Continuous versus cyclical transdermal estrogen replacement therapy in postmenopausal women: influence on climacteric symptoms, body weight and bleeding pattern

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Abstract

Objectives: To compare continuous and cyclical transdermal estrogen replacement therapy (ERT) with or without an oral progestogen regarding climacteric symptoms, body weight and bleeding pattern. Methods: A total of 2459 postmenopausal women were treated for three cycles of 28 days in an open, randomized, parallel group multicenter study. Patients received an estrogen matrix patch (50 μg 17β-estradiol/day) twice weekly, either continuously (eight patches/cycle) or cyclically (six patches/cycle, i.e. 3 weeks on, 1 week off). A total of 1232 patients were treated continuously and 1227 cyclically. In the study group 1150 patients had an intact uterus (543 in the continuous and 607 in the cyclical treatment arm) and received, in addition to the estrogen patch, an oral progestogen in a transformation dose for 12 days of each cycle. Hysterectomized patients totaling 1309 (689 in the continuous versus 620 in the cyclical group) did not receive progestogen. Of the 2459 patients, 771 (31.4%) participated in a follow-up study with two further treatment cycles, which was offered to the patients at the end of the main study. The main outcome measures were climacteric symptoms, measured at the end of cycles 1–3 by a Visual Analogue Scale at baseline, and body weight measured at baseline at the end of cycles 3 and 5. In addition, the bleeding time per cycle (days) was evaluated in all patients with an intact uterus. Results: Continuous and cyclical transdermal ERT reduced, over three treatment cycles, the average climacteric symptom score by 1.77 and 1.70, respectively. The percentage remission and improvement rates for the ten climacteric symptoms ranged between 69.3 and 88.0% and did not differ between the two groups. In patients with a higher symptom score at baseline, the continuous treatment was slightly more effective. However, this effect was statistically not significant. After three treatment cycles body weight increased in both treatment groups by between 500 and 700 g. Further treatment during the follow-up study induced an additional average weight gain of 200–400 g. These results were not influenced by the addition of an oral progestogen.

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In patients with an intact uterus, the average bleeding time at the end of the first cycle (5.4 days in the continuous versus 5.3 days in the cyclical group) increased slightly during cycle 2 and returned to baseline values at the end of cycle 3. Conclusions: Continuous and cyclical transdermal ERT were equally effective in reducing climacteric symptoms. The short term use of five cycles transdermal ERT induced a slight increase in body weight which was independent of the treatment regimen. These results were not influenced by the type and mode of administration of a progestogen. Both ERT regimens were very well tolerated and are suitable alternatives for estrogen replacement therapy of postmenopausal women. © 1997 Elsevier Science Ireland Ltd.

Keywords: Climacteric symptoms; Menopause rating scale; Estrogen replacement therapy; Transdermal application; 17β-estradiol; Body weight; Systemic tolerance; Local tolerance; Continuous therapy; Cyclical therapy; Bleeding pattern

1. Introduction

Transdermal delivery systems for 17β-estradiol (E2), such as patches, reduce the frequency of drug administration and provide E2 plasma concentrations which, in contrast to the oral route, remain relatively constant over a period of 3–4 days [1,2].

The first commercially available transdermal system was a reservoir patch, which was launched nearly 10 years ago [3]. Subsequently, the development of matrix patches led to improved local tolerance, which made these delivery systems more acceptable to the patient [4,5]. In addition, the pharmacokinetic properties of matrix patches are superior to those of the reservoir patch [6–8].

Despite these improvements and the broad applicability of the therapeutic preparations, compliance with ERT in postmenopausal women is still rather low [9,10]. Bleeding problems and weight changes are the main reasons for discontinuation. Reduction of these negative side-effects can be expected to improve compliance. In addition, treatment regimens should be as uncomplicated as possible. The continuous twice weekly application of an estrogen patch, for example, is easier for a patient to handle than the cyclical 3 weeks on, 1 week off regimen. However, it is unclear whether these two treatment regimens are equally effective in relieving climacteric symptoms.

The aim of our study, therefore, was to compare the relief of climacteric symptoms achieved under either continuous or cyclical transdermal ERT using a matrix patch, over a treatment period of 3 months, in a multicenter, parallel group study. In addition, the safety of both treatments and their influence on body weight were investigated over a treatment period of 5 months. Any effects of a progestogen treatment on the relief of climacteric symptoms and/or weight gain were to be evaluated. Hysterectomized women, who did not receive progestogen, were compared, therefore, to non-hysterectomized women, who received a progestogen in a transformation dose for 12 days every 4 weeks.

2. Subjects and methods

2.1. Patients

A total of 2459 postmenopausal women, older than 40 years, who required estrogen replacement therapy (ERT), were included in this multicenter study. Further inclusion criteria were: surgical or natural menopause, the last natural bleeding having occurred at least 2 years before the start of the study and/or with a serum FSH-level of more than 30 IU/l and a 17β-estradiol level of less than 30 pg/ml; gynecological investigation before the start of the study, including mammography and PAP smear, without any contraindication for ERT. A progestogen at a transformation dose was prescribed for all patients with an intact uterus for 12 days/cycle. The type of progestogen was not specified by the protocol. However, the use of medroxyprogesterone acetate (MPA), at a dose of 5 mg/day, was recommended. Exclusion criteria were: undiagnosed vaginal bleedings, known or suspected malignant diseases or other
severe diseases; acute thromboembolism, relevant dermatologic diseases (including allergic reactions) and known allergies to patches or other topical drugs. In addition, the use of any other sex hormones within 14 days of the start and during the study was not permitted.

All patients were informed of the study design and the study procedures and gave their written informed consent to inclusion. The study protocol was approved by the Ethical Committee of the Benjamin Franklin University Hospital, Berlin and by 16 regional Ethical Committees in Germany.

Of the 2459 patients, 771 (31.4%) participated in a follow-up study, which was offered to the patients at the end of the main study. The inclusion and exclusion criteria were not changed for this study extension and all participants had to give again their written informed consent.

2.2. Treatment

The treatment period for both groups extended over three cycles of 28 days. Patients received an estrogen matrix patch (Menorest, 50 µg E2/day) twice weekly, either continuously (8 patches/cycle) or cyclically (6 patches/cycle, i.e. 3 weeks on, 1 week off). Each package of testmedication contained two (cyclical treatment) or three (continuous treatment) reserve patches and instructions on the use of the patch. The patches were to be applied to a dry and hairless skin area, alternately using the left and right side of the waist or abdomen for each application. Non-hysterectomized women received a progestogen at a transformation dose for the last 12 days of each cycle. The type of the progestogen was not directed by the protocol. However, the use of medroxyprogesterone in a dose of 5 mg/day was recommended. In addition the type and dose of the progestogens used were recorded.

In a subgroup of patients the treatment period was prolonged for two further cycles of 28 days. During this follow-up study all participants received the same treatment regimen as originally randomized.

2.3. Study design

The study was designed as an open, controlled, parallel group multicenter study. Target patients were recruited by 469 gynecologists in Germany. During the course of the study, two visits were to be made, at baseline and at the end of the last treatment cycle. During the baseline visit, all inclusion and exclusion criteria were checked and the patients were randomized to the continuous and cyclical treatment groups following their informed consent. All anamnestic data and concomitant drug therapy were recorded and efficacy parameters were evaluated. Compliance was controlled by counting the unused test medication at the end of the treatment.

Patients who were willing to participate in the extension study received the new study medication according to the original randomization code at their second visit (i.e. the visit after three cycles of therapy). All inclusion and exclusion criteria were checked again and the patients were asked to come back for a final visit after two further treatment cycles.

2.4. Efficacy variables

The main efficacy variable was the sum of climacteric symptoms and its reduction during the course of the study. The symptoms were evaluated using the Menopause Rating Scale (MRS), which was developed recently [11]. This scale allows a rating of ten different climacteric symptoms from 0.0 (no symptoms) to 10.0 (severe symptoms) and provides an individual symptom profile for each patient. The scale was to be filled out by the patients during the two study visits (i.e. at baseline and at the end of cycle 3) and at the end of cycles 1 and 2. Secondary efficacy variables were the change in body weight (determined at baseline and after three and five treatment cycles) and the duration of vaginal bleeding during cycles 1–3. All adverse events were recorded by the physicians and their possible causal connection with the testmedication was assessed.
Table 1
Use of different oral progestogens (type in % and dosage in mg) in non-hysterectomized women (n = 1150)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Total population (n = 1150)</th>
<th>Continuous group (n = 543)</th>
<th>Cyclical group (n = 607)</th>
<th>Average daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethisterone acetate</td>
<td>47.6</td>
<td>45.2</td>
<td>49.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>37.4</td>
<td>39.7</td>
<td>35.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Medrogestone</td>
<td>10.5</td>
<td>10.4</td>
<td>10.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Chlormadinone acetate and</td>
<td>4.5</td>
<td>4.7</td>
<td>4.1</td>
<td>2.3°</td>
</tr>
<tr>
<td>others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type in % and dosage in mg. ° Only chlormadinone acetate.

2.5. Data analysis

2.5.1. Sample size determination

The main efficacy variable (climacteric symptoms) included 10 items and the total sumscore was evaluated for each cycle. Additionally, a comparison was planned between the baseline score and the individual last observation. On the basis of a coefficient of variation of 500%, a sample size of 1167 patients was required (t-test for independent random samples, two-sided, experimentwise type-I-error rate of α = 0.05, type-II-error rate of β = 0.05, α-adjustment on the basis of 33 planned comparisons).

2.5.2. Statistical methods

The confirmatory comparison of efficacy and safety data was planned on an intention to treat basis. All treated patients were to be included, as randomized. All calculations, as well as table generations were performed using the statistical package SPSS 4.0 under the Interactive UNIX operating system at the computing facilities of the Institut für Numerische Statistik, Cologne.

3. Results

3.1. Study population

A total of 2459 postmenopausal women were included in this study (intention to treat population). Of these patients, 1232 were treated in the continuous estrogen group and 1227 in the cyclical estrogen group. Twenty five patients in the continuous and 23 in the cyclical group were excluded due to major protocol violations (i.e. age less than 40 years, therapy with sex hormones during the wash-out phase or during the course of the study). In the remaining continuous group and in the cyclical group 151 and 138 patients respectively terminated the study prematurely. This was largely due to adverse events (30 versus 23) or to withdrawal of informed consent and/or loss to follow-up (27 versus 26). Further reasons included missing data or violation of eligibility criteria.

Of the 2459 patients, 772 (31.4%) participated in the follow-up study (401 in the continuous and 371 in the cyclical estrogen group).

3.2. Demographic and baseline characteristics

The two treatment groups were comparable with regard to their baseline characteristics. The mean age of the patients was 54 ± 7 years in both treatment groups and their body weight was 69.8 ± 11.3 kg (continuous) and 69.2 ± 11.3 kg (cyclical), respectively. The mean pre-therapy MRS sumscore was 3.62 ± 1.62 for both treatment groups.

In total, 1150 patients (47.7%) had an intact uterus (543 in the continuous and 607 in the cyclical treatment arm) and received an oral progestogen at a transformation dose. The different progestogens and their mean dosages used for this purpose are given in Table 1. The most frequently prescribed compounds were norethisterone acetate (NETA, in 47% of cases) and medroxyprogesterone acetate (MPA, in 37% of cases, see Table 1). A total of 1309 patients were hysterectomized. These patients received only the
transdermal estrogen replacement therapy (689 continuous versus 620 cyclical treatment).

3.3. Climacteric symptoms

During the course of the study, the MRS sum-score decreased on average by 1.77 points under the continuous and by 1.70 points under the cyclical treatment regimen (Fig. 1). This difference was not statistically significant. The remission and improvement rates for all ten climacteric symptoms ranged between 70 and 90%, with the highest relief rate for hot flushes (88.0 versus 87.7%, Table 2). Again, this improvement was almost identical for both treatment groups (Table 2) and did not differ between patients either receiving only transdermal estrogen replacement therapy (i.e. the hysterectomized patients) or transdermal estrogen replacement therapy plus an additional oral progestogen (i.e. all women with an intact uterus, Table 3).

The greatest relief of climacteric symptoms was achieved during the first treatment cycle (Fig. 1). During this period, a tendency towards greater symptom relief could be seen on continuous treat-

ment in association with the magnitude of the symptom score at baseline. The higher the symptom score on inclusion, the higher was the difference in the average symptom sumscore between the two groups at the end of cycle 1 (Fig. 2). This result was statistically not significant (paired t-test, \( P \geq 0.05 \)).

3.4. Body weight

Body weight increased slightly during the course of the main study. This increase ranged between 500 and 700 g and was similar in the continuous and cyclical treatment groups. Moreover, there was no significant difference in weight gain between patients who did or did not receive an additional progestogen (i.e. non-hysterectomized and hysterectomized women, Fig. 3). Further treatment during the follow-up study induced an additional weight gain of 200–400 g, which was also independent from the treatment regimen (Fig. 3).

3.5. Vaginal bleeding

The mean bleeding time of 5.3 to 5.4 days at
3.6. Safety

A sum of 438 adverse events were reported by 272 patients (10.6%). A possible relationship to the medication was given for 211 patients (8.6% of the total population), equally divided between the cyclical and the continuous treatment groups. The most frequently reported adverse events were topical allergic reactions (2.8%) with erythema and pruritus in most of the cases and menorrhagia/dysmenorrhea (1.7%). Further frequently reported events were breast pain (1.5%), headache (0.9%), weight increase (0.9%) and depression (0.6%, Table 4). Serious adverse events were reported in 14 patients (0.6%), with a possible relationship to the medication in one case (acute depression requiring hospitalization). The intensity of the events was mild to moderate in the majority of cases.

4. Discussion

Continuous and cyclical transdermal estrogen treatment with a matrix patch at a dosage of 50 μg E2/day induced comparable relief of climac-
teric symptoms. This was true for the mean MRS symptom score and for the ten different climacteric symptoms measured separately. Similar results have been reported with oral HRT [12,13]. Nevertheless, the average symptom score in the continuous treatment group was reduced slightly more rapidly. In this group, a tendency for a higher degree of symptom relief could be shown in patients with a more severe baseline symptom score. This effect was statistically not significant and could only be demonstrated during the first cycle of therapy. Nevertheless, it should be further evaluated in controlled studies especially with women showing stronger climacteric symptoms (e.g. younger women after ovariectomy or women in the first postmenopausal years). It could also be of importance when using lower dosages of transdermal ERT (e.g. 37.5 μg E2/day), since differences in the efficacies of the two treatment regimens might become more evident at low plasma estradiol levels. With both treatment regimens, the highest remission and improvement rates were observed for hot flushes. This symptom affects approximately 70–80% of postmenopausal women. Over 80% of them will still be experiencing flushes a year after onset and about 25% for the 5 years thereafter [14].

The additional administration of a progestogen did not influence the symptom relief of any of the ten climacteric symptoms measured. This observation supports previous results with different oral combination regimens of estrogen and progestogen, showing no major differences between the effects of various treatment combinations on climacteric symptoms [15,16].

Different types of progestogen were used in the subgroup of non-hysterectomized patients. This was allowed according to the protocol provided the type and dose of the progestogen was stable over the study period and consistent with the respective transformation dose [17]. As demonstrated in Table 1 this prerequisite was fulfilled by the investigators. Under these prerequisites, the mean duration of vaginal bleedings per cycle was somewhat higher (0.1–0.3 days) in the continuous treatment group, but probably this is not clinically relevant. Additionally, the reported number of patients with dysmenorrhea and/or menorrh-
gia was similar in both groups (20 versus 21 patients). These results seem to be reasonable, since most investigators probably did not change the previous progestogen prescriptions for their patients during this study. Due to this fact major influences of the slightly different estrogen regimens on the bleeding pattern cannot be expected.

Weight gain is one of the main reasons why postmenopausal women discontinue ERT. As demonstrated in our investigation, a small increase in body weight occurred in both treatment groups over a period of three treatment cycles. The average weight gain was 500–700 g and did not differ between the two transdermal ERT groups nor between the subgroups of opposed and unopposed ERT. The further ERT over two cycles in the follow-up phase of the study slightly increased this effect. However, the average weight gain was less than 1 kg in both treatment arms. The main reason for this effect was probably acute retention of extracellular fluid under estrogen influence. Other authors have shown that prolonged HRT does not induce a major weight increase in postmenopausal women. Even over a

Table 4
Most frequently reported adverse events (number of patients (percentage of patients)) in postmenopausal women (n = 2459) during three cycles of continuous or cyclical transdermal estrogen replacement therapy (50 μg E2/day)

<table>
<thead>
<tr>
<th>Event</th>
<th>Total group (n = 2459)</th>
<th>Continuous group (n = 1232)</th>
<th>Cyclical group (n = 1227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical adverse event</td>
<td>69 (2.8%)</td>
<td>35 (2.8%)</td>
<td>34 (2.8%)</td>
</tr>
<tr>
<td>Menorrhagia/dysmenorrhea</td>
<td>41 (1.7%)</td>
<td>20 (1.6%)</td>
<td>21 (1.7%)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>37 (1.5%)</td>
<td>19 (1.5%)</td>
<td>18 (1.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (0.9%)</td>
<td>9 (0.7%)</td>
<td>12 (1.0%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>21 (0.9%)</td>
<td>9 (0.7%)</td>
<td>12 (1.0%)</td>
</tr>
<tr>
<td>Depression</td>
<td>15 (0.6%)</td>
<td>7 (0.6%)</td>
<td>8 (0.7%)</td>
</tr>
</tbody>
</table>
period of 15 years or more, the weight gain and central obesity that is commonly observed in postmenopausal women cannot be attributed to HRT [18–20]. However, the shift of gynoid to android fat distribution is possibly reduced by HRT [20]. Both treatment regimens were tolerated very well. The most frequently reported side-effects were local intolerance in both groups (2.8 versus 2.8%), followed by menorrhagia/dysmenorrhea (1.6 versus 1.7%) and breast pain (1.5 versus 1.5%). All side-effects were essentially equally distributed in both treatment groups. These results confirm the safety of transdermal ERT and underline especially the good local tolerance of the matrix patch used. Distinctions between continuous or cyclical ERT in this respect cannot be made on the basis of our results.

In conclusion, continuous and cyclical transdermal ERT were equally effective in reducing climacteric symptoms. The possible advantage of the continuous treatment regimen in patients with a higher symptom score at baseline needs further clarification in controlled clinical trials. The short term use of five cycles transdermal ERT induced a slight increase in body weight, which was independent of the treatment regimen. These results were not influenced by the type and mode of administration of the progestogen. Both ERT regimens were very well tolerated and are suitable alternatives for estrogen replacement therapy of postmenopausal women.

References