Objective: To compare two new transdermal, continuous, combined formulations and an oral regimen of hormone replacement therapy (HRT) with respect to endometrial hyperplasia, bleeding patterns, and climacteric symptoms in postmenopausal women.

Methods: This was a randomized, open, parallel-group trial during 1 year in 441 postmenopausal women who received either a 10-cm² patch of 0.025 mg estradiol (E₂) and 0.125 mg norethisterone acetate, a 20-cm² patch of 0.05 mg E₂ and 0.25 mg norethisterone acetate twice weekly, or tablets of 2 mg E₂ and 1 mg norethisterone acetate once daily. The efficacy variables were frequency of endometrial hyperplasia after 1 year of treatment, number of bleeding and spotting days from the fourth to sixth treatment months, relief of climacteric symptoms, and tolerability.

Results: The frequency of endometrial hyperplasia was no more than 2% after 1 year of treatment in all groups. One case of simple hyperplasia was detected among the women treated with 10-cm² patches and two among those treated with oral HRT. From the fourth to sixth treatment months, amenorrhea occurred in 73%, 47%, and 66% of the women in the 10-cm², 20-cm², and oral HRT groups, respectively. The 10-cm² patches and oral treatments were associated with fewer bleeding days than were the 20-cm² patches (P << .001). During the last 3 months of the treatment year, amenorrhea was found in 100 subjects (86%) for 10-cm² patches, 61 (65%) for 20-cm² patches, and in 85 (79%) for oral HRT. All treatments alleviated the climacteric symptoms to a comparable extent.

Conclusion: In postmenopausal women, 10-cm² patches relieved climacteric symptoms and prevented endometrial hyperplasia at least as effectively as oral HRT. Amenorrhea was induced early in a high percentage of women using 10-cm² patches and oral HRT, and these therapies seemed to be convenient, effective, and safe for estrogen deficiency symptoms in postmenopausal women.

Estrogen replacement therapy effectively alleviates vasomotor symptoms and considerably reduces overall mortality from cardiovascular diseases. However, it has been reported that adverse effects of higher estrogen doses may be problematic in older women. Lower doses than those commonly prescribed, such as transdermal administration of 20–25 μg estradiol (E₂) per 24 hours and 1 mg E₂ orally per day, relieved climacteric symptoms and prevented bone loss.

Hormone replacement therapy (HRT) given cyclically or sequentially is often accompanied by recurrence of uterine bleeding in postmenopausal women with intact uteri. These withdrawal bleeding episodes are unacceptable to a majority of women and may reduce compliance with HRT. Continuous, combined regimens were developed to reduce bleeding disturbances. Most studies of continuous, combined regimens have shown that bleeding episodes occur early in therapy and gradually decrease with treatment duration. Oral formulations of continuous, combined regimens have been available for many years. Transdermal administration of HRT might offer an advantage because it obviates the first liver passage, minimizing the synthesis of several unwanted hepatic proteins and triglycerides.

The objective of the present study was to compare two new transdermal, continuous, combined formulations and an oral regimen of hormone replacement therapy with respect to endometrial hyperplasia, bleeding patterns, and climacteric symptoms in postmenopausal women.
two doses of a new continuous, combined transdermal treatment (Estragest 10 cm² and 20 cm²; Novartis Pharma AG, Basle, Switzerland) with a commercially available oral combination (Kliogest; Novo Nordisk, Bagsvaerd, Denmark). The preparations were compared for efficacy in preventing endometrial hyperplasia and for rates of amenorrhea, frequency of climacteric symptoms, and tolerability.

Methods

Women who met the inclusion criteria for the study were healthy postmenopausal women with intact uteri who needed HRT for moderate vasomotor symptoms, with a last menstrual period (LMP) at least 2 years before baseline screening. Women who had not taken HRT or had been treated for less than 6 months had to be over 48 years old. Women taking sequential, combined HRT had to have less than 2 years of treatment and be over 52 years of age. Exclusion criteria were endometrial thickness greater than 5 mm assessed by transvaginal ultrasound (without a normal result at follow-up biopsy), past endometrial hyperplasia, malignancy of the breast or ovary, thromboembolic disease, active skin disease, unopposed estrogen treatment, estrogen treatment with less than monthly addition of progestogen during the last 2 years, or any previous treatment with continuous, combined HRT. All other HRT was discontinued before study treatment. No woman received any medication that would interfere with the absorption, action, or metabolism of the study medicines. The women gave written consent to participate before study treatment. The trial was approved by local Ethics Review Boards.

This study was an open, parallel-group, comparative trial with active control and balanced randomization with a treatment duration of 1 year. The study could not be masked because of the different drug administration routes and different patch sizes. It was a multicenter study conducted in 49 centers in Sweden and Germany. During a washout period of at least 5 weeks, the women received medroxyprogesterone acetate 10 mg/day for 14 days to induce endometrial shedding before starting the study treatment. Eligible women were randomly allocated by computer to one of three groups of equal number and were given a 10-cm² patch (daily delivery of 0.025 mg E2 and 0.125 mg norethisterone acetate), a 20-cm² patch (daily delivery of 0.05 mg E2 and 0.25 mg norethisterone acetate), or a daily oral dose of 2 mg E2 and 1 mg norethisterone acetate. All treatments were given continuously for 13 cycles of 4 weeks. Patches were applied twice weekly and tablets were given daily.

Women were assessed at baseline and at 12, 24, 36, and 52 weeks of treatment. Climacteric symptoms were assessed at each visit using the Women’s Health Questionnaire, which consisted of 24 questions that allowed four different answers, ranked from 1 to 4, assessing symptoms such as hot flashes and insomnia.12 Daily bleeding diaries were collected from the women at each visit. Severity of bleeding was classified as spotting, normal bleeding, or heavy bleeding. At each visit, weight, blood pressure (BP), climacteric symptoms, breast tenderness, adhesion, local tolerability of patches, and any adverse experiences were recorded. General and gynecologic examinations, cervical smears, transvaginal ultrasonography, and mammography were done at baseline and at the final visit. Endometrial biopsies were done at baseline if the endometrial thickness was greater than 5 mm, but should be taken in all women whose cervical canals were not too narrow for sampling at the end of the study. The endometrial biopsy specimens obtained were evaluated according to recognized standards by a peer pathologist who was masked to the treatment.13

At the end of the study, we made an overall assessment of therapeutic efficacy and tolerability based on a four-point scale. In case of premature discontinuations, all final-visit assessments were done at the time of discontinuation. Primary efficacy variables were the frequency of endometrial hyperplasia after 1 year of treatment and the number of bleeding and spotting days during months 4–6 of treatment. Secondary variables were evaluation of climacteric symptoms at 12, 24, and 36 weeks. The criteria for tolerability and safety included details of adverse experiences, body weight, BP, and the investigators’ overall assessment of tolerability.

A sample of 150 women per group was considered sufficient to detect clinically relevant differences between groups in bleeding patterns and climacteric symptoms, based on an incidence of endometrial hyperplasia of 2% for effective combined HRT and a frequency of hyperplasia of 10% for unopposed estrogen treatment. The dropout rate was expected to be one-third. We calculated that 100 evaluated women per group were needed to show an increased frequency of endometrial hyperplasia in each treatment group, with a power of 95% and an α level of 5% for within-group comparison. A two-sided binomial test at the 5% significance level was done to determine whether the frequency of hyperplasia within specific treatment groups was 10% (which was used as an external standard). For the analysis of differences in bleeding patterns (bleeding and spotting days) between the groups in months 4–6, the odds ratio (OR) was analyzed using a continuation ratio model for eight categories corresponding to ranges in the numbers of bleeding and spotting days. We calculated two-sided 95% confidence interval (CI) for the OR of the 10-cm² patch and 20-cm² patch versus oral HRT.

Two subject data sets were analyzed. The intent-to-treat data set for efficacy and safety analyses included all subjects with at least one post-treatment measure-
ment. Missing values were not replaced. The number of subjects differed per time point, depending on the number of premature discontinuations. The acceptable-subject data set included women who received treatment for at least six cycles, or a total of 348 women. All randomized subjects were included in the safety analysis, which was descriptive.

Results

The 441 randomized subjects included 147 in the 10-cm² patch group, 150 in the 20-cm² patch group, and 144 in the oral-treatment group. The mean age was 54.8 years (range 32–74) and the mean time elapsed since menopause was approximately 6 years. Sixty-one percent of the subjects reported that their LMP was more than 4 years before the start of the study. Baseline data and demographic characteristics did not differ among the groups (P > .05) (Table 1). The 1-year trial was completed by 328 subjects (75%). Premature discontinuation occurred most frequently in the 20-cm² patch group (49 subjects, 33%), followed by the oral-treatment group (36 subjects, 25%), and was least frequent in the 10-cm² patch group (28 subjects, 19%). No cases of endometrial hyperplasia were detected in these women.

Endometrial biopsies were done in 313 of 328 eligible women who completed the study. There were 289 samples, or 66% of the intent-to-treat population available for evaluation by the pathologist. The remaining biopsy specimens lacked endometrium (n = 14) or had been handled inappropriately (n = 10). Most of the endometrial biopsies (75%) were reported as inadequate for assessment by the pathologist. In all of these cases, an endometrial thickness up to 5 mm was confirmed by transvaginal sonography.

The frequency of endometrial hyperplasia is shown in Table 2. Three cases of simple hyperplasia but no complex hyperplasias were observed. One case of cervical or endometrial carcinoma was found in the 10-cm² patch group, although the origin could not be determined.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Time since last menstrual period (mo)</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
</tr>
<tr>
<td>No. taking HRT in the previous 2 y</td>
</tr>
</tbody>
</table>

HRT = hormone replacement therapy. Data are presented as mean (range) or n (%).

<table>
<thead>
<tr>
<th>Table 2. Endometrium After 12 Months of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
</tr>
<tr>
<td>Evaluable specimens</td>
</tr>
<tr>
<td>Hyperplasia</td>
</tr>
<tr>
<td>Within-group tests, P (two-sided)</td>
</tr>
<tr>
<td>Upper limit of 95% CI (one-sided)</td>
</tr>
</tbody>
</table>

HRT = hormone replacement therapy; CI = confidence interval.

The statistical hypothesis tested was frequency of hyperplasia per group = 10.

Twenty-five subjects discontinued participation prematurely because of bleeding and spotting, and of these, 12 left the study during the first 6 months of treatment. The highest number of dropouts due to bleeding during the first 6 months was in the 20-cm² patch group (n = 9), compared with the 10-cm² patch (n = 2) and oral treatment (n = 1). During the last 6-month period, another nine women in the 20-cm² patch group discontinued because of bleeding. The majority of women in all groups had fewer than 6 bleeding and spotting days from the fourth to sixth treatment months. The highest frequency was recorded in the 10-cm² patch (83%) and oral (79%) treatment groups, compared with the 20-cm² patch group (51%).

More than 20 bleeding and spotting days were experienced by 2% of the women using the 10-cm² patch, 22% with the 20-cm² patch, and 9% taking oral HRT. A test of treatment differences for bleeding patterns between the groups showed fewer bleeding days in women taking oral HRT than in those using 20-cm² patches (OR 4.09; 95% CI 2.36, 7.10; P < .001), but no differences were found between oral HRT and 10-cm² patches (OR 0.75; 95% CI 0.39, 1.42; P = .375).

Amenorrhea was reported more frequently among women in the 10-cm² patch group than in the other groups, which was consistent for all time periods (Figure 1). The 20-cm² patch group had the lowest rate of amenorrhea. For all three groups, there was a tendency toward fewer bleeding days with longer duration of therapy. During the first 3 months of therapy, 64% of women in the 10-cm² patch group reported amenorrhea, compared with 35% in the 20-cm² patch group and 45% in the oral group. During the last 3 months of treatment, the corresponding figures were 86%, 65%, and 79%. Amenorrhea over the year was registered in 60% of women who used the 10-cm² patch, compared with 36% for oral treatment and 28% for the 20-cm² patch. In this respect, the women in the 10-cm² patch group differed from the women in the other treatment groups (P < .05).

The Women’s Health Questionnaire showed that the relief of symptoms such as hot flashes, insomnia, and
joint or limb pain improved during the trial. No major differences were detected among the treatment groups (Table 3), confirmed by pairwise comparisons of treatment groups by analysis of covariance after 9 months of treatment ($P > .4$).

The investigators’ assessment of the overall therapeutic effect was very good or good in the majority of women (92% on the 10-cm$^2$ patch, 86% on the 20-cm$^2$ patch, and 96% on oral therapy). Of 441 women included in the safety analysis, 327 (74%) reported adverse experiences. The lowest frequency of adverse experiences was in the 10-cm$^2$ patch group (52%). For all treatment groups, the urogenital system was involved most frequently, including bleeding and mastalgia. The lowest percentage of subjects who reported urogenital adverse experiences was in the 10-cm$^2$ patch group (35%), compared with 52% for the women using the 20-cm$^2$ patch and 60% of those taking oral treatment. Application-site reactions in women using transdermal patches were reported over the year by 34 women (23%) using the 10-cm$^2$ patch and by 51 women (34%) using the 20-cm$^2$ patch. Adhesion of patches was good in both transdermal groups. No significant changes in body weight or BP occurred in any of the groups. The investigators’ opinions of treatment tolerability were rated very good or good in 114 subjects (83%) using 10-cm$^2$ patches, 105 (75%) using 20-cm$^2$ patches, and 117 (89%) taking oral treatment.

**Table 3. Subjects Reporting Climacteric Symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>10-cm$^2$ patch ($n = 147$)</th>
<th>20-cm$^2$ patch ($n = 150$)</th>
<th>Oral HRT ($n = 144$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>83/140 (59.3%)</td>
<td>76/137 (55.5%)</td>
<td>78/138 (56.5%)</td>
</tr>
<tr>
<td>36 wk</td>
<td>10/119 (8.4%)</td>
<td>4/107 (3.7%)</td>
<td>6/116 (5.2%)</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>52/136 (38.3%)</td>
<td>64/138 (46.5%)</td>
<td>60/136 (44.1%)</td>
</tr>
<tr>
<td>36 wk</td>
<td>21/118 (17.8%)</td>
<td>23/107 (21.5%)</td>
<td>21/115 (18.3%)</td>
</tr>
<tr>
<td>Pain in joints or limbs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>53/138 (38.4%)</td>
<td>56/137 (40.9%)</td>
<td>52/136 (38.2%)</td>
</tr>
<tr>
<td>36 wk</td>
<td>34/117 (29.0%)</td>
<td>23/107 (21.5%)</td>
<td>35/116 (30.2%)</td>
</tr>
</tbody>
</table>

HRT = hormone replacement therapy.

Data were not available from all subjects.
Data are presented as number of subjects who always had the symptom/often had the symptom.

**Discussion**

The frequency of endometrial hyperplasia after 1 year of treatment was less than 2% with all three regimens tested, which agrees with reports on continuous, combined HRT$^{9,14}$ and is lower than the spontaneous prevalence of hyperplasia in postmenopausal women without treatment.$^{15}$ The annual rate of hyperplasia was reported as 20% in women who received unopposed estrogen therapy.$^{14}$ The woman with carcinoma of the cervix or endometrium in this study might have harbored pre-existing disease of any origin. There was probably no causal relation between the carcinoma and the trial medication. In the endometrium, it can take 5 years or more to develop carcinoma from hyperplasia. In that woman, the endometrial thickness was 4.9 mm before treatment, and no biopsy was taken. She was later treated conventionally and has been healthy during a follow-up of 2 years. This case illustrates that transvaginal sonography is not always trustworthy for assessing the endometrium because it cannot differentiate hyperplasia or carcinoma from a normal finding when the endometrium has a homogeneous sono-

graphic density.$^{16}$ In the current study, the endometrial specimens obtained at the end of treatment were considered inadequate for assessment in three-quarters of the women. The inability to obtain endometrial tissue may indicate endometrial atrophy.$^{13,17}$ There is no reason to believe that the sampling procedure was inadequate because all physicians were experienced and well acquainted with the biopsy methods used.

The majority of women in all three treatment groups had fewer than 6 days of bleeding or spotting during the 3 months between the fourth and sixth treatment.
cycles. Most women were amenorrheic after three treatment cycles. The rate of amenorrhea increased with increasing duration of therapy, which is consistent with previous observations for orally administered, continuous, combined HRT.5,8,18 A long-term study showed that further bleeding was uncommon once amenorrhea was achieved.5 It has been proposed that amenorrhea rates in some other studies may have been biased because of dropouts due to bleeding. The bleeding results in the current study should be reliable for the 10-cm² patch and the oral-treatment groups because very few women in these groups discontinued participation because of bleeding disturbances. The higher dropout rate due to bleeding among the 20-cm² patch users may overestimate amenorrhea frequency for that group. The 20-cm² patch was associated with too much bleeding to be well accepted by women. Despite equal ratios between estrogen and progestogen components in the patches, the formulation with the higher dosage did not control for bleeding as well as the lower dosage, which probably induced less endometrial stimulation, leading to fewer bleeding disturbances.

Regardless of the doses of E2 given, subjective symptoms of estrogen deficiency were relieved, as measured by the Women’s Health Questionnaire. There was an overall improvement in hot flashes, insomnia, and joint or limb pain. No reports have been found showing that a low dose of continuous, transdermal E2 alleviates climacteric complaints as effectively as 2 mg of daily E2 given orally. However, lower doses of orally administered estrogens than those commonly prescribed were reported to control climacteric complaints of moderate severity.4 A low dose of estrogen may be preferable in elderly women because of poor compliance due to side effects such as bleeding and breast tenderness.16

All preparations alleviated climacteric symptoms and did not induce an unacceptable rate of endometrial hyperplasia. Transdermal application of a low dose of combined estrogen-progestogen may be an alternative treatment for elderly women requesting HRT. However, long-term data are needed to show whether low-dose estrogen prevents bone loss and cardiovascular disease.

References

5. Evans SF, Davie MW. Low and conventional dose transdermal oestradiol are equally effective at preventing bone loss in spine and femur at all post-menopausal ages. Clin Endocrinol (Oxf) 1996;44:79–84.

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Received July 16, 1998.
Accepted January 13, 1999.

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