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Transvaginal estriol administration in postmenopausal women: a double blind comparative study of two different doses

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Abstract

A group of 72 postmenopausal women were treated for 4 weeks with vaginal suppositories containing 0.5 or 1.0 mg of estriol. The two different doses achieved an identical significant improvement of urogenital symptoms, while a dose-related effect seen to be on climacteric complaints, according to a good absorption of estriol by the vaginal epithelium. Minimal side effects were observed and the safety of vaginal estriol treatment could advise further study about the effect of this kind of treatment on the climacteric syndrome.

Keywords: Estriol; Vaginal Administration; Menopause

1. Introduction

Estriol has been succesfully applied in postmenopausal women in several countries for more than 30 years, while in the literature there are several publications on its effect on the urogenital trophism [1–4].

On the other hand, the effect of estriol on the climacteric syndrome has been rarely investigated [5–8] especially after vaginal treatment [9–11], although it is considered active without the potential risks associated with systemic estrogen therapy [12]. It is known that the vaginal administration of estrogens, estriol included, gives rise to a rapid increase of hormonal levels in the peripheral blood [13–17], resulting in general pharmacological effects, of which the urogenital activity plays the main role [12].

The degree and quality of this response depends, instead, on the strength of the receptor binding [18–20], on the basis of which estriol is already defined a "short acting" estrogen [21].

The present study was carried out to evaluate and compare the efficacy and safety of two dif-

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ferent doses of estriol administered by vaginal route in patients with postmenopausal gonadal insufficiency.

2. Subjects and methods

A double-blind, randomized clinical trial was carried out at the Center for the Study of the Climaterium and the Postmenopause of the University of Bologna, and the Clinic of Obstetrics and Gynaecology of the University of Cagliari.

2.1. Subjects

Eighty women aged 45–62 years were admitted to the trial all in natural or surgically-induced postmenopause for at least 60 months and not receiving hormonal replacement therapy for at least 3 months prior to admission.

Exclusion criteria comprised women with a case history of thromboembolic diseases, estrogen-related neoplasms, biliary lithiasis, all breast disorders, bronchial asthma, epilepsy, allergy or idiosyncrasy to drugs or contrast mediums; uterine bleeding and/or severe micotic or viral vaginal infection, BMI > 25; respiratory, heart, liver and kidney insufficiencies and severe debilitating diseases.

The experimental design comprised two parallel groups, one group received the estriol as a vaginal suppository at the dose of 0.5 mg daily for 28 days, and the other at the dose of 1.0 mg daily for the same time [22]; the patients were randomly assigned in groups of ten to the two test groups without the prior knowledge of the investigators.

Before the beginning of the trial all patients were submitted to:

1. A complete physical and gynaecological examination, including case history;
2. Colpocytology;
3. Colposcopy;
4. Endometrial and/or hysteroscopic biopsy;
5. Mammography;
6. Biohumoral tests of the lipid picture, liver function and hemocoagulation;
7. Radioimmunological plasma levels of E_2, FSH and LH.

Evaluation parameters assessed at baseline (T_0), intermediate (T_1) and end-point (T_2) included:

(a) Genital-urinary symptoms (itching, burning, dyspareunia and dysuria) rated with a score from 0 (absent) to 3 (marked);
(b) Cervicovaginal findings (mucosal appearance, thickness and vascularization of mucous) scored from 0 (normal) to 2 (atrophy);
(c) The Schiller's test rated 1 (normal iodo-captation) to 3 (no iodo-captation);
(d) Degree of colpocytoepithelial trophism calculated with the cell maturation index according to Meisels and Van der Verlden [23];
(e) The intensity of the climacteric syndrome according to the Kupperman Index [24].

2.2. Statistical analysis

The homogeneity of the two treatment groups at baseline (T_0) was assessed with the *t*-test for quantitative variables and the χ^2-test for qualitative variables. Efficacy parameters evaluated with a categorical scale, were submitted to non-parametric analysis of variance with the Friedman test "within dose" in order to assess response over time; if results were rated as statistically significant then multiple comparisons with the Wilcoxon test were made. The Mann-Withney test was used to evaluate any difference between the two drug formulations. An alpha level equal to 0.01 was used in both the Wilcoxon and Mann-Withney tests to enable multiple comparisons.

Clinical assessment of therapeutic efficacy was analyzed with the χ^2-test. Total score and continuous variables were submitted to Split-plot analyses which give a correct estimate of the error 'within' and 'between' factors; this error was then used in the Tukey test to perform all possible multiple comparisons. Analysis of variance for repeated measures was carried out on the colpocytoepithelial maturation index to test the dose-effect. Multiple comparisons were analyzed with the Helmert test to compare intermediate and end-point values and global assessments with baseline values.

Table 1
Clinical results after 4 weeks of estriol treatment with different doses of vaginal suppositories

E_3 Dosage (mg/daily)	Clinical improvement (%)				Total N
	>75	75–51	50–25	<25	
(A) 0.5	11	13	9	2	35
(B) 1	20	15	2	0	37
A + B	31	28	11	2	72

$\chi^2 = 9.1618$, $P < 0.05$.

Because of the marked variability at basal time, statistical analysis of the Kupperman index was performed on the differences with baseline at various times, using baseline ad the co-variant.

Analysis was also carried out on sub-groups divided according to the postmenopausal period and the covariance analysis was used for comparison between doses, considering 30 months as the cut-point among the sub-populations. Global clinical assessment of tolerance was analyzed with the χ^2-test and laboratory parameters with the *t*-test to compare mean baseline and end-point values. Normal values in each test were used to detect any abnormalities.

3. Results

Five patients refused to undergo treatment after enrolment. The randomization code disclosed at the termination of the trial showed 37 women as having received vaginal suppositories at the dose of 0.5 mg daily and 38 having received vaginal suppositories at the dose of 1.0 mg daily.

Mean age of the total group ($n = 75$) was 53.2 ± 3.2 years and mean time of postmenopause was 34.6 ± 17.6 months: baseline comparison of the clinical characteristics (age, postmenopausal time, symptom scores) of the two sub-groups showed no statistical difference thus confirming group homogeneity.

Three patients discontinued therapy before the intermediate visit (T_1): two women who did not tolerate the dose of 0.5 mg daily (local burning) were rated only for tolerance and not efficacy, and one woman who received 1.0 mg daily and dropped out for personal reasons was excluded from both assessments.

Table 1 reports the final result according to the clinical improvement registered at the end of estriol treatment and shows a positive dose-drug relation ($P < 0.05$) confirmed by statistical analysis with the Mantel-Haenzel test, which verifies the association between rising doses and values of clinical global impression.

Fig. 1 shows the course of the total clinical symptomatology, the score of which rises a significant improvement, 50% after 2 weeks ($P < 0.01$) and to 67.7% after 28 days ($P < 0.01$), both in all patients and in each dosage group, with a statistically significant reduction between the two, compared with the initial values ($P < 0.02$).

Table 2 reproduces the mean initial and final scores of every parameter used in the study:

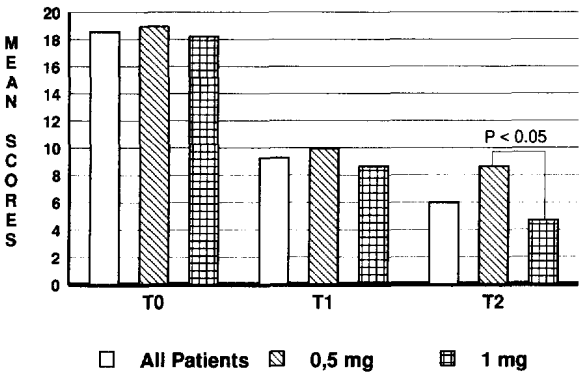

Fig. 1. Mean symptomatological score before (T_0) during (T_1) and after (T_2) transvaginal therapy with two different doses of estriol.

Table 2
Mean scores (±S.E.) of clinical parameters before (T_0) and after (T_2) estriol transvaginal treatment

Clinical parameters	Estriol dosage					
	0.5 mg			1 mg		
	T_0	T_2	P	T_0	T_2	P
Vaginal symptomatology	3.15 ± 0.18	0.18 ± 0.07	0.01	2.86 ± 0.17	0.17 ± 0.06	0.01
Schiller's test	2.03 ± 0.09	1.00 ± 0.00	0.01	2.14 ± 0.10	1.00 ± 0.00	0.01
Colpocytology	1.03 ± 0.03	0.16 ± 0.07	0.01	1.15 ± 0.07	0.15 ± 0.07	0.01
Maturation value	42.34 ± 1.92	73.49 ± 1.86	0.01	42.07 ± 1.98	73.78 ± 1.90	0.01
Kupperman Index	15.29 ± 1.57	6.89 ± 0.87	0.01	15.03 ± 1.03	4.27 ± 0.57	0.01
F.S.H.(mu/ml)	93.34 ± 4.44	68.15 ± 0.87	0.01	88.81 ± 5.20	62.09 ± 4.58	0.01
L.H. (mu/ml)	32.86 ± 2.58	28.74 ± 2.32	0.01	35.33 ± 2.60	27.26 ± 2.38	0.01

— the vaginal trophism reaches a significant improvement with both 0.05 mg ($P < 0.01$) and 1 mg suppositories ($P < 0.001$), though they are not statistically different;

— no significant difference between doses was observed in vaginal symptomatology, whereas its improvement was significant with both suppositories ($P < 0.01$). Similarly, no dose-related difference was noted in objective findings although their improvements are significant for both 0.5 mg and 1 mg doses ($P < 0.001$);

— the Schiller's test score was decreased by 33.8% after 14 days ($P < 0.01$) and by 50.7% at end-point ($P < 0.01$) with 0.5 mg daily and by 39.3% ($P < 0.01$) and 53.2% ($P < 0.01$), respectively with 1 mg daily. No significant difference was observed between the two treatments;

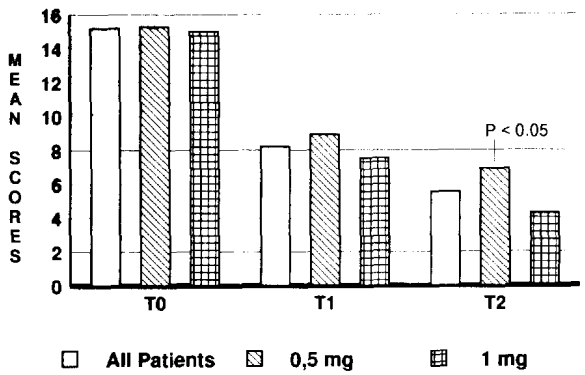

Fig. 2. Mean Kupperman's Index before (T_0) during (T_1) and after (T_2) transvaginal therapy with two different doses of estriol.

— the Maturation Volume, according to Meisels and van der Velden formula, showed a 60.1% increase after 2 weeks ($P < 0.01$) and of 73.6% at end-point ($P < 0.01$) with 0.5 mg and an increase of 69.8% ($P < 0.01$) and 75.4%, respectively with 1 mg daily;

— the Kupperman Index (Fig. 2) significantly decreased by 41.7% with 0.5 mg ($P < 0.01$) and 49.8% with 1 mg ($P < 0.01$) after 2 weeks, while was reduced by 55% ($P < 0.01$) and 71.6% ($P < 0.01$), respectively at the end of treatment. This second difference is statistically significant ($P < 0.013$). For mastering this field, the dose/effect ratio was assessed in relation to the postmenopausal time, according with the notion of climacteric symptoms predominance during the first postmenopausal years. The data obtained show that up to 30 months' postmenopause there is a significant difference between doses ($P < 0.05$) while there is no difference in over 30 months' menopausal women (Table 3);

— gonadotropins plasma levels were significantly decreased in both groups, but no differences were found between estriol doses (Fig. 3). Investigators assessed local and general tolerance as being very good in 86.5% (64/74) of the patients, fair in 10.8% (8/74) and poor in 8.7% (2/74); patients who discontinued therapy prior to the T_1 visit were not assessed for severity of adverse reactions but in relation to the suspension of treatment. When tolerance was judged fair ($n = 8$), but did not require the suspension of therapy or dose reduction, the

Table 3
Percent reduction (mean ± S.D.) of Kupperman index according to the menopausal period (cut point 30 months)

Time	Post menop. (Mths)	E_3 Daily dosage (mg)			
		All patients	0.5 mg	1 mg	*P*
T_0	<30	−44.7 ± 29.7	−39.5 ± 30.4	−49.4 ± 28.9	0.025
	>30	−42.8 ± 30.0	−41.5 ± 30.9	−44.2 ± 30.0	NS
T_2	<30	−67.9 ± 23.8	−58.5 ± 24.6	−70.7 ± 22.1	0.025
	>30	−57.6 ± 29.3	−46.6 ± 29.8	−68.5 ± 25.2	NS

patients described their disturbances as being transient, of mild entity and associated with vaginal dystrophy (burning and/or local itching) or estrogen activity (mastodynia and breast tenderness). No significant variations were observed in laboratory tests with either treatments.

4. Discussion

The results of our study confirm the well-known efficacy of vaginally administered estriol in postmenopausal therapy. There are several previous controlled trials about the effect of E_3 vaginal administration, but they mainly considered the urogenital tract disorders. Therefore, the effect of the drug proved not to be dose-related [3] because the vaginal symptoms were almost subsided with the E_3 lowest dose [1–8]. Also in our study no significant differences were observed between E_3 0.5 mg and E_3 1 mg daily for all genital, subjective and objective parameters. Nevertheless according to a systemic effect of this treatment, in agreement with data from literature, E_3 efficacy is also evident on the climacteric symptoms and, in this case, a significant difference between the two different dosages of estriol are surveyed on Kupperman Index.

Particularly, the dose/effect ratio was assessed in relation to the postmenopausal period, cutting this time at 30 months: there is a significant difference in the first group, while there is not in the over 30 months menopausal women. It is not unusual that climacteric symptoms vary considerably during the first postmenopausal years and many factors

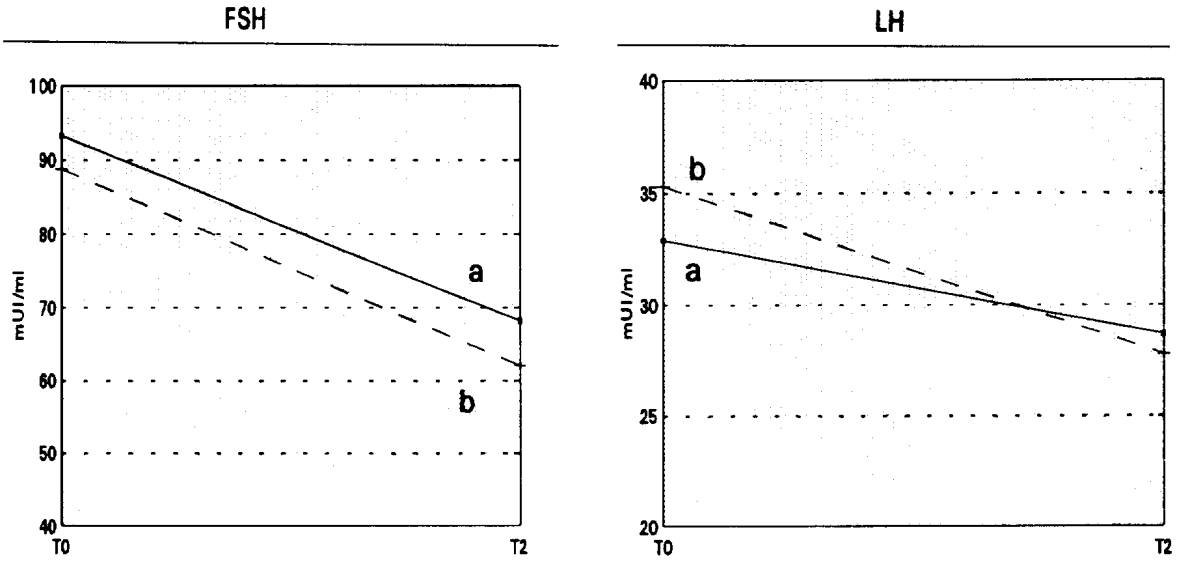

Fig. 3. FSH and LH mean values before (T_0) and after (T_2) transvaginal therapy with 0.5 (a) and 1 mg (b) of estriol.

(i.e. body weight, smoking, etc.) could render this period as easier. Nevertheless, the admission's strict rules (Body Index <25, no previous hormonal treatment, 5 years of maximal postmenopausal period) and the unusual smoking habit among patients, allow the thought that this effect was related to the drug. In fact, FSH and LH plasma levels (Fig. 3) were lower after 1 mg E_3 treatment than with 0.5 mg, while no statistical difference between them was noted.

In conclusion, further studies are necessary to confirm these findings and to propose E_3 transvaginal therapy as a possible alternative to conventional hormonal replacement without the potential risks of other estrogens.

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