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ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

The effect of tibolone on biochemical markers of bone metabolism in late postmenopausal women

OBJECTIVE **The aim of this study was to evaluate the effect of tibolone on bone metabolism in late postmenopausal women with decreased bone mineral density (BMD), as estimated by markers of bone remodelling.** METHOD **Sixteen women with a mean age of 56.4±4.6 years, mean duration of the postmenopausal period 9.5±5.2 years, and BMD −1 SD, estimated by quantitative computed tomography (QCT) were assigned to treatment with 2.5 mg tibolone plus 600 mg calcium and 200 U vitamine D daily for 6 months. The control group comprised 11 women matched for age and years after menopause, who received only 600 mg calcium and 200 U vitamine D per day. Markers of bone metabolism were determined at baseline and after the treatment period of 6 months.** RESULTS **In the tibolone group there was a significant decrease of serum alkaline phosphatase (P<0.01), deoxypyridinoline (P<0.01), serum phosphate (P<0.01) and urinary calcium excretion (P<0.05), while in the control group these parameters did not show significant changes. No change in the levels of liver enzymes was observed in either group.** CONCLUSIONS **Tibolone was found to be effective in suppressing bone remodeling markers in women in late postmenopause with low BMD. The effect on bone resorption markers appears to be expressed earlier and more significantly compared with markers of bone formation. Tibolone was well tolerated and can be used as an alternative to hormone replacement therapy (HRT) in elderly women with low BMD, in which HRT is undesirable.**

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2007, 24(5):458–462

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Η επίδραση της τιμπολόνης στους βιοχημικούς δείκτες οστικού μεταβολισμού γυναικών όψιμα μετά την εμμηνόπαυση

Abstract at the end of the article

Key words

Calciuria
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Late postmenopause
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Postmenopausal bone loss is the main reason for osteoporosis and its subsequent osteoporotic fracture. Many studies, including the Women's Health Initiative (WHI), have shown a protective effect of hormone replacement therapy (HRT) on osteoporotic vertebral and femoral fractures. Recent studies, however, significantly restrict the indications for HRT to a specific population of early postmenopausal women who are symptomatic and have a low risk of cardiovascular disease (CVD) and breast cancer. New treatment options such as SERMS and tibolone were therefore introduced in clinical practice to prevent bone loss.

Tibolone is a synthetic tissue-specific steroid [(7α, 17α)-17-hydroxy-7-methyl-19-norpregn-(10)-en-20-yn-3-one] with estrogenic, progestagenic and androgenic properties. It has been shown to be effective in relieving climacteric symptoms[1] with almost no stimulatory effect on the breast and the endometrium.[2,3]

Studies evaluating the effect of tibolone on bone are less numerous compared with those on HRT, and most have estimated the effect on bone in early postmenopausal women with normal bone mineral density (BMD).[4] It was shown that in this population tibolone prevented bone loss and maintained skeletal integrity. Less is known about the efficacy of tibolone in late postmenopausal women with advanced bone loss.

In order to evaluate the effect of an anti-osteoporotic treatment, it is recommended to measure BMD at baseline and again after 1 to 2 years.[5] It is known that some women (10–50%) continue to lose bone while receiving antiresorptive therapy and might benefit from a different or additional antiresorptive therapy.[6] Therefore the early estimation of the effect of therapy is of considerable importance. While different methods for the measurement of BMD are used for the diagnosis of osteoporosis, the biochemical markers of bone metabolism are useful

in the early monitoring of the efficacy of antiresorptive therapy, and the evolution of bone metabolism.

The aim of this study was to estimate the early effects of tibolone on bone metabolism in late postmenopausal women with low BMD using markers of bone remodeling.

MATERIAL AND METHOD

A six-month prospective, case-control, non-randomized, open study of postmenopausal outpatients was performed.

Subject selection

The subjects in the study were recruited from among the postmenopausal women attending the Clinic of Endocrinology, Medical University, Sofia. The inclusion criteria were as follows: clinically healthy Caucasian women, age <65 years; BMD (lumbar spine) T-score −1 SD, without gynecological and or mammologic contraindications. Exclusion criteria were: history of sex-hormone dependent malignancies, use of HRT or other steroid medication during the 6 months before the start of the study, hypertension, presence of history of cardiovascular, cerebrovascular or thrombotic disorders.

After signing written informed consent 31 women were included in the study. In the tibolone group 20 women started the treatment, of whom 16 completed the study until the 6th month. The discontinuations occurred within the first two months after the beginning of treatment. The reasons for dropout were: two women due to vaginal bleeding; one due to headache and one for personal reasons unrelated to the study. The control group consisted of 11 women, matched for age, years of amenorrhea, body mass index (BMI) and BMD. Only the subjects who completed the study were included in the analysis.

Study protocol

The treated women received tibolone 2.5 mg/day (Livial, Organon, OSS, The Netherlands), plus 600 mg calcium and 200 U vitamine D daily for six months. The subjects in the control group received only 600 mg calcium and 200 U vitamine D for the same period of time. Before and after the discontinuation of the treatment the following biochemical parameters were measured: 24 hours urine calcium excretion (UCE); serum calcium (Ca) and phosphorus (P); total serum alkaline phosphatase (sAP); deoxypyridinoline (DPD). At these time points the liver enzymes (AST, ALT and γGT) were measured in order to eliminate any liver AP interference during the treatment.

BMD measurement

Quantitative computed tomography (QCT) (Osteo-CT, Somatom Plus 4, Siemens) was used for estimation of the trabecular bone density of the lumbar vertebral bodies (L1–L3) at baseline. Mid-vertebral slices were using an automated procedure. For measurement within the vertebrae a computerized selection of the trabecular area was used. Trabecular bone density was expressed as mg calcium hydroxyapatite (Ca-HA) per mL, using a standard reference device.

Assays

DPD was measured by a highly specific competitive immunoassay using direct chemiluminescent technology – ACS: 180, Automated Chemiluminescence System, Bayer HealthCare. UCE, serum Ca and P, total sAP, and liver enzymes (AST, ALT and γGT) were assayed using commercial reagents of Bayer Diagnostics and measured with Hitachi 917, Japan.

Statistical methods

The data were analyzed using SPSS 12.01 software (SPSS, Chicago, IL, USA). The one-sample Kolmogorov-Smimov test was used to estimate the distribution of samples. The mean values of each variable were compared using analysis of variance. The independent t-test was used for comparing means between the control and patient groups, and the paired t-test was used for comparing the data within each group. All results are expressed as mean±SD. Statistical significance was fixed at $P<0.05$.

The baseline data of the patients of the tibolone and the control groups are given in table 1.

RESULTS

There was no significant difference between the tibolone and control groups with respect to the age, postmenopausal status, smoking, BMI, BMD, and baseline biochemical parameters (tables 1 and 2). DPD and UCE in the tibolone group decreased significantly after 6 months compared with the baseline values, by 36.5% and 24.5%, respectively, and with the control group, while in the controls no change was observed. Serum AP decreased significantly in the tibolone group by 19.4%, but not in the controls. Serum Ca levels did not change during the study period in either group, and serum P decreased significantly in the tibolone group at the sixth month. In the tibolone group the liver enzymes did not change during the follow up period and no differences were observed from the control group.

DISCUSSION

The aim of the study was to examine the effect of tibolone on markers of bone metabolism and to esti-

Table 1. Baseline data of the patients in the tibolone and the control group.

Parameter	Tibolone (n=16)	Control (n=11)	P
Age (years)	56.4±4.6	54.8±4.0	ns
Age of menopause (years)	46.9±4.0	47.4±5.3	ns
Duration of amenorrhea (years)	9.5±5.2	7.5±5.3	ns
BMI (kg/m^2)	24.3±3.2	24.1±2.5	ns
BMD (mg/mL Ca-HA)	89.8±20.5	102.7±27.5	ns
T-score (SD)	-2.5±0.8	-2.1±1.0	ns
Number of smokers (%)	4 (25)	3 (27)	ns

Note: Values are means±SD except as noted, BMI: Body mass index, BMD: Bone mineral density, ns: Statistical non significant

mate whether it exerts an early antiresorptive effect in late postmenopausal women with low BMD. Formerly tibolone was predominantly used to treat women with climacteric complaints, for whom bleeding was unacceptable, or who had experienced side-effects during conventional HRT.[7] However, the estrogenic properties of tibolone imply estrogen-like effects not only on climacteric symptoms and the vagina, but also on bone. Unlike HRT, the effects of tibolone on BMD and bone biochemistry parameters have not been so well elucidated and conclusive fracture data on tibolone are still lacking. Although estrogen and tibolone both act on bone through the estrogen receptors (ER), they differ considerably in their mechanism of action and their side effects on tissues other than bone.[8] The positive effects of tibolone on bone were first demonstrated by Lindsay et al.[9]

Animal studies have demonstrated that bone strength achieved after tibolone treatment is similar to, or better than that observed with estrogens, depending on the species used.[10] After treatment for 16 weeks, tibolone decreased the serum levels of deoxypyridinoline and pyridinoline in mature ovariectomized rats compared with an ovariectomized control group.[11]

The highest rate of bone loss is observed during the early postmenopause, although the activation of bone metabolism is initiated during the premenopausal period.[12] Clinical trials with tibolone refer predominantly to the bone-preserving effects of tibolone in the early postmenopausal period of women with normal BMD.[4,13] Short-term (3 months) administration of tibolone produced a decrease of DPD by 22.9%.[14] During the same period the authors found a slight decrease in AP of 4.5% and UCE of 13.6%, that were no significant. The significant decrease in DPD by 36.5%, sAP by 19.4% and UCE by 24.5% in this study after 6 months of treatment points to a more marked efficacy. The explanation should be sought in two aspects: in the pretreatment BMD state of the study patients and the longer period of testing. It is expected that the effect of an antiresorptive agent on the osteopenia/osteoporosis state would be more pronounced than in women with normal BMD.

Two randomized, double-blind placebo-controlled, dose-finding studies of 2 years' duration showed that tibolone was effective for osteoporosis prevention in early menopausal women with normal BMD.[4] These studies also showed a dose-dependent increase of BMD in the lumbar spine and the total hip, and made it possible to individualize the antiresorptive therapy for postmenopausal women according to the clinical response after an appropriate treatment period. The results of long-term studies (8 and 10 years) on the effects of tibolone on bone in early menopause were reported by Reymer et al.[15,16] The authors found a significant decrease in

Table 2. Values of biochemical parameters of the tibolone (n=16) and control (n=11) groups at baseline and after 6 months of follow-up.

Parameters	Tibolone basal values	Tibolone 6th month	Controls basal values	Controls 6th month
AST (U/L)	23.0±4.3	24.1±4.0	24.3±5.3	25.1±5.7
ALT (U/L)	20.0±4.9	21.7±12.5	23.0±8.9	22.5±8.4
γGT (U/L)	22.3±8.4	24.4±10.9	21.0±5.5	19.9±5.4
sAP (U/L)	84.4±23.8	68.0±28.9**	91.5±41.8	94.0±35.7
DPD (nmol/mmol creatinine)	9.6±5.1	6.1±3.1**	9.0±4.4	9.1±3.7#
Serum calcium (mmol/L)	2.33±0.13	2.31±0.11	2.29±0.15	2.26±0.11
UCE (mmol/24 hours)	4.37±2.01	3.30±1.73*	4.47±1.53	4.65±1.57#
Serum phosphorus (mmol/L)	1.08±0.13	0.95±0.15**	1.10±0.13	1.08±0.17#

* P<0.05 for the 6th month vs baseline in the tibolone group, ** P<0.01 for the 6th month vs baseline in the tibolone group, # P<0.05 for the control group compared with the tibolone group at the 6th month, sAP: Serum alkaline phosphatase, DPD: Deoxypyridinoline, UCE: 24 hours urine calcium excretion

sAP, while the bone formation marker osteocalcin stayed approximately the same.

In 1996 Brajanson et al reported the results of a study on the effects of tibolone on bone in late postmenopausal women with normal BMD, measured in the lumbar spine, and the forearm. The study showed a similar bone-preserving effect of the two doses administered (1.25 and 2.5 mg) in both skeletal areas. The results of most studies generally support a bone preserving effect of 2.5 mg tibolone daily, although the only study describing late menopause did not reveal significant effects of tibolone on bone-related biochemistry.[17] The authors reported an S-shaped upward pattern of increase of the spinal bone mass, and assumed that the drug acts initially as a depressor of bone resorption and subsequently as an activator of bone formation.[17] The data from the present study support such an assumption. Although the decrease of both biochemical markers was significant in comparison with baseline data, the results favor an earlier and more robust depression of bone resorption.

A major problem with menopausal women is their tendency to discontinue or change therapy because of side effects. Previous studies of various doses of tibolone indicated that a dose of 5 mg tibolone increased the frequency of vaginal bleeding considerably,[9] and that 1.25 mg tibolone was insufficient to control climacteric symptoms.[7] In the present study a dose of 2.5 mg/day tibolone was well tolerated, and none of the women who completed the study complained of bloating or rapid weight gain, or had a thrombotic incident. This study supports the theory of a beneficial effect of tibolone on bone by reduction the bone resorption rate after 6 months of treatment. This favorable effect, combined with its neutral effect on the breast and endometrium, suggests that tibolone may constitute a potential alternative to hormone therapy for the treatment of low BMD and of menopausal symptoms as stated in the recently published International Consensus.[18]

In conclusion, tibolone was found to be effective in suppressing bone remodeling markers in women in late menopause with low BMD. The effect on bone resorption markers appears to be expressed more significantly and earlier than that on markers of bone formation. Tibolone was well tolerated and can be used as an effective alternative to HRT in elderly women with low BMD, for whom HRT is undesirable.

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ΠΕΡΙΛΗΨΗ

Η επίδραση της τιμπολόνης στους βιοχημικούς δείκτες οστικού μεταβολισμού γυναικών όψιμα μετά την εμμηνόπαυση

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ΣΚΟΠΟΣ της μελέτης ήταν η αξιολόγηση της επίδρασης της τιμπολόνης στον οστικό μεταβολισμό γυναικών που βρίσκονται σε εμμηνόπαυση για μεγάλο χρονικό διάστημα και παρουσιάζουν μειωμένη οστική πυκνότητα (bone mineral density, BMD), όπως αυτή εκτιμάται από τους δείκτες οστικής ανακατασκευής. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Σε 16 γυναίκες ηλικίας 56,4±4,6 ετών, διάρκειας μετεμμηνοπαυσιακής περιόδου 9,5±5,2 ετών και BMD 1 SD υπολογισμένης με τη χρήση ποσοτικής υπολογιστικής τομογραφίας, χορηγήθηκε θεραπεία με 2,5 mg τιμπολόνης, σε συνδυασμό με 600 mg ασβεστίου και 200 U βιταμίνης D, ημερησίως για 6 μήνες. Η ομάδα ελέγχου αποτελείτο από 11 γυναίκες της ίδιας ηλικίας και της ίδιας μετεμμηνοπαυσιακής περιόδου, οι οποίες έλαβαν μόνο 600 mg ασβεστίου και 200 U βιταμίνης D ημερησίως. Οι δείκτες οστικού μεταβολισμού προσδιορίστηκαν πριν και μετά από τη θεραπεία των 6 μηνών. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Στην ομάδα που χορηγήθηκε τιμπολόνη παρατηρήθηκε σημαντική μείωση της αλκαλικής φωσφατάσης του ορού (P<0,01), της διοξυπυριδινολίνης (P<0,01), του φωσφόρου του ορού (P<0,01) και του ασβεστίου των ούρων (P<0,05). Αντίστοιχες διαφορές δεν παρατηρήθηκαν στην ομάδα ελέγχου. Σε καμία από τις ομάδες δεν παρατηρήθηκαν

διαφορές στα επίπεδα των ηπατικών ενζύμων. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Παρατηρήθηκε ότι η τιμπολόνη προκαλεί μείωση των δεικτών οστικής ανακατασκευής σε γυναίκες που βρίσκονται σε εμμηνόπαυση για μεγάλο χρονικό διάστημα και παρουσιάζουν μειωμένη BMD. Η δράση της στους δείκτες οστικής απορρόφησης φαίνεται ότι εκδηλώνεται νωρίτερα και είναι πιο εκσεσημασμένη, σε σύγκριση με εκείνη επί των δεικτών οστικού σχηματισμού. Η τιμπολόνη ήταν καλά ανεκτή και φαίνεται ότι μπορεί να χρησιμοποιηθεί εναλλακτικά ως θεραπεία ορμονικής υποκατάστασης, σε γυναίκες μεγαλύτερης ηλικίας με χαμηλή BMD και ανάλογες ανάγκες.

Λέξεις ευρετηρίου: Αλκαλική φωσφατάση ορού, Ασβεστιουρία, Εμμηνόπαυση, Τιμπολόνη

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