We compared the angiotensin II receptor antagonist valsartan to losartan as an antihypertensive agent in an 8-week trial. Adults with uncomplicated essential hypertension (baseline seated diastolic blood pressure < 115 mm Hg and ≥ 95 mm Hg) were randomized to receive 80 mg valsartan, 50 mg losartan, or placebo once daily. After 4 weeks doses of active medication and placebo were doubled. Seated systolic and diastolic blood pressures were measured and the response rate evaluated. Tolerability was assessed by the incidence of adverse events.

Both angiotensin II receptor antagonists produced similar significant reductions in mean blood pressures at 4 and 8 weeks compared to placebo. Valsartan produced a significantly higher number of responders (62%) than losartan (55%, \( P = .02 \)) at the 8 week treatment endpoint. The incidence of adverse experiences (AE) was similar in all three groups, with headache and dizziness reported most often.

Valsartan (80/160 mg) monotherapy in this trial was as effective and well tolerated as 50/100 mg losartan in treating mild to moderate essential hypertension, and at 160 mg has a significantly higher responder rate than 100 mg losartan. Am J Hypertens 1999;12:414 – 417 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Valsartan, losartan, angiotensin II antagonist, angiotensin II receptor blocker (ARB), AT₁ antagonist, essential hypertension.

Valsartan is a novel angiotensin II receptor antagonist\(^1\)\(^,\)\(^2\) that dose-dependently lowers blood pressure in patients with mild-to-moderate essential hypertension.\(^3\)\(^–\)\(^5\) The aim of this trial was to compare the efficacy of once daily valsartan with that of another angiotensin receptor blocker, losartan,\(^6\)\(^,\)\(^7\) and with placebo over a period of 8 weeks. A multicenter trial was performed to provide large enough treatment groups to make meaningful comparisons.

PATIENTS AND METHODS

Patients Outpatients aged 18 to 80 with mild-to-moderate uncomplicated essential hypertension were recruited from a total of 74 hypertension clinics. Patients were required to have a mean sitting diastolic blood pressure (MSDBP) ≥ 95 mm Hg and ≤ 115 mm Hg at the start of the 14-day placebo run-in and at randomization. The most important criteria for exclusion from the trial included the presence of overt heart disease or angina pectoris, a history of myocardial infarction or heart failure, or the inability to tolerate the absence of hypertensive medication during the
14-day run-in. Fertile women were required to use an effective method of contraception for the duration of the trial.

All patients gave their written informed consent to participate in the trial, which was approved by the relevant local Institutional Review Boards.

**Study Design**  This study was a randomized double-blind trial using parallel group placebo and active controls and up-titration of the active regimens. After an initial 14-day single-blind placebo run-in (which was omitted in the case of newly diagnosed, previously untreated patients), subjects were randomized into groups to receive either placebo, 80 mg valsartan, or 50 mg losartan. The study drugs were supplied as capsules of identical appearance to maintain blinding and were to be taken orally once daily in the morning.

After 4 weeks, patients were either continued on placebo or their dose of active medication was doubled (to 160 mg valsartan or 100 mg losartan) for another 4 weeks to the 8 week endpoint. If their MSDBP was ≤ 60 mm Hg or ≥ 120 mm Hg, or the mean sitting systolic blood pressure (MSSBP) was ≤ 100 mm Hg, patients were discontinued from the trial.

The primary efficacy variable was the change from baseline in trough MSDBP. The change from baseline in trough MSSBP and in peak MSDBP and MSSBP were secondary, and the changes from baseline in standing diastolic and systolic blood pressure (BP) were also evaluated as supplementary efficacy variables. Trough BP was measured 23 to 26 h after and peak BP 4 h after intake of the study medication. At each visit, BP was measured using a mercury sphygmomanometer in the same arm and wherever possible by the same clinician. All BP were measured using World Health Organization (WHO) criteria to the nearest 2 mm Hg. For the measurement of diastolic pressure, Korotkoff phase V was used.

To evaluate safety and tolerability, adverse events (AE) were recorded. At each visit after the first, any signs noted by the physician or symptoms reported by the patient were recorded and assessed for their severity and possible relationship to the trial medication. Any worsening of a preexisting condition was considered as a new AE. The secondary criteria for tolerability, changes in pulse rate and body weight, were also assessed at each visit.

**Statistical Considerations**  The sample size of 1000 patients (400 in each treatment group and 200 in the placebo group) was calculated to allow the null hypothesis, that the effect of valsartan on the reduction of trough MSDBP is less than or equal to the effect of losartan, to be rejected with 80% or more power at the .05 significance level.

Appropriate statistics, principally ANOVA with co-variance adjustment, were used to evaluate the change in mean blood pressures and the proportion of patients successfully responding to each treatment by a reduction in MSDBP to < 90 mm Hg or a ≥ 10 mm Hg decrease in MSDBP compared to baseline.

**RESULTS**

**Patients**  A total of 1369 hypertensive patients were randomized into the active treatment and placebo groups in approximately the ratio 2:2:1 (valsartan, n = 551; losartan, n = 545; placebo, n = 273). There were no statistically significant differences between the treatment groups with respect to demographic or baseline characteristics or in medical history (Table 1). Of the 1369 randomized patients, 779 (56.9%) were men and 590 (43.1%) were women. The age of the patients ranged from 24 to 80 years, with a mean of 55 ± 11 years, and the majority (90%) of the patients were white. The median duration of exposure to trial medication was 56 days for all groups.

A total of 1289 patients completed the full 8 weeks of the trial. Most premature discontinuations were
due to adverse experiences (n = 26) or an unsatisfactory therapeutic effect (n = 20), with a smaller number due to withdrawal of consent, administrative problems, loss to follow-up, patient not meeting the protocol criteria, or patient noncompliance.

Efficacy Both valsartan and losartan were significantly better (P < .001) than placebo at reducing the trough MSDBP (Figure 1) at both the 8 week and the 4 week endpoints (mean change from baseline at 4 weeks: 160 mg valsartan, −8.3 mm Hg; 100 mg losartan, −8.0 mm Hg; placebo, −4.9 mm Hg, and at 8 weeks: 160 mg valsartan, −10.5 mm Hg; 100 mg losartan, −9.7 mm Hg; placebo, −5.0 mm Hg). When valsartan was directly compared to losartan there was no statistically significant difference between treatments. Both trial drugs showed comparable efficacy regardless of patient age, race, or gender.

Similar results were obtained from the analysis of the secondary variable, change from baseline in trough MSSBP (Figure 1). For the secondary and supplementary variables (change from baseline in peak MSDBP and MSSBP, and in trough and peak standing diastolic and systolic BP), two-sided ANCOVA showed that both active drugs were statistically significantly superior to placebo (data on file at Novartis).

Both 80 mg valsartan and 50 mg losartan gave better patient response rates than placebo at week 4 (valsartan, 46.2%; losartan, 44.0%; placebo, 24.5%). Valsartan showed a slight superiority to losartan in response rate that reached statistical significance at 8 weeks (valsartan, 61.6%; losartan, 54.5%; placebo, 29.3%).

Safety and Tolerability The evaluation of safety was primarily based on the AE reported from week 0 to week 8. One or more AE (irrespective of relationship to trial medication) were reported by 87 of 272 patients (32.0%) in the placebo group, 174 of 551 patients (31.6%) in the valsartan group, and 159 of 542 patients (29.3%) in the losartan group. Overall the most commonly reported AE was headache (placebo 10.3%, losartan 6.8%, valsartan 6.7%) followed by dizziness (placebo 4.0%, valsartan 3.4%, losartan 2.4%).

Of the AE that were considered to be at least possibly related to trial medication, only headache occurred with an incidence > 3%, and was reported by 23 (4.2%) patients in the valsartan group, 16 (3.0%) in the losartan group, and 7 (2.6%) in the placebo group. Thirty-three patients reported AE that were serious or led to premature discontinuation from the trial (valsartan 13 [2.3%], losartan 13 [2.4%], placebo 7 [2.6%]). The proportion of serious AE was very low and similar in all treatment groups, confirming the high degree of safety of the two active treatments.

The other safety and tolerability criteria, changes from baseline in sitting and standing pulse rate and in body weight, showed no changes between treatments. No cases of orthostatic hypotension or clinically relevant changes in standard hematologic or biochemical measurements were reported.

DISCUSSION After 8 weeks of treatment 80 and 160 mg valsartan proved to be as effective as 50 and 100 mg losartan, respectively, in reducing trough MSDBP. Comparison of the effects of valsartan and losartan on peak and trough MSDBP and MSSBP and on standing BP at weeks 4 and 8 showed small but statistically nonsignificant differences between treatments. Thus by these
efficacy criteria, valsartan is as effective as losartan. Notably, however, the difference in responder rates between the two active treatments at 4 weeks widened by 8 weeks to give a statistically significant difference ($P = .021$) in favor of valsartan. Both valsartan and losartan were equally well tolerated, which is a confirmation of previous reports.7,10

Previous studies showing that valsartan is effective and well tolerated in the management of patients with essential hypertension have compared valsartan to placebo or other established classes of antihypertensive drugs. Our results in this 8-week multicenter study show that valsartan is as effective and as equally well tolerated as losartan, with a better response rate than losartan at the higher dose. The significant difference in response rate is worth investigating further in longer-term studies.

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REFERENCES