**INTRODUCTION**

The World Health Organization (WHO), in conjunction with The International Menopause Society, defines menopause as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Symptoms associated with the menopause transition begin during the climacteric phase and extend through the postmenopause phase. The climacteric phase begins the transition from reproductive to a non-reproductive state.

The perimenopausal period is defined as the time prior to menopause, when the endocrinologic and biologic components begin, until the first year following menopause.

Postmenopause is inaugurated from the final menstrual period, whether menopause is induced mechanically or whether it occurs naturally.

In the U.S., the fastest-growing segment of the population comprises women older than 50 years, in the age group usually corresponding with the onset of menopause. Approximately 80% to 85% of American menopausal women report that menstruation resulting from the loss of ovarian follicular activity. Symptoms associated with the menopause transition begin during the climacteric phase and extend through the postmenopause phase. The climacteric phase begins the transition from reproductive to a non-reproductive state.

The menstrual cycle is regulated by the hypothalamic–pituitary–ovarian axis with a feedback system involving gonadotropins, gonadotropin–releasing hormone (GnRH), ovarian hormones, neurotransmitters, and neuropeptides. GnRH, discharged from the hypothalamus, regulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations. Estrogen levels are decreased in the beginning of the follicular phase, leading to an elevation in FSH and LH and resulting in regeneration of follicular growth.

After the follicle matures, estrogen production increases. Because increased estrogen levels are a precursor to the elevation of LH, ovulation is stimulated. In the absence of fertilization, the corpus luteum dissipates, culminating in a decline in estrogen and progesterone and ultimately triggering degeneration of the uterine lining and menstruation.

During the fourth decade of life, a decline in the activity of the ovarian follicles is commonly noted. During perimenopause, follicular activity is diminished at an accelerated rate, and the follicles become less responsive to FSH stimulation. By the time menopause has occurred, only a few ovarian follicles are present.

In September 2005, the U.S. Food and Drug Administration (FDA) approved a combination of estradiol 1 mg and drospirenone 0.5 mg (Angeliq, Berlex Labs) for the treatment of moderate-to-severe vasomotor symptoms associated with menopause. To date, this is the only hormone replacement therapy (HRT) that contains the synthetic progestin drospirenone. The estradiol component of the drug mimics the actions of estrogen, which is normally produced by the ovaries before menopause. Because of the health risks associated with estrogen monotherapy (e.g., endometrial hyperplasia and an increased risk of endometrial carcinoma), concurrent administration of progestin has been recommended.

Within four weeks of treatment, drospirenone/estradiol relieved moderate-to-severe vasomotor symptoms such as hot flashes, night sweats, and vulval and vaginal atrophy.

**PHARMACOLOGY**

Drospirenone is a spironolactone analogue with anti-mineralocorticoid and anti-androgen activity, and it specifically counters estrogenic effects. It is worth noting that unopposed estrogen has been associated with an increased risk of endometrial carcinoma in women with an intact uterus. Drospirenone substantially reduces this risk by decreasing the number of nuclear estradiol receptors and by suppressing epithelial DNA synthesis in endometrial tissue.

Specifically, progestins diffuse freely into target cells (e.g., the female reproductive tract, mammary glands, hypop-
thalamus, and pituitary gland) and bind to the progesterone receptor. After progesterone is bound, it converts a proliferative endometrium into a secretory one, reducing endometrial growth.

Estradiol is the principal intracellular human estrogen; it plays a vital role in modulating the pituitary secretion of LH and FSH through a negative feedback mechanism. In postmenopausal women, the most abundant circulating estrogens are estrone and its sulfate-conjugated form, estrone sulfate. Estrone and estriol are also metabolites of estradiol; they possess estrogenic activity but to a lesser degree. Estradiol, estrone, and estriol influence cervical secretions, proliferation of the endometrium, and the elasticity and tone of urogenital structures.

Estrogens have weak anabolic activity and can affect the deposition of bone calcium. Moreover, estrogens appear to prevent osteoporosis associated with menopause, primarily by preserving bone mineral density.6,7

PHARMACOKINETICS

The relative oral bioavailability of drospirenone/estradiol tablets is 102% and 107%, respectively, compared with an oral suspension of the combination. Serum peak concentrations are reached six to eight hours after oral dosing. The bioavailability of drospirenone and estradiol in other combinations is not affected when the tablet is taken with food; however, the effects of administering this medication with food have not been studied.

Drospirenone has a mean volume of distribution of 4.2 L/kg. After administration, it is 97% bound to serum plasma proteins, whereas estradiol is 37% bound to sex hormone–binding globulin and 61% bound to albumin (Table 1).

Patients with renal or hepatic impairment should not take this medication. To illustrate, although drospirenone is not metabolized via the cytochrome P450 (CYP 450) system, it is extensively converted to inactive metabolites after oral administration. By contrast, estradiol undergoes sulfation and glucuronidation in the liver to form estrone. Studies suggest that estrogens are partially metabolized via CYP 450 isoenzyme 3A4; therefore, medications that inhibit or induce this isoenzyme may affect estradiol’s metabolism.

Estradiol and estrone coexist in a dynamic equilibrium; both may be converted to their major urinary metabolite—estriol. Because drospirenone is extensively metabolized by the liver, approximately 20 various metabolites have been found in urine and feces. Estradiol, estrone, and estriol, as well as their sulfate and glucuronide conjugates, are excreted via the urine.1

As a consequence of drospirenone’s aldosterone antagonistic activity, serum potassium levels may become elevated when the hormone is taken with medications such as angiotensin-converting enzyme (ACE)–inhibitors, angiotensin-receptor blockers (ARBs), or non-steroidal anti-inflammatory agents (NSAIDs). Nonetheless, no clinically significant changes in serum potassium levels resulting in hyperkalemia have been observed in patients treated with drospirenone/estradiol therapy.6,8

The goal of the study was to determine the effect of 13 28-day cycles of drospirenone combined with estradiol, compared with estradiol alone, on the endometrium. The women had not previously exposed to hormonal therapy.

The presence of endometrial hyperplasia served as the primary efficacy variable; the observation of bleeding patterns, the frequency and severity of hot flashes, urogenital symptoms, and health-related quality of life (HRQoL) were secondary efficacy variables.

The authors assessed the effects of the study medications on endometrial proliferation over a one-year period via biopsy or transvaginal ultrasonography (Table 2). The participants subjectively reported bleeding patterns, the incidence and severity of hot flashes, and urogenital symptoms (e.g., vaginal dryness, pain during sexual intercourse, frequent urination, involuntary urination, and nocturia).

The Medical Outcomes Study Short Form-36 Health-Related Quality-of-Life Questionnaire (SF-36) and the Women’s Health Questionnaire were used to assess the medication’s effects on the participants’ quality of life.

Combinations of drospirenone and estradiol, when compared with estradiol alone, were protective against endometrial hyperplasia. This combination was also effective in reducing menopausal symptoms, thereby elucidating improvements in HRQoL measures without significant adverse drug events (ADEs).9

CLINICAL TRIALS

The Archer Study9

In a double-blind, parallel, multicenter trial, Archer et al. randomly assigned postmenopausal women between 42 and 75 years of age with an intact uterus to receive one of these combinations:

- 0.5 mg of drospirenone/1 mg of estradiol
- 1 mg of drospirenone/1 mg of estradiol
- 2 mg of drospirenone/1 mg of estradiol
- 3 mg of drospirenone/1 mg of estradiol
- 1 mg of estradiol alone

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Table 1 Pharmacokinetics of Drospirenone/Estradiol

<table>
<thead>
<tr>
<th></th>
<th>Cmax (ng/ml)</th>
<th>AUC (ng/ml · hour)</th>
<th>Relative Bioavailability*</th>
<th>Protein Binding</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>18.3</td>
<td>208</td>
<td>107%</td>
<td>98%†</td>
<td>GI mucosa; hepatic Hepatic</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>43.8</td>
<td>665</td>
<td>102%</td>
<td>97%</td>
<td></td>
</tr>
</tbody>
</table>

* Compared with an oral combination suspension.

† 37% sex hormone–binding globulin; 61% albumin.

AUC = area-under-the-curve-concentration; Cmax = peak plasma concentration; GI = gastrointestinal.

The Schurmann Study

Schurmann and associates evaluated the effect of drospirenone/estradiol in 225 healthy postmenopausal Caucasian women between 45 and 65 years of age. Two weeks prior to the start of the study, the women were asked to self-report if they had at least five moderate-to-severe hot flashes per day. The study was randomized, and the participants were assigned as follows:

- Group 1: drospirenone 1 mg/estradiol 1 mg
- Group 2: drospirenone 2 mg/estradiol 1 mg
- Group 3: drospirenone 3 mg/estradiol 1 mg
- Group 4: placebo

The women received one tablet, given at the same time each day, for 16 weeks. Inclusion criteria were as follows:

- The women had to have an intact uterus with a normal endometrium.
- Estradiol levels had to be 20 pg/ml or below.
- Serum FSH levels had to be 50 U/L or greater.
- No history of cardiovascular disease, hypertension, type-1 diabetes mellitus, or previous estrogen or progestin hormone therapy.
- No recent myocardial infarction, unstable angina, or congestive heart failure.
- No liver or renal disease.
- No a history of stroke, venous thromboembolic disorders, or type-1 diabetes mellitus.
- No hormone therapy preparations within six weeks of the trial.
- No recent myocardial infarction, unstable angina, or congestive heart failure.
- No liver or renal disease.
- No a history of stroke, venous thromboembolic disorders, or type-1 diabetes mellitus.

The primary endpoint of the study was to identify changes in the frequency and intensity of hot flashes from baseline evaluation. Secondary endpoints consisted of identifying changes in the frequency and intensity of other menopausal symptoms: sweating, sleep disturbances, depression, nervousness, urogenital symptoms, vaginal bleeding, and ADEs.

The results demonstrated the effectiveness of the drospirenone/estradiol combination in decreasing the number of hot flashes per week in all treatment arms by 86% to 90% (P < .001) compared with the rate for placebo—45% (Table 3). For the three active study arms, the combination therapy was also more effective than placebo in relieving sweating episodes, sleep disturbances, depression, nervousness, and urogenital symptoms. The most commonly reported ADE was breast pain.

The White Study

Postmenopausal women between 45 and 80 years of age were recruited for this randomized trial. The primary objective was to determine the antihypertensive effects of drospirenone with estradiol.

In order to be included in the study, the women had to have an untreated systolic blood pressure reading of greater than 140–159 mm Hg and/or a diastolic blood pressure reading of 90 to 99 mm Hg. Exclusion criteria were as follows:

- had a history of cardiovascular disease, depression, diabetes mellitus, hypertension, alcohol or drug abuse, or thromboembolic disease.
- had been exposed to oral, transdermal, or vaginal, or implanted hormonal preparations within six weeks of the trial.
- had previously received estrogen or progestin hormone therapy.
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- had previously received estrogen or progestin hormone therapy.
- had a history of stroke, venous thromboembolic disorders, or type-1 diabetes mellitus.

Two hundred thirteen participants were divided into two treatment arms, receiving either placebo or drospirenone 3 mg/estradiol 1 mg every morning for 12 weeks. This combination lowered both clinical and daytime ambulatory blood pressures by an average of 7 mm Hg (systolic) and 4 mm Hg (diastolic) in these postmenopausal women with stage I hypertension.

The most commonly reported ADE was dizziness. Hyperkalemia was also noted, but no one in the study had to withdraw as a result of increased serum potassium levels (above 5.5 mEq/L).

The researchers suggested that the combination might be cardioprotective in a population with increased cardiovascular risk. However, the FDA cautions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>Mean Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>59</td>
<td>-47.0</td>
</tr>
<tr>
<td>Group 1</td>
<td>55</td>
<td>-85.6</td>
</tr>
<tr>
<td>Group 2</td>
<td>52</td>
<td>-88.0</td>
</tr>
<tr>
<td>Group 3</td>
<td>57</td>
<td>-84.5</td>
</tr>
</tbody>
</table>

Group 1 = drospirenone 1 mg/estradiol 1 mg; Group 2 = drospirenone 2 mg/estradiol 1 mg; Group 3 = drospirenone 3 mg/estradiol 1 mg.

against taking estrogen plus progestin to reduce the risk of cardiovascular disease. Moreover, the rate of women who experienced cardiovascular disease increased by 29% in those taking estrogen plus progestin, in comparison with those taking placebo.10,11

ADVERSE DRUG INTERACTIONS

As noted in the package insert, the Women’s Health Initiative (WHI) documented an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis (DVT) for participants 50 to 79 years of age who were treated for five years with oral conjugated equine estrogens combined with medroxyprogesterone acetate (e.g., Premphase, Prempro, Wyeth) or placebo. The WHI Memory Study also reported a potentially increased risk of dementia in postmenopausal women 65 years of age or older during four years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate and 5.2 years of treatment with conjugated estrogens (e.g., Premarin, Wyeth; Cinestin, Duramed) alone relative to placebo.

Although medroxyprogesterone was the progestin used in these studies, a boxed warning mentions these potential adverse risks; such risks should be assumed to be similar with drospirenone/estradiol.6,11 Other serious ADEs included breast pain, vaginal hemorrhage, upper respiratory infection, headache, and abdominal pain (Table 4).6,9

INDICATIONS

Drospirenone/estradiol is indicated for women with a uterus for the treatment of moderate-to-severe vasomotor symptoms and symptoms of vulval and vaginal atrophy associated with the menopause.

CONTRAINDICATIONS AND PRECAUTIONS

Drospirenone/estradiol and other estrogen/progestin combinations are contraindicated in patients with undiagnosed abnormal genital bleeding; a known or suspected history of breast cancer or estrogen-dependent neoplasia; a history of or active DVT, pulmonary embolism, or arterial thromboembolic disease; a known or suspected pregnancy; and renal, hepatic, or adrenal impairment (Table 5). This medication should not be used by patients with a hypersensitivity to its ingredients.6

DOSAGE AND ADMINISTRATION

The recommended dose is one tablet daily, with re-evaluations scheduled periodically to determine whether treatment is still needed.

Special Populations

After seven days of oral drospirenone 3 mg/day, drospirenone concentrations were approximately 37% higher in patients with a creatinine clearance between 30 and 50 ml/minute. No pharmacokinetic studies have been conducted in geriatric populations. Differences in the pharmacokinetics of drospirenone/estradiol in various ethnic groups have not been investigated.5,7

OTHER TREATMENT OPTIONS

Therapeutic options for the management of vasomotor symptoms associated with menopause include lifestyle modifications, nutrition and diet, herbal therapies, and nonhormonal therapies. Exam...
variables of lifestyle changes include limiting caffeine and alcohol intake, smoking cessation, and regular exercise.

Phytoestrogens (plant estrogens) contain estrogen-like properties and are found in many foods. Three primary food sources that contain phytoestrogens include isoflavones (legumes and soy products), lignans (cereals, vegetables, seeds), and coumestans (alfalfa).

Although alternative plant-based and herbal therapies may be helpful for menopausal symptoms and are sometimes associated with fewer ADEs than traditional HRT, the evidence is not definitive. Herbals and supplements that have been widely used to manage menopausal symptoms are black cohosh, dong quai, ginseng, evening primrose oil, vitamin E, and wild yam. Nonhormonal pharmacological agents used as an alternative to HRT for managing vasomotor symptoms are alpha2-adrenergic agonists (e.g., clonidine [Catapres, Boehringer Ingelheim]), antidepressants such as selective serotonin reuptake inhibitors (SSRIs), and selective serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine [Effexor, Wyeth]).

CONCLUSION
For postmenopausal women with an intact uterus, drospirenone/estradiol (Angeliq) is the newest form of HRT to be approved by the FDA for the treatment of moderate-to-severe vasomotor symptoms or symptoms of vulval and vaginal atrophy.

Women with a history of breast cancer, estrogen-dependent neoplasms, or hepatic or renal insufficiency should not use this medication. Like other HRTs containing a progestin and estrogen combination, Angeliq is effective in reducing symptoms associated with menopause; however, physicians and patients should weigh the benefits and risks of therapy.

REFERENCES