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-hour 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

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 120 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 Practice 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 2). 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 (clinical) 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. Recordings 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