Hormone Therapy in Postmenopausal Women

Effects of a New Hormone Therapy, Drospirenone and 17-β-Estradiol, in Postmenopausal Women With Hypertension

William B. White, Vladimir Hanes, Vijay Chauhan, Bertram Pitt

Abstract—Drospirenone (DRSP), a progestin with antialdosterone activity, has been developed for hormone therapy in combination with 17-β-estradiol (E2) in postmenopausal women. We evaluated the antihypertensive efficacy and safety of various doses of DRSP and E2 and estradiol alone in postmenopausal women with hypertension using ambulatory and clinic blood pressure (BP) monitoring. This was a randomized, double-blind clinical trial of 3 doses of DRSP combined with estradiol, estradiol alone, and placebo in 750 postmenopausal women with stage 1 to 2 hypertension between 45 to 75 years. Ambulatory and clinic BPs, potassium, aldosterone, and lipid measurements and adverse events were evaluated in postmenopausal women with stages 1 to 2 hypertension during 8 weeks of double-blind therapy. DRSP and E2 induced dose-related reductions in the ambulatory and clinic systolic BP with physiological increases in serum aldosterone. Significant decreases in 24-hour systolic pressure were observed at doses of 2 and 3 mg of DRSP combined with estradiol but not by estradiol alone or 1 mg of DRSP with estradiol. There were no significant changes from baseline in potassium in any treatment group. Small, significant reductions in total and low-density lipoprotein cholesterol occurred on all of the active treatments, and serum triglycerides did not change. Adverse event rates were low and similar across treatment groups. In conclusion, these data show that DRSP combined with E2 significantly reduces BP in postmenopausal women with hypertension and did not induce significant increases in serum potassium. These characteristics may lead to a new benefit for this novel hormone therapy in postmenopausal women with hypertension. (Hypertension. 2006;48:246-253.)

Key Words: drospirenone ■ hormones ■ aldosterone ■ blood pressure ■ hypertension, renal

Although postmenopausal estrogen deficiency has been associated with increases in cardiovascular risk, recent randomized clinical trials of standard formulations of hormonal therapy have not demonstrated a benefit of these therapies in reducing cardiovascular disease in postmenopausal women.1–5 Although the mechanisms for these generally negative results are not clear, it is apparent that innovative alternative strategies for hormone therapy in postmenopausal women are warranted.

Recently, experimental and clinical studies have implicated aldosterone, independent of angiotensin II, in the pathogenesis of significant cardiovascular and renal disease and demonstrated the benefit of aldosterone blockade in reducing a variety of cardiovascular and renal events.6–13 Drospirenone (DRSP) is a novel progestin with antialdosterone effects that, in combination with 17-β-estradiol (E2), has been developed for use in postmenopausal women as a hormone therapy.14–16 The combination DRSP/E2 is approved for estrogen deficiency symptoms in postmenopausal women. During its development for relief of menopausal symptoms, DRSP/E2 was shown to have significant antihypertensive effects in studies of postmenopausal, hypertensive women alone or in combination with enalapril.17–19 Furthermore, DRSP/E2 was found to have a significant antihypertensive effect in patients with and without type 2 diabetes mellitus and concomitant use of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists.20 When compared with other hormone therapies and oral contraceptives, DRSP results in a significantly greater increase in plasma aldosterone14–16 in response to the antialdosterone effect of the compound.

The primary objective of this study was to determine whether this new hormone therapy has clinically significant effects on 24-hour ambulatory and clinic blood pressure (BP) in a large population of hypertensive postmenopausal women using varying doses of DSRP with 1 mg of E2 compared with placebo. In addition, because there are conflicting data on the effects of estrogens on ambulatory BP, we included a treatment arm of E2 alone in this trial. Lastly, we evaluated the metabolic effects of DSRP/E2, because drugs that induce
aldosterone blockade have been associated with significant increases in serum potassium.14–16

Methods

Patient Population
Postmenopausal women (aged 45 to 75 years) were included if their mean seated clinic systolic BPs were 140 to 179 mm Hg and the diastolic BP was between 90 to 109 mm Hg in the untreated state (either untreated previously or removed from previous antihypertensive therapy). Postmenopausal women were defined in our protocol as women with natural menopause for ≥1 year (ie, no menstruation for 1 year) before screening or women who had a bilateral oophorectomy ≥3 months before study participation. Patients were excluded from the trial if they had had an acute myocardial infarction or unstable angina, symptomatic congestive heart failure, clinically significant liver or renal disease, known secondary hypertension, history of stroke or transient ischemic attack, venous thromboembolic disorders, or uncontrolled diabetes mellitus. Women with serum creatinine levels >2.0 mg/dL or whose serum potassium was >5.0 mEq/L were also excluded from study participation. Exclusionary and concomitant medications included antihypertensive medications, potassium supplements, potassium-sparing diuretics, anticoagulants (heparin or warfarin), antiarrhythmic agents, and hormone therapy.

Study Design
The study was a multicenter (42 centers in the United States and 22 centers in Europe), double-blind, randomized, placebo-controlled, parallel arm trial. The randomization numbers were generated in blocks of 5 using the RANDO System (Randomization User Manual, Version 3.0, 2000, Schering A.G.), and the 5 potential treatments were allocated equally. Patients were placed in a single-blind placebo phase for 3 to 4 weeks to establish baseline BP values and laboratory parameters. At random assignment, patients received placebo or DRSP 1, 2, or 3 mg or E2 1 mg or E2 1 mg alone once daily each morning. The run-in medication and the double-blind medication tablets were identical in shape and color to prevent any unmasking. The treatment and placebo groups were continued for 8 weeks. If the systolic BP was >180 mm Hg or the diastolic BP was >110 mm Hg on 2 consecutive occasions within 24 hours at any time during the trial, the patient was removed from double-blind medication for safety considerations. In addition, if the patient’s serum potassium level was sustained in excess of 5.5 mEq/L on ≥3 consecutive days, the patient was removed from blinded medication and placed on conventional therapy. An independent Data Safety Monitoring Board was established to monitor safety data at regular intervals. All of the participating centers had approval from their local institutional review boards or ethics committees before any patient involvement in this trial. All of the participating protocol patients were pooled from largest to smallest until the 5 per protocol patients in each treatment group.

Patients were assessed at 2-week intervals during the trial for BP, heart rate, adverse events, and concomitant medications. At all of the sites, 24-hour ambulatory BP monitoring was performed at baseline and after 8 weeks of therapy.

Measurements of BP and Heart Rate
The clinic BP was measured by calibrated mercury column sphygmomanometry in triplicate (and averaged) in the seated position at all visits after a minimum of 5 minutes of rest. Women were instructed to take 1 tablet early each morning at the same time; office BPs were taken 24 hours after dosing to coincide with the end of the dosing period. Ambulatory BP and heart rate measurements were obtained with the SpaceLabs 90207 monitor (SpaceLabs Inc). Quality criteria used for an acceptable ambulatory BP recording included a minimum of 80% valid readings obtained within 24 hours after monitor hookup, ≤3 nonconsecutive hours with <1 valid reading and ≤2 consecutive hours with <1 valid reading. During the 24-hour ambulatory monitoring study, BP and heart rate were measured every 15 minutes from 6:00 AM to 10:00 PM and every 20 minutes between 10:00 PM and 6:00 AM. Monitoring hookup was initiated between 7:00 and 10:00 AM, and patients were dosed with study medication at the time of monitor hookup. Study coordinators recorded medication dosing and monitor hookup in the case report forms.

Laboratory and Safety Assessments
Serum lipid levels and chemistries, including electrolytes and renal function testing, were determined at baseline and after 2, 4, 6, and 8 weeks of double-blind therapy. Serum aldosterone levels were performed at baseline and at the end of the study. An ECG was performed at screening and after 4 and 8 weeks of therapy. Adverse event data were obtained throughout the study via observation and indirect questioning. Each adverse event was assigned the medical term from Hochest Adverse Reaction Terminology System (HARTS) Dictionary Version 2.3. Events of special interest in the trial included hyperkalemia, hypotension, diziness, palpitations, syncope, and arrhythmias (including tachycardia and bradycardia). The laboratory protocol specified that all of the elevated serum potassium levels (≥5.5 mEq/L) were to be checked for hemolysis and repeated within 1 to 3 days for confirmation.

Statistical Analyses
The comparability of patients in the treatment groups was determined from the demographic data and baseline hemodynamic values. Continuous variables (age, body weight, body mass index, waist circumference, baseline values of BP, serum potassium, and lipids) were analyzed with an ANOVA model with factors for treatment and clinical center. Discrete variables (eg, ethnicity and smoking history) were examined with the Cochran–Mantel–Haenszel test for general association controlling for clinical center effect. All of the analyses were conducted using SAS 9.1 software. The statistical analyses for efficacy were performed on an intent-to-treat basis, which included all of the patients randomly assigned to the study with a baseline BP assessment and ≥1 postbaseline assessment during the double-blind dosing period. The last observed BP values were carried forward for dropouts. A sensitivity analysis was also performed by replacing the last observed values of BP by worst measurement for dropouts. The safety analysis population was the same as the intent-to-treat population.

The coprimary efficacy end points of the trial were to compare the mean change from baseline at week 8 in clinic and in ambulatory sphygmomanometry in triplicate (and averaged) in the seated position at all visits after a minimum of 5 minutes of rest. Women were instructed to take 1 tablet early each morning at the same time; office BPs were taken 24 hours after dosing to coincide with the end of the dosing period. Ambulatory BP and heart rate measurements were obtained with the SpaceLabs 90207 monitor (SpaceLabs Inc). Quality criteria used for an acceptable ambulatory BP recording included a minimum of 80% valid readings obtained within 24 hours after monitor hookup, ≤3 nonconsecutive hours with <1 valid reading and ≤2 consecutive hours with <1 valid reading. During the 24-hour ambulatory monitoring study, BP and heart rate were measured every 15 minutes from 6:00 AM to 10:00 PM and every 20
Adverse events were coded and summarized by treatment group and tabulated by treatment group and body system. Clinical laboratory data were summarized by treatment groups. For each parameter, the treatments were compared with respect to mean change from baseline using an ANCOVA. Shifts in baseline laboratory values were also compared between treatment groups.

The planned sample size of 675 patients (ie, 135 subjects per treatment group) provided 80% power to detect a difference of 4.0 mm Hg each between active treatment and placebo in change from baseline in office systolic BP with a 2-sample t test of the null hypothesis at the 0.05 level of significance. A common sample SD of 10.4 mm Hg used in the calculation was obtained from the results of a previous study. The sample size calculation was based on an assumed dropout rate of 20%.

**Results**

**Patient Characteristics and Disposition**

The disposition of the study population during the trial is shown in Figure 1. There were 750 patients randomly assigned into the 5 treatment arms with similar demographics (Table 1) and baseline clinic and ambulatory BP values with the exception of a slightly but significantly higher clinic diastolic BP in the DRSP 2 mg/E2 group (Table 2). Of these, 748 patients received 1 dose of study medication and were included in the intent-to-treat analysis. During the single-blind placebo run-in period, the major reasons for study exclusion were:

- 436 withdrew after the run-in period
- 106 withdrew because of withdrawal of consent
- 338 because of other inclusion/exclusion criteria not met
- 3 adverse events
- 4 patient lost, no information available
- 26 other

**Figure 1.** Disposition of the patient population during the conduct of the clinical trial.

**TABLE 1.** Patient Characteristics (Mean±SD) at the Baseline of the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRSP 3 mg/E2</th>
<th>DRSP 2 mg/E2</th>
<th>DRSP 1 mg/E2</th>
<th>E2</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>151</td>
<td>149</td>
<td>151</td>
<td>150</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>57±6</td>
<td>57±6</td>
<td>57±6</td>
<td>57±6</td>
<td>57±6</td>
<td>0.69</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>131 (87)</td>
<td>123 (83)</td>
<td>131 (87)</td>
<td>129 (86)</td>
<td>123 (84)</td>
<td>0.91</td>
</tr>
<tr>
<td>Black</td>
<td>20 (13)</td>
<td>26 (17)</td>
<td>20 (13)</td>
<td>21 (14)</td>
<td>24 (16)</td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>80.6±16.6</td>
<td>82.1±17.9</td>
<td>80.8±17.1</td>
<td>81.7±14.8</td>
<td>79.6±15.2</td>
<td>0.73</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>94.7±14.3</td>
<td>95.1±17.0</td>
<td>93.4±16.8</td>
<td>94.5±12.5</td>
<td>91.6±14.3</td>
<td>0.23</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.6±5.8</td>
<td>31.0±6.8</td>
<td>30.5±6.2</td>
<td>30.5±4.9</td>
<td>30.0±5.2</td>
<td>0.66</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>11 (7.3)</td>
<td>17 (11.4)</td>
<td>13 (8.6)</td>
<td>13 (8.7)</td>
<td>12 (8.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Serum potassium, meq/L</td>
<td>4.3±0.4</td>
<td>4.3±0.4</td>
<td>4.3±0.4</td>
<td>4.3±0.4</td>
<td>4.3±0.4</td>
<td>0.99</td>
</tr>
<tr>
<td>Lipoproteins, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>225±44</td>
<td>218±34</td>
<td>226±38</td>
<td>224±41</td>
<td>224±35</td>
<td>0.43</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>141±73</td>
<td>135±69</td>
<td>148±74</td>
<td>138±70</td>
<td>137±74</td>
<td>0.47</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>60±13</td>
<td>60±14</td>
<td>61±16</td>
<td>62±14</td>
<td>61±13</td>
<td>0.96</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>145±39</td>
<td>140±32</td>
<td>146±37</td>
<td>143±36</td>
<td>143±33</td>
<td>0.53</td>
</tr>
</tbody>
</table>

SBP indicates systolic BP; DBP, diastolic BP; BMI, body mass index; LDL, low-density lipoprotein.
discontinuation included failure to meet inclusion criteria (typically unacceptably low baseline BP), lost to follow-up, protocol violations, or patient withdrawal of consent. The percentage of patients withdrawn from the study after random assignment was low (Figure 1). Of note, no patient was withdrawn because of hyperkalemia.

Clinic BP
The adjusted mean changes in BP in the clinic setting are shown in Table 2 and unadjusted means in Figure 2. The reductions in clinic BP were significantly greater on 2- and 3-mg DRSP/E2 compared with placebo at the end of the study, whereas changes from baseline for 1-mg DRSP/E2 and E2 alone were similar to placebo. Reductions in BP occurred at 4 weeks of DRSP/E2 therapy and stabilized by 6 weeks of therapy (Figure 2). At the end of the study, the mean reductions in clinic BP in the 3- and 2-mg DRSP/E2 groups averaged -13.8/-8.5 mm Hg and -12.1/-9.2 mm Hg respectively, whereas the reductions for placebo were -8.7/-5.0 mm Hg (systolic BP reductions: P=0.0004 and 0.0195 for 3 and 2 mg, respectively, for diastolic BP reductions, P<0.0001 for both doses). The changes from baseline in heart rate were similar for DRSP/E2 and placebo.

Ambulatory BP
The mean changes from baseline in the 24-hour ambulatory BP are shown in Table 2 and Figure 3. Significant reductions from baseline in the coprimary end point of mean 24-hour systolic BP were observed in the 2- and 3-mg DRSP/E2 treatment group compared with placebo. In contrast, there were no differences in ambulatory BP for 1-mg DRSP/E2 and E2 alone versus placebo (Table 2). As shown in the 24-hour curves of the systolic BP in Figure 3, the reductions in systolic BP were greater as the dose of DRSP increased and persisted for all 24 hours of the dosing period. Less pronounced dose-related reductions in 24-hour diastolic BP were observed on DRSP/E2 compared with E2 alone or with placebo (Table 2).

Laboratory Findings
Five patients in each of the 3 DRSP/E2 groups and 5 patients in the placebo group developed a serum potassium of ≥5.5 meq/L. The mean maximal change from baseline in the DRSP group was not significantly different for the 5 treatment groups and ranged between 0.29 meq/L and 0.37 meq/L (P=0.48; Table 3). In addition to no differences in the proportion of patients developing predefined hyperkalemia (>5.5 meq/L), there were also no differences for ≥1 increase of serum potassium between >0.5 meq and <1.0 meq as noted here: 3 mg DRSP/E2: n=44 (29.1%); 2 mg DRSP/E2: n=45 (30.2%); 1 mg DRSP/E2: n=25 (16.6%); 1 mg E2: n=41 (27.3%); and placebo: n=43 (29.3%). Reductions in total and low-density lipoprotein cholesterol were significantly greater with all of these active treatment groups compared with placebo (Table 3), with the largest reduction on 3-mg DRSP/E2. There were no changes in serum triglycerides in any of the treatment groups. There were mixed findings for the high-density lipoprotein cholesterol as shown in Table 3. Dose-related increases in the serum aldosterone concentrations were observed on 2- and 3-mg DRSP/E2 (Table 3).

Adverse Events
There were no deaths in the study. The incidence rates of serious cardiovascular and noncardiovascular events were

### Table 2. Mean Changes From Baseline (±SD) in Clinic and Ambulatory BP After 8 Weeks of Therapy for DRSP/E2 Versus Placebo (Intent-to-Treat)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRSP 3 mg/E2</th>
<th>DRSP 2 mg/E2</th>
<th>DRSP 1 mg/E2</th>
<th>E2 Alone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>125</td>
<td>123</td>
<td>123</td>
<td>125</td>
<td>117</td>
</tr>
<tr>
<td>Baseline clinic systolic BP, mm Hg</td>
<td>138±15</td>
<td>139±15</td>
<td>142±14</td>
<td>138±15</td>
<td>137±14</td>
</tr>
<tr>
<td>Systolic BP change, mm Hg</td>
<td>-6.1±11.2</td>
<td>-4.7±10.4</td>
<td>-4.6±9.5</td>
<td>-1.0±9.9</td>
<td>-1.2±9.3</td>
</tr>
<tr>
<td>Adjusted mean (95% CI)</td>
<td>-5.0 (-7.3 to -2.6)</td>
<td>-3.2 (-5.6 to -0.8)</td>
<td>-2.2 (-4.6 to -0.2)</td>
<td>0.1 (-2.3 to 2.4)</td>
<td></td>
</tr>
<tr>
<td>P value (vs placebo)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.957</td>
<td>0.957</td>
</tr>
<tr>
<td>Baseline clinic diastolic BP, mm Hg</td>
<td>82±9</td>
<td>83±9</td>
<td>84±10</td>
<td>82±10</td>
<td>83±10</td>
</tr>
<tr>
<td>Diastolic BP change, mm Hg</td>
<td>-3.5±7.1</td>
<td>-2.8±6.6</td>
<td>-3.6±6.3</td>
<td>-1.0±6.3</td>
<td>-0.6±6.6</td>
</tr>
<tr>
<td>Adjusted mean (95% CI)</td>
<td>-3.3 (-4.9 to -1.8)</td>
<td>-2.4 (-4.0 to -0.9)</td>
<td>-2.6 (-4.2 to -1.1)</td>
<td>-0.8 (-2.4 to 0.7)</td>
<td></td>
</tr>
<tr>
<td>P value (vs placebo)</td>
<td>&lt;0.0001</td>
<td>0.0024</td>
<td>0.0008</td>
<td>0.2999</td>
<td></td>
</tr>
</tbody>
</table>

N are the number of subjects with baseline and postbaseline values.
women with hypertension. The focus of our analysis was on treatment with selective aldosterone blocking properties, our results demonstrate that DRSP with E2, a new hormone selected cardiovascular events (arrhythmia, bradycardia, dizziness, palpitations, and syncope) on DRSP/E2 versus placebo. The overall incidence of adverse events was 277 (61.4%) of 451 patients taking DRSP/E2 versus 83 (56.5%) of 147 patients taking placebo or 86 (57.3%) of 150 taking E2 only. The most common events were vaginal bleeding/spotting and breast tenderness (13.9% to 19.2% of DRSP patients versus 0.7% and 2.0% of the placebo patients, respectively; Table 4). The mean change from baseline in body weight was not statistically significantly different in any treatment group compared with placebo.

Discussion

Principal Findings

Our results demonstrate that DRSP with E2, a new hormone treatment with selective aldosterone blocking properties, provides significant reduction of BP in postmenopausal women with hypertension. The focus of our analysis was on the systolic BP, because it is associated with greater cardiovascular risk than diastolic BP in women with hypertension even at values >130 mm Hg.23 We used 24-hour ambulatory BP as a primary efficacy measurement tool, because it typically yields more reliable assessment of antihypertensive therapy because of the increased number of values taken over the dosing interval, the enhanced statistical reproducibility of ambulatory BP compared with clinical BP measurements, and less observer bias.22–24 One obvious attribute of ambulatory monitoring was the marked lower placebo effect compared with the BP measurements made in the clinic (Table 2) that allowed for superior discrimination of the effects of the various treatment doses used in our trial. An important safety finding in our trial was the lack of evidence for clinically important increases in serum potassium with DRSP/E2 up to 3 mg in this population of hypertensive postmenopausal women. Finally, DRSP/E2 significantly lowered total cholesterol because of reductions in low-density lipoprotein; the combination therapy reduced high-density lipoprotein compared with E2 alone (Table 3).

Clinic and Ambulatory BP

As shown in Table 2 and Figures 2 and 3, DRSP/E2 lowered both the clinic and 24-hour ambulatory BPs significantly compared with placebo, whereas E2 alone had no effect on BP levels. There was evidence of a dose-related reduction in both types of BP measurements, although the most distinct relationship was for the 24-hour systolic BP. The antihypertensive effect of DRSP/E2 becomes significant with 2-mg DRSP but the higher dose (3-mg DRSP) yielded more consistent and larger decreases in both clinic and 24-hour BP (Figure 3).

The level of ambulatory BP reductions observed in our study is comparable to many other antihypertensive agents, including the selective aldosterone blocker eplerenone.11 For example, the placebo-subtracted mean reduction from baseline in 24-hour BP on eplerenone was ≈7/4 mm Hg for the 50-mg dose, a value similar to what was observed with the 3-mg dose of DRSP both in the present study (Table 2 and Figure 3) and in our preliminary study with DRSP/E2.18 In addition, Preston et al.17 reported that 3-mg DRSP/E2 lowered 24-hour ambulatory BP by 9/5 mm Hg when the drug was added to enalapril after just 2 weeks of therapy. As in our present study, these reductions in BP were associated with increases in aldosterone by ≈3 ng/dL (40% above baseline), attesting to the pharmacological effect of DRSP in blocking the mineralocorticoid receptor.

Reductions from baseline in the clinic BP versus reductions in the 24-hour ambulatory BP for DRSP/E2 were variable (Table 2). Differential effects for clinic and ambulatory BP measurements are commonly observed in antihypertensive therapy trials, but typically the mean reduction in ambulatory pressures in clinical trials is ≈40% less than the average reduction in the clinic BP.18 In the present trial, there was a fairly large BP reduction in the placebo group for both the clinic systolic and diastolic pressure (≈8.6/≈5.0 mm Hg), which is attributable in part to both observer bias and in part to regression to the mean.22 Because each treatment group had between 119 and 129 patients who underwent ambulatory BP recordings, the findings for those data are exceedingly

Figure 2. Effects of DRSP/E2 vs placebo on clinic BP after 8 weeks of double-blind therapy. A is changes in systolic BP and B is changes in diastolic BP. Changes from baseline were significant for the 3- and 2-mg DRSP/E2 groups only (systolic BP, \( P = 0.0004 \) and 0.0195 for 3- and 2-mg DRSP/E2 groups, respectively; diastolic BP, \( P < 0.001 \) for both 3- and 2-mg groups).

Figure 3. Effects of DRSP/E2 vs placebo on 24-hour ambulatory BP after 8 weeks of double-blind therapy. A is changes in systolic BP and B is changes in diastolic BP. Changes from baseline were significant for the 3- and 2-mg DRSP/E2 groups only (systolic BP, \( P = 0.0004 \) and 0.0195 for 3- and 2-mg DRSP/E2 groups, respectively; diastolic BP, \( P < 0.001 \) for both 3- and 2-mg groups).
robust and, unlike the clinic BP measurements, show that 2 of 3 doses of DRSP/E2 have antihypertensive activity (Table 2 and Figure 3) and that a dose-related response occurs among the 3 doses tested in our study. Finally, it appears that the antihypertensive effect of DRSP/E2 is attributable primarily to the effects of DRSP, because E2 alone did not induce any reduction in either clinic or ambulatory BP. Alternatively, there may be synergism between DRSP and E2.

Figure 3. Effects of DRSP/E2 vs placebo on the coprimary end point of ambulatory systolic BP over 24 h ours at baseline and after 8 weeks of double-blind therapy that included placebo, E2 alone, 1-mg DRSP/E2, 2-mg DRSP/E2, and 3-mg DRSP/E2. Baseline period is the ○, —, and treatment period is the ●, —.

TABLE 3. Mean Changes in Laboratory Parameters After 8 Weeks of Therapy for DRSP/E2, E2 Alone, and Placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRSP 3 mg/E2</th>
<th>DRSP 2 mg/E2</th>
<th>DRSP 1 mg/E2</th>
<th>E2 Alone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium, meq/L</td>
<td>0.10±0.31</td>
<td>0.09±0.32</td>
<td>0.02±0.30</td>
<td>−0.03±0.33</td>
<td>0.01±0.33</td>
</tr>
<tr>
<td>Mean change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal change</td>
<td>0.36±0.39</td>
<td>0.37±0.37</td>
<td>0.26±0.36</td>
<td>0.26±0.39</td>
<td>0.29±0.37</td>
</tr>
<tr>
<td>Serum aldosterone, pg/mL</td>
<td>68.2±97.7*</td>
<td>40.9±91.6†</td>
<td>13.1±65.8</td>
<td>7.5±63.3</td>
<td>8.7±48.6</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>−18.0±32.5*</td>
<td>−11.5±27.4†</td>
<td>−10.6±32.3‡</td>
<td>−9.0±32.2</td>
<td>−2.1±28.0</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>−3.7±7.2†</td>
<td>−1.3±7.6</td>
<td>0.1±7.3</td>
<td>3.4±7.7‡</td>
<td>−1.0±6.7</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>−13.6±28.0*</td>
<td>−10.4±25.0†</td>
<td>−12.2±28.9*</td>
<td>−11.5±24.8†</td>
<td>−1.3±24.6</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>−9.8±57.2</td>
<td>−4.2±47.8</td>
<td>−2.1±61.0</td>
<td>−1.0±58.3</td>
<td>−5.4±49.3</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein.

*P<0.001; †P<0.01; ‡P<0.05 vs placebo.
Safety and Tolerability and Laboratory Assessments

Previous clinical studies showed that the use of DRSP combined with E2 provides protection against endometrial hyperplasia, reduces endometrial bleeding with time, and relieves menopausal symptoms.10 DRSP/E2 was well tolerated in this 750-patient trial with adverse event profiles similar to that for placebo (Table 4). Because of its antialdosterone effects, there were theoretical concerns that DRSP/E2 might induce hyperkalemia as has been observed in studies with both spironolactone12 and eplerenone.1,3,23 Extensive laboratory assessment at each visit did not show any clinically significant changes in serum potassium at any of the 3 doses of DRSP used in the trial (Table 4). Previous clinical studies with DRSP/E2 did not show greater incidence of hyperkalemia than with placebo in hypertensive postmenopausal women with and without type 2 diabetes mellitus and concomitant use of angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or ibuprofen.20 However, because our study did not study patients with serum creatinine levels in excess of 1.5 mg/dL, we would recommend caution in women taking DRSP/E2 who have moderate and/or severely reduced renal function. Lastly, DRSP/E2 induced small but statistically and clinically significant reductions in serum lipoproteins, a finding that has been observed with other estrogen-containing hormone therapies24 but has not been found to be predictive of cardiovascular effects. However, the higher doses of DRSP/E2 reduced the HDL cholesterol by ≈10%, whereas E2 alone raised HDL cholesterol by 10% (Table 3).

Conclusions

Our study demonstrated that DRSP/E2, a new hormone therapy with aldosterone blocking activity, was effective in reducing ambulatory systolic and diastolic BP with dose-related reductions between 1 and 3 mg of DRSP. The 2-mg DRSP is the lowest effective dose that provided significant and adequate BP reduction in postmenopausal hypertensive women. The hormone therapy was well tolerated for the 2-month period with modest subjective or objective adverse events.

Because reduction of systolic BP of the magnitude observed in our study has significant implications in postmenopausal women with hypertension,25–27 especially for reducing stroke and heart failure, DRSP/E2 may have an advantage for the treatment of menopausal symptoms over conventional progestins. Future studies designed to evaluate the longer-term (ie, ≈2 years) cardiovascular effects associated with these significant antihypertensive effects of DRSP/E2 might be warranted at this time.

Perspectives

During the postmenopausal period, hypertension is prevalent among those women who use hormone therapy. In the Women’s Health Initiative Observational Study,5 42.9% of postmenopausal women with hypertension and no known history of cardiovascular disease were classified as current users of hormone therapy, and users of estrogen with and without a progestin increased mean systolic BP an average of 1 to 2 mm Hg consistently over the course of the study. In addition, in the Estrogen in the Prevention of Atherosclerosis Study,28 estrogen use was associated with an increase in systolic BP in younger (<65 years) but not older postmenopausal women, an association that was positively correlated with changes in carotid intima–media thickness. These findings are particularly relevant, because younger women are more likely to receive hormone therapy under current guidelines. Use of DRSP, a unique progestin with antialdosterone effects, in combination with estrogen may help to mitigate the increase in BP observed with other types of combination hormone therapy. In our study, treatment with 2- and 3-mg DRSP with E2, was associated with a clinically and statistically significant reduction in systolic BP. At present, the approved doses of DRSP in combination with E2 are 2 mg in the European Union, 1 mg in Canada, and 0.5 mg in the United States. The present data are, therefore, being presented as an additional benefit of DRSP/E2 hormone therapy in

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**TABLE 4. Selected Adverse Events (With Frequency >2%) After 8 Weeks of Therapy for DRSP/E2, E2 Alone, and Placebo (Intent-to-Treat)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>DRSP 3 mg/E2 (n=151)</th>
<th>DRSP 2 mg/E2 (n=149)</th>
<th>DRSP 1 mg/E2 (n=151)</th>
<th>E2 Alone (n=150)</th>
<th>Placebo (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast discomfort</td>
<td>21 (13.9)</td>
<td>19 (12.8)</td>
<td>29 (19.2)</td>
<td>8 (5.3)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Vaginal bleeding/spotting</td>
<td>21 (13.9)</td>
<td>24 (16.1)</td>
<td>29 (19.2)</td>
<td>8 (5.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>10 (6.6)</td>
<td>4 (2.7)</td>
<td>15 (9.9)</td>
<td>9 (6.0)</td>
<td>13 (8.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (3.3)</td>
<td>9 (6.0)</td>
<td>9 (6.0)</td>
<td>10 (6.7)</td>
<td>10 (6.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (2.0)</td>
<td>3 (2.0)</td>
<td>4 (2.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breast enlargement</td>
<td>3 (2.0)</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3 (2.0)</td>
<td>3 (2.0)</td>
<td>2 (1.3)</td>
<td>7 (4.7)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>3 (2.0)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
<td>1 (0.7)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Breast engorgement</td>
<td>1 (0.7)</td>
<td>4 (2.7)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>1 (0.7)</td>
<td>0</td>
<td>2 (1.3)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>0</td>
<td>3 (2.0)</td>
<td>4 (2.6)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3 (2.0)</td>
<td>1 (0.7)</td>
<td>2 (1.3)</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>

Data are n (%).
hypertensive postmenopausal women. The projected indication in the United States at a future date for DRSP 2mg/E2 is “treatment of moderate-to-severe vasomotor symptoms in postmenopausal women with hypertension” as the antihypertensive effect DRSP/E2, alone or in combination with antihypertensive medications, has been conclusively demonstrated.

Sources of Funding
This study was supported by funding from Berlex, Inc.

Disclosures
W.B.W.’s academic department has received research funding from Berlex, Inc. and he has served as an academic consultant to Berlex, Inc, during the past 3 years; B.P. served as chair of the Data Safety Monitoring Committee for this study. In the past, B.P. has served as an academic paid consultant to Berlex, Inc. V.H. is a full time employee of Berlex, Inc, and V.C. is a statistician consultant of Berlex, Inc.

References
Effects of a New Hormone Therapy, Drospirenone and 17-β-Estradiol, in Postmenopausal Women With Hypertension

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Hypertension. 2006;48:246-253; originally published online June 26, 2006; doi: 10.1161/01.HYP.0000232179.60442.84

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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