Effectiveness of the selective aldosterone blocker, eplerenone, in patients with resistant hypertension

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Abstract

Resistant hypertension is defined as uncontrolled hypertension despite intensive treatment with at least three antihypertensive agents, one of which ideally should be a diuretic. To determine the efficacy and safety of the selective aldosterone antagonist eplerenone in this population, we studied patients with resistant hypertension (clinic blood pressure [BP] $>140$ mm Hg systolic or $>90$ mm Hg diastolic on maximal doses of more than three antihypertensive agents, including a loop or thiazide diuretic). At baseline and after 12 weeks of eplerenone therapy (50 to 100 mg daily titrated to effect), patients underwent clinic and 24-hour BP measurements, serum potassium, plasma renin activity, and serum aldosterone measurements. Patients ($n = 52$) completing the trial averaged 62 $\pm$ 10 years of age, were overweight (mean body mass index, $32.1 \pm 5.5$ kg/m\textsuperscript{2}), and had variable renal function (glomerular filtration rate, $106 \pm 38$ mL/minute); 70% were men and 74% were non-Black. The mean number of antihypertensive agents at baseline was $3.7 \pm 0.8$ (range, three to seven drugs) to achieve a clinic BP of $150.5/84.1$ mm Hg. The mean serum aldosterone was $12.9 \pm 7.6$ ng/mL and plasma renin activity was $2.3 \pm 2.7$ ng/mL/hour. After eplerenone, the change from baseline in the clinic BP was $-17.6/-7.9$ mm Hg ($P < .0001$ for both systolic blood pressure [SBP] and diastolic blood pressure [DBP]) and in 24-hour BP was $-12.2/-6.0$ mm Hg ($P < .0001$ for both). The number of antihypertensive drugs decreased to $3.3 \pm 0.9$ (range, one to seven agents). Plasma potassium increased by $0.30 \pm 0.45$ mEq/L ($P < .001$), but there were only three instances in two patients of mild hyperkalemia (potassium $>5.5$ mEq/L, but $<6.0$ mEq/L), despite all patients being on a background therapy that included an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Reductions in clinic and ambulatory BP were related to baseline clinic and ambulatory BP values ($r^2 > 0.3$ for both SBP and DBP, $P < .0001$), weakly related to baseline serum aldosterone ($r = -0.30$; $P = .05$), and unrelated to plasma renin activity, age, gender, or race. In conclusion, eplerenone demonstrated substantial efficacy in treatment-resistant hypertension and was well-tolerated with modest changes in plasma potassium. Serum aldosterone and plasma renin activity did not predict BP responses to eplerenone in this population. J Am Soc Hypertens 2008;2(6): 462–468. © 2008 American Society of Hypertension. All rights reserved.

Keywords: Ambulatory blood pressure; antihypertensive agents; glomerular filtration rate; serum aldosterone.

Introduction

Resistant hypertension, defined as uncontrolled hypertension despite treatment with three antihypertensive agents, is a common problem in clinical medicine and results in referrals from primary care physicians to hypertension specialists on a regular basis.\textsuperscript{1,2} Recently, there have been observations that aldosterone blockade with spironolactone or amiloride is an effective strategy for reducing both systolic blood pressure (SBP) and diastolic blood pressure (DBP) when added to existing antihypertensive regimens in patients with resistant hypertension.\textsuperscript{3,4} Furthermore, the addition of aldosterone antagonists has led to reductions in the overall number of antihypertensive medications. Despite these benefits, an important limiting factor for long-term
utility of spironolactone has been its poor tolerability, especially in male patients at higher doses. The incidence of gynecomastia with concomitant sexual dysfunction in men increases to 10% to 30% with daily doses of 25 mg and higher.5,6

Eplerenone is a highly selective aldosterone blocker with minimal sex hormone receptor activity.7 Eplerenone has a high degree of selectivity for the aldosterone receptor and a low binding affinity for progesterone (<1%) and androgen receptors (0.1%).7 Consequently, eplerenone is associated with a favorable tolerability profile with rates of gynecomastia, impotence, and menstrual cycle abnormalities similar to that of placebo.8–12 Because eplerenone has been shown to be an effective and well-tolerated agent when combined with renin-angiotensin blocking agents or diuretics when inadequate blood pressure (BP) control was observed,9–11 we hypothesized that it might be effective in patients with resistant hypertension who are taking these agents. To objectively evaluate the impact of eplerenone in this group of patients, we used ambulatory BP monitoring to evaluate the patient’s response to therapy.13,14 Because ambulatory BP monitoring removes all of the observer bias seen in antihypertensive drug trials and much of the “placebo” effect that is observed based on clinic measurements,14 we performed this trial with a prospective, open-label, blinded endpoint design as previously described.15

Methods

Study Design

The study was a prospective, open-label, two-center (Alabama and Connecticut) blinded endpoint (ambulatory BP measurements) clinical trial. After a screening visit, patients entered a 10- to 14-day run-in period to determine baseline BP stability. Ambulatory BP monitoring was used to establish the presence of true resistant hypertension (eg, vs. controlled hypertension and white-coat effect phenomenon). The screening period was followed by a 12-week, open-label treatment period in which patients received eplerenone, 50 to 100 mg daily. Prior antihypertensive agents were to be continued during the entire trial unless low BP values occurred as described below. Patients received eplerenone, 50 mg once daily for weeks and had serum potassium levels obtained at both 2 and 4 weeks after initiating the drug. If BP remained uncontrolled (clinic DBP ≥90 mm Hg or SBP ≥140 mm Hg) at week 4, and serum potassium was <5.0 mEq/L, the dose of eplerenone was increased to 50 mg twice daily. If BP was <140/90 mm Hg in the clinic at the initial dose level of 50 mg once daily, the patients remained on that dose until the end of the active treatment period. Serum potassium levels were performed at 2, 4, 8, and 12 weeks of the treatment period. If patients had reductions in SBP that led to symptoms judged to be due to hypotension (severe fatigue, lightheadedness, and postural

reductions in SBP >20 mm Hg) by the site investigator, reductions in antihypertensive drug doses or removal of those drugs were performed at both regular and ad hoc visits. At the end of 12-week active treatment period, patients underwent 24-hour ambulatory BP monitoring to evaluate the efficacy of treatment compared with baseline.

Patient Population

Men and women, 21 years or older, with uncontrolled, resistant hypertension in the clinic environment (SBP >140 mm Hg and <180 mm Hg or DBP >90 mm Hg and <110 mm Hg) despite treatment with three or more antihypertensive medications, including a diuretic (non–potassium sparing) and two of the following classes of therapies: renin-angiotensin blocking agent (angiotensin-converting enzyme [ACE] inhibitor or angiotensin II blocker), calcium antagonist, or beta-adrenergic blocker were eligible for the trial. The multi-drug antihypertensive regimen must have been stable for at least 4 weeks.

Patients with a history of stroke or acute myocardial infarction during the past 3 months, history of significant ongoing cardiac disease, including unstable angina pectoris and systolic heart failure, type 2 diabetes mellitus with microalbuminuria >300 μg/mg creatinine/day, and chronic kidney disease (serum creatinine >1.8 mg/dL in women and 2.0 mg/dL in men or known renal artery stenosis) were excluded from the study. Glomerular filtration rates were calculated according to the method of Cockcroft and Gault.16 In addition, patients whose baseline serum potassium was >5.5 mEq/L or who were taking potassium supplements or potassium-sparing diuretics (trimaterene, amiloride, and spironolactone) were excluded from the study. Patients were not excluded if there was an elevated serum aldosterone level or elevated aldosterone:renin ratio; however, patients with an adrenal tumor (Conn’s syndrome) amenable to surgery did not participate in the trial. This study was approved by the Human Subjects Protection Committees at both institutions.

Measurements of Efficacy and Safety Parameters

The office BP was measured in duplicate by a calibrated mercury column sphygmomanometer in the seated position at all visits. The pulse rate was measured in conjunction with the BP measurements at each visit. Study coordinators recorded times of medication dosing and BP measurements in the case report forms.

Ambulatory BP monitoring was performed using a Suntech Oscar II recorder (Suntech Medical Instruments, Morrisville, NC) during the 24-hour period before initiation of eplerenone and the 24-hour period before the final treatment visit (after 12 weeks of therapy). This ambulatory BP device has been independently validated according to rigorous guidelines of the British Hypertension Society.17 BP and heart rate measurements were obtained every 15 minutes between 6 AM and 10 PM (daytime, awake period) and every
20 minutes between 10 PM and 6 AM (nighttime, sleep period). Patients were instructed to be awake at least 2 hours before returning for device removal.

Safety was assessed by the evaluation of adverse events and vital signs at each visit of the study, and changes from baseline to the end of the study in laboratory parameters. All reported adverse events were categorized by body system and preferred term using the Medical Dictionary for Regulatory Activities (MSSO; MedDRA version 3.3., Reston, VA). The incidence of treatment-emergent adverse events in each treatment group was tabulated by severity and by relationship to study drug (as ascertained by the site study personnel). Treatment compliance was assessed by a physical count of returned study medications at each visit.

Data Analyses

The primary endpoint for assessing efficacy was the change from baseline to the end-of-study visit in 24-hour SBP. Changes from baseline in the 24-hour DBP was a secondary endpoint in the trial. Clinic systolic and diastolic BP measured 22 to 24 hours after the morning dose of study drug and other conventional therapies or 10 to 12 hours after the evening dose of study drug and conventional therapies were calculated as secondary endpoints. Further analyses of the ambulatory BP measurements were performed for the awake and sleep periods according to patient-kept diaries. All analyses performed on the primary endpoint and all testing on secondary endpoints was performed at a two-sided α = 0.05 using a per-protocol analysis that required a baseline and end of treatment 24-hour BP measurement study. For safety, all statistical testing was performed on the intent-to-treat efficacy population that included all patients who had baseline BP measurements, received at least one dose of study drug during the treatment period, and had at least one post-baseline BP measurement.

The primary objective of the study was to determine the effects of eplerenone on ambulatory SBP when added to the complex medication regimens that were not achieving adequate BP control. In this population, based on trials with other aldosterone antagonists, the expectations for reductions in 24-hour SBP on eplerenone were large (approximately 10 mm Hg). With a predicted baseline 24-hour SBP of approximately 145 mm Hg (and assuming a common standard deviation of 10 mm Hg), there would be 82% power to show a mean change from baseline of 7 mm Hg with 55 patients participating in the trial. A dropout rate of approximately 10% was estimated during the treatment period. Thus, approximately 60 patients were to be enrolled into the treatment period.

The primary endpoints as well as all secondary continuous variables were analyzed using an analysis of covariance model involving treatment group and study site, with baseline value as a covariate. Treatment group comparisons were based on the least square means obtained via the SAS general linear model procedure (SAS version 9.1.3; SAS Institute, Cary, NC). Response rates for both clinic (proportion of patients achieving a clinic BP <140/90 mm Hg) and ambulatory (proportion of patients achieving a 24-hour BP <135/85 mm Hg) BPs were calculated. Exploratory analyses included evaluating the efficacy of eplerenone according to baseline BP, plasma renin activity, and serum aldosterone values.

Safety and Tolerability

Incidence of treatment-emergent adverse events and results of clinical laboratory tests, physical examination, and 12-lead electrocardiograms were evaluated. Events of special interest are defined as hyperkalemia (K ≥ 5.5 and 6.0 mEq/L), impotence (reduced libido, erectile dysfunction, and inability to engage in sexual intercourse), gynecomastia, menstrual abnormalities, and breast pain.

Results

Patient Enrollment and Disposition

A total of 67 patients were screened for the study, of which 52 patients met all of the inclusion criteria and were initiated on eplerenone therapy. All patients who entered the eplerenone treatment phase of the study completed the trial. The two reasons for screening failures not qualifying for continuation in the study were out-of-range clinic BP values (n = 10) or ambulatory BP values (n = 5).

Baseline Characteristics of the Study Population

The baseline characteristics of the study population are shown in the Table. The mean age of the group was 62 years, with a greater percentage of males (70%), predominantly non-Black (74%) and with baseline office BPs of 151/84 mm Hg while being treated with an average of 3.7 antihypertensive medications. The 24-hour average BP at baseline was 150/78 mm Hg. The patient population was moderately obese (body mass index [BMI], 32 kg/m²) and had normal kidney function (estimated glomerular filtration rate, 106 mL/minute). Serum aldosterone levels were elevated (>20 ng/dL) in three patients at baseline and plasma renin activity was low (<1.0 ng/mL/hour) in 22 patients. Two of the three patients with elevated serum aldosterone levels had low plasma renin activity values. Ten of the study patients (19%) had type 2 diabetes mellitus.

Changes in the Clinic Trough (24 Hours Post-dose) and Ambulatory BPs

The average final dose of eplerenone was 70 mg daily; 31 patients were treated with 50 mg once daily and 21 patients with 50 mg twice daily. The effects of eplerenone treatment on trough clinic BPs are shown in Figure 1. After eplerenone, the change from baseline in the clinic BP was −17.6/−7.9 mm Hg (P < .0001 for both systolic and
Table

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tr>
<td>Age (years)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Number of antihypertensive drugs</td>
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<td>Clinic BP (mm Hg)</td>
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<td>Systolic</td>
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<tr>
<td>Diastolic</td>
<td>84.1 ± 12.0</td>
<td>59.3 – 104.0</td>
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<tr>
<td>Ambulatory BP (mm Hg)</td>
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<tr>
<td>24-hour systolic</td>
<td>150.2 ± 14.5</td>
<td>128.0 – 198.0</td>
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<tr>
<td>24-hour diastolic</td>
<td>78.7 ± 12.5</td>
<td>54.0 – 115.0</td>
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<td>154.9 ± 14.6</td>
<td>129.0 – 207.0</td>
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<td>82.2 ± 13.2</td>
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<td>70.4 ± 12.5</td>
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<td>Laboratory values</td>
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<td>Serum creatinine (mg/dL)</td>
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<td>Glomerular filtration rate (mL/minute)</td>
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<td>Serum potassium (mEq/L)</td>
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<td>Serum aldosterone (ng/dL)</td>
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<td>Plasma renin activity (ng/mL/hour)</td>
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<tr>
<td>Serum glucose (mg/dL)</td>
<td>125.5 ± 60.2</td>
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BP, blood pressure; SD, standard deviation.

diastolic BP) and in the 24-hour mean BP was $-12.2/-6.0$ mm Hg ($P < .0001$ for both systolic and diastolic BP). Reductions in the awake and sleep BP were similar ($-13/-6$ mm Hg and $-11/-5.5$ mm Hg, respectively) consistent with a sustained pharmacodynamic effect of eplerenone.

Impact of Eplerenone on Medication Utility

The mean number of antihypertensive agents fell slightly from $3.7 \pm 0.8$ drugs/patient to $3.3 \pm 0.9$ drugs/patient.

There were a total of nine patients who had reductions in antihypertensive agents because of low clinic SBP values ($<110$ mm Hg) after the initiation of eplerenone therapy. There were three patients who had reductions in doses of ACE inhibitors or angiotensin receptor blockers (ARB) because of elevated plasma potassium after the initiation of eplerenone. There were no clinical characteristics of these nine patients, including age, antihypertensive therapy at baseline, baseline SBP, BMI, renal function, or serum aldosterone levels that predicted the more substantial responses to eplerenone.

BP Control Rates (Clinic and Ambulatory)

The effects of eplerenone on prespecified BP control rates are shown in Figure 2. The proportion of patients whose clinic SBPs was $<140$ mm Hg was 63.5% and DBPs $<90$ mm Hg were 82.7%. For the ambulatory BP values, 40.1% met the criterion of SBP control using a value of $135$ mm Hg, whereas 73% met the criterion of DBP $<85$ mm Hg. Of note, 39% of patients had a 24-hour average ambulatory BP $<135/85$ mm Hg (Figure 2).

Predictors of BP Change on Eplerenone

The baseline level of the SBP was the best predictor of reductions in both clinic and ambulatory BP after treatment with eplerenone ($r = -0.51; P < .001$ for baseline clinic SBP and $r = -0.55; P < .001$ for baseline 24-hour SBP, respectively). Change from baseline in 24-hour SBP was weakly associated with the baseline serum aldosterone ($r = -0.29; P = .049$) (Figure 3), but not for the baseline plasma renin activity ($r = 0.09; P > .10$). In contrast, there was a weak, positive relationship between plasma renin activity and change from baseline in the clinic SBP ($r = 0.36; P = .02$).
Adverse Events

There were no deaths or serious adverse events reported during the study. Of the 52 patients who were in the study, a total of 14 (27%) had at least one non-serious adverse event with treatment during the 12-week treatment period. None of these adverse events resulted in withdrawal from the trial. The most common side effect was dizziness (7.6%) and in one case was associated with significant fatigue and a SBP of 105 mm Hg. Gradual tapering and discontinuation of two of the four baseline antihypertensive agents in this patient led to resolution of the adverse event.

There were no serious laboratory abnormalities seen in the trial. The serum potassium increased by an average of 0.3 mEq/L (from 3.9 to 4.2 mEq/L, \(P = .05\)) in the entire patient population by week 2 of the study and remained stable through week 12. There were three episodes in two patients in which the serum potassium rose above 5.5 mEq/L, but in no patient did the serum potassium increase to \(\geq 6.0\) mEq/L. The changes from baseline to end of treatment (week 12) and resultant values in serum potassium according to baseline renal function are shown in Figure 4.

There were no relations among baseline renal function, end-of-treatment serum potassium concentrations, or changes from baseline in serum potassium values.

Discussion

**Principal Findings**

Results from this trial in patients with uncontrolled hypertension despite taking nearly four antihypertensive drugs demonstrated that eplerenone, a highly selective aldosterone antagonist, substantially and significantly lowered both clinic and ambulatory BP (Figure 1). Furthermore, the addition of eplerenone to a regimen of standard antihypertensive therapy that included a diuretic, renin-angiotensin blocking agent and in two-thirds of patients, a calcium antagonist, led to normalization of BP in 60% of patients based on clinic BP values and in 40% of patients based on ambulatory BP values (Figure 2). Finally, this level of improvement in BP control occurred on eplerenone with minimal adverse events, both subjectively and from a biochemical perspective. Elevation of the plasma potassium to values of 5.5 to 5.9 mEq/L occurred in only two patients (3.8%) and was dealt with clinically by reduction of the doses of ACE inhibitors or ARBs.

**Reductions in Clinic and Ambulatory BP**

The primary endpoint in this study was the changes from baseline in the ambulatory SBP. As shown in Figure 1, reductions from baseline in the 24-hour awake and sleep SBPs were consistently about 12 mm Hg and less than that observed for the clinic SBP (\(-18\) mm Hg). This finding is expected because ambulatory BP recordings remove all of
the observer bias seen in clinical trials of antihypertensive drugs\textsuperscript{14,15} and much of the regression to the mean associated with acclimation by the patient to the research environment and the so-called “placebo” effect.\textsuperscript{18} By using ambulatory BP as our primary mode of measurement of effect, we could justify using the open-label study design as in past studies in which blinding is difficult to achieve\textsuperscript{15} or it is unethical to withhold therapy because of the comorbidities of the resistant hypertensive population.

**Comparison with Other Studies of Add-on Therapy to Patients with Resistant Hypertension**

The results of the present study compare favorably with other studies evaluating patients with resistant hypertension, defined as failing to achieve control despite three or more antihypertensive drugs. For example, Black et al\textsuperscript{19} recently showed that the new endothelin antagonist, darusentan, at a maximal dose of 300 mg daily, lowered the clinic SBP by approximately 18 mm Hg (11.5 mm Hg when the placebo effect was taken into consideration).

Other studies have examined the impact of using spironolactone in patients with resistant hypertension.\textsuperscript{4,21–23} Ouzan et al\textsuperscript{20} performed a small (n = 23), 4-week study with relatively high initial doses of spironolactone (1 mg/kg/day) in a selected patient population with resistant hypertension and demonstrated a substantial reduction in 24-hour BP (−36/−10 mm Hg). Because of the short-term nature of that trial, adverse events of gynecomastia and other indicators of androgen suppression would not have been likely to appear. In studies with low doses of spironolactone (25 mg daily or less), both Calhoun et al\textsuperscript{21} and Mansoor and White\textsuperscript{4} demonstrated that patients with and without primary hyperaldosteronism and resistant hypertension had remarkably similar reductions in clinic BP of 21 to 22/10 mm Hg after 6 weeks of therapy when added to a three-drug regimen that included a diuretic and ACE inhibitor or ARB. The Anglo Scandinavian Cardiac Outcomes Trial investigators\textsuperscript{22} performed a retrospective analysis of the effects of aldosterone blockade (median dose of spironolactone, 25 mg) in patients with resistance to the protocol regimen of the trial and observed a mean reduction in clinic BP of 22/10 mm Hg. The most common adverse event seen in the Anglo Scandinavian Cardiac Outcomes Trial population was gynecomastia or breast discomfort in men (6%). The results of the present study demonstrate that eplerenone at a median dose of 72 mg daily induces a similar level of BP reduction observed in the studies of spironolactone. Although the present study was not long enough to assess for the long-term incidence of gynecomastia in men, several prior studies of eplerenone that were carried out for 6 months to 3 years\textsuperscript{9,23–25} did not show increases in gynecomastia or sexual dysfunction compared with placebo or other classes of antihypertensive therapies. Of note, recently Lane and Beevers\textsuperscript{26} performed an audit analysis of amiloride, a potassium-sparing diuretic, that is not associated with gynecomastia, and found that it was much less effective than spironolactone with only 13% achieving a normal clinic BP.

**Predictors of Response to Eplerenone**

Studies of special populations with eplerenone\textsuperscript{11,12} have demonstrated that this drug lowers BP effectively in patients with low-renin status before initiation of therapy. In fact, Weinberger and colleagues\textsuperscript{1} reported that eplerenone was more efficacious than the ARB losartan in patients with low-renin hypertension. However, it was also noted in that study that eplerenone lowered BP regardless of renin status at baseline, whereas losartan reduced BP more effectively when patients had high baseline renin activity. In our study, plasma renin activity was not associated with a reduction in ambulatory BP on eplerenone, although there was a weak relationship with changes from baseline in the clinic SBP. In addition, a weak but significant relationship was observed between baseline serum aldosterone and reductions in ambulatory BP (Figure 3). However, the impact of the relation between serum aldosterone and the reduction in BP is modest and the serum aldosterone and plasma renin activity values should not be a prerequisite for considering eplerenone therapy in patients with resistant hypertension.

There was a fairly robust relationship between the level of the pretreatment clinic and ambulatory BP and reductions in BP on eplerenone. This is not a surprising observation because several studies have shown a strong relationship between pretreatment SBP, including ambulatory BP values, and responses to drug therapy.\textsuperscript{12,14,18} Because many patients with resistant hypertension have elevated systemic vascular resistance combined with a component of volume excess,\textsuperscript{1,2} agents that block aldosterone should provide appropriate hemodynamic mechanisms for reductions in SBP.\textsuperscript{3,4}

**Conclusions**

This is the first study that has evaluated the effects of the selective aldosterone receptor blocking agent, eplerenone, in patients with resistant or difficult-to-control hypertension. Data derived from both clinic and ambulatory BP monitoring demonstrate that highly significant reductions in BP occurred with eplerenone and that the drug was very well tolerated. BP control rates were as high as 60% based on clinic BP values and 40% based on ambulatory BP values. These findings support the use of eplerenone in patients with resistant hypertension, defined as those patients who have failed to achieve BP control on three or more drugs, one of which is a diuretic.
References

20. Lane DA, Beevers DG. Amiloride 10 mg is less effective than spironolactone 25 mg in patients with hypertension resistant to a multidrug regime including an angiotensin receptor blocking agent. J Hypertens 2007;25:2515–16.