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Effects of Tibolone on Depressive and Anxiety Symptoms in Symptomatic Postmenopausal Women

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ABSTRACT

Effects of tibolone on depressive and anxiety symptoms in symptomatic postmenopausal women

Aims: We investigated the effect of tibolone therapy on menopausal symptoms, depression and anxiety scores in women with symptomatic natural menopause compared to control group using Kupperman's Index, Hamilton Depression Rating Scale and Beck Anxiety Inventory.

Methods: One hundred thirty patients with menopausal symptoms enrolled into the study, and 121 patients completed. Group I patients were treated with tibolone 2.5 mg/day. Group II patients received placebo (calcium forte tablet 1000 mg/day). The menopausal, depressive and anxiety symptoms were assessed using Kupperman's Index, Hamilton Depression Rating Scale and Beck Anxiety Inventory before and at the end of the treatment. For statistical analysis, paired t, multivariate analyses tests were used.

Results: At the end of 3 months of therapy, we observed significant improvement in menopausal symptoms, depression and anxiety scores in both groups. When we compared two groups' Kupperman and Beck Anxiety Inventory (BDI) scores according to time before and after the treatment, Group I scored better than Group II. The superiority of tibolone comparing placebo on depressive symptoms could not be shown in this study.

Conclusion: Tibolone's effects in calming vasomotor symptoms and improving anxiety symptoms suggest it as an alternative when the possible side effects of estrogen and progesterone combination or estrogen alone are taken into account.

Key words: Menopause, tibolone, anxiety, depression

ÖZET

Semptomatik postmenopozal kadınlarda tibolonun aksiyete ve depresif belirtiler üzerindeki etkileri

Amaç: Semptomatik doğal yolla menopoza girmiş kadınlarda tibolonun menopozal semptomlar, depresyon ve anksiyete skorları üzerine etkilerini Kupperman Skalası, Hamilton Depresyon Skalası ve Beck Anksiyete Envanteri kullanarak kontrol grubu ile karşılaştırmalı olarak inceledik.

Yöntem: Menopoz semptomları olan 130 hasta çalışmaya dahil edildi, 121 hasta çalışmayı tamamladı. Grup I hastalar tibolon 2.5 mg/gün ile tedavi edildi. Grup II hastalara plasebo verildi (kalsiyum fort tablet 1000 mg/gün). Hastaların tedavi öncesi ve sonrası menopoz, depresyon ve anksiyete semptomları; Kupperman Skalası, Hamilton Depresyon Skalası ve Beck Anksiyete Envanteri kullanılarak değerlendirildi. İstatistik analiz için eşleştirilmiş t testi, çok değişkenli analiz testleri kullanıldı.

Bulgular: Üç aylık tedavi sonunda, her iki gruptaki hastalarda menopoz semptomları, depresyon ve anksiyete skorlarında belirgin düzelme gözlendi. İki grubun tedavi öncesi ve sonrası Kupperman ve Beck Anksiyete Envanteri skorları karşılaştırıldığında, Grup I'in skorları Grup II'ninkilerden daha iyi idi. Tibolonun depresif belirtiler üzerine plaseboya üstünlüğü gösterilemedi.

Sonuç: Östrojen ve progesteron kombinasyonunun veya tek başına östrojenin olası yan etkileri göz önüne alındığında, tibolonun vasomotor semptomları azaltıcı ve anksiyete semptomlarını düzeltici etkileri bir alternatif olarak düşünülebilir.

Anahtar kelimeler: Menopoz, tibolon, anksiyete, depresyon

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INTRODUCTION

Menopausal women frequently complain of psychological symptoms (1,2). Some studies report benefits of Hormone Therapy (HT) on psychological symptoms, others find no greater effect than placebo (3,4).

Tibolone is a synthetic steroid and it lacks the structural characteristics to explain its estrogen-like effects on vagina, brain and bone; these effects are attributed to the formation of two inactive estrogenic sulphated compounds, 3α and β, by the gastrointestinal

system (5). These compounds are then activated by the enzyme sulfatase that resides in target tissues. The effect of tibolone therefore is considered estrogenic. Estrogen increases serotonin synthesis and its metabolite 5-hydroxyindolacetic acid blood levels, so it effects as serotonin agonist (4). At the same time, estrogen could effect serotonin levels by increasing destruction rate of MAO enzyme. In addition, Bukulmez at al. (6) have shown that tibolone increases platelet tritiated [(3) H-] imipramine binding and improves mood. Mood-enhancing effects of tibolone may occur through the serotonergic system, as is the case with estrogen.

Tibolone has a mixed hormonal profile. Its estrogenic potency is about 1/50 of that of ethinyl-estradiol, its progestogenic potency is 1/8 that of norethisterone acetate (NETA) and the androgenic potency is about 1/3 that of norethisterone (7). It has been proven to relieve climacteric symptoms and improve libido.

This study was designed to evaluate the effects of tibolone and placebo on menopausal and psychological symptoms in women with symptomatic natural menopause by using Kupperman's Index, Beck Anxiety Inventory (BAI) and Hamilton Depression Rating Scale (HDRS).

METHODS

This prospective, single blind, randomized clinical study was performed at the menopause clinic between January 2005 and March 2007. Written informed consent was obtained from all patients. Study was approved by the local ethic committee. All study patients applied to our menopause clinic for menopausal symptoms. Inclusion criteria for the study were physiologic menopause with amenorrhea for at least 1 year and follicle stimulant hormone levels ≥35 mIU/ml and plasma estradiol levels <20 pg/ml, no previous HT history. Exclusion criteria were history of medical & psychological illness, use of psychoactive drugs within last 3 months, abnormal pelvic ultrasound findings and clinical contraindications to hormone therapy usage. As a rough control for sociodemographic factors, all patients were selected from urban community. After taking a detailed history and a physical examination, transvaginal ultrasonography, mammography, cervico-vaginal smear, routine laboratory studies and baseline psychiatric evaluation were performed for all participants.

The sample size needed to detect at least 20% difference on mood symptoms (2) between two drug groups and the control group was calculated to be 60 for each group, with an alpha error of 0.05 and 80% power.

At the beginning, 130 patients were enrolled into the study and 121 of them completed the study. Tibolone were applied in standard pharmaceutical packages. Randomization was done using a computer generated randomization table by an author and this author did not take any further place in the active conduction of the trial. Patients were randomly assigned to two groups:

1- Group I: Tibolone (Livial tablet 2.5 mg/day continuously; Organon, Istanbul, Turkey), n=60
2- Group II (control group): Placebo (Calcium Sandoz Forte 1000 mg/day; Roche,Istanbul, Turkey), n=61

Prestudy assessment and examinations were carried out by a different gynaecologist. Kupperman index was performed by another gynecologist. HDRS and BAI were performed by the same psychiatrist early in the afternoon between 2 and 4 p.m. in order to minimize day time difference effects. All of them were blind for patient's group. Statistical analysis was performed by a different professional person who has never seen the patients and who used the data only in the forms given to her. Participants were seen at the beginning and after 3 months of treatment. All patients completed the same tests before and at the end of therapy.

Kupperman Index: Menopausal symptoms were recorded during an interview using a 12 item (8).

Hamilton Depression Rating Scale (HDRS): HDRS is a structured tool used to measure the degree and the changes in severity of depression. It consists of 17 items, each of which should be assessed on a 0-4 scale. The scale was originally developed by Hamilton and

Table 1: Comparison of pre and post-treatment scores between and within the groups

		Group I (n=60)	Group II (n=61)	p
Kupperman Index	Pretreatment	24.63±4.70	24.79±4.23	NS*
	Posttreatment	14.95±4.18	18.03±3.22	0.006
	p	<0.001	<0.001	
Beck Anxiety Inventory (BAI)	Pretreatment	18.67±7.91	17.13±3.66	NS
	Posttreatment	13.53±7.24	15.10±3.14	0.041
	p	<0.001	<0.001	
Hamilton Depression Rating Scale (HDRS)	Pretreatment	11.12±4.75	10.02±2.79	NS
	Posttreatment	8.17±4.66	8.46±2.97	NS
	p	<0.001	0.003	

Mean +/- standard deviation, NS*: Not Significant

Williams (9). The validity and reliability study of Turkish version of the scale was assessed by Akdemir et al. (10).

Beck Anxiety Inventory (BAI): BAI is a frequently used self-report method for assessing the severity of anxiety. It has a 21 item form that requires subjects to indicate the presence and severity of symptoms. The scale was originally developed by Beck (11). The validity and reliability study of Turkish version of the scale was made by Ulusoy et al. (12).

Statistical calculations were performed with SPSS 13 program. Besides standard descriptive statistical calculations (mean and standard deviation) student t test was used in the comparison of groups, multivariate analyses test was utilized in the comparison of groups' scores changes by the time, paired t test was employed in the assessment of pre and post treatment values of each groups. Statistical significance level was established at $p<0.05$.

RESULTS

The median age of 130 women was 48.4 (SD: 2.29, range: 41-56) and 121 patients completed the study. Two women in tibolone group dropped out from the study because of the side effects of the drugs. Three women in the tibolone group and 4 women in the control group were lost to follow-up.

There were no significant differences between the groups with regard to age, duration of postmenopausal years (mean 2.03±0.91 years), parity, education, marital status, socio-economic status, smoking and history of psychiatric disorders.

The results of Kupperman index, depression and anxiety scores in the two groups at the beginning and at the end of therapy are shown in Table 1. All scores improved significantly after treatment in groups (Table 1).

Considering Kupperman index and BAI; there was no difference between the two groups before the treatment but there was statistically significant difference between the groups after the treatment. When we compare the two groups considering Kupperman index and BAI scores after the treatment, improvements in group I were higher than those seen in group II ($p=0.006$, $p=0.041$ respectively) (Table 1).

Patients had not severe depression scores at the beginning. When we examined the HDRS scores, there was no difference between the two groups before and after the treatment ($p= 1.66$, Table 1). No superiority of tibolone comparing placebo on depressive symptoms was shown in this study.

DISCUSSION

The present study was designed to investigate the psychological effects of tibolone and control group using a standardized psychological assessment. In the literature, there are many reports studying the effects of different combinations of HT regimens on perimenopausal mood disorders. Clinical observations in women suggest that low estrogen levels may be involved in the pathogenesis of depression (13).The

literature related with tibolone and its effects on postmenopausal mood changes reveals different results. Usually, menopause is associated with a reduction in endorphin levels that is believed to be involved in the pathogenesis of mood disorder (14). The reason for mood improvement may be an increase in plasma endorphin levels, which was shown to be induced with the use of tibolone (14). Genazzani et al. (4) suggested that increased β-endorphin levels in the pituitary and in plasma caused by tibolone may be related to the improvements in mood reported in these women. Since mood improvement can also be induced by androgens, the D4-isomer metabolite of tibolone formed locally in the brain may exert the effects of tibolone on mood (15). Tibolone has positive effects on mood as compared with placebo and alleviates several adverse mood parameters to a similar extent as conventional hormone therapy (4). With regard to the beneficial effects on mood parameters, Inan et al.'s study (2) data suggested that a slightly better effect was obtained with tibolone than in the sequential estrogen-progestogen therapy group at the end of 1 year. These findings are compatible with the results of Egarter et al. (16) and associates which reported that pre-existing depression and mood disorders were significantly improved by tibolone, while continuous conjugated estrogen (0.625 mg) combined with sequential medrogestone seemed to be less influential. This may be due not only to tibolone's positive effect on vasomotor symptoms but also on libido.

On the other hand, Ross et al. (17) found no effect of tibolone on anxiety or depression. Gulseren et al. (18) showed that there were no significant differences between tibolone and control group in the measurements of depressive symptom levels and cognitive function at the end of the follow-up period.

In our study, we found that tibolone was superior to placebo in anxiety and Kupperman index scores. In menopausal women, the psychological benefits of HT may occur because of the relief of vasomotor symptoms and a reduction in vaginal dryness, and this is known as the 'domino effect' (2). Probably, improvement in psychological symptoms are due to both improvement in vasomotor symptoms and increased β endorphin levels (4,14). Interestingly all scores of the control group were improved in our study. We can explain this condition with placebo effect.

The main restrictions of our study were shortness of the follow-up period and our patient's characteristics (mild anxiety and no depression at baseline). The data should be interpreted cautiously because of these restrictions. However, tibolone's effects in calming vasomotor symptoms and improving anxiety symptoms suggest it as an alternative when the possible side effects of estrogen and progesterone combination or estrogen alone are taken into account. To be able to better evaluate the effects of tibolone on anxiety and depression, further studies in postmenopausal women with mild, moderate and severe anxiety and depression should be carried out.

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