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Tibolone low dose (1.25 mg/d) therapy and postural balance in elderly women

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ABSTRACT

Most hip fractures occur in subjects without osteoporosis and are associated with a fall. Conventional menopausal hormone therapy (HT) improves postural balance, which might explain the rapid reduction in hip fracture risk. It is unclear whether tibolone improves postural balance, which might determine its effects on peripheral fracture risk.

Objective: To study the short-term effects of low-dose tibolone therapy on postural balance in elderly women.

Methods: Eighty healthy women (70 evaluable), aged 60 years or more, were recruited through advertising in the local media. They were randomly allocated to receive either tibolone (1.25 mg/d) or placebo for 6 months. Postural balance was assessed as sway velocity, using a force platform.

Result(s): Baseline characteristics, including serum estradiol values and postural balance, were similar in the two study groups. On average, the overall dosing compliance was very high, over 97% in both groups. After 6 months, sway velocity had decreased (improved) by 7.6% (−0.97 cm/s; $P = 0.16$ vs. baseline) in the tibolone arm and by 2.5% (−0.30 cm/s; $P = 0.59$ vs. baseline) in the placebo group. The difference 0.67 cm/s was not statistically significant (95% CI −2.44, 1.10; $P = 0.45$). Adjustments for age, serum estradiol level and variable value at baseline, revealed similar results.

Conclusions: Short-term treatment with tibolone (1.25 mg/d), compared to placebo, did not significantly affect postural balance function in elderly women.

1. Introduction

Most fractures in the elderly (more than 80%) occur in those without osteoporosis in their peripheral bone mass [1]. Postural imbalance and falls become increasingly associated with the occurrence of hip fracture on aging [2]. Deterioration in balance function starts at relatively young ages and further accelerates from about 60 years upwards [3]. Interventions to prevent falls in older adults are therefore considered highly important [4].

We recently reported that 6 months of hormone therapy (HT), initiated soon after menopause (mean age 52 years), rapidly and significantly improved postural sway to values similar to those previously reported in young healthy women between 20 and 30 years of age [5]. Further, estrogen therapy started at the time of menopause and continued into high age, seems to preserve postural sway at values similar to those in young healthy women and substantially better than in age-matched elderly women [6]. When conventional continuous combined HT was initiated in elderly women, postural balance substantially improved only in those with low serum estradiol levels at baseline [7]. Peripheral fractures, like hip fractures, are more common in elderly women and strongly dependent of a fall/imbalance [2]. In a recent study tibolone given in the normal dose (2.5 mg/d) to women soon after menopause (mean age 54 years) significantly improved handgrip strength, compared with placebo [8].

The aim of the present study was to examine the short-term effects of low-dose tibolone (an agent with combined estrogenic, progestogenic and androgenic) [9] on postural balance in elderly women. The dose of tibolone (1.25 mg/d), half of the standard dose (2.5 mg/d), was chosen because of its documented effect to preserve bone mass early after menopause [10], in elderly osteopenic women [11] and recently also shown to reduce fracture risk in elderly osteoporotic women [12].

2. Materials and methods

2.1. Participants and study design

In this randomized, blinded, placebo-controlled study, 80 Caucasian women, aged 60 years and older and with a BMI >18 and

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<30 kg/m^2, were recruited through advertising in the local media in Uppsala, Sweden. We excluded women with exposure to medium potent hormone replacement therapy, or vaginal 17-beta estradiol, during the last 6 months. In addition, we excluded those with contraindication for HT (e.g. known or suspected estrogen-dependent cancer or increased risk of thromboembolic disease or suspected cardiovascular disease). We also excluded women with hypertension (>170/105), use of drugs known to affect the postural balance (e.g. sedative-hypnotic agents, antiepileptic drugs), impaired locomotion or impaired auditory and visual function (glasses were allowed). In total 19 women had been on any form of HT before inclusion in the present study, with a mean time since HT use of 6.5 years.

2.2. Intervention

Subjects were randomly and blindly assigned to treatment with active tibolone or placebo for 6 months. Randomization was achieved with computer-generated assignment in blocks of 10, using sealed numbered treatment preparations that were prepared by the hospital pharmacy and consecutively dispersed after enrolment of each subject. Active therapy comprised tibolone 1.25 mg/d. Inactive tablets of identical appearance were given in the placebo arm. Follow-up visits were performed at 6 months.

Sixty-nine of the original 80 women completed the study. One woman, randomized to the tibolone arm, never took any study medication. In the tibolone arm, 5 subjects discontinued prematurely due to; abdominal pain, one due to headache, lack of time, nausea/depression and one without any given reason. In the placebo arm 5 women dropped out due to; one died due to subdural haematoma, high blood pressure, headache/nausea, foot fracture and one because of nausea/depression. All participants gave their informed consent. The study was approved by the ethics committee, Faculty of Medicine, Uppsala University, Sweden.

2.3. Study parameters

Postural sway was assessed using a computerized force platform (MAC III), based on the principles of Terekov [13], as described previously [5,6]. The magnitude of movements on the center point of force (CPF) is representative of the effort required to maintain postural balance. The sway velocity (movement in cm/s) was calculated as described previously and standardized for body weight [14]. During the test, the woman stood erect, with her arms by her sides and her heels together, with her feet at a 30° angle. Postural imbalance was provoked by blindfolding and by application of external vibrators to the calf muscles to disturb visual input and proprioception, respectively [14,15]. Stimulation via vibration induces body sway and gives an impression of forward propulsion [16]. The magnitude of this effect depends on the frequency of vibration stimulation, with maximum perturbation of posture at 80 Hz [17]. Sway velocity was measured at the vibration frequencies 0, 20, 40, 60, 80 and 100 Hz, applied in a mixed order to avoid habituation in the test situation [14]. The sum of the values obtained at the different frequencies was used as the end-point variable in our analysis.

Table 1
Baseline characteristics in the two study groups.

Baseline characteristics	Tibolone $N = 39$*	Placebo $N = 40$
Age (years)	67.3 (5.2)	68.5 (5.1)
Age at menopause (year)	50.3 (3.5)	50.3 (4.2)
Years since menopause	17 (6.7)	18.2 (6.8)
Body mass index (BMI) (kg/m^2)	25.7 (2.9)	24.9 (3.3)
Serum estradiol (pmol/L†)	79.0 (12.7)	76.4 (14.9)
HRT ever use		
No	27 (69%)	33 (82.5%)
Yes	12 (31%)	7 (17.5%)

Data are mean ± standard deviation or numbers (%).
† Detection limit, 25 pmol/L.
* One woman never started the study medication.

High values for sway velocity represent more impaired postural balance. The total duration of the measurement procedure was about 2.5 min.

Body mass index (BMI) was calculated as the weight (kg) divided by height (m) squared. Serum samples were drawn in the morning between 8 A.M. and 10 A.M., after an overnight fast, at baseline and at 3 and 6 months, and were analyzed for serum estradiol (detection limit 25 pmol/L) at the Department of Clinical Chemistry, using the kits AutoDelphia Estradiol and AutoDelphia human FSH, Wallac OY, Turku, Finland, with total coefficients of variation of 5.3%.

2.4. Sample-size and power calculation

A pre-study sample-size calculation was based on the magnitude of change in women early after menopause and differences in sway velocity between long-term estrogen users and non-users in our previous study [6]. Thus, thirty-one women would be needed to detect a mean group difference of 2 units (16% or 2/3 of the difference between long-term estrogen users and non-users) [6]. This was under the assumption of a standard deviation of 1.9, based on changes in early postmenopausal women [5], and to obtain a power of 80% at the 5% level.

2.5. Statistical methods

Paired *t*-test was used for within group changes over the study period. Two-sample *t*-test was applied as crude analysis. Since there were slight imbalances in the baseline values, analysis of covariance (ANCOVA) was used for adjustment with actual changes from baseline as a dependent variable, treatment as factor, and age, estrogen level and parameter value at baseline as covariates. All analyses were performed using SAS Version 8.2 on a PC under Windows NT.

3. Results

The baseline characteristics of the groups, including postural balance function, were similar (Table 1). After 6 months, sway velocity had decreased (improved) by 7.6% (−0.97 cm/s; $P = 0.16$ vs. baseline) in the tibolone arm and by 2.5% (−0.30 cm/s; $P = 0.59$ vs. baseline) in the placebo group. These changes differed by 0.67 cm/s,

Table 2
Changes over the 24 weeks study period for mean values of sway velocity, used as a measure of postural balance function. Intention to treat (ITT) analysis, within and between study groups. Mean (SD).

Estimate of postural balance	Tibolone $N = 36$	Placebo $N = 35$	Group difference
Sway velocity (cm/s)			
Baseline	12.74 (5.58)	11.94 (5.0)	−0.67 (−2.44, 1.10)*
Change (6–0 m)	−0.97 (4.10)	−0.30 (3.34)	
P value	0.16*	0.59*	0.45

* Analysis adjusted for age, estrogen level and actual parameter values at baseline: No significant values for any of the within- and between-group analyses after adjustment.