Evaluation of the 24-Hour Blood Pressure Effects of Eprosartan in Patients With Systemic Hypertension

William B. White, Yusra Anis Anwar, George A. Mansoor, and Domenic A. Sica

**Background:** Eprosartan is a new nonphenyl angiotensin II receptor blocker, which has been approved for the treatment of hypertension. Although the drug has a relatively short plasma half-life of 5 to 9 h, clinical studies have suggested that its antihypertensive effect persists for 24 h.

**Methods:** We assessed both the changes in 24-h and trough blood pressure (BP) (last 4 h of the ambulatory BP while the patient was awake) of eprosartan at doses of 600 and 1200 mg daily in a randomized, double-blind, placebo-controlled trial. Ambulatory BP was monitored at placebo baseline and after 8 weeks of double-blind therapy.

**Results:** Two hundred patients randomized in the study with 177 patients completing the trial. The 24-h change in BP from baseline was $0.2/0.1 \text{ mm Hg}$, $-7.9/-5.4 \text{ mm Hg}$ ($P < .0001$), and $-7.4/-5.0 \text{ mm Hg}$ ($P < .0001$) in the placebo, 600-mg eprosartan, and 1200-mg eprosartan groups, respectively. Changes in trough ambulatory BP showed significant reductions of $-6.3/-4.1 \pm 1.6/1.1 \text{ mm Hg}$ and $-7.7/-5.5 \pm 1.5/1.0 \text{ mm Hg}$ for 600 mg of eprosartan and 1200 mg of eprosartan, respectively.

**Conclusions:** These data demonstrate that eprosartan at doses of 600 or 1200 mg significantly reduced BP throughout an entire 24-h dosing period. There were no differences between the 600- and 1200-mg dose; thus, 600 mg once daily should be the only dose used in the treatment of hypertension with eprosartan. Am J Hypertens 2001;14:1248–1255 © 2001 American Journal of Hypertension, Ltd.

**Key Words:** Eprosartan, 24-h ambulatory blood pressure monitoring, trough–peak ratios, pharmacodynamics.

During the past decade, ambulatory blood pressure (BP) measurements have been consistently used in the evaluation of new classes of antihypertensive drugs. Such has been the case with a number of the older therapeutic drug classes, such as the angiotensin-converting enzyme inhibitors or the calcium channel blockers. More recently, this technology has been applied to the study of the BP-lowering effects of the angiotensin II receptor blockers (ARB).

Eprosartan is a nonphenyl, nontetrazole angiotensin receptor blocker highly specific for the AT₁ receptor. After oral ingestion of eprosartan, peak plasma concentrations are reached within 2 h and the plasma half-life is 5 to 9 h. Eprosartan is not significantly metabolized and approximately 70% of its systemic clearance being hepatic, and the remainder of its systemic clearance is renal in origin. Eprosartan reduces BP by selectively blocking the AT₁ receptor as well as by blockade of the presynaptic AT₁ receptors with a resultant diminution in sympathetic nerve activity. The purpose of this study was to formally evaluate the efficacy of eprosartan administered once daily using both clinic and the more sensitive modality of 24-h ambulatory BP monitoring.

**Methods Study Design**

This was a double-blind, placebo-controlled, prospective study conducted at 20 clinical centers in the United States (see Appendix). To be eligible for inclusion in the study,
patients were required to be ≥18 years of age and have essential hypertension. Patients were excluded from the study if they had secondary forms of hypertension, a history of malignant hypertension, sitting systolic BP >200 mm Hg or diastolic BP ≥115 mm Hg or advanced hypertensive retinopathy. Women who were pregnant or lactating were excluded, as were women of child-bearing potential, unless they were using an effective form of contraception.

The baseline clinic BP was established during the 2- to 4-week placebo run-in (single blind) period. To be randomized, the seated diastolic BP had to be ≥95 mm Hg and ≤114 mm Hg on two consecutive visits with no more than an 8-mm Hg difference in diastolic BP between the two visits. An ambulatory BP monitoring study was performed at the end of the placebo run-in period to determine eligibility for randomization to the double-blind treatment period. Patients were required to have an awake diastolic BP of ≥85 mm Hg with at least 35% of the readings ≥90 mm Hg during the daytime period (between 08:00 and 18:00) to progress into the double-blind treatment period.

The design of the trial is shown in Fig. 1. Patients were randomized to a single morning dose of eprosartan at 600 or 1200 mg or placebo for a total of 8 weeks. The patients were evaluated in the clinic at weeks 2, 4, and 8 during the double-blind treatment period. An ambulatory BP monitoring study was performed at the end of the 8-week treatment period to evaluate drug efficacy. If the ambulatory BP study at the end of the double-blind treatment was technically inadequate, it was repeated within 1 week. After completion of study-related procedures, a final follow-up visit was scheduled 1 week later, at a time when the patient was off all study medications.

**BP Measurements**

**Clinic BP**  Clinic BP was measured after the patient was seated quietly for 5 min. Three consecutive readings were taken (at 2-min intervals) with the arm supported at heart level. Trough BP (performed 22 to 26 h after dosing) was determined at baseline and after 4 and 8 weeks of eprosartan or placebo therapy.

**Ambulatory BP Measurements** Stringent requirements were set for ambulatory BP quality control as the results determined eligibility for randomization and the determination of trough pressures by ambulatory BP monitor was a key secondary efficacy end point for the study. To ensure consistent quality data, a minimum of 80% of the programmed readings had to be acceptable during the 24-h recording period, with no more than 2 h of consecutive missing data. During the trough period (last 4 h of monitoring), at least two valid readings every hour were required, with a minimum of 10 valid readings. It was also mandatory that the patient be awake and out of bed during the last 4-h period of the 24-h study to avoid a confounding reduction in BP associated with sleep. Alarm clocks were provided to each study patient and at monitoring hook-up each patient was reminded of the need to be awake and active during the final 4 h of the monitoring period.

---

**FIG. 1.** Diagram of the study design. ABPM = ambulatory blood pressure monitoring.
Table 1. Characteristics of patient population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 55)</th>
<th>Eprosartan 600 mg (n = 59)</th>
<th>Eprosartan 1200 mg (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54 ± 9</td>
<td>54 ± 9</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87 ± 18</td>
<td>91 ± 19</td>
<td>87 ± 18</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 9</td>
<td>173 ± 9</td>
<td>171 ± 10</td>
</tr>
<tr>
<td>M/F</td>
<td>39/16</td>
<td>40/19</td>
<td>42/21</td>
</tr>
<tr>
<td>White</td>
<td>36</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>African American</td>
<td>13</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Clinic SBP (mm Hg)</td>
<td>152 ± 20</td>
<td>152 ± 12</td>
<td>154 ± 13</td>
</tr>
<tr>
<td>Clinic DBP (mm Hg)</td>
<td>100 ± 10</td>
<td>100 ± 9</td>
<td>101 ± 9</td>
</tr>
<tr>
<td>24-h ABPM SBP (mm Hg)</td>
<td>148 ± 5</td>
<td>150 ± 4</td>
<td>151 ± 4</td>
</tr>
<tr>
<td>24-h ABPM DBP (mm Hg)</td>
<td>93 ± 7</td>
<td>93 ± 6</td>
<td>95 ± 6</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; ABPM = ambulatory blood pressure monitoring.
Values shown are mean ± standard deviation.

Data Analyses

The primary efficacy end point was the mean change from baseline in 24-h diastolic BP on either 600 or 1200 mg of eprosartan versus placebo. Analyses of covariance (ANCOVA) were performed to assess the effects of active drug treatment versus placebo; covariates taken into consideration in the analyses included age, baseline BP, dose, center, and treatment-by-center interaction.

A sample size of 56 patients per treatment arm was determined to be necessary for at least 90% power to detect a 4-mm Hg difference in mean change from baseline in 24-h diastolic BP. This power calculation assumed a standard deviation of 6.0 mm Hg and used .05 level of significance with two-sided testing with Bonferroni adjustment for each active group compared to placebo.

The secondary efficacy end points were to assess the effects of once daily eprosartan on trough clinic and ambulatory BP. Clinic trough pressures were defined as the predosing BP at the week 4 visit of the double-blind period and ambulatory trough pressures were calculated from the mean of the last 4 h of the dosing period at double-blind treatment week 8.

Results

A total of 200 patients were randomized to receive placebo (n = 67), 600 mg of eprosartan once daily (n = 62), or 1200 mg of eprosartan once daily (n = 71). One hundred seventy-seven patients completed the study: 55 patients in the placebo group, 59 patients in the 600-mg eprosartan treatment group, and 63 patients in the 1200-mg eprosartan treatment group. A total of 21 patients (19.4% placebo and 11.8% eprosartan) terminated the study prematurely. Reasons for premature discontinuation included adverse events (placebo, 4.5%; 600 mg of eprosartan, 3.2%; 1200 mg of eprosartan, 2.8%) or lack of efficacy with BP falling out of the pre prescribed limits (placebo, 7.5%; 600- and 1200-mg eprosartan groups, 0 and 1.4%, respectively). Other reasons for premature termination included non-compliance or protocol violations. The demographic and hemodynamic characteristics of the group discontinuing the study and those who remained in the study were similar.

The characteristics of the evaluable patient population are shown in Table 1. The demographic characteristics were comparable in the individual treatment groups except that the 600-mg eprosartan group had fewer African American patients compared to the 1200-mg eprosartan group, although this difference was not statistically significant (Table 1).

Primary Efficacy Analyses

The mean change in 24-h diastolic BP from baseline in the placebo group was 0.1 ± 1.0 mm Hg, whereas in the 600-mg eprosartan group it was −5.4 ± 1.0 mm Hg (P < .0001) and in the 1200-mg eprosartan group, −5.0 ± 0.9 mm Hg (P < .0001) (Table 2, and Figs. 2 and 3). The reductions in 24-h diastolic BP in both eprosartan groups were significantly greater than that in the placebo group. Reductions in BP between the two active treatment groups were not significantly different from each other.

Evaluation of the mean change in 24-h systolic BP from baseline showed differences of 0.2 ± 1.4 mm Hg on placebo, whereas 600 mg of eprosartan induced a reduction of −7.4 ± 1.3 mm Hg (P < .0001) and 1200 mg of eprosartan reduced systolic BP by −7.4 ± 1.3 mm Hg from baseline (Figs. 2 and 3). The changes from baseline in 24-h systolic ambulatory BP was not statistically different for the 600-mg versus the 1200-mg doses.

Secondary Efficacy Analyses

Changes in clinic diastolic BP from baseline, as assessed by 24-h after dosing BP measurements, were −1.5 ± 1.1 mm Hg, −2.2 ± 1.2 mm Hg, and −5.4 ± 1.1 mm Hg in the placebo, 600-mg eprosartan, and 1200-mg eprosartan groups, respectively. The corresponding mean systolic BP changes were −1.1 ± 1.8 mm Hg, −5.6 ± 1.9 mm Hg,
The changes from baseline in clinic BP did not differ statistically for either diastolic or systolic BP (P = .082 and P = .065, respectively) in the placebo versus the 600-mg eprosartan treatment group. In contrast, 1200 mg of eprosartan significantly lowered both diastolic and systolic BP more than placebo (P = .009 and P = .014, respectively) compared to clinic BP. The percentage of completed patients who reached a clinic diastolic BP of ≤90 mm Hg was 18.5% in the placebo group, 21% in the 600-mg eprosartan group, and 31.4% in the 1200-mg eprosartan group.

The change in BP from baseline during the trough period (final 4 h of the dosing period) was evaluated by ambulatory BP monitoring (Fig. 4). The change in diastolic BP at trough was −0.2 ± 1.1 mm Hg, −4.1 ± 1.1 mm Hg, and −5.5 ± 1.0 mm Hg for the placebo, 600- and 1200-mg eprosartan groups, respectively. The corresponding systolic BP change at trough was −0.1 ± 1.6 mm Hg, −6.3 ± 1.6 mm Hg, and −7.7 ± 1.5 mm Hg for the placebo, 600- and 1200-mg eprosartan treatment groups, respectively. These trough ambulatory BP changes from baseline represented statistically significant reductions in each of the eprosartan treatment groups and differed from clinic BP determinations in that regard (Fig. 4).

Assessment of average awake and sleep BP changes were also determined because of the use of 24-h ambulatory BP monitors (Table 2). The BP reductions in the awake hours of the two eprosartan treatment groups were

![Fig. 2](https://example.com/fig2.png)

**FIG. 2.** Changes from baseline in the systolic (SBP) and diastolic (DBP) blood pressure on 24-h ABPM for placebo, 600 and 1200 mg of eprosartan. Other abbreviations as in Fig. 1.
FIG. 3. Top) Twenty-four-hour ambulatory blood pressure curves for systolic blood pressure for placebo, 600 and 1200 mg of eprosartan treatment groups. Bottom) Twenty-four-hour ambulatory blood pressure curves for diastolic blood pressure for placebo, 600 and 1200 mg of eprosartan treatment groups.
similar, however, there was a larger reduction noted in the 1200-mg eprosartan arm during the sleep hours.

Group Analyses

Clinic systolic and diastolic BP responses in the study were analyzed according to age (<65 or ≥65 years), gender, race, severity of hypertension at baseline (clinic diastolic change BP <95 or ≥95 mm Hg) and by use of antihypertensive agents at baseline. Changes from baseline BP across all of these groups were generally consistent with the observed BP reduction in the overall study population. The exception was the response seen in the African American patients, although this represented a small percentage (<25%) of the overall patient sample. The changes in 24-h BP in the eprosartan treatment groups were not dissimilar to the changes observed in the placebo group in the African American patients. The mean reduction from baseline in 24-h diastolic BP in this population was -1.4 ± 1.9 mm Hg, -0.3 ± 1.9 mm Hg, and -0.6 ± 1.9 mm Hg for the placebo (n = 13), 600 mg of eprosartan (n = 8), and 1200 mg of eprosartan (n = 16), respectively. Diastolic BP reductions in the African American group by ambulatory BP monitoring did not significantly differ from the response observed with placebo.

Adverse Events

Ninety-six of the 200 patients in the study reported an adverse event during the double-blind treatment period. The distribution was 52.2% in the placebo arm and 48.4% and 43.7% in the 600- and 1200-mg eprosartan treatment arms, respectively. On therapy, adverse events, which exceeded 2%, did not differ significantly between the placebo and active treatment groups. Adverse events considered by the investigator to have probable relationship to the study medication were similar in the placebo and eprosartan-treated groups. Cough was not observed as a significant side effect in any of the treatment arms.

Discussion

This double-blind, placebo-controlled study demonstrated that eprosartan at doses of either 600 or 1200 mg effectively lowered ambulatory BP when given once daily. However, the higher dose of eprosartan did not induce a greater mean 24-h BP reduction than the lower eprosartan dose. The ambulatory BP monitoring curves (Fig. 3) also confirmed that both 600- and 1200-mg doses were effective over the entire 24-h dosing period. The 1200-mg dose showed numerically larger BP reductions at trough than the 600-mg dose, but this finding was not statistically significant. Enhanced duration of effect at increasing doses of angiotensin II receptor blockers has been shown with some of the agents in this class.15–17

The effects of eprosartan on ambulatory BP is comparable with other angiotensin II receptor blockers that have intermediate plasma half-lives. For example, BP changes using a 24-h ambulatory BP monitoring were reduced by 9/7 mm Hg, on 50 mg of losartan once daily, and to a slightly greater extent when dosed twice daily (50 mg twice daily).18 Neutel and colleagues19 carried out a sim-
ilar study to assess the antihypertensive efficacy of once daily valsartan in 217 patients at four different doses versus placebo after 8 weeks of therapy using 24-h BP monitoring. The BP reductions were relatively flat with values of $-11/-6.6$ mm Hg and $-10.6/-5.5$ mm Hg for 80 mg and 160 mg, respectively. Finally, irbesartan was evaluated by Fogari et al by 215 non-black patients from Italy. Changes in ambulatory BP of $-8.3/-5.4$ mm Hg and $-10.5/-7.2$ mm Hg were seen for 75 mg of irbesartan and 150 mg of irbesartan once daily, respectively.

In an earlier study performed by White et al, eprosartan had been studied using lower doses (50 mg twice up to 200 mg twice daily) using 12-h ambulatory BP measurements as the primary efficacy end points. These data showed that eprosartan was, in fact, effective at lowering ambulatory BP at the highest dose used in this study (200 mg twice a day). Because the design of that study and the present one used different dosing schedules, the ambulatory BP data are difficult to compare directly. In the present study, group analyses showed that eprosartan was effective independent of age, gender, or severity of BP. However, African Americans did not show a significant decline in BP on eprosartan monotherapy. In contrast to our findings, in the study reported by Gradman et al, a 42% response rate was observed in African Americans compared with an 18% responder rate in the corresponding placebo group. These discrepancies between studies suggest that a larger prospective trial of this agent in African American patients with hypertension is needed.

In conclusion, the results of this trial demonstrated that eprosartan, given once daily at a dose of 600 mg will be the primary effective dose in patients with systolic hypertension and that eprosartan was well tolerated at doses of up to 1200 mg daily. Furthermore, the data described herein demonstrated the usefulness of ambulatory BP in establishing the boundaries of treatment effect. Although clinic BP determinations are more easily obtained, they may miss important treatment effects and thereby provide a deceptive view of a compound’s true pattern of pharmacodynamic response.

Appendix
Eprosartan Ambulatory BP Multicenter Investigators: David A. Calhoun, MD, University of Alabama School of Medicine, Birmingham, AL; Jennifer HM Hamilton, MD, Baltimore VA Medical Center, Baltimore, MD; Paul G. Hammond, MD, VA Medical Center, Loma Linda, CA; Gabor S. Jilly, MD, Peoria, IL; Thomas J. Littlejohn, MD, Winston-Salem, NC; Joel M. Neutel, MD, University of California, Irvine, CA; Alan L. Niederman, MD, Ft Lauderdale, FL; Robert J. Noveck, MD, New Orleans, LA; Vasilios Papademetriou, MD, Springfield, VA; Warren W. Peskow, MD, Encinitas, CA; Marc S. Randell, MD, Omaha, Nebraska; Sidney Rosenblatt, MD, Irvine, CA; Andres Patron, MD, Hollywood, FL;Stephen S. Sharp, MD, Nashville, TN; Domenic A. Sica, MD, Medical College of Virginia, Richmond, VA; Addison Taylor, MD, PhD, Baylor College of Medicine, Houston, TX; Mel J. Tonkon, MD, Anaheim, CA; Ronald G. Victor, MD, University of Texas, Southwestern Medical School, Dallas, TX; William B. White, MD, University of Connecticut School of Medicine, Farmington, CT.

References

