Analysis of Recent Papers in Hypertension

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DROSPIRENONE, A PROGESTIN, SIGNIFICANTLY REDUCES BLOOD PRESSURE WHEN COMBINED WITH ESTRADIOL IN POSTMENOPAUSAL WOMEN WITH STAGE 1 HYPERTENSION

Drospirenone (DRSP), a progestin with antimineralocorticoid and antiandrogenic effects similar to spironolactone, has previously been shown to have blood pressure (BP)-lowering ability. It has been developed for use in combination with ethinyl estradiol for premenstrual syndrome and with 17β-estradiol (E2) for use as postmenopausal hormone therapy. The current investigation sought to determine the BP-lowering effects of DRSP when used in combination with E2 in postmenopausal women with stage 1 hypertension. Untreated postmenopausal women, 45–80 years of age, had to have a seated clinic systolic BP of 140–159 mm Hg and/or a diastolic BP of 90–99 mm Hg to be included in the study. Patients were excluded from the trial if they had received prior estrogen or progestin hormonal therapy; had sustained a recent myocardial infarction, unstable angina, stroke, or transient ischemic attack; or had heart failure, clinically significant liver or renal disease, known secondary hypertension, a history of venous thromboembolism, or type 1 diabetes mellitus. Women whose calculated creatinine clearance was <50 mL/min or whose serum potassium was >5.5 mEq/L at baseline were also excluded from participation.

After a 3–4 week run-in period to establish baseline BPs and laboratory parameters, 213 subjects from 30 clinical centers in the United States were randomized in double-blind fashion to DRSP 3 mg + E2 1 mg or matching placebo, each given once daily in the morning. Subjects were seen at 2-week intervals and evaluated for BP, heart rate, adverse events, and concomitant medications. If the systolic BP was >160 mm Hg or the diastolic BP was >100 mm Hg on two consecutive occasions 1–3 days apart at any time during the trial, the patient was removed from the trial for safety reasons. The primary efficacy end point of the trial was the mean change from baseline at Week 12 in clinic systolic and diastolic BP in each treatment arm. The incidence of significant hyperkalemia (serum potassium >5.5 mEq/L) and other adverse events was also compared. At 10 selected sites, a subset of subjects also underwent 24-hour ambulatory BP monitoring (Spacelabs 90207, Spacelabs Medical, Inc., Issaquah, WA) at baseline and after 12 weeks of double-blind treatment.

At baseline, subjects had similar demographic and clinical characteristics and baseline clinic and ambulatory BP values. The subjects' mean age was 56±5 years in the DRSP/E2 group and 57±5 years in the placebo group. Mean clinic BP was 145/89 mm Hg in the DRSP/E2 group and 146/89 mm Hg in the placebo group. Twenty-four hour ambulatory BP was 136/83 mm Hg in the DRSP/E2 group and 135/82 mm Hg in the placebo group. The percentage of patients who withdrew from the study was 9.8% in the DRSP/E2 group and 14.4% in the placebo group; the majority of withdrawals after randomization were due to adverse events or treatment failure. No patient was withdrawn because of hyperkalemia.

Using an intention-to-treat analysis, treatment with DRSP-E2 led to significantly greater reductions in clinic systolic BP by 2 weeks and diastolic BP by 4 weeks. At the end of the 12-week study,

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the mean reductions in clinic BP in the DSRP/E2 group (n=102) averaged –14.1/–7.9 mm Hg compared with reductions of –7.1/–4.3 mm Hg in the placebo group (n=111), a difference of 7.0/3.6 mm Hg. Pulse pressure was also significantly reduced in the DRSP/E2 treatment arm, with no change in heart rate. Significantly greater reductions in 24-hour mean ambulatory systolic BP were also seen with DRSP/E2 compared with placebo (–8.5 vs. –1.8 mm Hg). No significant difference was seen in 24-hour mean ambulatory diastolic BP (–4.2 mm Hg, DRSP/E2 vs. –1.6 mm Hg, placebo). The reductions in ambulatory BP with DRSP/E2 were mostly seen during the daytime, with little change in nighttime ambulatory BP, perhaps due to the low baseline nighttime ambulatory BP in the DRSP/E2 group (125/73 mm Hg).

There were no deaths during the study; one subject in the DRSP/E2 group sustained an acute myocardial infarction. The overall incidence of side effects was 6.9% in the DRSP/E2 group compared with 2.7% with placebo. Dizziness was the most common adverse event (4% of DRSP/E2 patients vs. 2% of the placebo patients). Because of the antimineralocorticoid effect of DRSP, changes in serum potassium were carefully monitored. There were no patients treated with DRSP who developed a serum potassium >5.5 mEq/L at any time during the study; the mean maximal change from baseline in serum potassium was 0.24±0.38 mEq/L in the DRSP/E2 group compared with 0.16±0.43 mEq/L in those treated with placebo.

These data suggest that the combination of DRSP 3 mg and E2 1 mg given in the morning is well tolerated and is associated with significant reductions in clinic and 24-hour ambulatory systolic BP in postmenopausal women with stage 1 systolic hypertension. This suggests possible benefit for cardiovascular (CV) risk reduction in this population.—*White WB, Pitt B, Preston RA, et al. Antihypertensive effects of drospirenone with 17β-estradiol, a novel hormone treatment in postmenopausal women with stage 1 hypertension.* Circulation. *2005;112:1979–1984.*

COMMENT

Postmenopausal hormone replacement therapy has been shown to have a number of health benefits, including the relief of menopausal symptoms, maintenance of bone mineral density, and a decreased risk of colon cancer. In the Women's Health Initiative (WHI) study, however, these benefits were outweighed by an increased risk of stroke, CV events, and thromboembolic events. Accordingly, developing innovative, alternative strategies for hormone replacement therapy with a better CV risk profile is potentially attractive.

In the present study, DRSP/E2 was associated with reduced clinic systolic and diastolic BP as well as daytime ambulatory systolic BP. No patients developed hyperkalemia, and the combination was well tolerated. The incidence of minor electrocardiographic abnormalities (22%) was identical in the two randomized groups and no deaths occurred in this short-term study.

As a result of its mineralocorticoid blocking effect, an effect similar to that seen with spironolactone, DRSP appears to lower BP when used in combination with oral estrogen in postmenopausal women with hypertension. Previous studies with DRSP/E2 in postmenopausal women demonstrated not only an additional reduction in BP when added to the angiotensin-converting enzyme inhibitor, enalapril, but also an association with increases in serum aldosterone, attesting to the effect of DRSP on blocking the mineralocorticoid receptors. Aldosterone blockade may provide additional benefits over and above BP lowering in patients with established CV disease; therefore, DRSP/E2 may have advantages for the treatment of menopausal symptoms in older women, especially those with hypertension, who remain at risk for CV disease.

While this approach appears promising, there are additional studies that should be done before the combination of DRSP/E2 is utilized for postmenopausal women with hypertension. We do not yet know its effects on the lipid profile. Is it, like traditional hormone replacement therapy, associated with significant elevations in high-density lipoprotein cholesterol? The demonstration of improvement in BP will not necessarily translate into a reduction in CV risk if other risk factors and risk markers are negatively affected. Future studies should evaluate the effects of DRSP on additional risk factors for CV disease, such as plasma lipids and serum glucose, and surrogate markers for CV risk like high-sensitivity C-reactive protein and carotid intimal thickness. As the authors note, future studies in hypertensive patients comparing DRSP/E2 with E2 alone and with other progestins and other estrogens will be necessary to better understand the benefits of these agents for the aging female population. Additional randomized controlled trials will be needed before DRSP/E2 can be considered a reasonable treatment option in postmenopausal women with hypertension.