A Multicenter, Randomized, Double-Blind Comparison of the Efficacy and Safety of Irbesartan and Enalapril in Adults with Mild to Moderate Essential Hypertension, as Assessed by Ambulatory Blood Pressure Monitoring: The MAPAVEL Study

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ABSTRACT

Background: When blood pressure (BP)–lowering efficacy is assessed by measurements taken in a clinic setting, angiotensin II–receptor antagonists show similar efficacy to angiotensin-converting enzyme inhibitors and better tolerability. A search of MEDLINE to date, however, reveals no randomized, double-blind studies using ambulatory BP monitoring (ABPM) to compare the BP-lowering efficacy of irbesartan and enalapril in a large number of patients (>200) with essential hypertension.

Objective: This study compared 24-hour BP reduction and BP control, as assessed by ABPM, in patients with mild to moderate essential hypertension treated with irbesartan or enalapril. The relative tolerability of the 2 treatments was also evaluated.

Methods: This was a multicenter, randomized, double-blind study in patients with mild to moderate essential hypertension (office diastolic BP [DBP] 90–109 mm Hg or systolic BP [SBP] 140–179 mm Hg). After a 3-week, single-blind placebo washout phase, patients with a mean daytime DBP ≥85 mm Hg, as measured by ABPM between 10 AM and 8 PM, were randomized to 12 weeks of active treatment with irbesartan or enalapril. Starting doses were 150 and 10 mg/d, respectively, with titration to 300 or 20 mg/d if clinic DBP was ≥90 mm Hg at week 4 or 8. Based on clinic measurements, BP control was defined

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as a BP reading <140/90 mm Hg after 12 weeks of treatment; patients achieving a reduction in DBP of ≥10 mm Hg at 12 weeks were considered responders. The ABPM criterion for BP control, independent of clinic values, was achievement of a daytime BP <130/85 mm Hg after 12 weeks of treatment; patients achieving a reduction in 24-hour DBP ≥5 mm Hg at 12 weeks were considered responders, independent of clinic values.

Results: A total of 238 patients were randomized to treatment, 115 to irbesartan and 123 to enalapril. The study population was ~52.0% female and 48.0% male, with a mean (±SD) age of 52.7 ± 10.6 years. The study was completed by 111 patients in the irbesartan group (dose titrated to 300 mg/d in 72.0% of patients) and 115 patients in the enalapril group (dose titrated to 20 mg/d in 76.5% of patients). BP reductions were similar in the 2 groups, both as measured in the clinic (DBP, 12.7 ± 8.8 mm Hg irbesartan vs 12.4 ± 7.4 mm Hg enalapril; SBP, 19.0 ± 14.1 mm Hg vs 17.5 ± 14.0 mm Hg) and by 24-hour ABPM (DBP, 9.4 ± 8.5 mm Hg vs 8.8 ± 8.5 mm Hg; SBP, 14.7 ± 14.7 mm Hg vs 12.6 ± 13.1 mm Hg). As assessed by ABPM, rates of BP control were 40.5% (45/111) for irbesartan and 33.9% (39/115) for enalapril, and the response rates were a respective 71.2% (79/111) and 71.3% (82/115). The overall incidence of adverse events (40.0% irbesartan, 51.2% enalapril) was not statistically different between groups, although the incidence of adverse events considered probably related to antihypertensive treatment was significantly higher with enalapril than with irbesartan (24.6% vs 9.2%, respectively; $P = 0.026$), essentially because of the higher incidence of cough (8.1% vs 0.9%).

Conclusions: As assessed by ABPM, irbesartan 150 to 300 mg/d was as effective in lowering BP and achieving BP control as enalapril 10 to 20 mg/d. Based on the number of treatment-related adverse events, irbesartan was better tolerated than enalapril.

Key words: irbesartan, enalapril, hypertension, ambulatory blood pressure monitoring. (*Clin Ther.* 2002;24:126–138)

INTRODUCTION

Blockade of the renin-angiotensin system through angiotensin-converting enzyme (ACE) inhibition has been widely used in the treatment of hypertension and associated conditions for the past 20 years.[1–7] However, angiotensin II (AT II) is also produced through non–ACE-dependent pathways, and treatment with ACE inhibitors does not completely prevent its production.[8] In addition, these drugs tend to increase circulating levels of bradykinins,[9] which may be related to the increased incidence of cough in patients treated with ACE inhibitors.[10]

AT II–receptor antagonists were introduced in 1994 for the treatment of hypertension. Their mechanism of blocking the renin-angiotensin system—selective blockade of AT II subtype 1 (AT_1) receptors—differs from that of ACE inhibitors.[11–13] Based on clinic BP measurements, AT II–receptor antagonist monotherapy has shown similar antihypertensive efficacy (defined as blood pressure [BP] reduction plus BP control) to that of ACE-inhibitor monotherapy[14–16]; however, their high selectivity for the AT_1 receptor confers better tolerability on AT II–receptor antagonists compared with ACE inhibitors.

When assessed by clinic BP measurements, the AT II–receptor antagonist irbe-

sartan has demonstrated similar efficacy to ACE inhibitors in the treatment of essential hypertension, while achieving better tolerability.[14–16] Based on a search of MEDLINE from 1995 to the present, it appears that no randomized, double-blind studies enrolling >200 patients have been conducted in which the efficacy of irbesartan and enalapril was assessed by 24-hour ambulatory BP monitoring (ABPM).

Several groups have reported that unlike clinic BP measurements, 24-hour mean BP obtained by ABPM involves no placebo effect,[17–19] allowing more accurate assessment of the magnitude of BP reduction with a simpler study design. In addition, mean BP values tend to be more reproducible from day to day, with smaller SDs than are obtained with clinic BP measurement. For these reasons, assessment of efficacy by ABPM allows a substantial reduction in the number of patients required to compare the efficacy of antihypertensive drugs and still maintain the necessary statistical power.[20]

Another advantage of using ABPM is that it makes it possible to exclude those patients who are subject to the white-coat effect.[21] In these patients, differences between BP obtained in the clinic and by ABPM persist over several weeks of antihypertensive treatment, although clinic BP measurements decline progressively with repeated visits[22]; this leads to overestimation of the effectiveness of antihypertensive treatment when assessed based solely on clinic BP. If more patients with the white-coat effect were randomized to one treatment group than another, this phenomenon could confound comparisons between drugs. Moreover, ABPM provides information on the effect of antihypertensive drugs on the 24-hour BP profile[23] and on the duration of antihypertensive effect.[24]

The objective of the MAPAVEL (Monitorización Ambulatoria Presión Arterial APROVEL) study was to use ABPM to compare the antihypertensive efficacy of irbesartan and enalapril monotherapy over a 24-hour period in patients with mild to moderate essential hypertension. The primary outcome measure was reduction in 24-hour diastolic BP (DBP) after 12 weeks. The relative tolerability of the 2 treatments was also evaluated.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Eligible patients were identified from the outpatient hypertension clinics of 17 centers in Spain. All patients had mild to moderate essential hypertension (clinic DBP 90–109 mm Hg on ≥3 occasions, systolic BP [SBP] 140–179 mm Hg) or uncontrolled hypertension (BP ≥140/90 mm Hg) despite monotherapy with antihypertensive drugs other than ACE inhibitors or AT II–receptor antagonists. Essential hypertension was diagnosed when complete clinical, biochemical, and radiologic assessment suggested no other cause for BP elevation.

Exclusions were renal impairment (serum creatinine level >1.5 mg/dL [132 μmol/L]), papilledema, or evidence of coronary heart disease or cardiac failure during the previous 3 months. Patients with any severe concomitant disease were also excluded, as were women who were pregnant or of childbearing potential. No other antihypertensive agents or any other drugs with effects on the cardiovascular system could be taken concurrently with the study treatments.

All patients gave their written informed consent. The study was approved

by the ethics committees of the 17 participating centers and by the Spanish Health Authority.

Study Design

This was a multicenter, randomized, double-blind, comparative trial. In an initial 3-week, single-blind placebo phase, patients underwent washout of previous antihypertensive drug therapy, with 24-hour ABPM conducted during the third week. To avoid the effect of white-coat hypertension, patients with a mean daytime DBP <85 mm Hg, as measured by ABPM between 10 AM and 8 PM, were excluded. The remaining patients were randomized to receive treatment with irbesartan or enalapril in the 12-week, double-blind phase. Starting doses were 150 and 10 mg/d, respectively, provided in identical capsules. If office DBP was ≥90 mm Hg after 4 or 8 weeks of treatment, the dose was titrated to irbesartan 300 mg/d or enalapril 20 mg/d, as appropriate.

There were 5 clinic visits: 1 at the start of the placebo washout period, 1 at the start of active treatment, and 1 each at weeks 4, 8, and 12 (24 hours after the last dose of study medication). Patients were instructed to take their medication between 8 and 9 AM and were seen by the study assistants at approximately the same time in the morning on each visit. Compliance was defined as having taken between 80% and 110% (the blister pack contained 7 extra pills) of the assigned medication and was assessed by pill counts at each visit.

A clinic BP reading was obtained at each visit. The second, and final, 24-hour ABPM was conducted during the last week of treatment. Laboratory tests (red blood cell count, hematocrit, hemoglobin, platelet count, leukocyte count, and such serum variables as glucose, creatinine, uric acid, total cholesterol, low- and high-density lipoprotein cholesterol, triglycerides, sodium, and potassium) were performed and a 12-lead electrocardiogram was obtained at the end of the placebo period and the end of the treatment phase.

Clinic BP Measurement

At each center, clinic BP measurements were obtained by the same study assistant using the same mercury sphygmomanometer and a standard adult cuff (unless a larger cuff was required). After the patient had rested for 10 minutes in a seated position, the nondominant arm was supported on a cushion and the cuff placed on the arm at heart level. Three successive readings were obtained at 3-minute intervals. DBP was recorded at disappearance of the Korotkoff sounds (phase V). The mean of the 3 values was recorded.

Patients whose clinic BP was <140/90 mm Hg after 12 weeks of treatment were considered to have achieved BP control. Patients achieving a DBP reduction of ≥10 mm Hg at 12 weeks were considered responders.

24-Hour ABPM

ABPM was performed using a noninvasive, automated oscillometric device (Spacelabs 90207, Spacelabs Inc, Redmond, Wash). The appropriate cuff was placed on the nondominant arm, and BP was recorded automatically at 20-minute intervals throughout a 24-hour period while patients performed their usual work and home activities. Short windows were used to define the daytime period (from 10 AM to 8 PM) and the nighttime period

(from 12 midnight to 6 AM) to avoid those periods in which some patients are awake but not others. Mean (±SD) deviations in SBP, DBP, and pulse pressure were recorded for the entire 24-hour period and for the daytime and nighttime periods.

The ABPM criterion for BP control was a daytime BP <130/85 mm Hg after 12 weeks of treatment, independent of clinic BP values. Patients exhibiting a reduction in 24-hour DBP ≥5 mm Hg at 12 weeks were defined as responders, independent of clinic BP values.

Statistical Analysis

The sample size was calculated to detect a 4–mm Hg between-group difference in mean 24-hour DBP reduction with 90% statistical power at a significance level of $P < 0.05$. Assuming a 20% prevalence of white-coat effect and a 10% dropout rate, it was determined that 230 patients were needed at the beginning of the double-blind phase to ensure completion by at least 208 patients.

Data obtained from ABPM recordings were processed and analyzed using SPSS for Windows, version 9.0 (SPSS Inc, Chicago, Ill). Baseline homogeneity between groups was assessed by 1-way analysis of variance and the Pearson chi-square test.[25] The efficacy assessment employed analysis of covariance to compare BP changes from baseline between treatment groups. All values were expressed as mean ± SD.

RESULTS

The study enrolled 295 patients with essential hypertension, 238 of whom were randomized to double-blind treatment. Of these, 226 completed the study (111 irbesartan, 115 enalapril). Twelve patients discontinued treatment during the double-blind phase (4 irbesartan, 8 enalapril), 5 due to adverse events (2 and 3, respectively), 4 lost to follow-up (1 and 3), and 3 (1 and 2) due to lack of efficacy (BP ≥180/110 mm Hg despite full-dose treatment). Dose titration to 300 mg/d took place in 80 patients (72.0%) in the irbesartan group and to 20 mg/d in 88 patients (76.5%) in the enalapril group.

Of the patients randomized to treatment, all were white, ~48.0% were male and 52.0% female, and their age ranged from 22 to 73 years (mean [±SD], 52.7 ± 10.6 years). There were no significant differences between groups with respect to age, sex, body mass index, biochemical parameters, or office BP values. Basal mean 24-hour DBP values obtained by ABPM were also similar between groups, with the exception of 24-hour SBP, which was significantly higher in patients randomized to irbesartan (mean of 4 mm Hg; $P = 0.003$) (Table I).

Table II lists baseline and final BP values obtained by ABPM for the entire 24-hour period, the daytime period, and the nighttime period. At the end of treatment, mean (±SD) reductions in both 24-hour DBP (irbesartan, 9.4 ± 8.5 mm Hg; enalapril, 8.8 ± 8.5 mm Hg) and 24-hour SBP (14.7 ± 14.7 mm Hg and 12.6 ± 13.1 mm Hg) were similar between groups (Figure 1). Although the 24-hour reduction in pulse pressure was greater in the irbesartan group than in the enalapril group (5.8 ± 10.6 mm Hg and 3.8 ± 9.0 mm Hg, respectively), the difference was not statistically significant between groups. Reductions in SBP, DBP, and pulse pressure during the daytime and nighttime periods were also similar between groups. There were no significant differences in reductions in clinic DBP (12.7 ± 8.8 mm Hg

Table I. Baseline characteristics and blood pressure (BP) measurements obtained in the clinic and by 24-hour ambulatory BP monitoring (ABPM) in patients randomized to irbesartan 150 mg/d or enalapril 10 mg/d. Values are expressed as mean ± SD, unless specified otherwise.

	Irbesartan (n = 115)	Enalapril (n = 123)
Age, y	52.7 ± 10.0	50.9 ± 11.6
Sex, no. (%*)		
Male	52 (45.2)	61 (49.6)
Female	63 (54.8)	62 (50.4)
Body mass index, kg/m^2	29.3 ± 4.0	28.8 ± 4.3
Years with hypertension	6.0 ± 5.9	5.5 ± 5.5
Clinic BP, mm Hg		
SBP	160.3 ± 14.1	158.2 ± 13.8
DBP	101.6 ± 4.7	102.0 ± 5.2
PP	58.7 ± 12.2	56.2 ± 11.4
24-Hour ABPM, mm Hg		
SBP	144.2 ± 11.5†	140.1 ± 11.9
DBP	89.9 ± 6.3	89.6 ± 7.9
PP	54.3 ± 10.9	50.5 ± 11.2

SBP = systolic BP; DBP = diastolic BP; PP = pulse pressure.
*Percentages may exceed 100 due to rounding error.
†P = 0.003 versus enalapril.

and 12.4 ± 7.4 mm Hg) or SBP (19.0 ± 14.1 mm Hg and 17.5 ± 14.0 mm Hg). As illustrated in Figure 2, the unsmoothed curves of mean hourly SBP and DBP over 24-hour monitoring periods at the end of the placebo phase and the end of 12 weeks of treatment with irbesartan or enalapril indicate preservation of the circadian SBP and DBP profiles with both drugs.

With respect to BP control as assessed by clinic measurements, 36.0% (40/111) of patients treated with irbesartan and 34.8% (40/115) of those treated with enalapril achieved strict BP control (BP <140/90 mm Hg) at the end of treatment. The respective response rates based on the clinic criterion (DBP reduction of ≥10 mm Hg) were 64.0% (71/111) and 67.8% (78/115). When ABPM criteria were applied, 40.5% (45/111) of patients treated with irbesartan and 33.9% (39/115) of those treated with enalapril achieved strict BP control (daytime BP <130/85 mm Hg), with no significant difference between groups. The corresponding response rates (24-hour DBP reduction of ≥5 mm Hg) were 71.2% (79/111) and 71.3% (82/115).

Compliance with treatment was similar in the 2 treatment groups. Mean compliance for all visits was 98.3% in patients treated with irbesartan and 98.4% in those treated with enalapril.

There was no significant difference in the overall incidence of adverse events between groups (40.0% irbesartan, 51.2% enalapril) (Table III). Adverse events considered probably related to treatment by the study investigators were mild and oc-

Table II. Changes in blood pressure (BP) from baseline after 12 weeks of treatment with irbesartan 150 to 300 mg/d or enalapril 10 to 20 mg/d, as recorded by 24-hour ambulatory BP monitoring.* Values are expressed as mean ± SD.

	Irbesartan		Enalapril	
	Baseline (n = 115)	12 Weeks (n = 111)	Baseline (n = 123)	12 Weeks (n = 115)
Entire 24-hour period, mm Hg				
SBP	144.2 ± 11.5†	128.8 ± 13.8	140.1 ± 11.9	127.2 ± 11.1
DBP	89.9 ± 6.2	79.9 ± 8.8	89.8 ± 7.7	80.5 ± 8.1
PP	54.2 ± 9.9	48.9 ± 9.8	50.4 ± 8.9	46.8 ± 8.3
Daytime, mm Hg				
SBP	150.0 ± 12.4	132.9 ± 15.3	145.6 ± 12.2	130.9 ± 11.4
DBP	94.8 ± 6.7	83.6 ± 9.8	94.9 ± 8.1	83.9 ± 8.6
PP	55.2 ± 10.6	49.3 ± 9.8	50.8 ± 9.1	47.0 ± 7.6
Nighttime, mm Hg				
SBP	131.4 ± 14.0	117.3 ± 13.3	126.8 ± 13.8	116.5 ± 12.8
DBP	79.7 ± 8.9	70.1 ± 8.6	78.6 ± 9.4	71.0 ± 9.4
PP	51.7 ± 10.4	47.2 ± 8.7	48.2 ± 8.9	45.5 ± 8.1

SBP = systolic BP; DBP = diastolic BP; PP = pulse pressure.
*BP data were collected for the entire 24-hour period, the daytime period (from 10 AM to 8 PM), and the nighttime period (from 12 midnight to 6 AM).
†$P = 0.003$ versus enalapril baseline.

curred significantly less frequently in patients treated with irbesartan than with enalapril (9.2% vs 24.6%, respectively; $P = 0.026$). The risk of experiencing an adverse event probably related to treatment was 2.6 times higher in patients receiving enalapril than in patients receiving irbesartan (OR = 2.6; 95% CI, 1.1–6.1).

Irbesartan given once daily was better tolerated than enalapril given once daily, and no severe side effects were reported with either treatment. Discontinuations due to adverse events occurred in 2 of 115 patients (1.7%) in the irbesartan group (gastric disturbance, nausea and vomiting) and 3 of 123 patients (2.4%) in the enalapril group (1 with skin rash, 2 with persistent cough). Cough was reported as an adverse effect in 10 patients (8.1%) treated with enalapril and 1 patient (0.9%) treated with irbesartan. Neither irbesartan nor enalapril induced changes in the laboratory parameters studied.

DISCUSSION

Based on a search of MEDLINE, this study was the first to compare monotherapy with irbesartan and enalapril in the treatment of >200 patients with mild to moderate essential hypertension using 24-hour ABPM data. Both drugs lowered BP during the entire 24-hour period while preserving the circadian profile. The mean 24-hour BP reduction achieved with irbesartan 150 to 300 mg/d was ~9 mm Hg

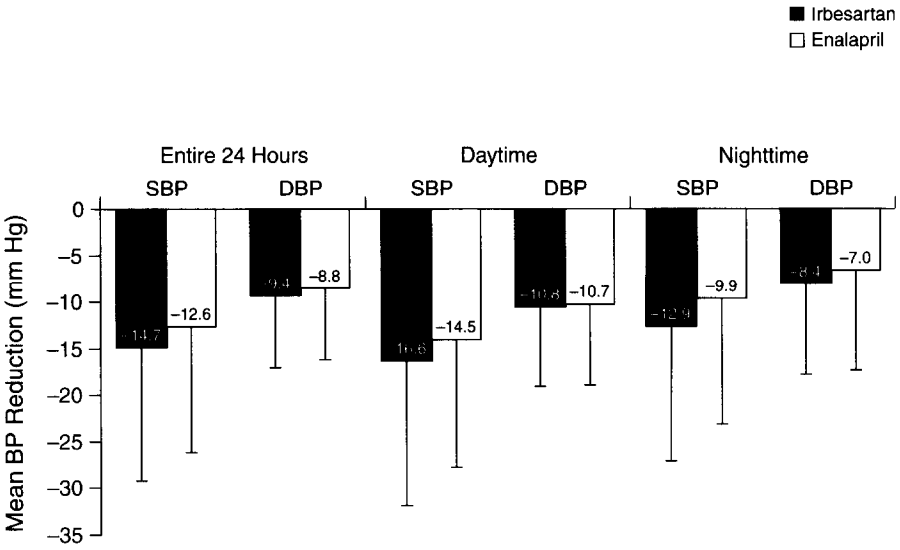

Figure 1. Mean reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) values obtained by 24-hour ambulatory BP monitoring after 12 weeks of treatment with irbesartan 150 to 300 mg/d or enalapril 10 to 20 mg/d. Data are presented for the entire 24-hour period of monitoring and for the daytime (from 10 AM to 8 PM) and nighttime (from 12 midnight to 6 AM) periods.

for DBP and ~14 mm Hg for SBP, reductions similar to those obtained with enalapril. The magnitude of BP reduction was similar to that observed in smaller studies in which efficacy was assessed by ABPM.[15] In addition, because there is no placebo effect when 24-hour ABPM is used to compare the efficacy of antihypertensive drugs over the short term (<12 weeks),[17] the absolute magnitude of reductions in mean SBP and DBP in the present study was comparable to that seen in large (>200 patients), placebo-controlled studies in which irbesartan-induced BP changes were assessed by clinic measurements adjusted for the placebo effect.[16,26,27]

Clinic DBP was reduced by >10 mm Hg in >60% of patients treated for 12 weeks with irbesartan or enalapril, although BP was normalized (clinic BP <140/90 mm Hg) in an average of only 35%. These results are also consistent with findings from the aforementioned studies.[16,26,27] The response rates and incidence of BP control were slightly higher when ABPM criteria were used rather than clinic BP. Strict BP control is of great importance in reducing morbidity and mortality in patients with hypertension, particularly in high-risk patients such as those with diabetes mellitus or associated cardiovascular clinical conditions (BP target, ≤130/85 mm Hg).[28,29] However, no antihypertensive monotherapy is able to produce BP reductions of 10 to 20 mm Hg in >50% of patients, making it difficult to achieve strict BP control

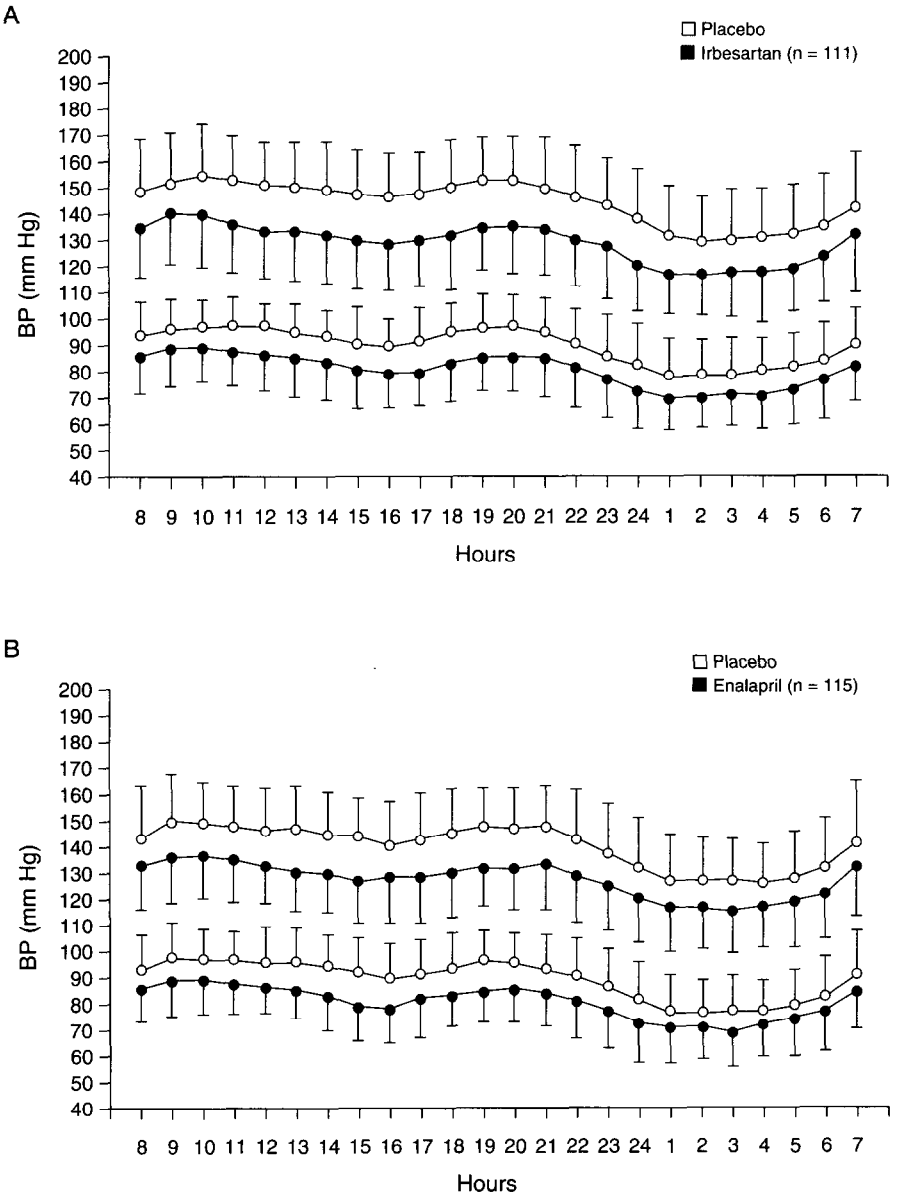

Figure 2. Unsmoothed curves of mean hourly systolic (top 2 curves) and diastolic (lower 2 curves) blood pressure (BP) values over two 24-hour periods of ambulatory BP monitoring conducted at the end of the 3-week placebo phase and the end of the study in patients who completed 12 weeks of treatment with (A) irbesartan 150 to 300 mg/d, or (B) enalapril 10 to 20 mg/d. For ease of viewing, SDs are shown in 1 direction only.

Table III. Adverse events (AEs) in patients treated with irbesartan 150 to 300 mg/d or enalapril 10 to 20 mg/d.

	No. of Patients (%)	
	Irbesartan (n = 115)	Enalapril (n = 123)
Any AE	46 (40.0)	63 (51.2)
Discontinuations due to an AE	2 (1.7)	3 (2.4)
Most common AEs*		
Nervous system	22 (19.1)	33 (26.8)
General (fatigue, back pain, fever)	16 (13.9)	10 (8.1)
Gastrointestinal system	12 (10.4)	8 (6.5)
Headache	11 (9.6)	18 (14.6)
Dizziness	9 (7.8)	17 (13.8)
Cardiovascular system	8 (7.0)	9 (7.3)
Palpitations	7 (6.1)	8 (6.5)
Upper respiratory tract	4 (3.5)	18 (14.6)
Cough	1 (0.9)	10 (8.1)
Skin disorders	–	5 (4.1)

*Occurring with an incidence of >5% in either group.

with a single drug in patients having an SBP >160 mm Hg.[30–32] Both irbesartan and enalapril may be combined with drugs in any other antihypertensive class, particularly diuretics, to increase efficacy. Current evidence suggests that most hypertensive patients will require combination therapy.[28–32]

The incidence of overall adverse events was similar in both treatment groups in the present study, and the rate of discontinuations due to adverse events was low (~2% in each group). No severe side effects were reported. However, the incidence of adverse events considered probably related to antihypertensive treatment was significantly higher among patients treated with enalapril ($P = 0.026$), essentially because of the higher incidence of cough in these patients. Although this study was not designed to compare the incidence of cough with irbesartan and enalapril, the results support other evidence that the incidence of cough with AT II–receptor antagonists is similar to that with placebo.[16,33,34] ACE-inhibitor therapy, on the other hand, is known to be associated with an increased incidence of cough.[9,10,35,36] Use of antihypertensive drugs that have a tolerability profile similar to that of placebo, even at the highest doses, may aid compliance with treatment.

CONCLUSIONS

When BP was assessed by 24-hour ABPM, irbesartan 150 to 300 mg/d and enalapril 10 to 20 mg/d achieved similar BP reductions and BP control in adult patients with mild to moderate essential hypertension. Irbesartan, however, was significantly better tolerated than enalapril.

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