Placebo-controlled cross-over study of effects of tibolone on premenstrual symptoms and peripheral β-endorphin concentrations in premenstrual syndrome

O.Taskin¹, R.Gökdeniz¹,³, A.Yalcinoglu¹, A.Buhur¹, F.Burak¹, R.Atmaca¹ and U.Ozekici²

¹Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, Inonu University School of Medicine, Malatya, Turkey and ²First University School of Medicine, Elazig, Turkey

Introduction

Premenstrual syndrome (PMS) is a combination of mental and physical symptoms arising in the luteal phase of the menstrual cycle. It is a common complaint among women of reproductive age, particularly women aged ≥30 years and among women of greater parity (Reid and Yen, 1981). The symptoms, which can severely affect quality of life, begin after ovulation and disappear after the onset of menstruation. During the rest of the follicular phase the patient is free from symptoms. More than 90% of women are affected by one or more of the signs and symptoms of PMS, which cause problems at work and in family relations. The cyclical nature of the symptoms is characteristic of PMS.

Since first described by Frank (1931), numerous hypotheses have been adopted to explain the aetiology of PMS, but no definitive cause has been established. This obscure aetiology is further complicated by the lack of a commonly accepted definition and objective criteria to diagnose PMS, which has led to contradictory results in treatment. PMS is thought to result from changes of brain opioid activity during the luteal phase (Facchinetti et al., 1987). It has been proposed that the altered premenstrual concentrations of β-endorphin (β-EP) peripherally may reflect a decrease in central concentrations of β-EP and may be responsible for the PMS symptom complex (Chuong et al., 1985, 1989). To date, due to inaccessibility, data on the central concentrations of β-EP in PMS patients are lacking, and most of the peripheral β-EP is thought to be secreted from the pituitary gland (Frederickson and Geary, 1982). Although β-EP has been the major proposed mechanism in the aetiology of PMS and its relevance to the reproductive system and its functions, the role of central β-EP activities in relation to PMS needs to be further investigated.

As pathophysiological mechanisms causing PMS are still undetermined, therapy for the condition is largely empirical. In this trial, the efficacy of a synthetic weak oestrogenic steroid, tibolone (Org OD 14) was investigated in the treatment of PMS and on β-EP activities.

Materials and methods

Women with premenstrual tension at the PMS clinic participated in an open interview to describe the natural history of the problem and the degree of interference in their lives. All patients were aged between 20 and 36 years, had had regular menses for at least six previous cycles, and were in general good health. Pregnant patients, patients being treated for PMS, patients with a history of psychiatric disorders, and those on oral contraceptives were excluded from the study. Each patient included in the study underwent a psychiatric consultation and physical examination. All the chosen patients were tested the efficacy of the synthetic steroid Org OD 14 (tibolone) in the treatment of PMS. This prospective, randomized, placebo-controlled, double-blind cross-over study included 18 ovulatory women with PMS as ascertained by a visual linear analogue scale (VLAS). The women in each group received either 2.5 mg per day Org OD 14 (n = 9) or a multi-vitamin pill as placebo (n = 9) for 3 months. Treatments were then crossed over to a placebo for a further 3 months. VLAS ratings were evaluated at the end of each menstrual cycle throughout the study. Peripheral β-EP concentrations were determined by radioimmunoassay on days 7 and 25 of each menstrual cycle. Changes in VLAS score and β-EP concentrations from baseline were calculated and analysed by Student’s paired t-test. Improvements in VLAS scores and β-EP concentrations were evident during the second and third months of tibolone treatment. At the end of the third month, there was a significant improvement in VLAS scores of all symptom categories compared with pretreatment and placebo during treatment with tibolone (P < 0.05). Similar results were obtained in the first placebo group when switched to tibolone, β-EP concentrations were not significantly different between the study groups at the initial cycle (15.9 ± 3.6 versus 17.2 ± 2.3 pg/ml). The increase in β-EP concentration was significantly greater on day 25 of the menstrual cycle in women treated with tibolone compared with baseline and placebo group (22.5 ± 4.4 versus 15.9 ± 3.6 and 17.2 ± 2.3 pg/ml respectively, P < 0.05). Our data confirm the clinical efficacy of tibolone in PMS-related symptoms, as well as its effects on serum β-EP concentrations in patients with PMS.

Keywords: β-endorphin/premenstrual syndrome/tibolone/therapy

Presented in part at the 51st Annual Meeting of the American Society for Reproductive Medicine Seattle, Washington DC, October 7–12, 1995

© European Society for Human Reproduction and Embryology
assessed using the premenstrual tension observer-rating scale. Only women fulfilling the research diagnostic criteria and scoring higher than 18 in the ratings on the interview day, completed the visual linear analogue scale (VLAS) (Steiner et al., 1980; Haskett and Abplanalp, 1983). The basal body temperature (BBT) chart was maintained daily for one cycle from the first day of the menstrual cycle following the initial visit. The VLAS is a 16-item scale composed of mood-related and somatic symptoms. All participants were re-evaluated at the end of one menstrual cycle, when the VLAS and BBT charts were completed. Patients were instructed to use a barrier contraceptive (condoms) method throughout the study.

Eighteen ovulatory women with premenstrual complaints gave their consent and were included in the study. Ovulation was documented in each patient by urinary luteinizing hormone (LH) testing and measuring serum progesterone concentrations. Patients screened by interview and the VLAS consented for the study. PMS was diagnosed when there was a 30% increase in at least one of the three mood-related symptoms and in one of the three main somatic symptoms in the ratings during the luteal phase. The women in each group received either 2.5 mg per day tibolone (group 1) or placebo (group 2) from the first day of the menstrual cycle following the initial visit. The VLAS is a 16-item scale composed of mood-related and somatic symptoms. All participants were re-evaluated at the end of one menstrual cycle, when the VLAS and BBT charts were completed. Patients were instructed to use a barrier contraceptive (condoms) method throughout the study.

Results

The mean (± SD) age of patients was 29.8 ± 4.7 years. There was no difference in the demographic characteristics, mean age, body weight or VLAS scores between the women allocated to either the placebo or the tibolone groups (Table I). All patients were multiparous and the numbers of living children were similar between groups. The BBT charts of all patients and controls showed biphasic patterns with a sustained temperature rise during the luteal phase of the cycle. All patients had normal thyroid function tests (Table I). The results of the patients’ VLAS during the study revealed that all 18 subjects fulfilled the PMS criteria as described above.

The improvement in β-endorphin concentrations and VLAS scores was evident during the second and third months of treatment (P < 0.05; Figures 1 and 2). At the end of the third month, there was a significant improvement in VLAS scores of all symptom categories compared with pre-treatment and the placebo during treatment with tibolone (P < 0.05). Similar results were obtained in the initial placebo group when they switched to tibolone. In both study groups, serum concentrations of β-endorphin on days 7 and 25 were similar, as were β-endorphin concentrations on day 25 of the initial cycle (15.9 ± 3.6 versus 17.2 ± 2.3 pg/ml). The increase in β-endorphin concentrations was significantly greater on day 25 of menstrual cycle in women treated with tibolone compared with the baseline and placebo group (22.5 ± 4.4 versus 15.9 ± 3.6 versus 17.2 ± 2.3 pg/ml, respectively, P < 0.05).

The β-endorphin values and VLAS scores for the tibolone and placebo groups at the end of the third month (when the tibolone group switched to placebo) were 26.5 ± 2.4 versus 15.1 ± 3.9 pg/ml and 54 ± 10 versus 90 ± 5 pg/ml respectively. Also, when the tibolone group was switched to placebo, the β-endorphin values and VLAS scores at the end of the sixth month had returned again almost to basal values.

Discussion

PMS continues to be an unsolved problem as there is no consensus on its pathophysiology, and effective treatment. It
has been reported that central nervous system neurotransmitters and peptides are related to behavioural and mood changes in women. Recent reports have supported the hypotheses that PMS results from luteal phase changes in β-EP concentrations (Chuong et al., 1985; Facchinetti et al., 1987). Dye and Blundell (1997) have considered the premenstrual phase as a time when women are vulnerable to overconsumption and depression due to low serotonin activity. Sleep disturbances also form an important component of PMS, including insomnia, nightmares and hypersomnia which is not uniformly defined in the literature (Halbreich et al., 1983; Chuong et al., 1997). Trials with an opiate receptor antagonist naloxone, which produces PMS-like symptoms when administered to volunteers with no PMS symptoms, further support the endogenous opiate hypothesis (Cohen et al., 1981). However, there is sufficient evidence to show that ovarian function is closely related to PMS, including the onset after puberty and cessation after natural or surgical menopause (Casson et al., 1990; Mezrow et al., 1994).

β-EP, a proopiomelanocortin (POMC)-related peptide, is involved in important reproductive events (puberty, pregnancy, menopause) or ageing processes (Genazzani et al., 1983, 1987). Reproductive life in women is associated with β-EP concentrations that peak at the midcycle with no observed differences between the follicular phase and the luteal phase in normal ovulatory women (Genazzani et al., 1987; Chuong et al., 1989). A continuous decline until old age is evident after the menopause. Chuong et al. (1985) found that PMS patients have lower concentrations of plasma β-EP during the luteal phase of the menstrual cycle, than during the follicular phase and compared with controls during the luteal phase. They proposed that the premenstrual decrease of β-EP may be responsible for the PMS symptom complex, these findings being supported by Facchinetti et al. (1987) and Tulenheimer and Laatikainen (1987), who demonstrated a decrease in plasma β-EP in PMS patients near to menses. Although direct measurements of β-EP in the peripheral blood may not reflect changes in the central site, various studies have been reported, using indirect measurements in the peripheral blood or the assessment of endocrine activity modulated by opioids (Aleem and McIntosh, 1984; Facchinetti et al., 1987; Seifer and Collins, 1990; Lewis et al., 1995). In the present study we have measured and compared the β-EP concentrations in the peripheral blood both in the follicular and luteal phases. The blood samples were obtained after 15 min of rest, between 8:00 a.m. and 10:00 a.m. in a fasting state, as it has been shown that exercise can increase β-EP concentrations (Carr et al., 1981).

β-EP is well known for its role in behavioural, analgesic, thermoregulatory and neuroendocrine functions (O’Donohue and Dorsa, 1982). These functions are closely related to the pathogenesis of the symptoms commonly seen in PMS (Dye and Blundell, 1997). Its role in mood and behavioural disorders is further supported by the fact that climacteric symptoms are associated with decrease in POMC-related peptides, mainly β-EP (O’Donohue and Dorsa, 1982; Trevoux et al., 1983; Lindsay et al., 1989). Several studies have shown that tibolone, a weak oestrogenic, progesterational and androgenic steroid, alleviated climacteric complaints by increasing β-EP concentrations. These studies confirmed that behaviour and mood changes during menopause may be related to the reduction of central and peripheral concentrations of β-EP (Trevoux et al., 1983; Casson et al., 1990). The above beneficial effects on climacteric symptoms and β-EP concentrations have alerted us to evaluate the effectiveness of tibolone on β-EP concentrations and symptoms in patients with PMS.

To our knowledge, the present study is the only one evaluating the effect of tibolone in patients with PMS. Our results are encouraging as tibolone has significantly alleviated PMS symptoms compared with placebo, as observed in VLAS scorings.

Moreover, the observed increase in β-EP with improved PMS symptoms may further support the role of POMC-related peptides in the pathogenesis of PMS. Although not supported in our study, there are studies reporting a decrease in HDL-C levels with tibolone in climacterics. However, these adverse effects are off-set by recent studies reporting no differences in either LDL-C and HDL-C levels, or a decrease in lipoprotein(a) levels (Haenggi et al., 1993).

In conclusion, our study provides the first supporting clinical and laboratory evidence for the positive effects of tibolone on PMS symptoms and increasing β-EP concentrations. Our data provide further information on the effects of β-EP on PMS-related symptoms than in previous observations. In addition, clinical efficacy of the synthetic steroid tibolone on PMS-related symptoms, as well as its effect on serum β-EP concentrations, were confirmed in a group of patients with PMS. However, further studies with larger patient groups are needed to outline the exact role of tibolone on PMS and β-EP dynamics.

References


