Comparison of Candesartan Versus Enalapril in Essential Hypertension

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on behalf of the Italian Candesartan Study Group

Background: The objective of this study was to compare the antihypertensive efficacy and tolerability of candesartan cilexetil (CC) with that of enalapril (E) and placebo (P) in hypertensives by clinic and ambulatory blood pressure (BP).

Procedures: The study was an Italian multicenter, randomized, double-blind, parallel group trial including 227 mild to moderate essential hypertensives (age range, 18 to 70 years). After 4 weeks of P, patients were randomized to 8 weeks of treatment with P or CC (4 mg) or E (10 mg) once daily, which was eventually increased to 8 mg and 20 mg once daily in nonresponders. At the end of each study phase, trough BP was measured by conventional sphygmomanometry and ambulatory BP was monitored over 24 h by a Spacelabs device. Analysis of 24-h BP profile included calculation of 24-h, daytime, nighttime, and hourly average values.

Results: In the 178 patients evaluable per protocol, at the end of 8 weeks of treatment, trough systolic (S) and diastolic (D) BP were similarly reduced by both active treatments (13 ± 12 and 10 ± 7 mm Hg for CC and 14 ± 12 and 10 ± 7 mm Hg for E) and significantly more by both treatments than by P (6 ± 11 and 7 ± 8 mm Hg, $P < .01$ *v* CC and E). In the 85 patients with valid 24-h recordings reduction in 24-h BP was again similar for the two active groups. The antihypertensive effect was still evident during h 23 and 24 after the last dose for both active treatments (8 ± 20 *v* 5 ± 18 mm Hg for SBP and 4 ± 12 *v* 6 ± 13 mm Hg for DBP, CC *v* E, respectively) but not for P. Heart rate was not significantly modified by either active treatment. The incidence of adverse events was greater in the E than in the CC group.

Conclusions: Our study provides evidence that CC at a dose of 4 to 8 mg is as effective as E at a dose of 10 to 20 mg over 24 h, but is better tolerated than E. Am J Hypertens 2001;14:129–134 © 2001 American Journal of Hypertension, Ltd.

Key Words: Essential hypertension, ambulatory blood pressure monitoring, antihypertensive treatment, candesartan cilexetil, enalapril.

Compounds selectively blocking the angiotensin II receptor subtype 1 have recently been introduced in the antihypertensive armamentarium. They have shown to be as effective as other classes of antihypertensive drugs and to cause very few adverse events, these being in most cases comparable to those observed with placebo.[1–3]

In the present study we compared the antihypertensive efficacy and tolerability of one of these compounds, candesartan cilexetil,[4–8] administered at a relatively low dose of 4 to 8 mg once daily, with those of enalapril at doses of 10 to 20 mg and placebo, also given once daily in patients with mild to moderate essential hypertension by clinic and ambulatory blood pressure (BP) measurement. Data concerning the effect of these drugs on clinic BP have partly been published in a preliminary paper.[9]

Methods

Study Population

The study included 227 male and female outpatients with mild to moderate essential hypertension who were never previously treated or whose BP was not satisfactorily controlled by current treatment. The main inclusion criteria were age between 18 and 70 years and a sitting diastolic BP between 95 and 109 mm Hg after 4 weeks of placebo treatment (see later here). Patients were excluded if they had any of the following: 1) sitting diastolic BP ≥ 110 mm Hg or < 94 mm Hg; 2) sitting systolic BP ≥ 200

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A complete list of study participants is provided in the Appendix.

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mm Hg; 3) secondary hypertension; 4) heart failure or other severe cardiac diseases; 5) major arrhythmias; 6) myocardial infarction within the last 3 months before starting the study; 7) cerebral arterial disease; 8) serum creatinine $\geq$ 1.6 mg/dL or serum potassium outside the normal range; 9) serious hepatic, gastrointestinal, metabolic, or immunological disorders; 10) malignancy; or 11) known hypersensitivity to angiotensin converting enzyme (ACE) inhibitors. Pregnant women and breast-feeding mothers were also excluded, as well as women of childbearing age who were not using acceptable methods of contraception.

Written informed consent was obtained from all patients before their inclusion in the study. The study was approved by the Ethics Committees of the centers involved.

Study Design

This was an Italian multicenter (17 centers), randomized, double-blind, three parallel group trial. After a 4-week period of placebo treatment, patients were randomized in a 2:2:1 fashion to one of the following: 1) active treatment with candesartan cilexetil, 4 mg once daily; 2) active treatment with enalapril, 10 mg once daily; or 3) placebo once daily. At the end of the first 4 weeks of treatment, the dose of candesartan cilexetil, enalapril, or placebo was maintained unchanged in responder patients, whereas it was doubled (from 4 to 8 mg for candesartan cilexetil, from 10 to 20 mg for enalapril, or from 1 to 2 tablets for placebo, respectively) in those patients whose diastolic BP had remained $>$ 90 mm Hg or in whom diastolic BP had been reduced by $<$ 8 mm Hg. In both cases treatment was continued for the next 4 weeks. The active drug or placebo was administered at 9 AM.

At the end of the placebo run-in treatment period and of the 8 weeks of double-blind treatment, BP was measured in the clinic environment and by ambulatory monitoring. Clinic BP was obtained in the sitting and standing positions by standard mercury sphygmomanometry from the dominant arm 24 h after the last drug intake. Three consecutive measurements, taken at 2-min intervals with the patient sitting for 10 min, were averaged and used as the clinic BP reference value. Two measurements were also taken in the standing position: the first immediately after standing, and the second after 2 min. Heart rate was measured by the palpatory method at the radial artery level over 1 min. Ambulatory BP monitoring was performed over 24 h by a Spacelabs 90207 device (Spacelabs, Redmond, WA).[10] The device cuff was wrapped around the nondominant arm and the patient was asked to keep her/his arm still during automatic BP measurements. Each recording started in the morning, immediately after clinic BP assessment and before administration of placebo or active treatment. The device was programmed to measure BP every 15 min throughout the 24 h. At each visit, patients were also asked to report the occurrence and type of adverse events (see Results).

Data Analysis

The primary efficacy criterion of the study was the reduction in sitting clinic diastolic BP with treatment. This parameter was statistically assessed by analysis of covariance, considering the value at the end of the placebo run-in period as the covariate. Sitting clinic systolic BP and heart rate values were analyzed in the same fashion as diastolic BP. These effects were further assessed by computation of the percentage of patients normalized (diastolic BP $\leq$ 90 mm Hg) or responding (reduction in diastolic BP of $\geq$ 10 mm Hg) to treatment. Comparisons of normalized and responding patients between the three treatment groups were performed using the Cochran-Mantel-Haenszel statistics.

The analysis of 24-h BP recordings was preceded by removal of artifacts according to previously described editing criteria.[11] Recordings were considered valid when a complete 24-h monitoring period was available, with at least two valid measurements per hour during the day and at least one valid measurement per hour during the night. The analysis included computation of 24-h, daytime (6 AM to 12 PM), and nighttime (12 PM to 6 AM) averages for BP and heart rate. As done for clinic BP, the effect of treatment on 24-h, daytime, and nighttime BP and on heart rate values was assessed by analysis of covariance. Hourly averages were also computed and displayed, starting from the time of drug intake.

Results

Demographic and Clinical Data

A total of 22 patients were not suitable for the analysis during the placebo run-in period; thus, the number of patients randomized to treatment was 205. The patients evaluable by protocol at the end of treatment were 178, with 39 randomized to placebo, 72 to candesartan cilexetil, and 67 to enalapril. The remaining patients were excluded from the analysis of BP data because of major protocol violations, poor compliance with medical visits, or withdrawal because of adverse events.

The demographic characteristics of the per protocol population are shown in Table 1. Before randomization the three groups were similar with respect to age, height, weight, clinic and 24-h BP, and heart rate values. A difference between the three groups was found for gender distribution and for 24-h systolic BP, which was slightly higher at baseline in the placebo than in the two active treatment groups ($P < .05$). Concomitant diseases were homogeneously distributed among the three groups and were not clinically relevant.

Clinic Blood Pressure and Heart Rate

Results of an intention-to-treat analysis of efficacy performed on clinic BP data have been already published.[9]

Table 1. Demographic and hemodynamic data of the patients before randomization to treatment (means ± SD)

	Placebo	*n*	Candesartan Cilexetil	*n*	Enalapril	*n*
Age (years)	48 ± 15	39	48 ± 11	72	50 ± 11	67
Sex (M/F)	23/16	39	48/24	72	33/34	67
Height (cm)	169 ± 10	39	170 ± 9	72	167 ± 9	67
Weight (kg)	76 ± 15	39	77 ± 13	68	75 ± 14	67
Clinic SBP (mm Hg)	152 ± 11	39	152 ± 11	72	154 ± 12	67
Clinic DBP (mm Hg)	101 ± 4	39	100 ± 4	72	101 ± 3	67
Clinic HR (beats/min)	75 ± 7	39	72 ± 8	72	73 ± 7	67
24-h SBP (mm Hg)	145 ± 12(*)	15	137 ± 13	37	140 ± 10	33
24-h DBP (mm Hg)	90 ± 10	15	88 ± 9	37	88 ± 7	33
24-h HR (beats/min)	72 ± 10	15	72 ± 10	37	73 ± 7	33

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate. Asterisk refers to statistical significance of placebo versus active treatments ($P < .05$).

This analysis was performed in 201 patients, 44 treated with placebo, 79 with candesartan cilexetil, and 78 with enalapril) and gave results similar to those obtained by analyzing the smaller per-protocol population of the present study. Clinic systolic and diastolic BP values were reduced by both active treatments significantly more than by placebo (Fig. 1, upper panel). The diastolic and systolic BP reduction achieved at the end of treatment was not significantly different for candesartan cilexetil and enalapril (Fig. 1, upper panel). The percentage of responders was similar in the two active treatment groups (60% and 63%, for candesartan cilexetil and enalapril, respectively) and was greater than that in the placebo group (36%, $P < .05$). This was the case also for the percentage of patients normalized by treatment (61% for candesartan cilexetil, 63% for enalapril, and 39% for placebo, $P < .05$ placebo *v* active treatments).

Neither active treatment induced any significant change

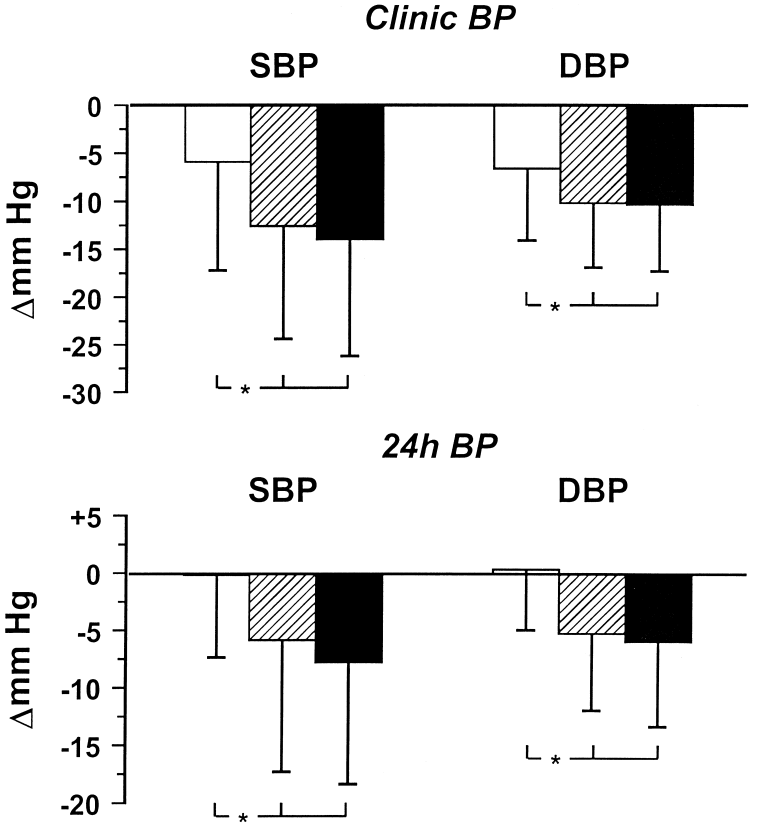

FIG. 1. Changes (Δ) in clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP) (**top panel**) and in average 24-h SBP and DBP (**bottom panel**) after treatment with placebo (**open bars**), candesartan cilexetil (**striped bars**), and enalapril (**filled bars**). Data are shown as means ± SD. Asterisks refer to the statistical difference between treatments (*$P < .05$).

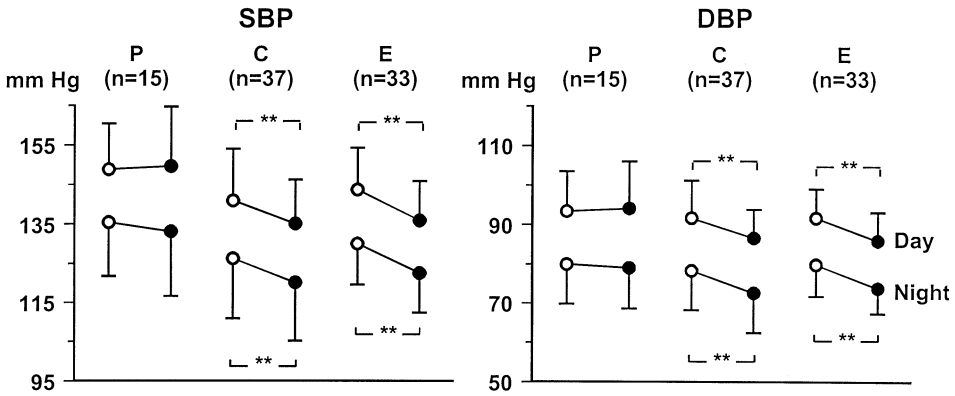

FIG. 2. Average daytime and nighttime systolic blood pressure (SBP; **left panel**) and diastolic blood pressure (DBP; **right panel**) before (**open circles**) and after (**full circles**) treatment with placebo (P), candesartan cilexetil (C), and enalapril (E). Data are shown as means ± SD. Asterisks refer to the statistical difference between baseline and treatment period (**$P < .01$).

in heart rate, which, at the end of treatment, was similar between the two groups (71 ± 8 beats/min for candesartan cilexetil and 72 ± 8 beats/min for enalapril) and which was not significantly different from that observed in the placebo group (74 ± 7 beats/min).

Ambulatory Blood Pressure and Heart Rate

A total of 85 patients had valid 24-h ambulatory BP recordings both at baseline and at the end of treatment: 15 treated with placebo, 37 with candesartan cilexetil, and 33 with enalapril. As shown in Table 1, in the patients with valid 24-h recordings, at randomization the 24-h average BP and heart rate values were similar in all treatment groups, with the exception of a significantly higher systolic BP in the placebo group. As previously observed for clinic BP, the 24-h diastolic and systolic BP fall after 8 weeks of treatment was similar in the two active treatment groups (Fig. 1, lower panel). Placebo did not induce any change in 24-h systolic or diastolic BP.

The BP lowering effect of the two active treatments was found to be statistically significant also when the 24-h period was subdivided, with daytime and nighttime BP averages calculated (Fig. 2), and no significant difference between the effects of the two drugs was observed. Placebo did not change daytime BP, although it seemed to induce a slight and nonsignificant systolic BP reduction during the nighttime. The BP changes obtained with candesartan cilexetil and enalapril during the daytime and nighttime were consistently significantly different from those obtained with placebo ($P < .05$).

Calculation of hourly average BP values showed that both candesartan and enalapril maintained most of their antihypertensive effect throughout the 24 h, including the hours farthest from the last drug intake (Fig. 3, middle and bottom panels). Hourly BP profiles during the pretreatment washout and at the end of placebo treatment were similar (Fig. 3, top panel). In the active treatment groups, in the last 2 h from the drug intake, the BP reduction from baseline was still statistically significant and not significantly different between candesartan and enalapril for both systolic BP (8 ± 20 *v* 5 ± 18 mm Hg candesartan *v* enalapril; NS) and diastolic BP (4 ± 12 *v* 6 ± 13 mm Hg candesartan *v* enalapril; NS).

Average heart rate values (24-h, daytime, and nighttime) were not significantly different among placebo (74 ± 12 beats/min), candesartan (74 ± 8 beats/min), and enalapril (73 ± 6 beats/min).

Safety and Tolerability

Safety analysis was performed in the 205 patients randomized to treatment who were subjected to ≥ 1 day of treatment. A total of 35 patients reported at least one adverse event: 16% of patients treated with placebo, 11% with candesartan cilexetil, and 24% with enalapril (Table 2). Not only the number of patients reporting adverse events but also the number of adverse events was greater in the enalapril ($n = 26$ in 67 patients) than in the placebo ($n = 8$ in 39 patients) and candesartan cilexetil group ($n = 15$ in 72 patients). All adverse events were mild to moderate in severity except for a case of severe leg pain in the placebo group. Only three patients were withdrawn from the study because of adverse events: one patient had a macular-papular rash; another had cough, throat sore, dizziness and dry eyes; and another suffered from thyroiditis. All of them were under treatment with enalapril. There were no clinically significant changes in electrocardiograms or in laboratory variables in any of the treatment groups.

Discussion

The present study has shown that candesartan cilexetil, at doses of 4 to 8 mg, reduces clinic and ambulatory BP significantly more than placebo in subjects with mild to moderate essential hypertension. The reduction in clinic and 24-h diastolic and systolic BP achieved with candesartan was not significantly different from that obtained

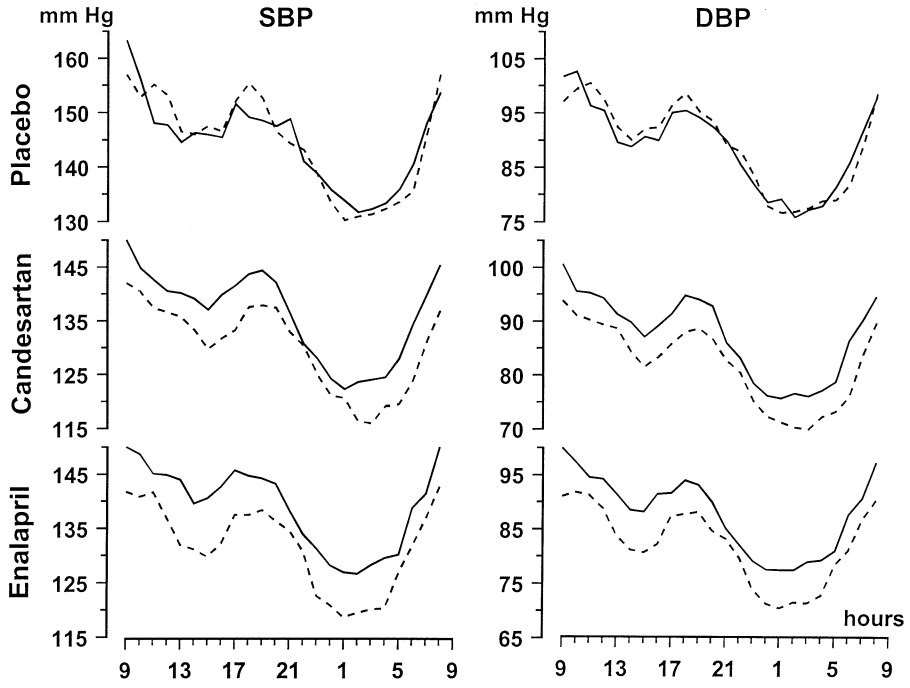

FIG. 3. Average hourly systolic blood pressure (SBP) and diastolic blood pressure (DBP) values at baseline (**continuous lines**) and at the end of treatment (**dashed lines**) with placebo (**upper panels**), candesartan cilexetil (**mid panels**), and enalapril (**lower panels**).

with enalapril at a dose of 10 to 20 mg. The number of normalized (diastolic BP during treatment $\leq$ 90 mm Hg) or responder patients (reduction in diastolic BP of $\geq$ 10 mm Hg with treatment) was similar among the patients taking candesartan and enalapril and was always significantly greater than with placebo.

Other results of our study should be examined in detail. First, the antihypertensive effect of candesartan and that of enalapril were similar not only when 24-h average values but also when daytime and nighttime average BP values were considered. This is important because not only does 24-h BP but also daytime and nighttime BP bear a relationship with end organ damage associated with hypertension, and thus are clinically relevant.[12–14] Second, both drugs lowered BP throughout the 24 h, and although an attenuation of the antihypertensive effect of both drugs was observed in the hours farthest from last drug intake, a BP reduction at trough was still evident and was similar for the two drugs. Thus, both candesartan and enalapril are capable of covering the between-dose interval with therapeutic efficacy.

The study has two limitations. The first is that only low and intermediate doses of the two compounds have been tested, and the high doses, such as 16 mg candesartan cilexetil and 40 mg enalapril, have not been compared, although these higher doses are sometimes used in practice. The second limitation is that enalapril is not the longest lasting ACE-inhibitor. However, our data show that 10–20 mg enalapril effectively lower BP for 24 h to the same extent as 4–8 mg candesartan cilexetil.

An important positive result of the present study concerns the safety analysis. The number of adverse events observed during treatment with candesartan was similar to that observed with placebo and was less than that observed with enalapril. Only three patients were withdrawn from the study because of adverse events: all of these patients were treated with enalapril, and two reported adverse events typical of ACE inhibitors (macular-papular rash, dry cough, throat sore, and dizziness). Thus, this study confirms what has been shown in previous studies,[5–8] ie, that candesartan is a better tolerated antihypertensive drug than ACE inhibitors.

A limitation of this study was that the number of patients included in the analysis of ambulatory BP was half of that included in the analysis of clinic BP. However, the balance of randomization was maintained in the smaller group of subjects with valid 24-h recordings, and the results of analysis of ambulatory BP recordings con-

Table 2. Type and number of adverse events reported by at least one patient during the treatment phase (n = 205)

	Placebo (n = 44)	Candesartan (n = 80)	Enalapril (n = 81)
Dizziness	—	—	2
Dry cough	—	—	3
Headache	2	2	5
Epigastralgia	1	1	2
Flu	1	1	1
Others	3	5	6
Total	7 (16%)	9 (11%)	19 (24%)

firmed and extended what were observed with clinic BP. Furthermore, 24-h BP measurements are more reproducible than clinic BP[15,16] and, as also seen in this study, they are devoid of any substantial placebo effect.[17] Thus, when the antihypertensive effect of a drug needs to be tested on ambulatory BP, fewer patients are required as compared with conventional BP.

In conclusion, our results provide evidence that in essential hypertensives, the new angiotensin II antagonist candesartan, at a dose of 4 to 8 mg (ie, at a dose lower than the maintenance dose currently recommended [16 mg]) is an effective and well tolerated drug. Its antihypertensive effect is sustained and balanced over 24 h and does not substantially differ from that of enalapril administered at a dose of 10 to 20 mg.

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Appendix: List of Participants in the Study

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