Local estrogen replacement therapy in postmenopausal atrophic vaginitis: Efficacy and safety of low dose 17β-estradiol vaginal tablets

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Summary

Purpose of investigation: To verify the effectiveness and safety of low-dose 17β-estradiol vaginal tablets in the treatment of the postmenopausal atrophic vaginitis.

Patients and methods: 325 postmenopausal women with atrophic vaginitis in estrogenic replacement therapy with 0.025 mg 17β-estradiol vaginal tablets, one application each day for two weeks, and a single application two times a week for the following 22 weeks (total treatment period: 24 weeks).

Results: Most of the women reported an improvement of symptoms just after two weeks and minimal incidence of adverse reactions. No patients showed abnormal endometrial thickness and no one had to interrupt the treatment for abnormal uterine bleeding because of systemic absorption.

Conclusion: Low-dose 17β-estradiol vaginal tablets in the treatment of the postmenopausal atrophic vaginitis constitutes an extremely valid approach in terms of effectiveness and safety.

Key words: Atrophic vaginitis; Estrogen replacement therapy; 17β-estradiol vaginal tablets.

Introduction

Postmenopausal women show atrophic vaginitis symptoms and, more generically, urogenital systemic atrophy, with an incidence between 10% and 40% [1]. However the percentage of symptomatic patients who go under medical observation is not beyond 20-25% [2], resulting in an underestimation of a disease that plays, with all the evidence, an important role in the quality of life of climacteric women [3].

Postmenopausal estrogen reduction (normally from 120 pg/ml to approximately 18 pg/ml) exposes the urogenital tract to recurrent infections and mechanical insults because of lack of hormonal stimulus to proliferation and epithelial maturation. The consequent vaginal epithelium thinning, mostly at the intermediate and superficial layers, which are particularly full of glycogen, induces Döderlein bacillus reduction and vaginal pH rising (from 4 to 7), resulting in a compromising of the main defence mechanism against infections. Moreover, numerous cytological transformations are a consequence of hormonal deficiency: connecting tissue proliferation, elastin fragmentation and collagen hyalinization, followed by granulation, fissures, ruise, teleangectasy and ulceration in the genital and urinary tract because of common embryological origin [4].

The first typical atrophic vaginitis symptom is dryness, because of lowering vaginal lubrication, and then dyspareunia, leucorrhoea, vulvae pruritus, followed by a sense of heaviness [5]. These symptoms can often be raised because of bacteria (faecal origin), mycosis and protozoa infections to which these patients are more exposed. Atrophic vaginitis signs are also characteristic: external genitalia pallor, smoothing and thinning, loosing of tissue elasticity, labra dryness, vaginal vestibulum narrowing, genital prolapse, vulval petechia and dermatosis [6]. Due to all these symptoms, there is a large uneasiness deriving from the frequently induced sexual dysfunctions [7]. Urologic symptoms are recurrent dysuria, pollakiuria, haematuria, infections (often post-coital cystitis), and incontinence. Common signs are the presence of urethral caruncola, urethral mucous eversion, cystouretrocele, and urethral polyposis [8]. Since estrogen deficiency is responsible for atrophic vaginitis, a logical approach to resolve symptomatology and function restoration is replacement therapy (HRT). HRT, hormonal estrogen counterbalanced by progesterone (without increasing incidence of endometrial hyperplasia) [10], given in a local or systemic way, can obtain the best compliance [9]. When the symptoms are limited to the urogenital tract, and a clear climateric syndrome with systemic symptoms is not found, the condition demands systemic HRT. Vaginal low-dose oestradiol treatment has been found effective in terms of clinical resolution, pH lowering, and low systemic absorption, without undesired side-effects and minimal endometrial exposure [11-14]. In fact, opposing a progressive increase of systemic absorption, due to vascularization restoration, there is the advantage of the vaginal approach that allows the use of a lower useful dosage [15], with unquestionable advantages in tolerability [16] and safety [17].

The aim of our study has been to verify, in patients treated with local substitutive estrogen therapy, the effec-

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tiveness and the safety of low-dose oestradiol vaginal tablets in postmenopausal atrophic vaginitis treatment.

Subjects and Methods

From June 2002 to March 2004, 325 postmenopausal women, with symptoms and signs of atrophic vaginitis, came under our observation. Age ranged between 51 and 67 years (medium 55.3 years), years after menopause between two and 15 (medium 7.8 years), and body weight from 54 to 77 kg (medium 61.1 kg). Vaginal substitutive estrogen therapy was chosen for these patients. Treatment was a single vaginal administration system (Vagifem®, Novo Nordisk, Denmark) with an HD applicator and a 0.025 mg synthetic 17β–estradiol pill, chemically and biologically equal to the human one, classified as natural (Novo 279). The particular formulation of the pills, consisting of an 80 mg cellulosed hydrophilic matrix when in contact with vaginal humidity, hydrates itself, releasing a constant oestradiol dose (drug/eccipient rate is 1:3200) (18,19). Therapy was a single application each day for two weeks, and a subsequent application two times a week for 22 weeks (total period of treatment 24 weeks). Inclusion criteria were: basal and para basal cell prevalence at upper level vaginal cytology, mixed flora at vaginal culture (degree III of Donders), vaginal pH > 5, and absolute hypoestrogen. Exclusion criteria were: a clear climacteric syndrome and need for systemic HRT; HRT in the last six months; vaginal infections or vaginosis, candidiasis, trichomoniasis; recent contact with soaps, scents, powders, deodorant, synthetic dresses, spermicidal creams; non menopausal hypoestrogen; oestrogen assumption contraindications, even via the vaginal way (hypersensitivity towards eccipients, unknown cause of metrorrhagia, oestrogen dependent cancer, and tromboembolic diseases). All the patients underwent a gynaecological exam, Pap test, vaginal pad, vaginal pH determination, and oestradiol blood sample before starting therapy (T0). At the end of the therapy, 24 weeks after (T3) a gynaecological exam, vaginal pH determination, oestradiol blood samples which were only repeated after two weeks (T1) and 12 weeks (T2).

At T1, T2 and T3 treatment effectiveness and tolerability were estimated. The effectiveness was expressed by evaluating symptom changes (vaginal dryness, dyspareunia): very improved, improved, no changes. Tolerability was estimated by adverse reaction incidence (haematic spotting, emphasized vaginal secretions, cutaneous rashes). Safety treatment was estimated by incidence of endometrial hyperplasia, with or without uterine bleeding. Ultrasound endometrial thickness was evaluated at T0 and T3, with an Esaote® apparatus with probe from 5 MHz. Thickness more than 4 mm at T0 or abnormal uterine bleeding during the treatment were considered, respectively, as exclusion criteria and suspension of therapy; an endometrial thickness more than 4 mm at the end of treatment (T3), instead, was subsequently evaluated at hysteroscopy with an endometrial biopsy. The percentages were always rounded off to the nearest decimal.

Results

At T0 all the 325 women had atrophic vaginitis symptomatology, especially dryness and dyspareunia. In all cases the Pap test, vaginal pad, vaginal pH and oestrogenemia respected inclusion criteria at the start of the study. After two weeks (T1), in 309 patients who returned for follow-up (drop-out to T1 4.9%), symptomatology was very improved in 257 cases (83.2%), improved in 41 (13.3%), with no changes in the remaining 11 (3.6%); best results were for dryness, while dyspareunia was harder to cure. There were vaginal secretions in 37 patients (12.0%) and cutaneous rashes in 13 (4.2%). Vaginal pH went towards acidity in 207 cases (67.0%), while serous oestradiol never significantly changed from pretreatment values. After 12 weeks (T2), 278 patients returned for follow-up (drop-out to T2 14.5%), and symptomatology was very improved in 252 cases (90.6%), improved in 17 (6.1%), with no changes in the remaining nine (3.2%). There were vaginal secretions in 31 patients (11.2%) and cutaneous rashes in ten (3.6%). Vaginal pH went towards acidity in 231 cases (83.1%), while hemetic oestradiol increased in 11 cases (4.0%) but no more than 3% of pretreatment values. At 24 weeks (T3), the end of the treatment, 266 patients returned for follow-up (drop-out total 18.2%). The symptomatology was very improved in 247 cases (92.9%), improved in 11 (4.1%), with no changes in the remaining eight (3.0%) (Table 1). There were vaginal secretions in 23 patients (8.6%) and cutaneous rashes in seven (2.6%) (Table 2). Vaginal pH went towards acidity in 236 cases (88.7%), hemetic oestradiol increased in 12 cases (4.5%) but no more than 5% of pretreatment values (Table 3). At vaginal cytology we observed superficial and intermediate cell increases in 218 patients (82.0%), and vaginal lactobacillus in 178 cases (66.9%). Transvaginal ultrasound scans at T0 found a medium endometrial thickness of 2.8 ± 0.4 mm. The same scan after 24 weeks of therapy (T3), showed medium values of 3.0 ± 0.5 mm, only excluding three cases (1.1%) with endometrial thickness more than 4 mm (but always inferior to 7 mm) (Table 4). No patient showed abnormal uterine bleeding during the entire treatment.

The three patients with abnormal endometrial thickness who underwent hysteroscopy and endometrial biopsy showed simple glandular hyperplasia in two cases and cystic hyperplasia in the remaining one.

Table 1. — *Efficacy of treatment.*

Improvement in symptomatology	T_1 (2 weeks of treatment 309 patients (100%)	T_2 (12 weeks of treatment 278 patients (100%)	T_3 (24 weeks of treatment 266 patients (100%)
High	257 (83.2%)	252 (90.6%)	247 (92.9%)
Mild	41 (13.3%)	17 (6.1%)	11 (4.1%)
None	11 (3.6%)	9 (3.2%)	8 (3.0%)

Table 2. — *Tolerance of treatment.*

Side-effects	T_1 (2 weeks of treatment 309 patients (100%)	T_2 (12 weeks of treatment 278 patients (100%)	T_3 (24 weeks of treatment 266 patients (100%)
Increased vaginal discharge	37 (12.0%)	31 (11.2%)	23 (8.6%)
Erythema	13 (4.2.%)	10 (3.6%)	7 (2.6%)
Vaginal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3. — *17β-estradiol systemic absorption.*

	T_1 (2 weeks of treatment 309 patients (100%)	T_2 (12 weeks of treatment 278 patients (100%)	T_3 (24 weeks of treatment 266 patients (100%)
Increased plasmatic 17β-estradiol	0 (0.0%)	11 (4.0%) (Less than 3% to pretreatment values)	12 (4.5%) (Less than 5% to pretreatment values)

Table 4. — *Endometrial survey.*

Endometrial thickness (TVE)	T_0 (Before treatment 325 patients) (100%)	T_3 (24 weeks of treatment 266 patients) (100%)
< 4 mm	325 (100.0%) (2.8 ± 0.4 mm)	263 (98.9%) (3.0 ± 0.5 mm)
> 4 mm	0 (0%)	3 (1.1%) (always < 7 mm)

Discussion

Postmenopausal women frequently show atrophic vaginitis symptoms (vaginal dryness, dyspareunia) because the reduction in oestrogen level exposes urogenital epithelium to recurrent infections and mechanical insults, thus lacking hormonal stimulus to epithelial regeneration. If symtomatology is limited to the urogenital apparatus and there is no clear climacteric syndrome needing systemic HRT, local substitutive estrogen therapy, when not contraindicated, is a valid therapeutic opportunity. In our experience, 266 postmenopausal women with atrophic vaginitis of 325 enlisted (drop-outs 18.2%) were treated for 24 weeks, respecting the criteria of inclusion and exclusion, with low-dose oestradiol vaginal pills. The treatment effectiveness and safety has been evaluated. Symptomatology was much improved just after two weeks in the majority of cases, with a minimum incidence of adverse reactions. Rise in lactobacillus number, vaginal pH elevation, superficial and intermediate cell increases at vaginal cell examination were found in the majority of patients at the end of therapy, with transcurable systemic absorption, tolerability and safety advantages, no undesired effects and minimal endometrial exposure. The transvaginal ultrasound scan at the end of the treatment showed minimal endometrial thickening only in 1.1%, and hysteroscopic biopsy showed simple typical hyperplasia. No patients had abnormal uterine bleeding during the entire treatment and no patients, therefore, had to interrupt therapy for this cause.

Conclusions

We can conclude that low-dose oestradiol vaginal tablets in the treatment of postmenopausal atrophic vaginitis is an extremely valid approach in terms of effectiveness and safety.

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