Introduction

Raloxifene hydrochloride, a nonsteroidal benzothiophene derivative, is a selective estrogen receptor modulator (SERM) which has beneficial estrogen-agonist effects on bone and on cardiovascular risk factors but estrogen-antagonist effects on the endometrium and on breast tissue (1, 2). The tissue specificity of SERMs may be related to the existence of (at least) two different isoforms of the estrogen receptor with distinct signaling properties (3, 4).

Data regarding the action of raloxifene on pituitary secretion are at present few and often conflicting. In fact, although some studies, performed in vitro or in rats, show that raloxifene acts as a pure estrogen antagonist at the pituitary level (3, 6), others show that it exerts an estrogenic action on the hypothalamic–pituitary structures (7). In male volunteers, raloxifene blunts estrogen-induced changes in serum anterior pituitary hormone levels (8), whereas in premenopausal women, it does not alter the length of the menstrual cycle or the day of luteinizing hormone (LH) surge, but stimulates follicle-stimulating hormone (FSH) secretion, increases serum 17β-estradiol (E2) levels and decreases serum prolactin (PRL) values (9). In postmenopausal women, the effect of raloxifene on...
pituitary function has been little investigated, even though this drug is currently approved for the prevention of postmenopausal osteoporosis.

In this study we report the changes in baseline serum PRL and gonadotropin levels and in the thyrotropin-releasing hormone (TRH)-stimulated PRL responsiveness induced by 6 months of raloxifene treatment in postmenopausal women.

Patients and methods

Patients

Sixteen healthy postmenopausal women, who gave their informed consent, were enrolled in this study and were divided into two groups on the basis of their bone status, evaluated by dual energy X-ray absorptiometry (Hologic QDR 4500, Hologic, Inc., Bedford, MA, USA) at the lumbar level. Eight women (group 1, chronological age 52.4 ± 4.1 (s.d.) years, menopausal age 42.4 ± 3.9 years), in whom T-score L2–L4 was less than –2.5 s.d., were treated with raloxifene (60 mg p.o.), administered daily for 6 months. Another eight women (group 2, chronological age 52.6 ± 2.5 years, menopausal age 42.1 ± 3.6 years), in whom T-score L2–L4 ranged between –1 and –2.5 s.d., were enrolled as controls. All 16 women were treated with calcium, 1 g/day p.o., and cholecalciferol, 880 U/day p.o., for the same length of time. In all cases, postmenopausal status was proven by serum FSH levels over 30 U/l and serum E2 concentrations under 10 pg/ml. None had previously undergone ovariectomy. Women with diabetes mellitus or other endocrinopathies requiring drug therapy, with impairment of liver or kidney function and with a history of alcohol or drug abuse, were excluded from the study. The study protocol was approved by the Ethics Committee of the University of Messina School of Medicine.

Methods

Serum hormone levels were evaluated at baseline and after 3 and 6 months of treatment. All samples were performed in the morning after an overnight fast and 30 min after an indwelling catheter had been placed into an antecubital vein of the forearm kept patent by the slow infusion of isotonic saline. At each examination, serum PRL, LH, FSH and E2 levels were measured in duplicate by immunometric assays provided by Diagnostic Products Corporation (DPC, Los Angeles, CA, USA). Specifically, PRL was measured by Immunolite 2000 Prolactin (normal range 40–530 mIU/l, analytical sensitivity 3.4 mIU/l, intra-assay coefficient of variation (CV) 2.2%, interassay CV 6.9%), LH by Immunolite 2000 LH (normal range for postmenopausal women 11.3–39.8 mIU/ml, analytical sensitivity 0.05 mIU/ml, intra-assay CV 3.5%, interassay CV 7.1%), FSH by Immunolite 2000 FSH (normal range for postmenopausal women 21.7–153 mIU/ml, analytical sensitivity 0.1 mIU/ml, intra-assay CV 2.5%, interassay CV 6.3%) and E2 by Immunolite 2000 Estradiol (normal range for untreated postmenopausal women < 30 pg/ml, analytical sensitivity 15 pg/ml, intra-assay CV 4.9%, interassay CV 7.1%). In all women, serum PRL responsiveness to exogenous TRH administration (200 µg i.v.) was evaluated.
at baseline and at the 6 month examination. Serum PRL peak was assessed between 20 and 30 min after TRH injection in all cases.

**Statistical analysis**

Data are expressed as means±S.D. Statistical differences were evaluated by applying Student’s t-test for paired or unpaired data. A value of \( P < 0.05 \) was considered statistically significant.

**Results**

At baseline, mean serum PRL, LH and FSH levels were not significantly different in the two groups (PRL 133.6±21.7 vs 136.7±28.1 mIU/l (NS), LH 25.1±6.8 vs 24.4±6.7 mIU/ml (NS), FSH 74.4±25.0 vs 71.1±24.1 mIU/ml (NS), in group 1 and group 2 respectively). In all patients, basal serum PRL values were in the normal range (<530 mIU/l) and basal serum E2 was not detected (<15 pg/ml).

In group 1, mean serum PRL values decreased significantly (third month: 100.1±47.7 mIU/l, \( P < 0.05 \); sixth month: 81.5±30.2 mIU/l, \( P < 0.001 \)), whereas mean serum LH (third month: 27.2±12.6 mIU/ml (NS); sixth month: 25.6±11.4 mIU/ml (NS) and FSH (third month: 75.4±33.1 mIU/ml (NS); sixth month: 72.6±27.1 mIU/ml (NS)) values were unchanged, after 3 and 6 months of raloxifene treatment. In group 2, no significant changes were observed in mean serum concentrations of PRL (third month: 139.7±29.8 mIU/l (NS); sixth month: 135.2±30.3 mIU/l (NS)), FSH (third month: 73.0±18.8 mIU/ml (NS); sixth month: 72.9±24.1 mIU/ml (NS)) and LH (third month: 24.9±5.6 mIU/ml (NS); sixth month: 22.4±6.1 mIU/ml (NS)) (Fig. 1). Serum E2 was not detected at each examination, in all patients.

At baseline, TRH-stimulated PRL peak was not significantly different between the two groups (1015.4±30.5 vs 1030.2±25.7 mIU/l in group 1 and in group 2 respectively (NS)). At the 6 month examination, mean PRL peak decreased significantly in group 1 compared with baseline values (770.5±47.4 mIU/l, \( P < 0.001 \)) but not in group 2 (1068.1±301.8 mIU/l (NS)). Mean PRL peak was also significantly lower in group 1 than in group 2 (\( P = 0.02 \)) (Fig. 2).

**Discussion**

Raloxifene hydrochloride is a SERM which shows tissue-specific estrogen agonistic and antagonistic activity (10). In animal models, raloxifene has estrogen agonistic activity on bone and circulating lipoproteins, but estrogen antagonistic activity on mammary tissue and the uterus (11, 12). In postmenopausal women, raloxifene has favorable effects on circulating lipoproteins and reduces bone turnover (1, 2). However, the raloxifene effect on endocrine function, mainly on pituitary hormone secretion, has so far been little investigated. In this study we report that long-term raloxifene treatment in healthy postmenopausal women induces a significant decrease of serum PRL levels, whereas it does not modify significantly serum gonadotropin concentration.

Some authors have shown that the effect of raloxifene on pituitary hormones is related mainly to its estrogen-antagonist activity (5, 6). Studies performed on rat pituitary cells show that raloxifene is a potent antagonist of both positive and negative estrogen actions in the pituitary gonadotropes, and that, after short-term treatment with high concentrations or after long-term treatment, raloxifene itself exerts an inhibitory effect on gonadotropin-releasing hormone-induced LH secretion (13). This antigonadotropic effect on pituitary hormone secretion is suggested by some studies which, in agreement with the present results, showed a significant decrease of serum PRL levels after long-term treatment with raloxifene in postmenopausal women. The effects of raloxifene on serum LH and FSH levels observed in this study are in agreement with those of other studies in which LH and FSH levels were significantly decreased after long-term treatment with raloxifene in healthy postmenopausal women (14).

**Figure 2** TRH-stimulated PRL peak in raloxifene-treated (open bars) and untreated (gray bars) women at baseline and after 6 months. Means±S.D.
effect of raloxifene was also demonstrated by Ortmann et al. (14) using a model in which phenol red exerts estrogenic activity on cultivated rat pituitary cells.

In vivo, the effect of raloxifene on pituitary secretion is more complex and previous studies produced conflicting results. In estrogen-treated ovariectomized rats, microimplants of raloxifene into the preoptic area of the hypothalamus block spontaneous surges in LH levels (15). Recently, Pinilla et al. (7) showed that raloxifene inhibited the pulsatile secretion of LH and increased PRL levels in ovariectomized rats which had not undergone estrogen replacement therapy. On the contrary, other authors (16) showed that in normally estrogenized rats, 6 months of raloxifene treatment increased serum LH and E2 concentrations, and blocked ovulation. Data about the action of raloxifene on human pituitary secretion are, at present, few. In male volunteers the drug blunts estrogen-induced changes in serum gonadotropin levels (8). In premenopausal women, Baker et al. (9) showed that raloxifene increases serum FSH and E2 levels, and reduces PRL concentrations by 10–35% of basal values. Studies performed in ovariectomized rats which had not undergone estrogen replacement therapy suggested that raloxifene can play an estrogen-like action on neuroendocrine opiate pathways, increasing β-endorphin concentrations in the anterior and neurointermediate pituitary lobe and in the hypothalamus (17). These data were recently confirmed also in postmenopausal women, in whom the administration of raloxifene 60 mg/day significantly increased circulating β-endorphin levels after 3 and 6 months of treatment (18).

In our study, 6 months of raloxifene treatment did not change serum gonadotropin levels but significantly decreased serum PRL values. The impaired responsiveness of serum PRL levels after TRH administration, observed after 6 months of raloxifene administration, enforces the evidence that pituitary PRL reserve and secretion could be consistent with the proven antineoplastic effect of raloxifene on lactotrope cells or to the increase of opiateergic tone, previously demonstrated in animal models and recently in postmenopausal women. Further studies are needed to confirm this evidence and to prove the relationship between this drug and the neuromodulator system.

References


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