Replens versus Dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women

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Abstract

Objectives: This study was designed to evaluate the efficacy of Replens, a non-hormonal moisturizing vaginal gel, on symptoms of vaginal atrophy in postmenopausal women, in comparison with Dienoestrol (Cilag), an estrogenic vaginal cream.

Methods: Thirty-nine patients were randomly allocated to either of the two treatments. Replens was given three times a week during the 12 weeks of the study, which Dienoestrol was administered daily during the first two weeks and thereafter three times a week. Vaginal dryness index, itching, irritation, dysparcunia, pH and safety were evaluated every week the first month and every month thereafter.

Results: Both treatments had a significant increase on vaginal dryness index as soon as the first week of treatment, and the hormonal compound was significantly better than the non-hormonal one. All symptoms as itching, irritation, dysparcunia significantly decreased or disappeared without any difference between the two treatments. For pH, no significant difference was seen either in each group or between the two groups. No adverse events related with the two drugs were related.

Conclusion: This study shows that Replens applied vaginally three times a week, is a *full* therapy for all symptoms of vaginal atrophy as well as local estrogen. No serious adverse event was related. Replens is an alternative treatment to local estrogen and perhaps a good complement of systemic HRT in patient suffering from vaginal dryness.

Key words: Vaginal, vaginal atrophy, vaginal dryness, vaginal moisturization, non-hormonal vaginal therapy, hormonal vaginal therapy, vaginal pH.

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1. Introduction

Vulvovaginal atrophy appears frequently at menopause secondary to progressive decrease in ovarian secretion of estradiol. It varies from one patient to another, in intensity, delay of onset and localization. In 45% of menopausal women, it is clinically manifested as a syndrome consisting mainly of vaginal dryness, itching, irritation and, if the woman is sexually active, dyspareunia (1). Common treatment is estrogen taken systemically or topically. Nevertheless, adverse effects of those treatments are now well known, particularly on the endometrium. Other non-hormonal therapies have shown some efficacy on those symptoms. Replens, a non-hormonal local bioadhesive vaginal gel, has shown to have a superior efficacy when compared to

common lubricants (2). Replens is a vaginal gel composed of purified water enmeshed in a carbomer-polycarbophil system. The overall aim of this study was to compare the efficacy, safety and tolerability of a vaginal moisturizing get. Replens (Meda AB) and a vaginal cream, Dienoestrol (Cilag AB) in the treatment of vaginal dryness, the major symptom of vaginal atrophy, in postmenopausal women.

2. Materials and methods

2.1. Subjects

Thirty-nine postmenopausal women complaining of vaginal dryness, aged 43-76 years (mean age 58.28 years) were enrolled in a comparative, randomized, open label study of three months duration. The following exclusion criteria were adopted: hormonal-dependent tumors, known or suspected other serious disease, abnormal genital bleeding, past history of active thromboembolic disorder, vaginal infection, hormonal replacement therapy in the last three months, vaginal use of any douche or lubricant. All gave their informed consent. A history was taken and all patients underwent clinical examination and a PAP smear.

The patients were randomly allocated to one of two treatments. Group A received Replens: 1 vaginal application three times a week for 3 months. Group B received Dienoestrol vaginal cream (0.01%): the dose per application was 0.5 mg given daily for 2 weeks then three times a week for up to 3 months.

2.2. Methods

After each patient had been assessed for this study suitability using the inclusion/exclusion criteria, the study design was explained to them and an oral informed consent obtained. A complete medical history has been taken with specific reference to vaginal atrophy symptoms, vaginal dryness, dyspareunia, itching… A complete physical examination has been performed and a vaginal examination conducted, vaginal pH and vaginal dryness index measured and a PAP smear obtained for vaginal cytology. Diaries have been dispensed and patients instructed as to their completion. Then the patients will be examined every week for the first month, as week 8 and at week 12 for the final evaluation.

Efficacy criteria were:

- Vaginal dryness index, as previously published by Bachmann (2). This index allows for scoring of vaginal moisture, vaginal fluid volume, vaginal elasticity, and vaginal mucosa on a scale of 1 (poorest) to 5 (best) for each individual data and on a score of 5 to 25 for the total.
- Vaginal pH (strips colorpHast), itching, irritation, dysparcunia for patient who had intercourse; patient's overall feeling, length of moisturizing effect as measured on a five-point scale; up to six hours, six to twelve hours, twelve to eighteen hours, eighteen to twenty-four hours, greater than twenty-four hours.

Safety was assessed in terms of adverse events, vaginal cytology.

2.3. Statistical evaluation

All demographic and efficacy parameters will be analyzed for differences between groups using an analysis of variance for the data which are parametric or can be considered parametric and either a Wilcoxson Sigh Rank Test for remaining non-parametric ordinal data or other appropriate non-parametric tests for non-ordinal data. The comparability of the two groups before treatment was assessed using one-way ANOVA tests for quantitative variables such as age, weight levels. The duration of menopause was compared using a non-parametric test (Kruskall-Wallis). Qualitative data such as vaginal dryness, elasticity, were analyzed using the Fisher exact text.

3. Results

Altogether 40 postmenopausal women were recruited for the study from September 1991 to June 1993; one didn't start treatment. There was no clinically significant difference in the measurable parameters among the two groups. All women were deprived of ovarian function as a result of either natural menopause (n = 37) or oophorectormy (n=2).

3.1 Efficacy on vaginal dryness index

Both treatments resulted in a significant increase in the vaginal dryness index when compared to the baseline values. This was significant for all women treated with Dienoestrol and for all but one following treatment with Replens. The comparison between the two groups was also significantly different in favor of Dienoestrol after the first week of treatment.

Week	0	1	2	3	4	8	12
DIENOESTROL Mean + SD n p / visit 1*	 13+4.33 19	 18.32+3.25 19	 20.74+2.60 19 0.0001	 21.28+3.29 18 0.0001	 22+3.07 18 0.0001	 21.89+2.85 18 0.0001	 21.78+2.76 18 0.0001
REPLENS Mean + SD n p / visit 1**	 13.43+3.45 20	 17.53+2.50 19	 17.35+2.61 20 0.0003	 17.74+2.85 19 0.0005	 17.63+3.13 20 0.0013	 17.3+2.6 20 0.0011	 17.32+2.50 19 0.0026
p Replens/Dien.***		0.2164	0.0024	0.0014	0.0003	0.0001	0.0001

* p from ANOVA comparison before and during treatment with Replens
** p from ANOVA comparison before and during treatment with Dienoestrol
*** p from ANOVA comparison between groups

3.2. Efficacy on vaginal pH

No significant difference was seen between the two groups of treatment while the pH, at the start of the study, was between 5 and 6.

Week	0	1	2	3	4	8	12
DIENOESTROL Mean + SD n	5.91+1.10 15	3.17+0.78 16	4.7+0.67 17	4.96+0.72 16	4.87+0.74 16	4.95+1.08 17	4.98+1.06 16
REPLENS Mean + SD n	5.24+1.19 17	4.95+1.04 17	4.77+0.82 17	4.92+1.10 17	5.02+1.15 17	5.32+1.10 18	4.74+0.78 16
p Replens/Dien.		0.5077	0.7847	0.9349	0.6635	0.3267	0.4651

p from ANOVA comparison between groups

3.3. Efficacy on itching irritation

In the two groups of treatment, most of the patients who suffered from itching or irritation had a disappearance of those symptoms as soon as the first week of treatment. There was no significant difference between the two groups.

Week	Grade	0	1	2	3	4	8	12
DIENOESTROL	1 2 3 4	7 (18.92%) 3 (8.11%) 5 (13.51%) 3 (8.11%)	15 (42.86%) 0 2 (5.71%) 0	16 (41.03%) 0 2 (5.13%) 1 (2.56%)	18 (47.37%) 0 0 0	18 (47.37%) 0 0 0	16 (42.11%) 7 (5.26%) 0 0	16 (44.44%) 0 1 (2.78%) 0
REPLENS	1 2 3 4	8 21.62%) 2 (5.41%) 5 (13.51%) 4 (10.81%)	14 (40.0%) 1 (2.86%) 1 (2.86%) 2 (5.71%)	16 (41.03%) 2 (3.13%) 1 (2.56%) 1 (2.56%)	18 (47.37%) 1 (2.63%) 0 1 (2.63%)	19 (50.0%) 1 (2.63%) 0 0	16 (42.11%) 3 (7.89%) 0 1 (2.63%)	15 (41.67%) 3 (8.33%) 0 1 (2.78%)
Grade: 1 (none) to 4 (severe).								

3.4. Efficacy on dyspareunia

Only 11 patients in each group had intercourse during the trial. All of them had a disappearance of pain with intercourse at three months, and most after two weeks. No significant difference between the two groups was found.

Week	Grade	0	1	2	3	4	8	12
DIENOESTROL	1 2 3 4 5	1 (2.63%) 0 7 (18.42%) 3 (7.89%) 7 (18.42%)	7 (17.95%) 0 3 (7.69%) 0 9 (23.08%)	7 (17.93%) 2 (3.12%) 0 0 10 (25.6%)	7 (18.42%) 0 0 0 11 (28.95%)	7 (18.42%) 0 0 0 11 (28.95%)	9 (23.68%) 0 0 0 9 (23.68%)	9 (24.32%) 0 0 0 9 (24.32%)
REPLENS	1 2 3 4 5	3 (7.89%) 1 (2.63%) 3 (7.89%) 4 (10.53%) 9 (23.68%)	4 (10.26%) 0 1 (2.56%) 0 15 (38.46%)	4 (10.26%) 0 2 (5.12%) 1 (2.56%) 13 (33.33%)	5 (13.16%) 0 2 (5.26%) 0 13 (34.21%)	6 (15.79%) 0 2 (5.26%) 0 12 (31.58%)	4 (10.53%) 1 (2.63%) 1 (2.63%) 2 (5.26%) 12 (31.58%)	6 (16.22%) 0 0 0 13 (35.14%)
Grade: 1 (none) to 4 (severe); 5 (no intercourse)								

3.5. Efficacy on onset of action

Replens group had a mean time until improvement of 5.8 days whereas Dienoestrol group had 3.9 days. However, this difference is not significant due to the large variability of the measurement.

3.6. Patient assessment of overall feeling

The effect of the treatment was also subjectively evaluated by the patient. For Replens, 60% of the patients judged the effect to be good, very good or excellent. The corresponding rate for Dienoestrol was 84%. Only one patient in each treatment group regarded the effort as poor.

At the end of the study, no significant difference was seen between the two groups. The only difference was seen at 3 weeks and 1 month.

3.7. Safety

No patients had abnormal gynecological findings, or were reported as having poor tolerance to the gel. Two adverse events were reported, one in each group of treatment. At week 2, one patient with Dienoestrol had pain in abdomen and was withdrawn from the study. At week 8, one patient with Replens had vaginal odor and wad withdrawn from the study. In both these cases, it has not been made a casual relationship to the study drug.

4. Discussion

Both drugs efficiently reversed symptoms of vaginal atrophy, vaginal dryness, itching and/or irritation, discomfort during intercourse in sexually active women. Replens and Dienoestrol resulted in significant improvement of vaginal dryness index, and the comparison between the two drugs was in favor of Dienoestrol. All women but one in each treatment group reported they felt better or much better at the end of the treatment. For other symptoms, itching and/or irritation, discomfort during intercourse in sexually active women, both treatments were equal with the disappearance of those symptoms as soon as the first week of treatment.

A large proportion of women don't take hormones for menopause. Estimates of the incidence of hormone therapy in different countries range from 3% in Italy to 32% in California (3,4). Substantial number of women also start HRT but stop within a few months; up to two-thirds will abandon it within one year (5). So, many symptomatic postmenopausal women need non-hormonal treatments.

As shown by Bachmann, Replens is active on vaginal dryness not only in women without HRT, but also with HRT (2). One of the explanations of this efficacy has been shown by Sarrel in a preliminary study (6); he found that Replens increased the vaginal blood flow comparable to HRT. Moreover, in patients under HRT, an additional increase of 25% of vaginal blood flow has been shown.

Nachtigall, in a comparative study with a local estrogen therapy, found the same results as us and has shown that 60% of the Replens group with vaginal atrophy as seen on PAP smear at baseline had reversed in 12 weeks as well (7).

This study showed that Replens applied vaginally three times a week, is a *full* therapy for all symptoms of vaginal atrophy as well as local estrogen. No serious adverse event was related. Replens is an alternative treatment to local estrogen and perhaps a good complement of systemic HRT in patients suffering from vaginal dryness.

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