring recordings (see Methods), the final analysis was based on 259 patients (83.5%): 133 patients in the valsartan- and 126 in the amlodipine-based treatment. All of the variables had a normal distribution except the T/P ratios, which had a positively skewed distribution for both SBP ($P < 0.0001$) and DBP ($P < 0.0001$).

There were no significant differences between the treatment groups in terms of sex, age, or baseline blood pressure (Table 1). In comparison with placebo, clinic and ambulatory SBPs and DBPs were significantly lower after either 4 weeks or 12 weeks of therapy ($P < 0.0001$ for all, data not shown). The changes in ambulatory blood pressure and heart rate from baseline to week 4 and week 12 are summarized in Table 2: the two regimens led to a similar fall in ambulatory blood pressure at both time points. However, when only the subjects considered to be responders were taken into account, the patients assigned to the valsartan/HCTZ treatment ($n = 111$, 84% of total) showed a greater reduction in night-time SBP ($P = 0.03$, Fig. 1) and DBP ($P = 0.02$, Fig. 2) after 12 weeks than those assigned to amlodipine ($n = 101$, 80% of total). The average hourly pressure differences from placebo in the responders of the two

Table 2 Changes from baseline in ambulatory blood pressure and heart rate after 4 weeks and 12 weeks of therapy in the population as a whole. Values are expressed as mean (±SD). *SBP* systolic blood pressure, *DBP* diastolic blood pressure in mmHg, *HR* heart rate in bpm, Δ difference from baseline, *NS* not significant

Change	4 weeks			12 weeks		
	Valsartan-based treatment ($n = 133$)	Amlodipine-based treatment ($n = 126$)	*P value*	Valsartan-based treatment ($n = 133$)	Amlodipine-based treatment ($n = 126$)	*P* value
Δ 24 h SBP	–6.12 ± 8.95	–7.41 ± 8.26	NS	–11.15 ± 10.72	–9.55 ± 9.17	NS
Δ 24 h DBP	–4.19 ± 6.04	–4.78 ± 5.92	NS	–7.58 ± 6.82	–6.93 ± 6.31	NS
Δ 24 h HR	–0.05 ± 5.49	1.31 ± 5.08	0.036	0.39 ± 5.82	1.73 ± 4.68	NS
Δ Day SBP	–6.61 ± 9.64	–7.47 ± 8.84	NS	–11.71 ± 11.37	–10.42 ± 9.90	NS
Δ Day DBP	–4.34 ± 6.71	–4.92 ± 6.36	NS	–7.73 ± 7.27	–7.70 ± 6.84	NS
Δ Day HR	0.27 ± 6.39	1.81 ± 5.97	0.042	0.84 ± 6.66	2.12 ± 5.56	NS
Δ Night SBP	–5.07 ± 9.93	–7.11 ± 9.81	NS	–9.99 ± 11.87	–7.99 ± 10.32	NS
Δ Night DBP	–3.78 ± 6.81	–4.47 ± 7.25	NS	–7.22 ± 8.22	–5.48 ± 7.65	NS
Δ Night HR	–0.69 ± 5.12	0.36 ± 6.23	NS	–0.47 ± 6.68	0.87 ± 6.11	NS
SBP trough	–5.19 ± 13.82	–8.01 ± 12.99	NS	–11.88 ± 14.73	–10.75 ± 12.99	NS
DBP trough	–3.88 ± 9.84	–4.84 ± 9.08	NS	–7.92 ± 9.52	–8.10 ± 9.08	NS
SBP peak	–17.50 ± 12.40	–18.70 ± 11.87	NS	–23.07 ± 13.55	–21.41 ± 11.87	NS
DBP peak	–12.54 ± 9.05	–13.08 ± 8.92	NS	–16.42 ± 8.98	–16.19 ± 8.92	NS

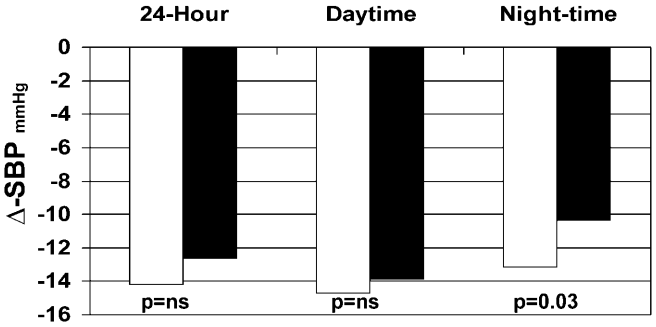

Fig. 1 Changes in ambulatory systolic blood pressure from baseline (Δ-SBP) in the valsartan-based (*open bars*) and amlodipine-based (*solid bars*) treatment groups after 12 weeks of therapy in responders

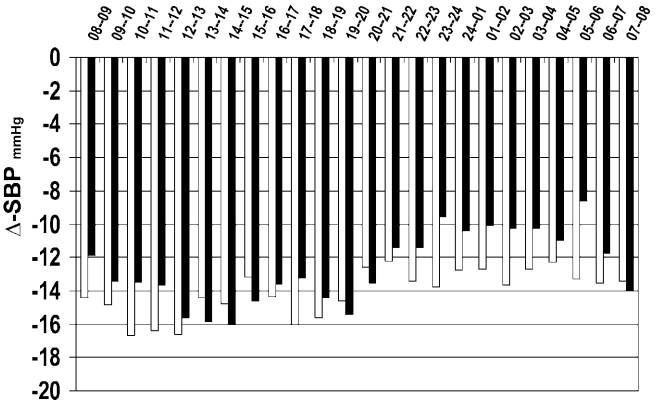

Fig. 3 Mean hourly changes in ambulatory systolic blood pressure from baseline (Δ-SBP) in the valsartan-based (*open bars*) and amlodipine-based (*solid bars*) treatment groups after 12 weeks of therapy in responders

treatment groups are shown in Fig. 3 (SBP) and Fig. 4 (DBP). Both regimens led to significant decreases in systolic and diastolic ambulatory pressures during each of the 24-h intervals. However, after 12 weeks, the valsartan/HCTZ combination induced a significantly greater reduction in night-time SBPs and DBPs (from 2300 hours to 0600 hours). Ambulatory heart rate did not change with the valsartan/HCTZ combination and slightly increased with amlodipine; the between-treatment difference was statistically significant after 4 weeks (Table 2).

T/P ratio and smoothness index

After 4 weeks

The T/P ratios of the groups as a whole were first calculated by dividing the average change in systolic and diastolic trough pressures by the average change in peak systolic and diastolic pressures (Table 3): all of the patients were included in this analysis. For both treatments, T/P ratios were less than 0.5 and slightly but insignificantly greater for amlodipine than valsartan. Among the responders, that is those subjects whose peak blood pressure and average 24-h blood pressure were lower on therapy than on placebo, T/P ratios were still less than 0.5 for DBP and were greater than 0.5 for SBP with higher values for amlodipine. However, between-drug differences were not statistically significant. The smoothness index, either calculated from the responders or from all patients, was less than 1 for both treatments.

After 12 weeks

After 12 weeks of treatment, the T/P ratios of the responders and the groups as a whole were greater than 0.5 for both treatments. The T/P values in the valsartan-based treatment group were slightly higher than those in the amlodipine-based treatment group, especially when the responders were considered alone (>0.7 for both SBPs and DBPs). However, the between-group differences were not statistically significant. The smoothness index also increased after 12 weeks of therapy and was slightly higher in the valsartan- than the amlodipine-based treatment group, with higher values in the responders than the groups as a whole. Again, the between-group differences did not reach the level of

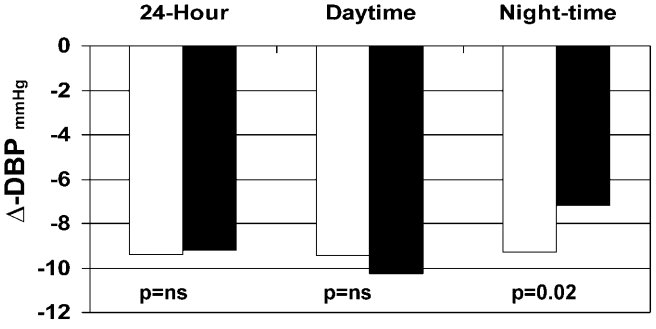

Fig. 2 Changes in ambulatory diastolic blood pressure from baseline (Δ-DBP) in the valsartan-based (*open bars*) and amlodipine-based (*solid bars*) treatment groups after 12 weeks of therapy in responders

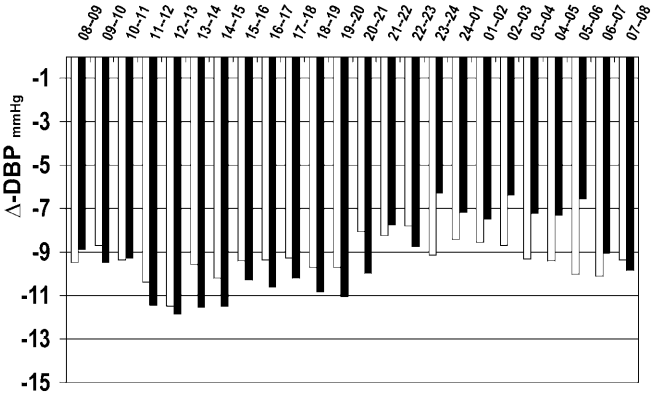

Fig. 4 Mean hourly changes in ambulatory diastolic blood pressure from baseline (Δ-DBP) in the valsartan-based (*open bars*) and amlodipine-based (*solid bars*) treatment groups after 12 weeks of therapy in responders

Table 3 Trough:peak ratio and smoothness index in the two study groups after 4 weeks and 12 weeks of treatment. Values are expressed as mean (±SD). *SBP* systolic blood pressure, *DBP* diastolic blood pressure in mmHg

Index	4 weeks		12 weeks	
	Valsartan-based treatment	Amlodipine-based treatment	Valsartan-based treatment	Amlodipine-based treatment
SBP trough:peak ratio in responders	0.56 ± 3.03	0.65 ± 1.17	0.76 ± 1.35	0.66 ± 0.72
DBP trough:peak ratio in responders	0.37 ± 4.58	0.38 ± 1.21	0.74 ± 1.59	0.62 ± 0.58
SBP smoothness index in responders	0.72 ± 0.71	0.87 ± 0.64	1.34 ± 0.83	1.22 ± 0.64
DBP smoothness index in responders	0.64 ± 0.69	0.77 ± 0.64	1.17 ± 0.76	1.16 ± 0.64
SBP trough:peak ratio (all patients)	0.29	0.43	0.61	0.56
DBP trough:peak ratio (all patients)	0.31	0.37	0.57	0.56
SBP smoothness index (all patients)	0.58 ± 0.78	0.71 ± 0.73	1.06 ± 1.00	0.94 ± 0.84
DBP smoothness index (all patients)	0.52 ± 0.71	0.60 ± 0.71	0.95 ± 0.88	0.90 ± 0.82

statistical significance. No serious side effect was observed with either treatment [15].

Discussion

The results of the present trial show that the once-daily administration of amlodipine and the valsartan/HCTZ combination led to a clinically relevant reduction in ambulatory blood pressure, with the combination having a greater antihypertensive effect during the night. The valsartan/HCTZ combination had a similar blood pressure-lowering effect during the day and the night, whereas the antihypertensive efficacy of amlodipine tended to decline from 2300 hours to 0700 hours (Fig. 3 and Fig. 4).

When evaluating the antihypertensive efficacy of a drug regimen, a rigorous approach is necessary to verify whether the blood pressure-lowering effect is homogeneous throughout the 24 h [1, 2, 3, 4, 5]. Ambulatory monitoring is now an established technique for this purpose, and the determination of T/P ratios is a well-known means of providing clinical evidence that a formulation possesses a satisfactory duration of action [6, 7, 8]. Although the U.S. Food and Drug Administration has recommended for several years that new antihypertensive agents should have a T/P ratio of greater than 50% [23], there is a lack of standardized guidelines as to how T/P ratios should be calculated. They may be derived from a relatively unselected population of hypertensive patients or from the subset showing reduced blood pressure after drug administration [6, 7]. Responders can be selected using arbitrary measures such as predetermined reductions in blood pressure versus placebo. In previous analyses, we have shown that two conditions must be satisfied in order to obtain meaningful individual T/P ratios: a lower peak and lower average 24-h blood pressure on treatment than on placebo [22]. According to Omboni et al., T/P ratios should be calculated in individual patients and limited to those who respond to treatment [21] on the grounds that the exclusion of non-responders removes often erratic values and leads to less interindividual variation. However, ratios derived from responders alone have statistical limitations and should be supported by T/P ratios calculated from group means of all of the individual troughs and peaks [6, 7, 21]. That is why in the present study we calculated both individual and global T/P ratios.

In this study, the T/P ratios were good after 12 weeks (always >0.5) and tended to be higher for valsartan- than the amlodipine-based treatment, especially when calculated on the basis of the individual values of the responders, but the between-treatment differences did not reach the level of statistical significance. These findings are in keeping with those of Ford et al. [24], who reported that fosinopril led to T/P ratios greater than 0.5 for responders but ratios of 0.32–0.36 if all patients were included.

The smoothness index does not seem to suffer the consequences of the methodological, interpretative, and practical problems encountered with T/P ratios, and recent evidence suggests that it permits a better assessment of homogeneity of antihypertensive treatment [8]. In the present report, the smoothness index showed 25–30% greater values when calculated from the subjects considered responders to treatment than when calculated from the whole study group, suggesting that in our nonresponders more artifactual readings had occurred, which likely accounted for the increased SD of mean hourly changes. The smoothness index showed slightly greater values for the valsartan/HCTZ combination than for amlodipine, but the between-group differences were not statistically significant.

We found generally lower ambulatory heart rate values in the patients with valsartan/HCTZ than in those on amlodipine. This may be clinically relevant for

hypertensive patients as a lower heart rate leads to a reduction in cardiac workload and oxygen need. Furthermore, epidemiologic studies indicate that a lower heart rate might be associated with a better prognosis in terms of cardiovascular morbidity and mortality [25, 26].

In conclusion, the results of the present study showed that both valsartan 80 mg plus HCTZ 12.5 mg and amlodipine 5–10 mg were effective in lowering ambulatory blood pressure in mild to moderate hypertension. However, the valsartan/HCTZ combination produced a more homogeneous blood pressure control over the 24 h. Although T/P ratio and smoothness index were greater in the valsartan/HCTZ than the amlodipine group, the between-treatment differences failed to reach the level of statistical significance indicating that these indices may not reflect accurately 24-h blood pressure control exerted by antihypertensive treatment.

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