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Effects of Raloxifene, One of the Selective Estrogen Receptor Modulators, on Pituitary–Ovary Axis and Prolactin in Postmenopausal Women

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To investigate the clinical effects of raloxifene, one of the selective estrogen receptor modulators (SERMs), on the pituitary–ovary axis and prolactin, a prospective, randomized, double-blinded study on 59 healthy postmenopausal women was performed. Forty-eight women received raloxifene 60 mg daily. The other 11 received combined conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 5 mg daily (CCEP) as active controls. Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and prolactin were measured at baseline and 1 yr after treatment. The mean levels of FSH and LH were significantly decreased in the raloxifene group (FSH: –10.7%; $p < 0.01$, LH: –10.3%; $p < 0.05$) and CCEP group (FSH: –53.7%, $p < 0.001$; LH: –46.8%, $p < 0.001$). The prolactin level decreased in the raloxifene group but not in the CCEP group (–17.0%; $p < 0.001$ vs +13.3%, p = no significance; NS). Consequently, long-term administration of raloxifene up to 1 yr decreases serum prolactin level significantly and may be a therapeutic alternative for postmenopausal osteoporotic women with hyperprolactinemia.

Key Words: Raloxifene; prolactin; FSH; LH.

Introduction

Hormone replacement therapy (HRT) is one of the main regimens for preventing and treating postmenopausal osteoporosis *(1)*, although adverse effects such as uterine bleeding and breast engorgement, and the increased risks of endometrial cancer, breast cancer, cardiovascular events, and dementia have prevented many postmenopausal women from taking HRT long term *(2–5)*. To circumvent these untoward effects, selective estrogen receptor modulators (SERMs) have been developed and raloxifene is among one of these compounds. It has agonistic effects of estrogen on bone and serum lipids, and antagonistic effects of estrogen on the breast and endometrium *(6)*. In some postmenopausal women, however, raloxifene may aggravate hot flushes, an indication that this compound may have antiestrogenic effects in the central nervous system *(7)*. Previous large-scale clinical trials had shown that raloxifene can increase bone mineral density and reduce vertebral fracture *(8)*. Currently, raloxifene is recommended as one of the first-line drugs for the prevention and treatment of postmenopausal osteoporosis *(1)*. But other clinically relevant effects of this drug are not yet completely understood. The effect of raloxifene on serum prolactin levels is one of these issues. Long-term use of estrogen has been shown to increase serum levels of prolactin *(9)*, which is unfavorable for women with hyperprolactinemia. On the other hand, tamoxifen, a SERM that is a triphenylethylene derivative used in the treatment of breast cancer, has been shown to decrease the serum level of prolactin *(10)*. In this study, we examine the changes in serum prolactin level as well as levels of estradiol (E2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) after usage of oral raloxifene 60 mg daily for 12 mo in healthy postmenopausal women.

Results

Seventy-five of all 79 subjects (94.9%) completed the treatment program. The remaining four subjects dropped out due to various adverse effects (one in the CCEP group due to vaginal spotting; three in the raloxifene group, due to headache, dyspepsia, and flatulence, respectively). Specimens from 16 of these 75 subjects were used up in a previous study *(11)* (12 and 4 in raloxifene and CCEP groups, respectively). In the remaining 59 subjects (48 in raloxifene group and 11 in CCEP group), the compliance was good. Pill counting showed that each patient consumed 85–100% of the medication. Table 1 shows the basic characteristics of the two groups. The average age, body weight, body height,

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Table 1
Baseline Characteristic Data[a] of the Postmenopausal Women Treated with Raloxifene or CCEP Regimen

	Raloxifene	CCEP
n	48	11
Age (yr)	57.0 ± 0.5	56.7 ± 0.8
Weight (kg)	57.7 ± 0.8	54.9 ± 0.6
Height (cm)	154.2 ± 0.5	154.0 ± 1.0
YSM[†] (yr)	7.5 ± 0.5	7.2 ± 1.0

[a]Mean ± standard error of mean (SEM).
[†]Year since menopause.

Table 2
Serum Levels of FSH, LH, E2, and Prolactin at Baseline and 12 Mo after Treatment in Raloxifene and CCEP Groups[a]

	Raloxifene			CCEP		
	Baseline	12 months	Changes	Baseline	12 months	Changes
FSH (IU/L)	44.8 ± 2.6	40.0 ± 2.5	–10.7%	60.1 ± 7.5	27.8 ± 5.7	–53.7%
LH (IU/L)	19.4 ± 1.5	17.4 ± 1.2	–10.3%	22.0 ± 3.5	11.7 ± 3.1	–46.6%
E2 (pmol/L)	102.4 ± 6.4	108.6 ± 10.6	+6%	97.3 ± 12.9	196.3 ± 23.2	+101.7%
Prolactin (μg/L)	6.29 ± 0.62	5.22 ± 0.53	–17.0%	6.03 ± 0.75	6.83 ± 0.77	+13.3%

[a]Mean ± standard error of mean (SEM). The significances are shown in Fig. 1.

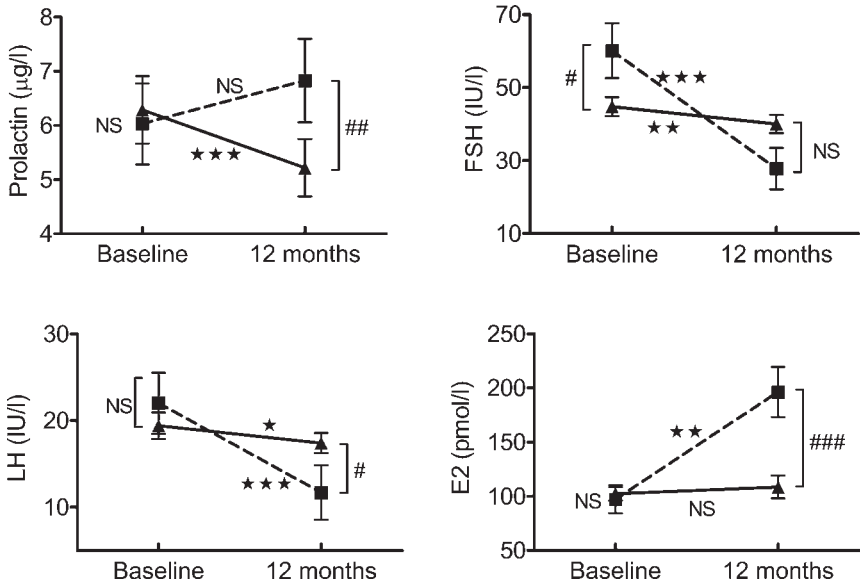

Fig. 1. Mean (± SEM) FSH, LH, E2, and prolactin levels in patients at baseline and 12 mo after raloxifene (circle and solid-line) and CCEP (square and dashed-line) treatment. #, ## and ###: $p < 0.05$, 0.01, and 0.001 between the two treatment groups by Mann–Whitney *U* tests, respectively; *, **, and ***: $p < 0.05$, 0.01, and 0.001 between baseline and 12 mo after treatment by Wilcoxon matched pairs tests, respectively; NS: nonsignificant.

and years-since-menopause were not significantly different between the raloxifene and CCEP groups. The hormonal levels at baseline and 12 mo after treatment and their percentage changes for the raloxifene and CCEP groups are shown in Table 2. A comparison of the two groups is plotted in Fig. 1. Baseline levels of prolactin, LH, and E2 were not significantly different between the two groups, but baseline FSH levels were higher in the CCEP than the raloxifene group. After 12 mo of treatment, however, the serum levels of FSH and LH of the raloxifene group were higher than that of the CCEP group (p = NS and $p < 0.05$, respectively). E2 and prolactin levels were lower in the raloxifene group

than in the CCEP group ($p < 0.001$ and $p < 0.01$, respectively). After 1 yr of treatment, the CCEP group revealed significant and marked decreases in FSH (–53.7%, $p < 0.001$) and LH (–46.8%, $p < 0.001$) levels and an increase in E2 levels (+101.7%, $p < 0.01$) from baseline. In the raloxifene group after 1 yr of treatment, serum levels of FSH and LH also showed decreases of 10.7% ($p < 0.01$) and 10.3% ($p < 0.05$) respectively, but the E2 level did not show significant change from baseline. The prolactin levels showed an insignificant trend of increase after CCEP treatment for 1 yr (+13.3%, p = NS). In contrast, prolactin levels decreased significantly (–17.0%, $p < 0.01$) after 1 yr of raloxifene treatment (Table 2 and Fig. 1).

Discussion

HRT is a common modality for the treatment of osteoporosis in postmenopausal women *(1)*. However, HRT is associated with a number of adverse effects, including an increased incidence of breast cancer, endometrial cancer, thromboembolism, cardiovascular events, and dementia *(2–5,12)*. All of the therapeutic and adverse effects of estrogen are currently believed to be modulated through estrogen receptors (ER) distributed over the related organs. There are two known types of ER, ER-α, and ER-β, both of which can be found in the human central nervous system, cardiovascular system, bone tissue, urogenital tract, and reproductive organs, but with different distributions *(7)*. SERMs are a group of compounds that bind to the two ERs with different affinity, thereby showing different estrogenic or antiestrogenic effects in various organs *(13)*. Raloxifene is one of the SERMs; it is an estrogen agonist for bone metabolism but an antagonist for the endometrium and breast *(6,14)*. Currently it is used to increase the bone mineral content and decrease the incidence of osteoporotic fractures for postmenopausal osteoporosis, without some of the side effects of conventional HRT such as endometrial proliferation and breast cancer.

Previous studies have shown increases of prolactin levels with postmenopausal estrogen therapy *(15)*. We also found 13.3% increases in serum prolactin levels following CCEP treatment for 1 yr. Although the increases from baseline did not reach statistical significance, it is likely that our small sample size accounted for the nonsignificant results. Regarding prolactin levels, previous reports have shown that the serum levels decrease after administration of clomiphene, an antiestrogen, or tamoxifen, another SERM *(10,16)*. In our study, we found that raloxifene intake for 12 mo in postmenopausal women decreases prolactin level significantly by 17.0%. Thus, the three triphenylethylene or benzothiophene analogs, raloxifene, tamoxifen, and clomiphene, show opposite effects on serum prolactin level as compared to conjugated equine estrogen. Moreover, raloxifene showed the smallest reductions in serum prolactin level (raloxifene: –17%; tamoxifen: –33%; clomiphene: –20%, respectively) under the usual clinical dosages.

Various aspects regarding the mechanisms of estrogen action have been elucidated. As nuclear receptors, both ER-α and ER-β can enhance, suppress, or transactivate target gene expression through the classic estrogen response elements (ERE) or activator protein-1 complex *(17)*. After binding to ER-α, E2 and benzothiophenes have opposite effects through the classic ERE pathway but similar agonistic effects through the activator protein-1 pathway *(13)*. On the other hand, after binding to ER-β, benzothiophenes exert opposite effects through both the classic ERE and activator protein-1 pathways as compared to E2. Therefore, it is likely that raloxifene decreases serum prolactin levels through some pathways other than the classical ER-α/activator protein-1 pathways in the hypothalamus and/or pituitary gland.

Lasco et al. *(18)* reported a decrease of prolactin level (by 39.0%) without changes in FSH or LH levels following 6 mo treatment of raloxifene in postmenopausal women aged 44–60 yr. Our patients, however, showed a decrease of approx 17% in prolactin levels after 12 mo of raloxifene therapy. In addition, our patients showed decreases (about 10%) in FSH, and LH levels. The duration of treatment varied in these two studies and may have affected the amplitude of changes in prolactin, FSH, and LH levels. In Lasco et al., the small case number ($n = 8$) may have resulted in some selection bias. Studies in men have shown that following raloxifene administration, FSH and LH levels increased markedly *(19)*. However, Palomba et al. reported that the menstrual cycle and levels of FSH, E2, and progesterone did not change significantly in premenopausal women following 180 mg daily administration of raloxifene for 6 mo *(20)*. Clearly, there are gender differences as well as between pre- and postmenopausal women with respect to the effects of raloxifene on FSH and LH. Currently, the reason for such differences among men, pre-, and postmenopausal women is unclear and awaits further investigation.

In conclusion, raloxifene significantly decreased serum prolactin level in healthy postmenopausal women. FSH and LH were less affected by raloxifene than by CCEP. It appears that for hyperprolactinemic postmenopausal women, raloxifene may be a viable therapeutic alternative.

Materials and Methods

This study was conducted in a randomized, active-controlled, double-blind fashion in a university hospital setting. Because of an accessibility issue, samples were taken from only one of the two participating university hospitals, the National Taiwan University Hospital, of a prior randomized, active-controlled, double-blind study comparing the bone densitometric and biochemical effects of raloxifene to conjugated equine estrogen and medroxyprogesterone (CCEP).

A detailed description of subject recruitment, characteristics, and randomization has been published *(11)*. Briefly, for this analysis, a total of 79 healthy, postmenopausal Taiwanese women, living in Taipei urban area and aged 47–66 yr, were enrolled. Subjects were excluded if they have had a hysterectomy, any prevalent vertebral fractures (evaluated by lateral spine radiograph), any treatment for osteoporosis within the preceding 6 mo, or any medical history that was known to affect bone metabolism. No subjects had a history of Colles' or hip fracture. The subjects were randomly assigned to receive raloxifene as the study intervention or CCEP as active controls in a 4:1 ratio based on previous reports of less prominent changes in bone mineral density with raloxifene than conventional HRT *(21)*. Thus, 63 women were randomized to the raloxifene group, receiving 60 mg oral raloxifene daily for 1 yr, and the 16 remaining women to the CCEP group, receiving combined oral regimen of conjugated equine estrogen 0.625 mg and medroxyprogesterone 5 mg daily (CCEP) for a year. Serum levels of hormones including FSH, LH, E2, and prolactin (Immulite, DPC®, Los Angles, CA, USA) were measured at baseline and after 1 yr of treatment. The analytical sensitivities of FSH, LH, E2, and prolactin are 0.1 IU/L, 0.05 IU/L, 55 pmol/L, and 0.5 μg/L, respectively. The intraassay and interassay precisions of FSH at 40 IU/L are 2.1% and 4.0%, respectively; those of LH at 20 IU/L are 3.4% and 6.6%, and 9.9% and 14% for E2 at 330 pmol/L. The intraassay and interassay precisions of prolactin at 8 to 51 μg/L are 5.7% to 6.8%, and 6.4% to 9.6%, respectively. All blood samples were drawn in the morning following overnight fasting. Then the serum samples were separated and obtained by centrifugation within 2 h. All of the specimens were then stored in −70°C until we analyzed them in one batch for batch assay. All subjects gave informed consent. This protocol has been approved by the Pharmacy and Therapeutic Committee of the National Taiwan University Hospital.

Statistical Analyses

To study the effects of raloxifene, we used Wilcoxon matched pairs test to test the difference between serum levels before and after treatment. The effects of CCEP were analyzed in the same manner. To investigate whether the effects of raloxifene and CCEP were significantly different, we used Mann–Whitney *U* test to compare serum FSH, LH, E2, and prolactin levels between the raloxifene and CCEP groups after 12 mo of treatment. We also used Mann–Whitney *U* test to compare the baseline serum hormonal levels and basic characteristics of the two groups. We used nonparametric analyses (Wilcoxon matched pairs test and Mann–Whitney *U* test) instead of their parametric counterparts (paired-*t* test and *t* test, respectively) because of the small number or skewed distribution of samples. All statistical calculations were performed using GraphPad Prism® software package (version 4.00, GraphPad Software Inc., San Diego, CA, USA).

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