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A GROUP-COMPARATIVE STUDY OF EFFECTS OF OVESTIN CREAM VERSUS PREMARIN CREAM IN POST-MENOPAUSAL WOMEN WITH VAGINAL ATROPHY *

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Fourteen post-menopausal women with vaginal atrophy applied, intravaginally, Ovestin® cream (0.5 mg oestradiol/day; 7 patients) or Premarin® cream (1.25 mg conjugated oestrogens/day; 7 patients) for 3 wk. Effects on plasma E₁, E₂, E₃, FSH, LH, PRL, TRH-stimulated PRL release, SHBG, and on maturation value (MV), ferning (F) and spinnbarkeit (S) were studied. Endometrial biopsies at pre-treatment and at 2 wk were obtained from 2 patients from each group.

Premarin induced a significant and progressive rise in E₁ and E₂ levels and in SHBG, whereas Ovestin induced no changes. Both creams increased E₃ slightly and suppressed FSH and LH, Premarin suppression of FSH and LH being significantly greater. No significant changes in PRL or TRH-stimulated PRL release occurred with either cream. A similar, marked rise in the MV occurred, but the effect of Premarin on F and S was significantly greater. Endometrium remained atrophic in the 2 Ovestin-treated patients, but moderate proliferation occurred in the 2 Premarin-treated patients. The data showed Ovestin cream to be superior to Premarin cream because of the absence of undesirable effects on E₁ and E₂ levels and the subsequent changes in SHBG and endometrium.

(Key words: Vaginal atrophy, Ovestin-Premarin creams, Plasma hormone levels, Endometrium)

INTRODUCTION

Speert [1] reported as early as 1948 that oestrogens could be readily absorbed from the vagina in amounts sufficient to cause endometrial stimulation and bleeding. It has also been known for a long time that reproductive tissues undergo a marked stimulation of growth and differentiation in response to sex steroid hormones in general, and to oestrogens in particular.

The possibility of a relationship between certain forms of oestrogen replacement therapy and cancer of the endometrium has led to extensive discussions in recent years. Interestingly enough, vaginal creams containing oestrogens have been widely used for a considerable amount of time in the treatment of post-menopausal vaginal atrophy and associated complaints, the most frequently used being Premarin cream. Despite clinical experience that such creams could induce uterine bleeding, no attention was paid to the

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pharmacodynamic aspects of this finding until the recent studies of Widholm and Vartiainen [2], Englund and Johansson [3], and Whitehead et al. [4].

A number of recent publications on a vaginal cream containing oestriol (Ovestin cream) have shown the cream to provide a safe and efficient therapy for post-menopausal vaginal atrophy [5-9].

An open-group comparative study of the effects of Ovestin and Premarin creams on post-menopausal women with vaginal atrophy was performed to compare the effects of the two preparations on plasma hormone levels, sex hormone binding globulin (SHBG) capacity, vaginal epithelium and cervical mucus. Endometrial biopsies were also performed.

MATERIALS AND METHODS

Patients

The 14 patients who participated in the study were 53-65 yr old and met the following selection criteria: at least 8 yr since the last menstruation and presenting with vaginal atrophy and related symptoms, absence of any cervico-vaginal infection, and not treated with steroids for at least 6 mth prior to the present study. No other therapy or self medication was permitted during the study.

Patients with a history of malignancies and/or cervico-vaginal lesions were excluded. Informed consent was obtained from all participants.

Preparations

Patients were randomly assigned to treatment with either Ovestin or Premarin cream.

A daily dose of 0.5 mg of oestradiol was applied for 3 wk before retiring, using a plastic applicator calibrated to deliver 0.5 g of Ovestin cream.

A daily dose of 1.25 mg of conjugated oestrogens was applied for 3 wk before retiring, using a plastic applicator calibrated to deliver 2 g of Premarin cream.

Parameters and times of assessment

The following parameters were studied: oestrone (E_1), oestradiol (E_2), oestriol (E_3), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), thyrotrophin-releasing hormone (TRH)-stimulated PRL release, sex hormone binding globulin (SHBG) capacity, maturation value (MV), ferning (F), spinnbarkeit (S) and endometrial biopsy.

Assessment was at pre-treatment and on days 8, 15 and 21, except for TRH-stimulation and endometrial biopsy which were performed at pre-treatment and on day 15. Blood samples were obtained between 0800 and 0830 h, after an overnight fast (to ensure that base-line values were obtained).

Methods

E_1 and E_2 were determined by radioimmunoassay according to Emmert et al. [10], using test kits from Medical Systems and Biodata, respectively. Unconjugated E_3 was

measured by radioimmunoassay according to Rotti et al. [11], using reagents provided by Medical Systems. For enzymatic hydrolysis β -glucuronidase, isolated from *Helix pomatia*, was used. FSH and LH were determined by a radioimmunosorbent method according to Wide et al. [12], using Biodata test kits. PRL was determined according to Ciardella et al. [13], using a test kit from Biodata. SHBG capacity was measured as previously described by Rudd et al. [14].

All hormone determinations were run in duplicate, in a single assay using the same batch of reagents.

Synthetic TRH (200 μ g) was administered intravenously as a bolus injection at time 0 via an indwelling catheter inserted into a scalp vein. Blood samples were obtained at -15, 0, 15, 30, 60 and 120 min.

Each blood sample was immediately centrifuged and the plasma was separated and kept at -20°C until analyzed.

Vaginal smears were obtained from the upper third of the vaginal wall and stained according to the Papanicolaou method. For the evaluation the MV was calculated from the maturation index by multiplying the percentages of the cell types by different factors: 0 for basal-parabasal cells, 0.5 for intermediate cells and 1 for superficial cells. The total sum after applying this score is defined as the MV [15].

Cervical-mucus samples were aspirated from the cervical canal. F was scored as 0, 1, 2 or 3. S was measured in cm immediately after collection of the sample.

Endometrial specimens were obtained by curette at pre-treatment and on day 15 in 2 patients from each treatment group.

For the statistical evaluation an analysis of covariance was applied to the variables: E_1 , E_2 , FSH, LH, PRL, SHBG capacity, TRH-stimulation (area under the response curve) and MV. Student's *t*-test for comparative groups was applied to E_3 . The non-parametric Wilcoxon test was applied to F and S.

RESULTS

Figure 1 shows that treatment with Ovestin cream had no effect on the mean plasma levels of E_1 and E_2 , whereas Premarin cream induced very pronounced and progressive increases in the mean plasma levels of these parameters. E_1 rose from a pre-treatment value of 45.9 pg/ml to 218.7 pg/ml at day 21, and E_2 rose from 26.3 pg/ml to 139.2 pg/ml at day 21. The difference between the mean E_1 and E_2 plasma levels for the two treatment groups was already significant ($P < 0.05$) at day 8. Both treatments led to an increase in the mean plasma levels of E_3 , from undetectable levels before treatment (<12 pg/ml) to mean values of 23.4 (Ovestin cream) and 23.9 (Premarin cream) pg/ml at day 21.

It can be seen from Figure 2 that Ovestin cream induced a slight suppression of FSH, from a mean pre-treatment value of 75.2 mIU/ml to a mean value of 70.5 mIU/ml at day 21. Premarin cream induced a greater suppression of FSH, from a mean pre-treatment value of 71.0 mIU/ml to a mean value of 55.6 mIU/ml at day 21. The mean plasma levels on days 8, 15 and 21 after Premarin cream were significantly lower than those after Ovestin cream.

A similar pattern is seen for LH. Ovestin cream induced a slight suppression of LH,

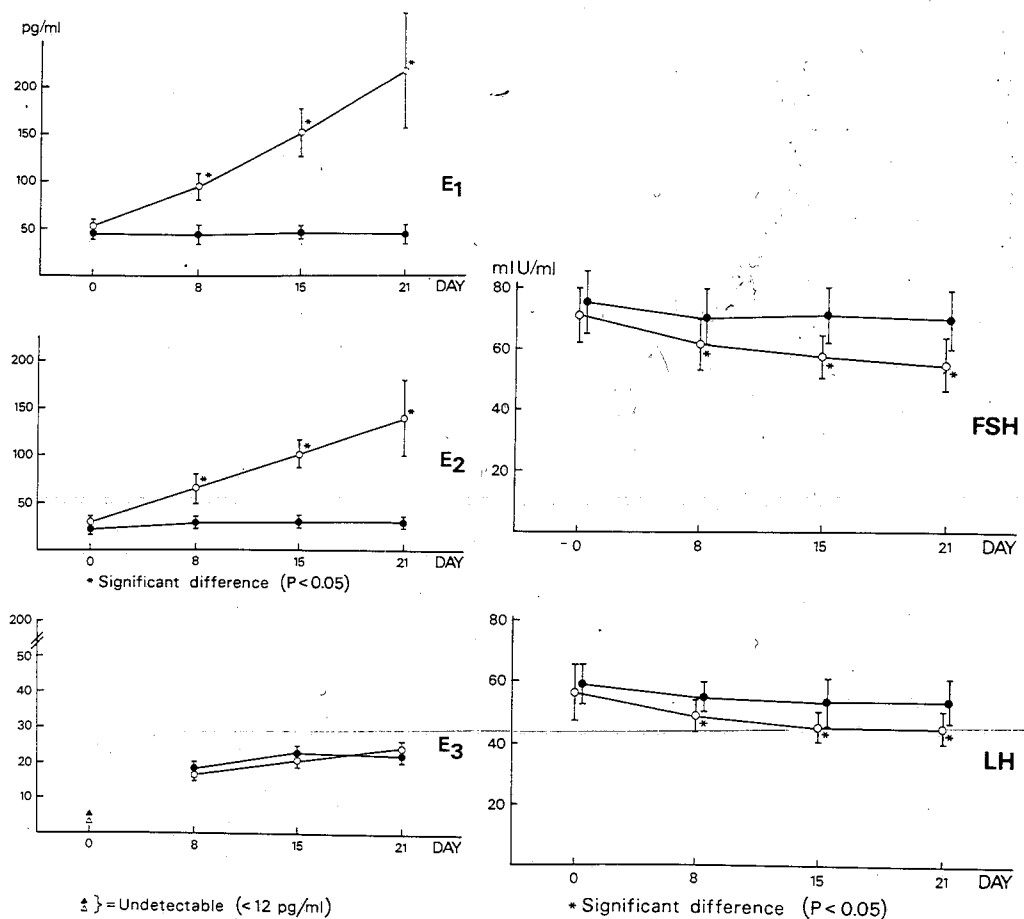


Fig. 1. Mean plasma levels (±SD) of E₁, E₂ and E₃ in Ovestin (●—●) and Premarin (○—○) treated patients.

Fig. 2. Mean plasma levels (±SD) of FSH and LH in Ovestin (●—●) and Premarin (○—○) treated patients.

from a mean pre-treatment value of 59.3 mIU/ml to a mean value of 53.1 mIU/ml on day 21. The suppression induced by Premarin cream was greater, from a mean pre-treatment value of 57.6 mIU/ml to a mean value of 44.4 mIU/ml at day 21. Mean plasma levels of LH on days 8, 15 and 21 after Premarin cream were significantly lower than those after Ovestin cream.

Figure 3 shows that neither preparation induced consistent changes in mean plasma PRL levels. It can also be seen that neither preparation induced changes in TRH-stimulated PRL release.

Premarin cream induced a progressive rise in mean SHBG capacity (Fig. 4), from 1.91 to 2.66 µg of testosterone bound/100 ml plasma at day 21. Following application of

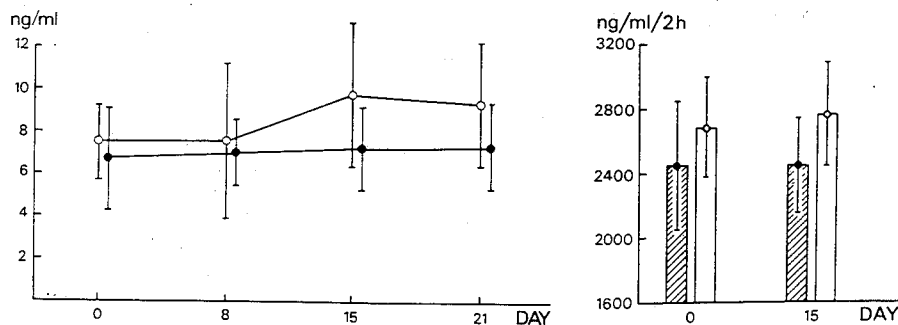


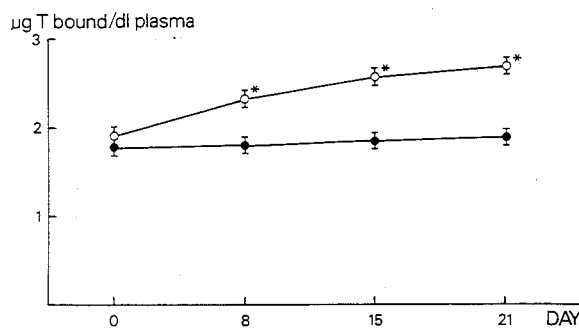
Fig. 3. Mean plasma levels (\pm SD) and PRL (left) and of TRH-stimulated PRL release (right) in Ovestin (\bullet — \bullet) and Premarin (\circ — \circ) treated patients.

Ovestin cream no changes were induced in mean SHBG capacity. The difference between the mean values for the two treatment groups was already significant ($P < 0.05$) at day 8.

Both preparations induced a pronounced and progressive rise in the mean MV; differences between the effects of the two preparations were not significant (Fig. 5). The rise in the MV reflects the beneficial effect of both preparations on post-menopausal vaginal atrophy.

Figure 5 also presents data on F and S. Whereas Ovestin cream induced a slight change in F, from a mean pre-treatment value of 0 to a mean value of 1.4 at day 21, Premarin cream induced a pronounced rise from a mean pre-treatment value of 0 to a mean value of 2.7 at day 21. Mean values on days 8, 15 and 21 after Premarin cream were significantly higher than those after Ovestin cream. A slight change in S was induced by Ovestin cream, the mean value rising from 0 cm at pre-treatment to 2.4 cm at day 21. Premarin cream induced a pronounced rise from a mean pre-treatment value of 0 cm to a mean value of 6.4 cm at day 21. Mean values on days 8, 15 and 21 after Premarin cream were significantly higher than those after Ovestin cream.

Endometrial specimens were obtained from 4 patients at pre-treatment and at day 15.



* Significant difference ($P < 0.05$)

Fig. 4. Mean plasma SHBG capacity (\pm SD) in Ovestin (\bullet — \bullet) and Premarin (\circ — \circ) treated patients.

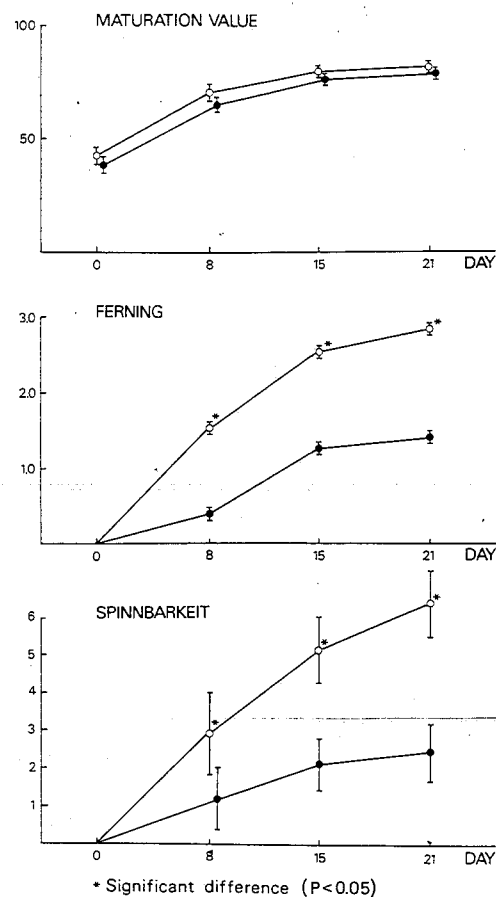


Fig. 5. Mean MV (\pm SD) in Ovestin (●—●) and Premarin (○—○) treated patients.

In the 2 patients applying Ovestin cream the endometrium was atrophic at pre-treatment and remained atrophic after 15 days of treatment. However, in the 2 patients applying Premarin cream, the endometrium, which was atrophic at pre-treatment, displayed moderate proliferation at day 15.

No side effects were reported.

DISCUSSION

The present study shows that oestrogens are readily absorbed following intravaginal administration, a finding which is in agreement with previous papers. It is known that preparations containing E_1 and/or E_2 give rise to unphysiologically high circulating oestrogen levels after intravaginal application [3,4,16–18], and this unfortunately leads to unwanted general effects, of which excessive endometrial stimulation is potentially the most dangerous [2,4]. The present data on the effects of Premarin cream on plasma E_1

and E₂ levels and endometrial stimulation are in agreement with previous findings, although our mean peak values at 3 wk for E₁ and E₂ were 219 and 139 pg/ml, respectively, compared to Whitehead et al.s' figures of 276 and 227 pg/ml, respectively, also after 3 wk of Premarin treatment. The reasons for these differences are not clear, but may be related to the very large inter-individual variation in the absorption pattern of E₁ and E₂ in both studies.

In the present study, endometrial biopsies were obtained after 2 wk of Premarin administration, and showed moderate proliferation in both cases; Whitehead et al. [4] obtained specimens after 4 wk (in one case cystic glandular hyperplasia was diagnosed and proliferative endometrium in the other). Taking into account the times of assessment, the endometrial findings of these two studies are in complete agreement. In an earlier study [2] Senikolp® Star, a vaginal ointment containing conjugated oestrogens, was applied for 10 days. In two cases, exploratory curettage was required because of uterine bleeding, and in both cases cystic glandular hyperplasia was diagnosed. Moreover, we observed a marked and significant rise in SHBG capacity following Premarin cream administration, indicating that these patients were being over-treated. Our data on changes in SHBG capacity fit nicely with the recent work of Pogmore and Jequier [19] who observed that orally-administered Premarin tablets induced SHBG levels in post-menopausal women that were significantly higher than those in normally-ovulating women. It is perhaps relevant to note here that, in addition to oestrone sulfate, Premarin preparations contain equilin and equilinin, both of which possess oestrogenic potency, but they cannot be assessed by current assays.

On the other hand, E_3 is also readily absorbed from the vagina after application of Ovestin cream and, although it exerts a local beneficial effect similar to that of Premarin cream, it does so without inducing undesirable general effects like those which follow the use of preparations containing E_1 and/or E_2 . The present study shows that, following Ovestin cream, circulating E_1 , E_2 and PRL, and SHBG capacity, remained unchanged. Histological examination showed no evidence of endometrial stimulation. The more pronounced and significant effects of Premarin cream on the plasma levels of FSH and LH, and also on F and S, are due to increased levels of circulating E_1 and E_2 .

In discussing the differences in general effects, one should keep in mind the differences between the amounts of conjugated oestrogens, which possess a considerable oestrogenic potency, and E₃, which is generally known as a weak oestrogen because of its brief duration of interaction with oestrogen receptor and rapid metabolic clearance. However, it should be pointed out that the aim of the present study was to compare the effects of the two preparations, using the doses recommended by the respective manufacturers, upon the local condition of vaginal atrophy.

The fact that neither preparation induced consistent changes in mean plasma PRL levels, or changes in TRH-stimulated PRL release is not surprising since Lind et al. [20] found that conjugated oestrogens indeed do not increase serum PRL levels after oral administration of recommended doses, and L'Hermite et al. [21] found that E_3 orally administered at doses of 2 and 6 mg/day did not alter circulating PRL levels. Furthermore, we have recently studied the effects of high oral doses of E_3 on PRL secretion and release. Even in high doses E_3 failed to induce any significant changes [22].

The present study again demonstrates that even by the vaginal route, similarly to what

is seen after oral administration, there is a clear-cut dissociation in the action of a single undivided daily dose of E_3 , since it displays a pronounced stimulatory effect on the vaginal mucosa and a total lack of such an effect on the endometrium. In view of the intended therapeutic use of vaginal creams this dissociation represents an ideal situation. There is no simple explanation for this remarkable dissociation in the action of E_3 . Speroff et al. [23] showed that, in post-menopausal women, the amount of endogenous oestrogens needed to develop or maintain proliferation of the vaginal epithelium is lower than that needed for proliferation of the endometrium. It is generally accepted that the E_3 -receptor complex is short lived. The studies of Katzenellenbogen et al. [24] and Clark et al. [25] suggest that this is one of the reasons why E_3 is a short-acting oestrogen and strongly support the concept that uterine growth requires prolonged influence of the oestrogen-receptor complex in the nucleus [26–28]. Hence the administration of a low undivided daily dose of E_3 is unlikely to lead to undesirable general effects, and in particular to endometrial proliferation.

It can be concluded, therefore, that although Ovestin and Premarin cream exert a similar favourable effect on post-menopausal vaginal atrophy, nevertheless clinical preference should be given to Ovestin cream in view of its lack of undesirable general effects.

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