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Effects of Tibolone in Thai Post-menopausal Women

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ABSTRACT

Objective To assess the effects of tibolone on climacteric symptoms, serum levels of sex hormones (FSH, LH, E_2), lipids and calcium as well as the bone mineral density in Thai post-menopausal women.

Design Prospective study.

Setting Menopause clinic, Chulalongkorn Hospital.

Subjects Thirty-one post-menopausal women without contraindication to hormonal replacement therapy were recruited. A daily oral dose of 2.5 mg tibolone was administered to all subjects for 6 months.

Main outcome measures Climacteric symptoms were assessed periodically. Serum levels of sex hormones, lipids and calcium as well as the bone mineral density were measured at the beginning and the end of the study.

Results Climacteric symptoms decreased over the study period. There was no significant change in the levels of sex hormones, total cholesterol, apolipoprotein A and B. A reduction in the levels of HDL and calcium was observed. Bone mineral density remained unchanged.

Conclusion Tibolone is suitable for the treatment of climacteric complaint and also potentially capable to prevent post-menopausal bone loss.

Key words : tibolone, post-menopausal women

In the past, menopausal symptoms were considered unpleasant but inevitable part of woman's life which had to be endured in silence. The treatment of the symptoms associated with the climacteric syndrome, namely: hot flushes, sweating, paresthesia, insomnia, loss of libido, irritability, dizziness, depression, muscle and joint pain, fatigue, palpitations and psychological instability included administration of estrogens, such as conjugated estrogens and estradiol or

one of its ester derivatives. However, long-term administration of these estrogens as a monotherapy (unopposed estrogen therapy) carries the risk of overstimulating the endometrium. The addition of a progesterone at regular intervals protects against endometrial overstimulation, but also results in regular post-menopausal withdrawal bleeding.[1,2] This regular withdrawal bleeding at the end of the progesterone cycle in conventional hormonal replacement therapy (HRT) is unacceptable to many women.[3] This fact leads to a need for a new drug that is able to alleviate these climacteric complaints and prevent bone loss in osteoporotic women, while not stimulating the endometrium, not having negative effects on the cardiovascular system and not increasing the risk of malignancies.[4]

Tibolone is a steroid compound formulated by Organon company. This compound is structurally related to the progestogens, norethynodrel and norethisterone, but has one additional double bond and additional 7-methyl group. Pharmacological studies in laboratory animals have demonstrated that the drug exerts mild estrogenic effect. Hormonal experiments with laboratory animals have shown the estrogenic effect of tibolone to be 1/50 that of ethinyl estradiol, the progestogenic effect to be less than half of that of norethynodrel and less than 1/8 that of norethisterone, the androgenic effect to be 3 times weaker than that of norethisterone, and the ovulation inhibiting effect to be the same as that of norethynodrel and 20 times greater than that of norethisterone, indicating a relatively strong central effect.[5,6] Other experiments with laboratory animals have shown tibolone to be able to reduce the frequency of ovariectomy-induced hot flushes, and inhibit bone loss.[7]

Some clinical studies with human subjects have shown tibolone to be able to reduce the symptoms of the climacteric syndrome as well as post-menopausal skeletal demineralization,[8] while not exerting any negative side effects such as endometriotrophic effects or post-menopausal bleeding.[9] However, these studies were done in European women.

The objective of this study was to assess the effects of tibolone on climacteric symptoms, bone mineral density, serum levels of sex hormones, lipids and calcium in Thai post-menopausal women.

Materials and Methods

Thirty-one post-menopausal women were recruited for the trial on the basis of the following criteria :

- voluntarily attended the menopause clinic at Chulalongkorn Hospital,
- time since has had the menopause for longer than one year,
- no hormone-dependent tumours,
- no cardiovascular or cerebrovascular disorders,
- no vaginal bleeding due to unkonwn causes,
- no severe liver or kidney disorders,
- no treatment for climacteric symptoms within the last 3 months.

A daily oral dose of 2.5 mg tibolone (Livial^{R}) was administered to each of the subjects for a period of 6 months. This dose was chosen on the results of a pre-test dose which had shown 5 mg/day to induce vaginal bleeding and 1.25 mg/day to be insufficient in alleviating vasomotor symptoms.

All 12 symptoms associated with the climacteric syndrome (mentioned in the introduction) were assessed by asking the women to rate the severity of each symptom by assigning a score of 0-3.

The scores of these 12 symptoms were assessed on four occasions during the study period : day 0, day 30 (1month), day 90 (3 months), and day 180 (6 months).

The incidence of vaginal bleeding was recorded monthly. Serum sex hormones : follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), serum lipids : total cholesterol, high-density lipoprotein (HDL), apolipoprotein A, apolipoprotein B and calcium were measured and recorded at day 0 and day 180. The bone mineral density of the lumbar spine and hip was measured by dual photon absorptiometry at the beginning and the end of the study. The body weight and blood pressure was recorded 3 times (day 0, day 90 and day 180).

Satistical analysis were expressed as mean with standard deviation (SD) and percentage as appropriate. The differences in the means were compared by student t-test. The P value of < 0.05 was considered as statistical significance.

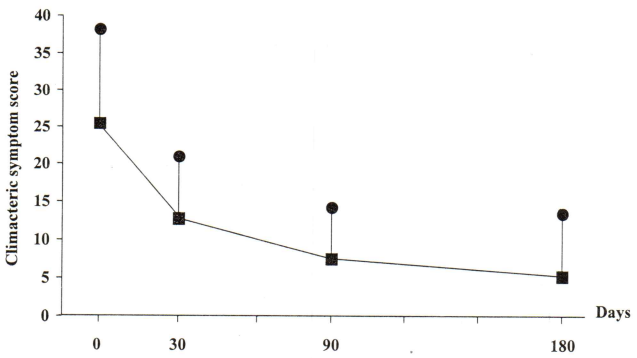

Fig. 1. Mean (+ SD) values for total climacteric symptom score in the tibolone treated patients (N = 31, P < 0.05).

Results

The women recruited ranged in age from 47-60, with a mean age of 53.3. The average number of years since the menopause was 4.3.

Climacteric symptom : Total scores of the 12 climacteric symptoms steadily decreased over the 6 month study period in almost all of the women (Fig. 1).

Vaginal bleeding : Vaginal bleeding occurred in 6 women while taking Tibolone in the first month. After that, the number of women experiencing vaginal bleeding decreased. There was no vaginal bleeding observed after the fourth month (Table 1).

Body weight and blood pressure : At the pre-trial examination, the body weight and blood pressure of all women admitted to the trial were found to be within the normal range. There were no significant changes in the mean values of body weight and blood pressure during the 6 month study period (Table 2).

Serum sex hormones : The mean values of serum FSH, LH and E_2 levels at the beginning and the end of the study are shown in Fig. 2. While no change was observed in the serum E_2

Table 1. The number of women experiencing vaginal bleeding (N = 31)

	Day						
	0	**30**	**60**	**90**	**120**	**150**	**180**
Number of women	0	6	3	1	1	0	0
Percent	0	19.4	9.7	3.2	3.2	0	0

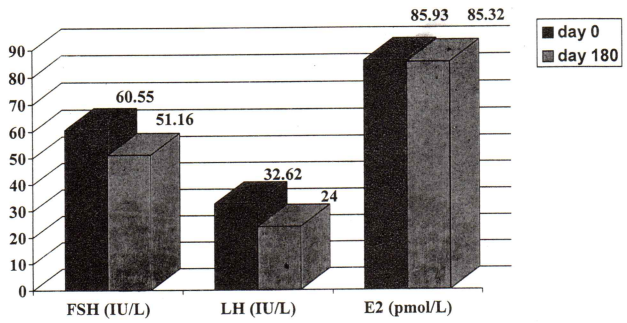

Fig. 2. The serum levels of sex hormones (N = 31).

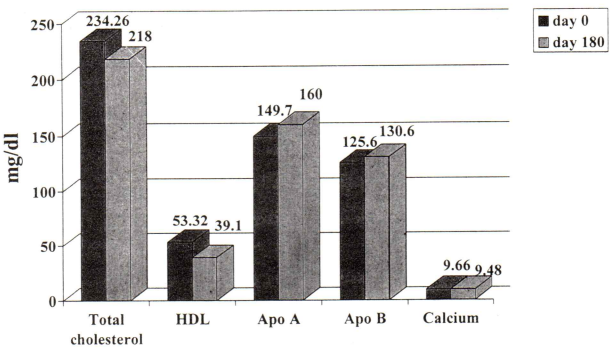

Fig. 3. The serum levels of lipids and calcium (N = 31).

level, there was a drop in the levels of serum FSH and LH, but these changes had no statistical significance.

Serum lipids and calcium levels : Fig. 3 shows the mean values for serum total cholesterol, HDL, apolipoprotein A, apolipoprotein B and calcium levels. There was a significant reduction in the levels of serum calcium and HDL. A reduction in the serum total cholesterol and a rise in the serum apolipoprotein A were observed although there was no statistical significance.

Bone mineral density : The data on the bone mineral density measured by dual photon absorptiometry in the lumbar spine and hip are shown in Table 3. During the 6 month study period, no significant change in these values was found.

Discussion

A rational approach to the therapy of climacteric symptoms and to the prevention of long-term sequelae of menopause like osteoporosis and cardiovascular accident, is the subsitiution of various sex hormones. The combination of estrogen-progestogen therapy has been recommended and applied successfully, but sometimes leads to regular or irregular bleeding especially during the initial months of treatment. These bleedings are regarded as unacceptable by many post-menopausal women, leading to poor compliances and high drop-out rates.

The benefits and risks of tibolone therapy in post-menopausal women have been shown in many recent studies. Our study clearly indicates that tibolone, orally administered in a daily dose of 2.5 mg, is an efficient mean of inhibiting the climacteric symptoms (Fig. 2). This finding is in agreement with previously published data.[5,6,8] Vaginal bleeding occurred in six cases during the first month of treatment, four of whom have had menopause within two years. Pathological diagnosis of sampling endometrium during bleeding revealed an atrophic endometrium. There was no vaginal bleeding observed after the fourth month (Table 1). The data presented shows that, unlike preparation containing estrogen, tibolone does not cause endometrial proliferation, which is of considerable clinical importance. This therapy does not cause weight gain or affect blood pressure during the study period of 180 days (Table 2).

Recent studies showed that at a dose of 2.5 mg/day tibolone significantly suppressed plasma FSH, and to a lesser extent, LH levels in climacteric patients.[6,7] In our study, there was

Table 2. Body weight and blood pressure (N = 31)

	Day			
	0	**30**	**90**	**180**
Body weight (kg)	58.1	57.9	59.2	58.1
Blood pressure (mmHg)				
Systolic	116 ± 13.1	116 ± 15.6	113 ±15.7	116 ± 17.1
Diastolic	75 ± 11.3	74 ± 1.0	75 ± 9.3	73 ± 6.6
P-value	-	NS	NS	NS

NS = No statistical significance

Table 3. The bone mineral density (N = 24)

	Day		
	0	**180**	**P-value**
Spine (g/cm^2)	0.86 ± 0.14	0.83 ± 0.10	NS
Hip (g/cm^2)	0.78 ± 0.12	0.78 ± 0.10	NS

also a drop in the level of FSH and LH, however, this finding was not statistically significant. The effect of tibolone on lipid metabolism appears to be complex. In short term studies, tibolone induced a clear decrease in HDL and apolipoprotein A1 in young oophorectomized women. However, long term clinical data showed no difference in HDL level in comparison with control group while triglycerides and very low density lipoprotein (VLDL), and cholesterol were significantly decreased.[10] During our six-month trial period, we observed a significant decline in HDL level which is in agreement with other studies. However, serum apolipoprotein A was observed to be increased but of no statistical significance. To clarify this finding, we recommended more study cases and longer period of follow up. Serum calcium was shown to be decreased with statistical significance. This finding again needs more cases with longer follow-up period, moreover, urine calcium concentration should be examined instead of serum calcium.

Tibolone, in several studies, was found to be a bone-active compound with anti-resorbing as well as anabolic activity.[8,11] Long-term prevention of bone loss as well as curative treatment of post-menopausal osteoporosis was shown in these studies. We found, from our study, that the bone mineral density of the lumbar spine and hip did not change during the six-month trial period. However, we need more time to follow up the cases.

In summary, tibolone appears to be particularly suited for the treatment of the

climacteric complaint in view of its efficacy in alleviating hot flushes and associated complaints, lack of stimulating effect on the endometrium, and capacity to prevent post-menopausal bone loss. Further studies should be designed to complete in clinical profile of this new drug for the post-menopausal patients.

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