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TITLE:	REPRODUCCION
PUBLISHER/PLACE:	Mtp Press Lancaster
VOLUME/ISSUE/PAGES:	1982 Apr-Jun;6(2):101-6 101-6
DATE:	1982
AUTHOR OF ARTICLE:	Trevoux R; van der Velden WH; Popovic D
TITLE OF ARTICLE:	Ovestin vaginal cream and suppositories for the tr
ISSN:	0303-5220
OTHER NUMBERS/LETTERS:	
	NLM Unique ID: 0427161
	PubMed ID: 7141096
SOURCE:	PubMed
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Reproduccion 6 (1982) 101–106

Ovestin® Vaginal Cream and Suppositories for the Treatment of Menopausal Vaginal Atrophy*

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Eighty-two postmenopausal women with vaginal atrophy and associated symptoms were treated with either Ovestin® vaginal cream (54 women) or vaginal suppositories (28 women) containing 0.5 mg of E_3/dose, daily for 3 weeks. A maintenance dose of 0.5 mg of E_3 twice weekly was applied by all patients for 5 weeks, and by 27 of them for up to 16 weeks. Variables studied were clinical and colposcopic findings, the Maturation Index (MI) and Maturation Value (MV), cervical mucus ferning (F) and spinnbarkeit (S) and endometrial biopsies (obtained pretreatment and after 3 weeks in 15 of the patients). Furthermore, the bio-availability of circulating unconjugated E_3 for up to 8 hours following a single dose of Ovestin cream was studied in 10 of the patients.

Clinical and colposcopic findings indicated that the treatment had a very favourable effect in all patients. This was reflected in the pronounced change in vaginal smears, indicating a strong oestrogenic effect. There was a slight to moderate effect on cervical mucus. Endometrial biopsies showed that endometrium remained atrophic in all 15 patients in whom biopsies were obtained. A maintenance dose of 0.5 mg of E_3 twice weekly appeared to be sufficient to maintain the beneficial effect. Tolerance was good, and patients commented favourably on the treatment.

INTRODUCTION

Postmenopausal vaginal atrophy with associated clinical symptoms is the most frequent problem in women of this age group. According to Kicovic *et al.*[1] about 20% of postmenopausal women refer to the Menopause Clinic because of some of these symptoms, and require topical treatment with creams containing oestrogens.

* Partly presented at the International Symposium on the Menopause, Viareggio, Italy, May 25–28, 1980 and at the 3rd International Congress on the Menopause, Ostend, Belgium, 9–12 June, 1982

Until recently creams containing conjugated oestrogens were used frequently in clinical practice. However several recent studies have shown that vaginal administration of these creams led towards marked rise in circulating E_1 and E_2 levels with resultant high urinary oestrogen levels and pronounced endometrial stimulation[2–5]. It is not therefore, surprising, that current clinical interest is focusing on E_3 which has very recently been shown to cure post-menopausal vaginal atrophy efficiently without any undesirable general effects[1–5]. The present study was undertaken to extend recent clinical experience in treating this syndrome with the new Ovestin® vaginal cream or suppositories containing 0.5 mg of E_3/dose[1].

MATERIALS AND METHODS

Patients

Eighty-two postmenopausal or ovariectomized women aged 36–79 years and presenting with vaginal atrophy and related symptoms, participated in the study. The menopause had occurred 4–28 years (mean 14.6 years) prior to the present study. None of the patients had used any hormonal treatment for at least 12 months preceding the present investigation; furthermore, no other therapy or self-medication that might have interfered with the present medication was allowed. Patients with a history of malignancies were excluded. The patients were divided into two groups: 54 of them were treated with Ovestin vaginal cream and 28 were treated with Ovestin vaginal suppositories, both containing 0.5 mg of E_3 per dose. The patients applied a daily dose of 0.5 mg of E_3 (0.5 g of cream by a plastic calibrated applicator, or one suppository) each day before retiring for 3 weeks. A maintenance dose of 0.5 mg of E_3 twice weekly was applied by all patients for 5 weeks, and by 27 of them for up to 16 weeks.

Variables

Vaginal smears obtained by drawing a disposable wooden spatula down the upper half of both lateral vaginal walls, were fixed in 95% alcohol and stained according to Papanicolaou. Results were expressed as the Maturation Index (MI). By multiplying the percentages of basal–parabasal cells, intermediate cells and superficial cells by factors 0, 0.5 and 1, respectively, the values of the MI were transformed into the Maturation Value (MV). Ferning (F) was scored as 0, 1, 2 or 3; spinnbarkeit (S) was measured immediately in centimetres. Endometrial biopsies were evaluated by means of light microscopy. The plasma levels of unconjugated E_3 were measured by radioimmunoassay according to Rotti *et al.*[6]; reagents were obtained from Medical Systems. For enzymatic hydrolysis β-glucuronidase, isolated from *Helix pomatia*, was used. Assays were carried out in duplicate, at the same time and with the same batches of reagents.

Clinical and colposcopic examinations were performed pretreatment and at weeks 3, 5, 8, 12 and 16. Besides patients' claims on the clinical symptomatology, particular attention was paid to the appearance of cervico-vaginal mucosa (colour, petechiae, elasticity, etc.). Furthermore, in 15 of the patients endometrial biopsies were obtained prior to, and after 3 weeks of, treatment.

RESULTS

The treatments with both cream and suppositories had a beneficial effect in all patients at 3 weeks, the improvement being maintained during the maintenance therapy. A good clinical effect was reflected in the change of the MV from 44.5 and 39.1 at pretreatment to 73.8 and 69.8 at 3 weeks following daily administration of the cream or suppositories, respectively. During the maintenance therapy MV remained more or less unchanged, thus demonstrating that the twice-weekly maintenance treatment appeared to be sufficient. As can be seen from Table 1, both cream and suppositories induced slight to moderate effect on cervical mucus F and S.

In ten of the patients absorption and bioavailability of E_3 following a single administration of Ovestin vaginal cream (0.5 g of cream, i.e. 0.5 mg of E_3) were studied by means of frequent measurements of the plasma levels of unconjugated E_3. Table 2 shows that there was a sharp rise in unconjugated E_3 levels to a mean peak value of 113.5 pg/ml at 1 hour, followed by a gradual decline during the following 7 hours, the mean value being 34.6 pg/ml at 8 hours.

Clinical examinations showed the treatments to have had a beneficial effect in all patients at 3 weeks, the improvement being maintained during maintenance therapy. A remarkable improvement in dyspareunia was reported by all 28 patients presenting with this complaint. A similar beneficial effect was reported by all patients who complained of vaginal dryness. Improvement of the local condition led toward a change in the libido and sexual activity in a number of patients, and this was indeed remarkable. Kraurosis vulvae was considerably improved in two patients presenting with this complaint, whilst pruritus vulvae et ani remained unchanged in one patient. Colposcopic examinations confirmed that the treatments had an excellent effect on vaginal mucosa: subepithelial petechiae disappeared completely and mucosa had normal appearance. Endometrial biopsies, obtained in 15 of the patients, showed that endometrium remained atrophic at 3 weeks in all of them.

Tolerance was very good and all 82 patients were satisfied with the treatments. Only one patient experienced slight, transient mastodynia at the beginning of treatment and one patient complained of a sensation of "fire in vagina" during the first 2–3 days of therapy with suppositories, but this side-effect was only transitory and did not re-occur. No other untoward effects were reported.

DISCUSSION

The present study confirms the recent data on efficacy and safety of Ovestin vaginal cream and/or suppositories for the treatment of postmenopausal vaginal atrophy, as well as on the absorption pattern of E_3 from these preparations through vaginal mucosa[1]. In view of the well-known facts about untoward effects of vaginal creams containing conjugated oestrogens[2–5], particularly with regard to unopposed endometrial stimulation, the natural hormone E_3 appears to be an ideal alternative for the treatment of this local condition which is so frequent in the older group of postmenopausal women. E_3 is a short-acting oestrogen and its long-term oral or intravaginal administration in individual daily doses leads toward normalization of the cervico-vaginal mucosa, whereas the endometrium remains unaffected. This is not

Table 1 Mean values of the MI, MV, F and S in patients using Ovestin cream and Ovestin suppositories

Variable	*Time of assessment*					
	Pretreatment	*3 weeks*	*5 weeks*	*8 weeks*	*12 weeks*	*16 weeks*
Ovestin cream						
MI	14.5/82 /3.5	0/52.5/47.5	0/59 /41	0/56.8/43.2	0/60.3/39.7	0/62.4/37.6
MV	44.5	73.8	70.5	71.6	69.9	68.8
F	0	1.7	1.4	1.5	1.4	1.5
S	0	2.1	1.9	1.8	2.1	2.0
Ovestin suppositories						
MI	23.5/74.8/1.7	0/60.5/39.5	0/65.4/34.6	0/63 /37	n.d.*	0/66.8/33.2
MV	39.1	69.8	67.3	68.5	n.d.	66.6
F	0	1.2	1.1	1.0	n.d.	1.1
S	0	1.8	2.0	1.9	n.d.	1.4

*n.d. = not determined

Table 2 Individual and mean (± SD) plasma levels of unconjugated E_3 (pg/ml) following single i-vaginal administration of Ovestin cream

Patient no.	*Hours*					
	0	*1*	*2*	*4*	*6*	*8*
1	—*	117	106	76	57	35
2	—	128	109	93	75	44
3	—	96	108	87	71	50
4	—	104	86	73	60	36
5	—	121	113	69	62	37
6	—	112	94	71	43	30
7	—	124	107	65	48	25
8	—	105	85	70	44	43
9	—	118	91	66	42	27
10	—	110	87	73	45	30
$\bar{x}$	—	113.5	98.6	74.0	54.7	34.6
SD		10.0	11.0	9.0	12.1	7.7

* Undetectable, i.e. < 12 pg/ml

surprising in view of (a) the pharmacokinetic profile of E_3 (rapid absorption following oral or intravaginal administration, rapid metabolism and excretion together with weak binding to plasma proteins), and (b) the finding that the E_3–receptor complex is much less stable than that of oestradiol (E_2)[7,8].

We found it very practical and suitable to have both pharmaceutical forms of this excellent preparation available for clinical practice as some patients do not accept or have difficulties in manipulating an applicator for the cream, while others nevertheless prefer the cream. Tolerance of both pharmaceutical forms was shown to be very good and we recommend these preparations as therapy of choice for postmenopausal vaginal atrophy and associated complaints.

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