The Effect of Postmenopausal Use of Oral Estriol Therapy on Endometrial Thickness and Pathology

POSTMENOPOZAL ORAL ESTRİOL TEDAVİSİNİN ENDOMETRIAL KALINLIK VE PATOLOJİYE ETKİSİ

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SUMMARY

Objective: The aim of this study was to evaluate the effect of daily single dose oral estriol succinate treatment on endometrium in postmenopausal women.

Material and Methods: *24 postmenopausal women received 6 mg estriol succinate daily for six months. At the end of this course of therapy endometrial thickness (evaluated via ultrasonography) and endometrial pathology was compared with the control group who received no medication.*

Results: The endometrium was atrophic in all cases of treated group same as the control group.

Conclusion: Orally once a day estriol has no effect on endometrium in postmenopausal women.

Key Words: Estriol, Endometrial thickness, Endometrial pathology

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ÖZET

Amaç: *Çalışmanın amacı postmenopozalhastalarda **günlük tek doz** ora! estriol tedavisinin endometriuma etkisinin değerlendirilmesi.*

Materyal ve Metod: *24 postmenopozal hastaya 6 ay süreyle 6 mg/gün estriol süksinat **verildi. Tedavi** sonunda **endometrial** kalınlık (ultrasonografi **ile) ve** endometrial patoloji tedavi almayan kontrol grubuyla karşılaştırıldı.*

Bulgular: *Endometrium tedavi verilen hastaların tümünde ve kontrol grubunda atrofik olarak bulundu.*

Sonuç: *Postmenopozal kadınlarda günlük **tek** doz estriol tedavisinin endometriuma etkisi yoktur.*

Anahtar Kelimeler: Estriol, Endometrial kalınlık, Endometrial patoloji

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The natural estrogens used in postmenopausal period are 17 b estradiol, piperazine estrone sulfate conjugated estrogen and estriol. They all have proliferative effect on endometrium depending on dosage, route of administration and duration of therapy except estriol. It is shown that neither oral nor local vaginal administration of estriol causes endometrial proliferation. As its clearence from serum is rapid and bounds the nuclear receptors of endometrium without endometrial proliferation (2). If it is administered in sufficient dosages it improves hot flushes (3,4) but it is ineffective in osteoporosis prophylaxis (5).

In this preliminary study we tried to evaluate the effect of oral single dose of 6 mg/day estriol succinate for 6 months duration on endometrial thickness and pathology.

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MATERIALS AND METHODS

37 Postmenopausal women with a duration of at least one or more years of menopause and plasma E2 and gonadotropin levels within the postmenopausal range (E2: 50 or less pg/ml FSH: 75 IU or more LH: 40 IU or more) were studied. They had no systemic illness expect symptoms related to estrogen deprivation. The study was held prospectively for a six months period. 24 of 37 women received oral single dose of 6 mg/day estriol succinate while 13 of 37 women who refused hormonal medication were accepted as control group. Systemic and pelvic examination were done at admittance. Complete blood count, urine analysis, routine biochemical tests, hormonal analysis, vaginal ultrasonography, papsmear, endometrial biopsy with pipelle and mammography were performed. No pathology could be detected in none of the patients. The procedures performed at follow up in the six months included systemic and pelvic examination, hormonal and biochemical analysis, vaginal ultrasonography and endometrial biopsy by pipelle. Endometrial thickness measured by ultrasonography was defined in terms of

Table 1. Demographic data
Tablo **1**, Demografik veriler

	Age (years) mean±SD	Duration meantSD
Treatment group (n-24)	52.7±4.2	5.8±5.1
Control group (n«13)	54,2±5.9	6.1+4.3

mm and atrophic endometrium evaluated by biopsy was defined by symbol "t".

RESULTS

The mean age was 52.6+4.1 and 54.2+5.9 and the duration of menopause was 5.7±5.1 and 8.1 ±4.3 years in medicated and control group respectively. Demographic characteristics are given in Table 1. The differences in mean age and duration of menopause between the groups by Mann-Whitney U test was not significant.

The mean E2, FSH and LH values are given in Table 3. Though there was no statistically significant difference between pre treatment and post treatment E2 and LH values according to Wilcoxon test, the supression of FSH was found to be significant (initial FSH: 84.1-13.1, at 6.month FSH: 61,9±15,4 $p<0.05$). In Table 2 endometrial biopsy reports and endometrial thickness is given. In the treated group endometrial biopsy revealed atrofic endometrium in all patients. In none of the cases neither proliferation nor endometrial hyperplasia was reported. As all of them were atrophic they were symbolized as "!". Pre and post treatment biopsy reports in means of endometrial thickness and biopsy reports were statistically not significant according to Wilcoxon test. Pre and post treatment endometrial characteristics are given in Table 4. No significant difference was found between treated and control group with Mann-Whitney U test.

DISCUSSION

Estriol is an effective hormone in the treatment of severe genito urinary symptoms in postmenopausal women with a long duration of years in menopause without causing unwanted vaginal bleeding (6,7). It not only improves urogenital symptoms by stimulating cervical and vaginai epithelium (6,7) also improves hot flushing (8). It increases picnotic index by stimulating maturation in vaginal epithelium (8,9). it doesn't cause unwanted vaginal bleeding because of the lack of proliferation in endometrium (10). Progesteron has to be added to the treatment regimen of the patients treated with estradiol because of its hyperplastic activity on endometrium depending on the dosage and duration. This may cause spotting even in continuous administration. It is shown that oral or local intravaginal administration of estriol don't cause endometrial hyperplasia (8,10,11). In a study Haskins reported only 3 cases of vaginal bleeding in 60 postmenopausal patients treated with orally 1 mg/day estriol and endometrial biopsy revealed atrophy in all cases (11).

The main reason in responsiveness of endometrium to single daily dose oral administration of estriol might be due to its short half life and weakly binding to estrogen receptors in endometrium. After administration at 30th minute free estriol levels reach the peak value and decline after 4 hours (1). It has a short half life because it is excreted from the kidneys rapidly due to the lack of binding to the sex hormone binding globuline (12). Weakly binding of estriol to nucleer receptors are shown in rats. It cannot show its uterotropik activity because of not posessing the ability to bind this receptors at least 6 hours (13,14). In our study in none of the 24 cases endometrial proliferation or hyperplasia could be detected and no significant endometrial change was found between two groups.

Divided daily doses of estriol versus single dose showed similar effects on endometrium with estradiol.

Table **2.** Pre treatment and post treatment endometrial thickness and resuls of biopsy (atrofic endometrium was symbolized as "1")
Tablo **2.** Tedavi öncesi ve sonrası endometrial kalınlık ve biobsi sonuçları (atrofik endometrium "1" şeklinde sembolize edilmiştir.)

	Endometrial thickness 1 mean-SD	Endometrial thickness 2 mean±SD	Biopsy 1	Biopsy 2
Treatment group (n-24)	1.7 mm±1.0	2.3 mm+1.1	1±0.0	1±0.0
Control group (n-13)	1,8mm±1.1	1,0 mrtwO.Q	1±0.0	1 ±0,0

Table **3.** Pre treatment and post treatment Estradiol, FSH, LH values
Tablo **3.** Tedavi öncesi ve sonrası Estriol, FSH, LH değerleri

	Estradiol 1 mean+SD	Estradiol 2 mean r SD	FSH 1 mean+SD	FSH 2 mean±SD	LH 1 meamSD	LH 2 mean+SD
Treatment group (n-24)	24.4+7.1	24.5±11.0	84.1+13.1	61.9ı 15,4	50.5±15.8	44.5±19.4
Control group (n-13)	29.2+10,1	23.3±16.0	60.1 + 17.6	56.3; 16.8	44.1+14.4	38.3+13.5

Table **4.** Post treatment endometrial thickness and results of biopsy
Tablo **4.** Tedavi sonrası endometrial kalınlık ve biobsi sonuçları

	Post treatment endometrial thickness (mm) mean+SD	Post treatment biopsy meantSD
Treatment group (n-24)	2.3 mm±1.1	1 ±0.0
Control group (n-13)	1.0 mmtO.O	1 ±0.0

For example if it is given with 8 hour intervals endometrial proliferation can be seen because of the long duration of binding to the receptors (1). Englund showed endometrial proliferation in patients treated with 3x2 mg estriol (1). Though he didn't mention the intervals of administration Hauser reported minimal or mild endometrial proliferation in 39 of 40 patients treated with 2-8 mg oral estriol. He should probably used divided doses (15).

As a conclusion in this preliminary study we showed that single daily administration of 6 mg estriol in the treatment of genitourinary symptoms in postmenopausal women is a safe and effective method without causing unwanted vaginal bleeding and endometrial proliferation and hyperplasia.

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