Clinical and endometrial effects of oestradiol and progesterone in post-menopausal women

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This study reports the clinical effects in a group of post-menopausal women after 4 months of treatment with 2 mg micronized 17β-oestradiol (E2) in combination with different doses of micronized progesterone (50, 100 or 200 mg) for 25 days each month. The 30 participants were divided into three groups. All of the subjects tolerated the preparation well and obtained relief from their climacteric complaints. None dropped out because of side effects and no changes were observed in blood pressure, weight or Papanicolaou cytology. Breakthrough bleeding was noted in the first cycle, mainly in the group receiving the lowest dose of progesterone. Endometrial biopsies performed before and after 4 months of treatment showed an atrophic endometrium in most of the women who received 100 mg progesterone and in all of the women on 200 mg progesterone. The results showed that this new combination of 2 mg E2 and micronized progesterone in different doses was both effective and well accepted.

Key words: Oestradiol, Progesterone, Endometrium, Clinical effects

Introduction

Climacteric complaints such as sweating and hot flushes are common among post-menopausal women [1,2]. It is well known that oestrogen replacement therapy relieves the symptoms effectively [3], but that the use of unopposed oestrogen therapy increases the risk of endometrial cancer [4,5]. The addition of progestogens for 10—13 days per month results in a secretory endometrium, which decreases the risk of cancer [6,7]. It has also been reported that maintenance of the endometrium in an atrophic state can lower the risk of endometrial cancer [8].

The use of synthetic oestrogens has been criticized, since these steroids have induced negative effects on coagulation and the fibrinolytic enzyme system when used in oral contraceptives [9]. Synthetic progestogens, on the other hand, can have adverse effects on the changes in lipid metabolism that are currently considered to be
beneficial with regard to the prevention of cardiovascular disease. However, oral progesterone has not been shown to oppose these oestrogen-induced lipid changes [10]. In one study, natural progesterone was shown to have an antihypertensive action [11].

In the present study, 30 women were treated for 4 months with 2 mg 17β-oestradiol (E2) and different doses (50, 100 and 200 mg) of progesterone (P). The aim was to determine whether the natural hormones gave symptomatic relief, to study the incidence of side effects and to investigate objective effects, such as changes in blood pressure, weight, Papanicolaou cytology or endometrial histology. The study was also designed to evaluate the effects of different doses of progesterone on the bleeding patterns.

Subjects and methods

Thirty healthy women, aged 43—67 years (mean 52.5 years), with characteristic climacteric complaints voluntarily participated in this study. None of them had received oestrogen therapy for at least 6 weeks previously or had experienced vaginal bleeding for at least 6 months. They were randomly divided into three groups of ten, which were treated for 4 months with 2 mg micronized E2 in combination with 50 mg, 100 mg or 200 mg micronized progesterone, respectively.

The tablets were taken every day for 25 days, followed by a 5-day treatment-free interval, and then again for another 25 days, and so on for 4 months. The subjects visited the clinic before therapy began, returning after 23—25 days of treatment (just before the first 5-day interval) and again just prior to the end of treatment.

Endometrial biopsies were taken under local anaesthesia (paracervical block using Mepivacain), before and after 4 months of treatment. All the biopsy material was examined by the same pathologist and where there was any uncertainty about the histology, the biopsies were checked by three different pathologists. Papanicolaou smears were taken before treatment and after four months. All the women were provided with bleeding records which they completed on a daily basis.

At the first visit, baseline assessments were made of the frequency of sweating episodes and hot flushes, and symptoms such as insomnia, vaginal dryness, nausea, oedema and tenderness of the breasts were recorded. These assessments were repeated at each follow-up. Sweating episodes and hot flushes were recorded as the number per day and the other symptoms were assessed on a scale of 0—3 (where 0 = no problems at all, 1 = some discomfort, 2 = substantial discomfort and 3 = great discomfort). Blood pressure was measured in the lying and standing positions and weight was also recorded at each visit.

Results

The preparation was well tolerated by all the subjects. After 1 month a significant reduction in the frequency of sweating episodes and hot flushes was observed (Figs. 1 and 2). Problems such as insomnia and vaginal dryness were also relieved, but to a less dramatic degree. The occurrence of other symptoms such as nausea, oedema
and breast tenderness was infrequent both before and during treatment in all three groups.

There were no statistically significant changes in blood pressure and no cases of weight gain during the treatment period. The average weight was 65.7 kg at the first visit, after which it fell to 64.7 kg after 4 months.

Two women had first-stage cervical intraepithelial neoplasia (CIN I), i.e. mild cervical dysplasia, at the start of treatment. After four months one of them had a normal smear, while the other had progressed to CIN II (moderate dysplasia). Histology of portio and cervical biopsies revealed CIN III (carcinoma in situ). Cold knife conisation was accordingly performed and the postoperative Papanicolaou smears were found to be normal.

Three women taking the largest dose of progesterone (200 mg) experienced slight dizziness shortly after tablet intake, but the problem disappeared when they took the tablet at bedtime instead of in the morning.

In the first group (2 mg E₂ + 50 mg P) 7 out of 10 of the subjects reported breakthrough bleeding. In the second group (2 mg E₂ + 100 mg P) 8 women had no
TABLE I

BREAKTHROUGH AND WITHDRAWAL BLEEDING DURING 4 MONTHS OF TREATMENT WITH 2 mg 17β-OESTRADIOL AND DIFFERENT DOSES OF PROGESTERONE

<table>
<thead>
<tr>
<th>Progesterone dose</th>
<th>Number of women with</th>
<th>Breakthrough bleeding</th>
<th>Withdrawal bleeding</th>
<th>No bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg (n = 10)</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>100 mg (n = 10)</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>200 mg (n = 10)</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

bleeding at all. In the third group (2 mg E₂ + 200 mg P) 4 women reported no bleeding (Table I). The bleeding records showed that most of the breakthrough bleeding occurred during the first and second months. Some of the women experienced both breakthrough and withdrawal bleeding.

One woman stopped therapy only 3 weeks after the study started since, despite the paracervical block, she found the endometrial biopsy procedure painful and was unwilling to continue. One woman dropped out after 6 weeks of treatment because she had ambivalent feelings about oestrogen replacement therapy. Another woman stopped tablet intake after 3 months of treatment owing to migraine-like headaches and one woman completed the therapy but was unable to attend for the last biopsy.

Table II gives the results of the endometrial biopsies. At the beginning of the study the endometrium was atrophic in 24 of the 30 subjects.

In the first group (2 mg E₂ + 50 mg P), one woman had a secretory endometrium at the start of treatment, but after 4 months it had become atrophic. Another woman had a proliferative endometrium which became secretory during treatment. This woman had a low follicle-stimulating hormone (FSH) serum level as well as bleeding during treatment, and was probably peri-menopausal. Two women in this group with an initially atrophic endometrium had a slightly proliferative endometrium after 4 months.

In the second group (2 mg E₂ + 100 mg P), one woman showed slight proliferation of the endometrial tissue. She also had a low FSH serum level and was considered to be peri-menopausal. Her final biopsy showed a secretory endometrium. The endometrium in all the other women in the group remained atrophic throughout therapy.

In the third group (2 mg E₂ + 200 mg P), all of the subjects had an atrophic endometrium after four months, despite the fact that two had had a proliferative endometrium at the start.
TABLE II

EFFECTS ON THE ENDOMETRIUM OF TREATMENT WITH 2 mg 17β-OESTRADIOL AND DIFFERENT DOSES OF PROGESTERONE

<table>
<thead>
<tr>
<th>Progesterone dose</th>
<th>Before treatment</th>
<th>After 4 months of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>50mg</td>
<td>8 A</td>
<td>6 A</td>
</tr>
<tr>
<td></td>
<td>1 S</td>
<td>1 S</td>
</tr>
<tr>
<td></td>
<td>1 P</td>
<td>2 P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Drop-out</td>
</tr>
<tr>
<td>100 mg</td>
<td>9 A</td>
<td>6 A</td>
</tr>
<tr>
<td></td>
<td>1 P</td>
<td>1 S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Drop-outs</td>
</tr>
<tr>
<td>200 mg</td>
<td>7 A</td>
<td>10 A</td>
</tr>
<tr>
<td></td>
<td>1 S</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 P</td>
<td></td>
</tr>
</tbody>
</table>

A = atrophic, S = secretory, P = proliferative endometrium.

Discussion

The present study showed that combinations of 2 mg E₂ with different doses of micronized progesterone were well tolerated by the 30 women involved. They all reported a reduction in their climacteric symptoms and very few side effects or sweating problems were noted in the treatment-free periods. In 1985 Rylance et al. showed that natural progesterone alone had a significant antihypertensive effect [11]. The combinations of progesterone and E₂ used in this study had no effect on blood pressure.

Both micronized E₂ and micronized natural progesterone are reported to be absorbed when administered orally [12, 13].

Vaginal bleeding was observed in earlier studies in which continuous oestrogen-progestogen therapy was used to treat climacteric complaints.

Some women treated with 2 mg E₂ and 1 mg norethisterone acetate without any treatment-free period were reported to have experienced breakthrough bleeding [14]. When 2.5—5 mg medroxyprogesterone was used to oppose oestrogens, the endometrium became atrophic, but half of the patients reported vaginal bleeding [15]. By giving the tablets for 25 days and having 5 treatment-free days, the aim in our study was to achieve some measure of bleeding control. Nevertheless, a number of the subjects still experienced breakthrough bleeding.

With the 100 mg progesterone regimen, bleeding episodes occurred in only 2 out of 10 women and then mainly in the initial cycles. However, the scale of this study does not permit definitive conclusions to be drawn with respect to bleeding control, and in view of its length (4 months) the findings should be regarded as only preliminary results. Future studies to investigate long-term effects on the bleeding pattern should provide interesting information, a likely hypothesis being that bleeding will occur in the treatment-free periods.
Siddle et al. treated post-menopausal women with 1.25 mg/day conjugated equine oestrogen in combination with either 1—10 mg/day norethisterone or 150—500 μg/day norgestrel for 10 days each month. They concluded that the doses of synthetic progestogens used earlier to suppress endometrial proliferation were excessive [16]. In a study using 100—300 mg/day oral micronized natural progesterone, only the highest dose induced a secretory phase [17].

We found that a dose of progesterone as low as 50 mg was generally sufficient to keep the endometrium atrophic. This could, of course, be due to different pharmaceutical formulations of the progesterone used and, consequently, different absorption rates. Furthermore, the doses of progesterone required to keep the endometrium atrophic when given continuously may differ from that needed to transform a proliferative into a secretory endometrium with sequential therapy. It is known that endometrial hyperplasia due to oestrogen therapy is avoided if progestogens are added for more than 10 days per month. Our results show that at least 100 mg progesterone should be used to achieve an atrophic endometrium and to provide optimum bleeding control. Nearly 100% of the women studied had an atrophic endometrium after 4 months of treatment with 100 mg or higher doses of progesterone.

We have shown that continuous use of 2 mg E2 combined with 50, 100 or 200 mg progesterone not only has a beneficial effect on oestrogen deficiency, with few side effects, but also renders the endometrium atrophic and provides good bleeding control. There have been reports of tiredness in patients treated with large doses of progesterone [18], but we found that changing the time the tablets were taken from the morning to the evening eradicated this problem for the small number of women who experienced transient tiredness after tablet intake.

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References


