Thai Journal of Obstetrics and Gynaecology
June 1998, Vol. 10, pp. 59-63

SPECIAL ARTICLE

Tibolone : a Unique form of Hormone Replacement Therapy

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ABSTRACT

Tibolone (Livial®) is an innovative synthetic steroid analogue for the treatment of postmenopausal climacteric symptoms which, in contrast to classical hormone replacement therapies, reacts with both estrogen, gestagen and androgen receptors. This is mainly due to three metabolites of tibolone, the 3α and 3β hydroxy metabolites and the Δ4 isomer.

One significant advantage of tibolone over conventional hormone replacement therapies is the low rate of vaginal bleeding. One investigation in 129 postmenopausal patients treated with either tibolone or conjugated estrogens plus medrogestone showed significantly lower bleeding rate in the tibolone group, with 10-15% of patients in the tibolone group experiencing vaginal bleeding in the first three months of treatment ; after that, vaginal bleeding was very rare. The virtual lack of endometrial stimulation of tibolone is thought to be due to the presence of a 3β hydroxysteroid dehydrogenase in the endometrium. This enzyme is responsible for the transformation of tibolone to the Δ4 isomer, which exhibits mainly progestogenic and androgenic activities.

Another study was designed to assess the tolerability and side effects of tibolone after four months of treatment in a large collective of patients. 1,189 postmenopausal patients were included in this study. Tibolone significantly relieved all of the classical menopausal complaints. The proportion of patients with bleeding problems dropped significantly from 15.9% to 6.8%. Other complaints, such as headache, nervousness, and breast tenderness, were also significantly less frequent than before treatment. Only 14.4% of women discontinued treatment prematurely. The use of tibolone in the postmenopause is only rarely associated with vaginal bleeding, a side postmenopausal women from taking hormones.

Key words : hormone replacement therapy, tibolone, bleeding rates

In the treatment of climacteric complaints, attention initially focused on estrogens, and because of their varied and favourable actions clinicians recommended now in most cases combined with a gestagen.[1] Another group of steroid hormones, the androgens, have so far

attracted less attention. Although the many effects that male sex hormones exert in women are not fully understood, androgens are known to be involved in libido and seem to have an effect on lipolysis and bone metabolism.

Tibolone is a relatively new synthetic steroid analogue, which in contrast to classical hormones reacts with both estrogen, gestagen, and androgen receptors. This is mainly due to the three metabolites of tibolone, the 3α and 3β OH metabolites and the so-called Δ4 isomer. These metabolites with their different biological activities may explain the many effects of tibolone. Studies into the relative binding affinities of tibolone and its metabolites to different receptors have shown that the estrogenic action is mainly caused by tibolone itself and the 3 and 3 OH metabolites, whereas the Δ4 isomer shows a relatively high affinity for both the progesterone and the androgen receptor.[2]

Concerning the estrogenic effect, a dose of 2.5 mg tibolone per day was shown in a comparative study to be as effective in reducing climacteric symptoms as a dose of 2 mg estradiol valerate and 0.625 mg conjugated estrogens.[3] In contrast to classical estrogen/progestogen therapy, one main advantage of tibolone is that there is almost no re-occurrence of vaginal bleeding. In a study[4] in which a total of 168 postmenopausal women were treated with tibolone and in which endometrial biopsies were performed at the beginning and during treatment, no stimulation or an atrophic endometrial pattern was observed in about 90% of all women for up to more than 5 years. In only about 10% of the women the endometrium was slightly proliferative ; however, no hyperplasia was found in any of the patients involved.

This low rate of vaginal bleeding under tibolone has since been confirmed both in numerous clinical studies and in daily practice. In one of our own investigations[5] in 129 postmenopausal women, we compared tibolone-treated women with a group of women taking conjugated estrogens and medrogestone, and we found a highly significant difference concerning unscheduled vaginal bleedings. In the tibolone group, between 10 and 15% of women showed some vaginal bleeding episodes in the first 3 months ; after that, these episodes were much more infrequent. In this study we also measured endometrial thickness sonographically and found no significant difference before and during tibolone therapy.

This obvious lack of a stimulatory effect on the endometrium may be explained by the presence of a so-called 3β -hydroxy-steroid dehydrogenase in endometrial cells.[6] This enzyme causes a metabolic conversion of tibolone to the more porgestogenic Δ4 isomer. As a result of this local metabolic process, tibolone loses its potential estrogenic action on the endometrium while retaining its estrogenicity for desirable actions on other tissues.

Looking at the compliance with hormone replacement therapy, this positive effect of tibolone on the endometrium cannot be overestimated. We know from several studies that, in addition to changes in body weight, the re-occurrence of vaginal bleeding is a central factor determining compliance with hormone replacement therapy.

When women on tibolone therapy do bleed, Habiba and colleagues[7] found in hysteroscopic investigations that all patients but one had an atrophic endometrium, and there was only one focal simple hyperplasia. However, they found 10 patients with benign endometrial polyps, 3 with fibroids and 2 with congenital uterine abnormalities. These data offer further reassurance of the

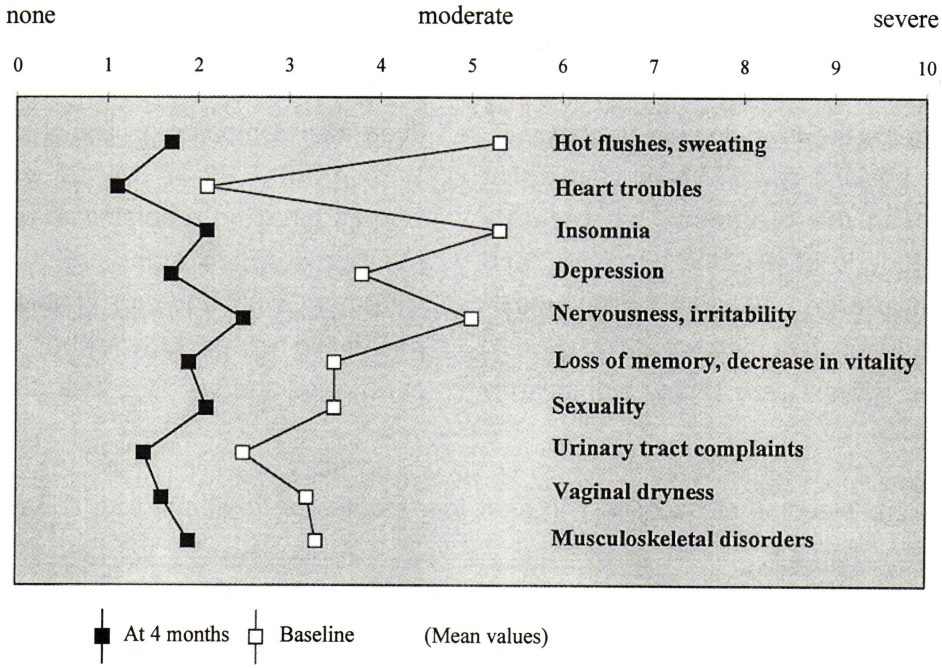

Fig. 1. Menopause Rating Scale (Hauser et al[10]).

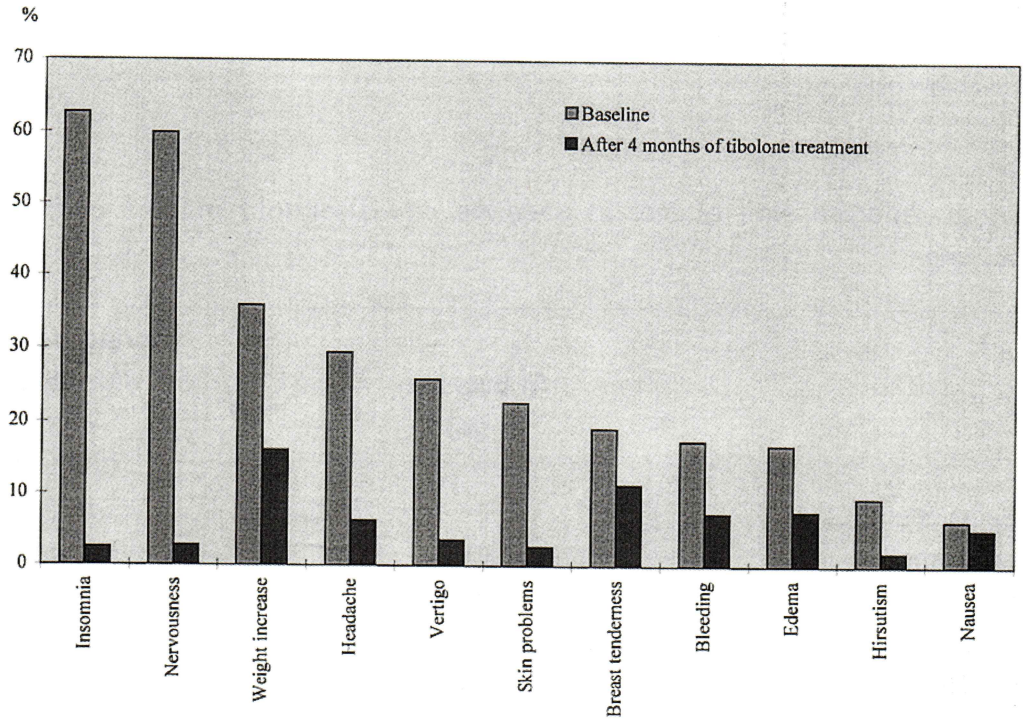

Fig. 2. Complaints at baseline and after four months of treatment with tibolone.

usually benign nature of bleeding with tibolone, although a high proportion of patients were found to have underlying uterine ormalities, suggesting hysteroscopy to be the investigation of choice.

Because tibolone is a synthetic steroid that is not present in the organism, we recently performed a study to assess the tolerability and side effects in a large collective of patients.[8] 1,189 postmenopausal women were recruited in this study. The typical were highly significantly improved with tibolone (Fig. 1.). Other pre-existing problems, such as headache, vertigo, and bleeding problems, were reported significantly less often after 4 months on tibolone (Fig. 2.)

A total of 15.9% of women recorded various bleeding problems at baseline, and this number dropped significantly to 6.8% during treatment with tibolone (Table. 1). In only 10 cases did we perform either hysteroscopy or curettage, and we also found one endometrial

Table 1. Vaginal bleeding at baseline and after four months of treatment with tibolone

	At baseline n (%)*	During treatment with tibolone n (%)*	Significance level
Spotting	55 (5.0)	47 (4.3)	n.s.
Metrorrhagia	47 (4.3)	11 (1.0)	$p < 0.001$
Both	28 (2.5)	3 (0.3)	$p < 0.005$
Unspecific	45 (4.1)	13 (1.2)	$p < 0.001$

* (%) of available data

Table 2. Other reported side effects at baseline and after four months of treatment with tibolone

	At baseline n (%)*	During treatment with tibolone n (%)*
Leg problems/edema	-	8 (0.7
Venous problems	5 (0.4)	8 (0.7)
Hair loss	7 (0.6)	9 (0.8)
Acne	1 (0.1)	4 (0.3)
Increase in RR	1 (0.1)	7 (0.6)

* (%) of all patients included

polyp and one case of a submucous fibroid.

Side effects, such as oedema or venous problems, were rare (Table 2.). Some patients may experience individual hypersensitivity to the partial androgenic effect of tibolone. Also, as we know from other orally administered medications,[9] there might sometimes be an increase in renin substrate production, which, in turn, may lead to an increase in blood pressure.

In conclusion, the data on tibolone show that it reliably alleviates climacteric symptoms and is only rarely associated with vaginal bleeding. It may at least partly meet the hopes placed in modern hormone replacement therapy and almost corresponds to the often demanded so-called "designer drug"

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