Hormone Combo Cuts Blood Pressure, Hot Flashes

BY FRAN LOWRY
Orlando Bureau

WASHINGTON — The combination of drospirenone (a progestin with antialdosterone effects) and 17-β-estradiol as hormone therapy for hypertensive postmenopausal women not only reduces hot flashes, but lowers blood pressure as well, according to a poster presented at the annual meeting of the American College of Obstetricians and Gynecologists.

Treatment with the combination of drospirenone and 17-β-estradiol for an 8-week period produced significant reductions in systolic and diastolic 24-hour ambulatory and clinic blood pressure at 2- and 3-mg doses of drospirenone, reported Dr. William B. White, professor of medicine at the University of Connecticut, Farmington.

Drospirenone plus estradiol has been used for the treatment of menopausal symptoms and is Food and Drug Administration–approved for this indication at a dose of 0.5 mg drospirenone/1 mg estradiol (marketed in the United States as Angeliq by Berlex Laboratories Inc.). During its development, it was noted that at a higher drospirenone dose, the combination also had antihypertensive properties. It is currently being used in Europe, Asia, and the rest of the world at a dose of 2 mg drospirenone/1 mg estradiol, Dr. White told this news organization. In a multicenter (42 U.S. centers and 22 European centers) trial, Dr. White and his colleagues evaluated the blood pressure–lowering efficacy of various doses of drospirenone (1, 2, or 3 mg) combined with 1 mg of estradiol in 750 postmenopausal women aged 45-75 years, with an untreated systolic blood pressure of 140-179 mm Hg and untreated diastolic blood pressure of 90-109 mm Hg. They also evaluated estradiol alone to elicit data on the effects of estrogen on ambulatory blood pressure, about which little is known, Dr. White wrote.

This novel progestin 'impacts upon aldosterone and therefore has a dose-related reduction in blood pressure—especially systolic blood pressure.'

In addition, because drugs which induce aldosterone blockade have been shown to increase serum potassium, the researchers evaluated the metabolic effects of the combination therapy.

Following a single-blind, placebo phase for 3-4 weeks to establish baseline blood pressure and laboratory values, the women were randomized to one of the three combination treatment arms, to estradiol alone, or to placebo. Twenty-four–hour ambulatory blood pressure monitoring was done at baseline and at 8 weeks.

Drospirenone at the 2-mg dose reduced clinical systolic and diastolic blood pressures by a mean of 12.1 and 9.2 mm Hg, respectively; and by a mean of 13.8 and 8.5 mm Hg, respectively, at the 3-mg dose. Drospirenone at the 1-mg dose was less effective, reducing systolic BP by a mean of 9.8 mm Hg and diastolic BP by a mean of 7.0 mm Hg. The blood pressure–lowering effect of estradiol (–7.6 mm Hg systolic and –5.9 mm Hg diastolic) was similar to that seen with placebo, Dr. White wrote.

Reductions in ambulatory blood pressure showed findings similar to clinic readings, although the combination with 1 mg of drospirenone also had marginal benefits compared with placebo and estradiol alone, he added.

Changes in potassium levels were similar in all groups: Five patients in each of the drospirenone groups and five in the placebo group developed a serum potassium less than or equal to 5.5 mEq/L. The mean maximal change from baseline in drospirenone-treated patients was not significantly different among the five treatment groups and ranged from 0.29 mEq/L to 0.37 mEq/L.

Regarding the combination's effect on lipid levels, total and LDL cholesterol levels also were lowered significantly in women taking drospirenone and estradiol, with a 13.6-mg/dL drop in LDL cholesterol at the 3-mg dose, a 10.4-mg/dL drop at the 2-mg dose, and a 12.2 drop at the 1-mg dose. Triglyceride levels were not affected, Dr. White wrote.

Side effects varied according to drospirenone dose; those seen with a frequency greater than 2% included breast discomfort, vaginal bleeding or spotting, and upper respiratory infection, according to the researchers.

"This is a novel progestin which actually impacts upon aldosterone and therefore has a dose-related reduction in blood pressure—especially systolic blood pressure—which is associated with cardiovascular risk.

"We actually studied a full spectrum of doses, along with estradiol alone and placebo, so the strength of the study is that we actually had these two control groups showing that, in fact, it was the drospirenone that was the important component that lowered the blood pressure. And it did that without any significant metabolic consequences," Dr. White said in an interview.

Dr. White disclosed that he serves as a consultant for Berlex Laboratories Inc., which markets Angeliq, as well as other pharmaceutical companies. ■

Low-Dose Estrogens Help Hot Flashes

BY MARY ELLEN SCHNEIDER
New York Bureau

WASHINGTON — A 0.45-mg daily dose of synthetic conjugated estrogens-A improves moderate to severe menopausal vasomotor symptoms, compared with placebo, according to data presented at the annual meeting of the American College of Obstetricians and Gynecologists.

The results indicate that postmenopausal women who start estrogen therapy at a low dose may be able to gain the efficacy of higher-dose treatments while having minimal side effects, Dr. James A. Simon of George Washington University in Washington and Dr. Sam S. Miller of the SAM Clinical Research Center in San Antonio wrote in a poster presented at the ACOG meeting.

At week 12 of therapy, nearly 38% of patients taking synthetic conjugated estrogens-A (SCE-A) reported no moderate to severe vasomotor symptoms vs. 7.8% of patients taking placebo, according to the researchers. In addition, the 0.45-mg daily dose of SCE-A reduced the mean weekly frequency of moderate to severe vasomotor symptoms by 67.8 from a baseline of 95.9 at 12 weeks, compared with a mean drop of 42.9 among placebo patients from the same baseline score.

The multicenter, double-blind trial included postmenopausal women, with or without a uterus, who had experienced at least 60 moderate to severe vasomotor symptoms per week. A total of 104 patients were randomized to receive either the 0.45-mg dose of SCE-A or placebo daily for 12 weeks. Approximately 91% of the patients taking SCE-A and 67% of the patients taking placebo completed the full 12 weeks of the study.

Nearly 38% of patients taking the estrogens reported no moderate to severe vasomotor symptoms at week 12.

DR. SIMON

The subjects were asked to keep a daily diary of the frequency and severity of their symptoms. Patients also had vital signs, body weight, and adverse events evaluated during six office visits. The investigators assessed the safety and tolerability of the treatment through standard laboratory evaluations at screening and at week 12 of the study.

The research was supported by Duramed Research Inc. of Bala Cynwyd, Pa., which markets SCE-A under the trade name Cenestin. Duramed is a wholly owned subsidiary of Barr Pharmaceuticals.

Cenestin 0.45 mg was approved by the Food and Drug Administration in 2004 for the treatment of moderate to severe vasomotor symptoms.

The patients recruited for the study were healthy women ages 30-80 years who had experienced spontaneous amenorrhea for 12 months prior to screening or who had a bilateral oophorectomy, with or without hysterectomy, at least 6 weeks before screening.

Patients taking SCE-A had a greater reduction in frequency of symptoms starting at week 2 and reaching statistical significance from week 3 on. The drug also resulted in greater reduction in severity of symptoms at week 2, reaching statistical significance from week 5 on. ■

Nonhormonal Treatments for Hot Flashes Rated Not So Hot

Despite the avid interest in finding nonhormonal therapies for menopausal hot flashes, most alternative treatments have demonstrated only limited efficacy, and their safety remains in question, according to a systematic review of the literature.

Dr. Heidi D. Nelson and her associates at Oregon Health and Science University, Portland, identified all randomized, placebo-controlled trials of nonhormonal treatments for hot flashes in the English literature and compared the efficacy and adverse effects of agents other than estrogens, progestins, progesterone, or androgens.

From an initial screening of 4,249 abstracts, they narrowed their focus to 43 trials with adequate study designs. However, even these trials were often flawed by high dropout rates, small study samples, short follow-up periods, and methodologic failings, they noted (JAMA 2006;295:2057-71).

The selected studies included 10 that assessed antidepressants, 10 assessing clonidine, 6 assessing other prescription drugs, and 17 assessing isoflavone extracts.

Eleven of the trials included women with breast cancer, many of whom were receiving tamoxifen. This is a population in whom hot flashes are particularly common and for whom estrogen therapy is contraindicated, the researchers said.

A metaanalysis was conducted using 24 of the 43 studies.

Overall, there was some evidence that selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, clonidine, and gabapentin reduce the severity and frequency of hot flashes. However, none of these agents approached the effectiveness of hormone therapy.

"Although these therapies may be most useful for highly symptomatic women who cannot take estrogen, they are not optimal choices for most women." Their safety as treatments for hot flashes has not been adequately studied, and the adverse effects they cause as well as their cost will make their use prohibitive for many women, Dr. Nelson and her associates said.

The evidence for soy isoflavone extracts was contradictory, "even among the largest and highest quality trials," they noted. No evidence supported the efficacy of red clover isoflavone extracts.

—Mary Ann Moon