Clinical Responses to the Combination of Estradiol and Drospirenone in Symptomatic Postmenopausal Thai Women

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Objectives: *To investigate the efficacy and tolerability of the oral hormone replacement therapy (HRT) containing 1 mg estradiol (E2) plus 2 mg drospirenone (DRSP) in Thai women with postmenopausal symptoms.*
Material and Method: *Fifty-five Thai women with postmenopausal symptoms participated in this multicenter, open-label, non-comparative Phase IV study. The primary endpoint was the reduction of hot flushes after 12 weeks of treatment. Secondary endpoints included changes in frequency and intensity of menopausal symptoms as well as safety assessments after 4, 8, and 12 weeks of treatment.*
Results: *Treatment with 1 mg E2 plus 2 mg DRSP reduced the frequency of hot flushes in 94.6% of women at the end of the 12-week treatment period. In 60% of women, the frequency of hot flushes was reduced to 10% or less, compared to baseline findings and 49.1% of women had no remaining hot flushes. Other postmenopausal symptoms such as vaginal dryness, urinary incontinence, dysuria, and dyspareunia improved. The most common adverse events were vaginal bleeding or spotting and breast tenderness.*
Conclusion: *The oral HRT of 1 mg E2 plus 2 mg DRSP was effective and well tolerated by Thai women suffering from postmenopausal symptoms.*

Keywords: *Drospirenone, Estradiol, Hormone replacement therapy (HRT), Menopause*

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Decreased estrogen levels during menopause can cause postmenopausal symptoms such as hot flushes and urogenital symptoms that may impair the quality of life of affected women. Estrogen therapy can relieve postmenopausal symptoms, including the symptoms related to atrophic changes in the urogenital tract, and prevent osteoporosis[1,2]. In a subset of women, hormone replacement therapy (HRT) may reduce the risk of cardiovascular events[3]. In women with an intact uterus, however, estrogen monotherapy induces endometrial proliferation, which increases risk of endometrial malignancies. Progestogens effectively prevent endometrial proliferation induced by estrogen and thereby reduce the risk of endometrial cancer[4,5].

The combination of 1 mg estradiol (E2) plus 2 mg drospirenone (DRSP) is an effective treatment for postmenopausal symptoms and osteoporosis prevention. DRSP is a novel synthetic progestogen with a pharmacodynamic profile similar to endogenous progesterone. Unlike other synthetic progestogens, DRSP has no androgenic activity[6]. Furthermore, DRSP is devoid of estrogenic, glucocorticoid, or antiglucocorticoid activity[7,8]. Notably, DRSP's unique aldosterone receptor-antagonist properties are also associated with antihypertensive effects in mildly hypertensive women[7,9,10].

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The efficacy and safety profile of 1 mg E2 plus 2 mg DRSP has been studied in a large number of clinical trials, mostly involving Caucasian women[2,3,7,10-12]. However, the prevalence and severity of postmenopausal symptoms as well as the sensitivity and responsiveness to treatment may differ among ethnic groups[13,14]. The purpose of the present trial was to investigate the efficacy and tolerability of 1 mg E2 plus 2 mg DRSP (Angeliq®, Bayer Schering Pharma AG, Berlin, Germany) as an oral HRT in postmenopausal Thai women suffering from hot flushes and other postmenopausal symptoms.

Material and Method

This multicenter, open-label, noncomparative Phase IV study was planned and conducted in five centers in Thailand according to Thai national laws and in compliance with the ethical principles from the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Good Clinical Practice (ICH-GCP) Guidelines of January 17, 1997. The Ethical Committees of all participating centers approved the present study protocol and all participating subjects gave written informed consent before trial entry.

Inclusion/exclusion criteria

Between September 2005 and December 2006, 111 postmenopausal Thai women 45 years or older were screened. Fifty-five women were enrolled. Women with amenorrhea for more than 12 months, or with amenorrhea for more than 6 months with serum follicle-stimulating hormone (FSH) levels > 40 mIU/ml, and women with bilateral oophorectomy were eligible to participate in the present study if they had at least 24 hot flushes over seven consecutive days within a 14-day time frame. In addition, women must have had normal clinical breast examination and normal mammograms within one year prior to screening. Women with an intact uterus had to have a double-layer endometrial thickness of < 5 mm and a negative pregnancy test.

Exclusion criteria included contraindications to HRT, treatment with an anticoagulant, known or suspected premalignant or malignant lesions, clinically significant abnormal laboratory values, a history of myocardial infarction less than 6 months prior to the present study entry, severe coronary heart disease or congestive heart failure, uncontrolled hypertension, a history of stroke or transient ischemic attacks, thrombophlebitis, or thromboembolic disorder. Women with uncontrolled thyroid disorders, insulin-dependent diabetes mellitus, a history of severe headaches during previous estrogen therapies, or a history of depression or vaginal bleeding of unknown cause were also excluded.

Study design

The present study was composed of four phases: screening, baseline, 12-week treatment phase, and 2-week follow-up phase. Six clinical visits were scheduled throughout the study, consisting of screening visit, baseline visit, visits during the treatment phase (weeks 4, 8, and 12), and one follow-up visit two weeks after the end of treatment (week 14).

During the screening phase of the present study, patients documented the number and intensity of hot flushes per day as well as vaginal bleeding patterns on diary cards for two weeks. If a cumulative total of at least 24 hot flushes of any severity over seven consecutive days was documented, the patient was eligible to undergo further screening examinations including gynecological, medical, surgical and medication history, physical and gynecological examination, laboratory studies including FSH and thyroid-stimulating hormone (TSH) levels, cervical cytology (Pap smear), transvaginal ultrasound (in cases with an intact uterus), and bilateral mammography (if not performed within one year prior to screening).

Eligible women entered the 12-week treatment phase, during which they received 1 mg E2 plus 2 mg DRSP (Angeliq®, Bayer Schering Pharma AG, Berlin, Germany) once daily without interruption for 12 weeks. During the treatment phase and the 2-week follow-up phase, patients continued to record the number and intensity of hot flushes and vaginal bleeding pattern on diary cards.

The primary endpoint was the change in frequency of hot flushes from baseline to the end of the 12-week treatment period. The reduction in the frequency of hot flushes was expressed as the individual relative change (%) in the number of hot flushes in week 12 compared with baseline values. Weekly rates (number of hot flushes per week) as well as absolute and relative change from baseline in weekly rates of hot flushes were described by giving summary statistics. According to their response, subjects were divided into three groups: women with any kind of reduction in the number of hot flushes, women with a 90% reduction, and women with a 100% reduction (no remaining hot flushes after treatment). The two-

sided 95% exact binomial confidence intervals for these proportions are reported.

Secondary efficacy endpoints included change in intensity (mild, moderate, or severe) of hot flushes and effects on urogenital symptoms. The absolute changes in the intensity of hot flushes from baseline to weeks 4, 8 and 12 were described for each woman in relation to the total number of hot flushes recorded during these periods. Urogenital symptoms (vaginal dryness, pollakiuria, nocturia, urinary incontinence, dysuria and dyspareunia) were assessed at baseline and at weeks 4, 8 and 12 as either present or absent and were summarized by using frequency counts and the relative percentage change across visits.

Safety variables included vaginal bleeding patterns recorded during the treatment period in women with an intact uterus. Bleeding intensities were graded as none, spotting, light, normal, or heavy and were presented using descriptive statistics. Other safety variables included adverse events (AEs), physical and gynecological examinations and laboratory evaluations and these were also evaluated descriptively.

Statistical analysis

Quantitative data were summarized as descriptive statistics, including number of patients and minimum, maximum, mean, standard deviation and median values. Qualitative data were displayed as frequency tables, including absolute counts, as well as relative frequencies in percent. For efficacy parameters, both per-protocol-set analysis (PPS; 42 subjects) and full-analysis-set analysis (FAS; 55 subjects) were performed. A patient was included in the PPS if she had no major protocol deviations that might have affected the primary target variable. A patient was included in the FAS if she had taken at least one dose of the present study medication and if at least one observation after dosing was available. The outcomes of both analysis sets were similar. In the present report the FAS is presented. A p-value of less 0.05 was considered statistically significant.

Results

One hundred eleven postmenopausal Thai women were screened for eligibility. Fifty-five women between 46 and 71 years of age were enrolled into the present study. The main reasons for screening failures were insufficient numbers of hot flushes during the screening period and abnormal baseline laboratory parameters. Mean age was 52.3 years old (SD 4.9) with average BMI at 23.3 kg/m^2 (SD 2.6). Mean time since last menstruation was 77.2 months (SD 106.6). Seventeen women (30%) underwent hysterectomy with or without oophorectomy.

Efficacy

After 12 weeks of treatment, the great majority of women (94.6%) had a reduced frequency of hot flushes compared to baseline. In more than half of the women (60.0%) the frequency of hot flushes was reduced to 10% or less and about half of the women (49.1%) had no remaining hot flushes at the end of the 12-week treatment period (Table 1).

At the first assessment (week 4) the mean number of hot flushes decreased from 51.1 at baseline to 21.4, translating to a relative reduction in mean hot flushes of 61.9% (SD 47.9%). Further reductions in the mean number of hot flushes to 15.2 and 13.2, respectively, were observed at weeks 8 and 12. This translates to a relative reduction in the mean number of hot flushes of 74.2% (SD 45.9%) and 74.5% (SD 52.1%) compared with baseline at weeks 8 and 12, respectively (Table 2).

As a secondary endpoint, changes in the intensity of hot flushes after 4, 8, and 12 weeks of treatment compared with baseline were measured. Fig. 1 shows the mean proportions of mild, moderate, and severe hot flushes among the total number of hot flushes at baseline and at treatment weeks 4, 8, and 12.

Table 1. Proportion of patients who showed a reduction in the frequency of hot flushes at treatment week 12 in the FAS

Patients with reduction in hot flashes compared to baseline (n = 55)	Responders	Proportion (%)	95% CI
Any reduction	52	94.6	(83.9-98.9)
90% reduction	33	60.0	(45.9-73.0)
100% reduction	27	49.1	(35.4-62.9)

FAS = full analysis set analysis; CI = confidence interval

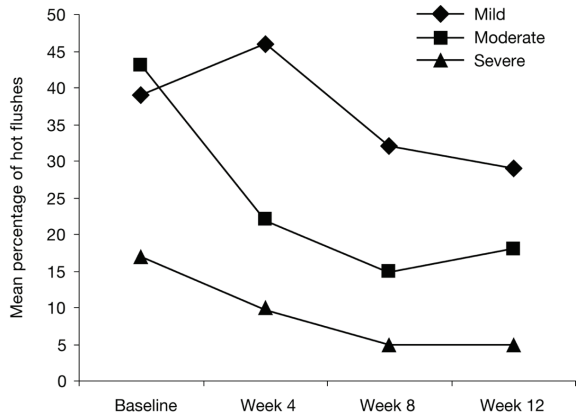


Fig. 1 Mean proportions of mild, moderate, and severe hot flushes at baseline and treatment weeks 4, 8, and 12 in the FAS

The mean proportions of moderate and severe hot flushes were markedly reduced at treatment weeks 4, 8, and 12 compared with baseline. The mean proportion of mild hot flushes transiently increased from baseline to week four before dropping below the baseline value at weeks 8 and 12.

The frequencies of urogenital symptoms such as pollakiuria, involuntary urination, dysuria, and dyspareunia as well as vaginal dryness were reduced after 12 weeks of treatment. For women with urogenital symptoms, improvement became apparent within the first four weeks of treatment. Nocturia was the only urogenital symptom that did not reduce in frequency during the treatment period.

Safety

One hundred forty nine AEs were recorded in 47 women. Seventy-six AEs (51%) were considered to be possibly, probably, or definitely related to treatment. Table 3 provides an overview of AEs occurring in at least 3% of women. The most frequent treatment-related AEs in the FAS were vaginal bleeding or spotting events (54.5%), and breast tenderness (25.5%).

Among 38 women with an intact uterus, 30 (78.9%) experienced vaginal bleeding or spotting events at some stage during the present study. Vaginal bleeding patterns in these women were analyzed for weeks 1-4, 5-8, and 9-12 to identify potential changes in frequency, duration, and intensity over time. During the first four weeks of treatment, 29.9% of women had vaginal bleeding or spotting events. During week five to eight, the proportion of women reporting bleeding or spotting events increased to 51.4% but remained stable after an additional four weeks of treatment. The mean duration of bleeding or spotting events was 1.9, 4.3, and 4.8 days during the first, second, and third 4-week-treatment periods, respectively. Overall, the bleeding intensities were assessed to be low in each treatment period analyzed, with spotting and light bleeding being the most predominant bleeding pattern (Fig. 2). All patients who experienced vaginal bleeding recovered within two weeks post-treatment.

Five women discontinued treatment prematurely. Two of the women had elevated fibrinogen levels prior to the start of treatment. One woman had vertigo, considered to be unrelated to

Table 2. Number of hot flushes at baseline, treatment weeks 4, 8, and 12, and follow-up visit in the FAS

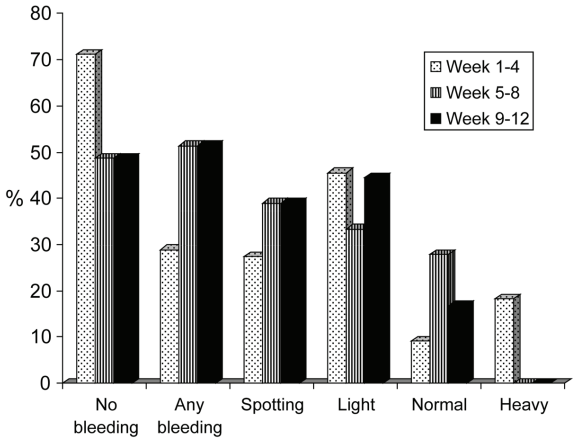
Treatment (n = 55)	Mean	SD	Min	Median	Max
Baseline	51.1	31.2	10.0*	48.0	199.0
Week 4	21.4	39.6	0.0	9.0	254.0
Week 8	15.2	36.7	0.0	1.0	231.0
Week 12	13.2	33.3	0.0	1.0	229.0

* Please note that the number of hot flushes needed to be at least 24 within 7 consecutive days during the 14-day screening period. The 7 consecutive days with at least 24 hot flushes were not necessarily the last 7 days of screening
FAS = full analysis set analysis

Table 3. Most frequently reported adverse events (AEs) with a prevalence of at least 3% in the FAS

	AEs (n = 107)	Subjects (n = 55)	
	n	n	%
Vertigo	4	4	7.3
Dry mouth	2	2	3.6
Pyrexia	2	2	3.6
Arthralgia	2	2	3.6
Back pain	2	2	3.6
Musculoskeletal pain	2	2	3.6
Dizziness	3	3	5.5
Headache	5	4	7.3
Breast tenderness	18	14	25.5
Vaginal bleeding or spotting	64	30	54.5*
Genital pruritus	2	2	3.6

*Among women with an intact uterus, 30/38 (78.9%) reported vaginal bleeding or spotting. Please also see Fig. 2
FAS = full analysis set analysis



Note: bleeding pattern was evaluated for women with an intact uterus.

* Three women with an intact uterus discontinued study participation. Of the three, one woman discontinued due to heavy vaginal bleeding

Fig. 2 Vaginal bleeding intensities during three consecutive 4-week treatment periods in women with an intact uterus

treatment, one woman had uterine bleeding pain, and another woman experienced dizziness, which was considered to be potentially treatment-related. Three AEs in two women were serious (pneumonia, subacute tracheobronchitis, and bronchitis). All serious AEs were considered to be unrelated to treatment.

The results of blood pressure monitoring at baseline, weeks 4, 8, and 12, and at follow-up did not change significantly.

Discussion

The present study demonstrated that the combination of 1 mg E2 plus 2 mg DRSP is effective in reducing the incidence and severity of hot flushes in postmenopausal Thai women. The primary endpoint of the present study was the change in frequency of hot flushes from baseline to treatment week 12. The vast majority (94.6%) of women benefited from treatment by a reduction in the incidence of hot flushes, with about half of women (49.1%) having no remaining hot flushes after 12 weeks of treatment. The mean number of hot flushes decreased by over 74%, from 51.1 to 13.2. The reduction in the frequency of hot flushes in the present study was slightly lower compared with previously reported reductions in Caucasian and Korean women using the same HRT, although in both other studies the treatment period was 4 weeks longer than in the present study. After 16 weeks of treatment, Schurmann et al reported a mean relative reduction in hot flushes of 85.6% in postmenopausal Caucasian women[2]. With a relative reduction of 84.4% after 16 weeks of treatment, Lee et al reported a virtually identical relative reduction in Korean women[15].

In the present study, the authors observed a steady decline in the frequency of hot flushes throughout the entire treatment period, suggesting that an extension of the treatment period to 16 weeks may have resulted in a similar reduction as reported in both previous studies. Lee et al reported a steady decline throughout the entire 16-week treatment period, suggesting that a further decline beyond 16 weeks of treatment may also be possible.

Consistent with Schurmann et al, the reduction in the frequency of hot flushes observed in the present study was accompanied by a decreasing intensity of the remaining hot flushes. In particular, the relative proportions of the more intensive hot flushes (severe and moderate) declined within the first four weeks of treatment, demonstrating rapid symptom relief after initiation of treatment. The transient relative increase in the proportion of mild hot flushes is likely caused by a conversion of pre-existing more intensive hot flushes into less intensive forms.

In the present study, secondary efficacy endpoints included changes in urogenital symptoms such as vaginal dryness, urinary incontinence, dysuria, dyspareunia, and nocturia. With the exception of nocturia, all urogenital symptoms improved within four weeks of treatment and remained improved until the end of the treatment period. The improvements in urogenital symptoms are similar to those previously reported[15]. However, in that study the authors further reported an improvement of nocturia from baseline to the end of the 16-week treatment period (from 28.6% of the valid-case population to 14.3%, respectively), whereas in the present study a slightly increase in the proportion of women reporting nocturia was observed throughout the entire study period. The reason for this discrepancy could be the timing of treatment administration. In the present study the great majority of women (> 95%) took their medication in the late evening before going to bed. The mild antidiuretic effects of DRSP, due to its aldosterone receptor-antagonist properties[7], may have contributed to an increased frequency of urination during the night.

All side effects reported in the present study have also been reported previously. No treatment-related serious AEs occurred in the present study.

In line with previous reports[15,17], vaginal bleeding or spotting was the most commonly observed side effect. At least one episode of vaginal bleeding or spotting was observed in 51.4% of women with an intact uterus during each treatment period analyzed. The result is virtually identical to the results in Caucasian women reported by Barnabei et al[17]. In their placebo-controlled, randomized study, the proportion of women experiencing vaginal bleeding in the treatment arm was 51% vs. 5% of women receiving placebo. In the present study, as well as in other studies[2,15,17], vaginal bleeding was mostly of a mild nature and short in duration. Consistent with the reports of others, the authors observed that after an initial increase in vaginal bleeding, the frequency and intensity of these events decreased with continued treatment. The second most common side effect in the present study, reported by 25.5% of women, was breast tenderness. This is a well-known side effect of HRT. However, in other studies using the same HRT, the proportion of women with breast tenderness was slightly lower (8.9%[15] and 18.5%[2]).

In conclusion, the oral HRT containing 1 mg E2 plus 2 mg DRSP was effective and well tolerated in Thai women suffering from postmenopausal symptoms. DRSP's efficacy and safety in the present study was comparable with studies of DRSP conducted in Caucasian women. The mild blood pressure-lowering effect distinguishes this combination HRT from others, thereby providing additional benefits to patients.

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Potential conflicts of interest

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การศึกษาการตอบสนองทางคลินิกต่อการรักษาด้วยฮอร์โมนทดแทนที่ประกอบด้วย estradiol และ drospirenone ในหญิงไทยวัยหมดประจำเดือน

สุกัญญา ชัยกิตติศิลป์, สุรศักดิ์ อังสุวัฒนา, สมศักดิ์ เชาว์วิศิษฐ์เสรี, มยุรี จิรภิญโญ, กิตติศักดิ์ วิลาวรรณ, กระเษียร ปัญญาคำเลิศ, อรรณพ ใจสำราญ, กิติรัตน์ เตชะไตรศักดิ์, นันทนา มรกต, ชาญชัย สุชาติวัฒนชัย, วรพงษ์ คงมีผล, นิมิต เตชไกรชนะ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิผล และความปลอดภัยของฮอร์โมนทดแทนชนิดรับประทาน ซึ่งประกอบด้วย estradiol 1 มิลลิกรัมและ drospirenone 2 มิลลิกรัม ในหญิงไทยวัยหมดประจำเดือน*

วัสดุและวิธีการ: *เป็นการศึกษาระยะที่ 4 แบบหลายสถาบัน เปิดฉลากและไม่มียาเปรียบเทียบในหญิงไทยวัยหมดประจำวันเดือน จำนวน 55 ราย วัตถุประสงค์หลัก คือ เพื่อศึกษาการลดอาการร้อนวูบวาบ หลังจากได้ยา 12 สัปดาห์ วัตถุประสงค์รอง คือ ศึกษาการเปลี่ยนแปลงความถี่ และความรุนแรงของอาการหมดประจำเดือนอื่น ๆ รวมถึงศึกษาความปลอดภัยของการใช้ยาภายหลังจากการรักษา 4, 8 และ 12 สัปดาห์ ตามลำดับ*

ผลการศึกษา: *การรักษาด้วยฮอร์โมนทดแทนที่ประกอบด้วย estradiol 1 มิลลิกรัมกับ drospirenone 2 มิลลิกรัม ช่วยลดความถี่ของการเกิดอาการร้อนวูบวาบลงถึงร้อยละ 94.6 เมื่อสิ้นสุดระยะการรักษา 12 สัปดาห์ ผู้หญิงในกลุ่มศึกษาร้อยละ 60 พบว่าอาการร้อนวูบวาบดีขึ้นโดยเหลือเพียงไม่เกินร้อยละ 10 เมื่อเทียบกับก่อนรักษา และผู้หญิงร้อยละ 49.1 ไม่มีอาการร้อนวูบวาบเหลืออยู่เลย นอกจากนี้ อาการอื่น ๆ ของวัยหมดประจำเดือน เช่น ช่องคลอดแห้ง, กลั้นปัสสาวะไม่อยู่, ปัสสาวะแสบ และเจ็บเมื่อมีเพศสัมพันธ์ ก็ลดลงด้วย อาการข้างเคียงที่พบบ่อยที่สุด คือ เลือดออกกะปริดกะปรอยทางช่องคลอดและอาการเจ็บหรือคัดหน้าอก*

สรุป: *การรับประทานฮอร์โมนทดแทนที่ประกอบด้วย estradiol 1 มิลลิกรัมและ drospirenone 2 มิลลิกรัม มีประสิทธิภาพและความปลอดภัยในหญิงไทยที่มีอาการขาดฮอร์โมนในวัยหมดประจำเดือน*