TREATMENT OF OSTEOPOROSIS

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FIELD OF THE INVENTION

The present invention relates in general to a method for the prevention or treatment of postmenopausal osteoporosis. Accordingly, the present invention relates to a new method for the prevention or treatment of postmenopausal osteoporosis which comprises initiating the treatment with a low dose of an estrogenic compound and after the initiation period increasing the dose of the estrogenic compound. The present invention also relates to the use of an estrogenic compound in the manufacture of a medicament for the prevention or treatment of postmenopausal osteoporosis characterized in that the treatment is initiated with a low dose of an estrogenic compound and after the initiation period the dose of the estrogenic compound is increased.

BACKGROUND OF THE INVENTION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. It is a significant cause of mortality and morbidity in the elderly people, both of individual and community perspective. Osteoporosis affects an estimeted 75 million people in Europe, the United States and Japan.

The number of postmenopausal women has been increasing steadily with the ageing population. One of the most common types of osteoporosis is associated with menopause. Annual losses of 2-6% of bone mass have been reported to occur in women in early postmenopause.

Conventional estrogen preparations are currently used for the treatment of postmenopausal osteoporosis. One such preparation is a sequentially administered preparation containing 2 mg of estradiol valerate combined with 10 mg of medroxyprogesterone acetate (Divina®, Orion Corporation, Espoo, Finland).

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SUMMARY OF THE INVENTION

The present invention provides use of an estrogenic compound in the manufacture of a medicament for the prevention or treatment of postmenopausal osteoporosis wherein the treatment is initiated with a low dose of an estrogenic compound for about 4 to about 8 months and after the initiation period the dose of the estrogenic compound is increased.

In a further aspect, the invention relates to use of an estrogenic compound in the manufacture of a medicament for the prevention or treatment of postmenopausal osteoporosis wherein the treatment is initiated with a low dose of an estrogenic compound and after the initiation period the dose of the estrogenic compound is increased and maintained at the increased amount for at least 6 months.

In a further aspect, the invention provides use of an estrogenic compound in the manufacture of a medicament for the prevention or treatment of postmenopausal osteoporosis wherein the treatment is initiated with a daily dose 1 mg of estradiol valerate for an initiation period of about 6 months and the daily dose of estradiol valerate is increased to 2 mg after the initiation period.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the change (%) in bone mineral density in osteopenic and osteoprotic women in lumbar spine.

Figure 2 shows the change (%) in bone mineral density in osteopenic and osteoprotic women in femoral neck.

DETAILED DESCRIPTION OF THE INVENTION

The inventors suprisingly discovered that when treating postmenopausal osteoporosis by initiating the treatment with a low dose of an estrogenic compound and increasing the dose of the estrogenic compound after this initiation period, the increase in bone mineral density was higher than when treating postmenopausal osteoporosis by administering the same dose of the estrogenic compound (either the low dose or the increased dose) for the whole term of the treatment. Particularly, it was found that in patients whose daily dose of the estrogenic compound was increased after the first 6 months of the treatment from 1 mg of estradiol valerate (E_2V) to 2mg of E_2V, the increase in bone mineral density in the vertebrae,

expressed as a percentage, was 8.9 % after the treatment term of 48 months. Analogously, the increase in bone mineral density, expressed as a percentage, was 6.2 % and 7.4 % in patients whose daily estrogen dose during the whole treatment term was either 1 mg of E_2V or 2 mg of E_2V respectively. The corresponding values in the femoral neck were 4.2 %, 2.9 % and 2.9 %. Further, it was found that in osteopenic and osteoporotic patients whose daily dose of the estrogenic compound was increased after the first 6 months of the treatment from 1 mg of E_2V to 2mg of E_2V, the increase in bone mineral density in the vertebrae, expressed as a percentage, was 9.4 % after the treatment term of 48 months. Analogously, the increase in bone mineral density, expressed as a percentage, was 7.7 % and 7.3 % in patients whose daily estrogen dose during the whole treatment term was either 1 mg of E_2V or 2 mg of E_2V, respectively. In osteopenic and osteoporotic patients the corresponding values in the femoral neck were 6.4 %, 3.8 % and 3.5 %.

Accordingly, an object of the present invention is a method for the prevention or treatment of postmenopausal osteoporosis which comprises initiating the treatment with a low dose of an estrogenic compound and after this initiation period increasing the dose of the estrogenic compound. Particularly, the present invention relates to a method for the prevention and treatment of postmenopausal osteoporosis which comprises initiating the treatment with a low dose of an estrogenic compound and after this initiation period doubling the dose of the estrogenic compound. The initiation period of the treatment usually lasts about 4 to 8 months, preferably 6 months.

The low dose of an estrogenic compound used during the initiation period is a dose equivalent in estrogenic activity to approximately 0.5 mg – 1.5 mg of estradiol valerate. Preferably, the low dose of an estrogenic compound is a dose equivalent in estrogenic activity to approximately 1 mg of estradiol valerate.

The increased dose of an estrogenic compound used during the rest of the treatment term is a dose equivalent in estrogenic activity to approximately 1 mg - 3 mg of estradiol valerate. Preferably, the increased dose of an estrogenic compound is a dose equivalent in estrogenic activity to approximately 2 mg of estradiol valerate.

The estrogenic compound of the present invention is preferably estradiol valerate. Other conventional estrogens such as estrone, estrone sulfate, estrone sulphate piperazine salts and their esthers as well as synthetic estrogens may also be employed.

EXAMPLE

In order to demonstrate the effectiveness of using the method of the present invention, and its advantages, a comparative study was undertaken to evaluate the efficacy and tolarability of the method. The subjects used in the study were 419 postmenopausal women, aged 45 to 65 years. Eligible women had to be at least 3 years postmenopausal with normal gynecological findings, an intact uterus and a body mass index of 30 or less. Major medical exclusion criteria included endometrial hyperplasia and pathological mammography findings, prior hormone-dependent malignancies, severe thyroid diseases, and other criteria typical for HRT studies. Excessive smokers and alcohol abusers were excluded. Otherwise the women were not required to change their daily diet or other lifestyle habits for the study period. The women did not take any calcium or vitamin D supplementation during the study period.

Subjects were randomly assigned to six treatment groups to receive one tablet daily containing one of the following dose combinations: 1 mg or 2 mg of estradiolvalerate (E_2V) combined to 2.5 mg or 5 mg of medroxyprogestrone acetate (MPA) (Indivina®, Orion Corporation, Espoo, Finland).

Group	Daily E_2V dose (First 6 mo/After 6 mo)	Daily MPA dose
Group I	1 mg / 2 mg	2.5 mg
Group II	1 mg / 2 mg	5 mg
Group III	2 mg /2 mg	2.5 mg
Group IV	2 mg / 2 mg	5 mg
Group V	1 mg / 1 mg	2.5 mg
Group VI	1 mg / 1 mg	5 mg

Groups changing from 1 mg E_2V to 2 mg E_2V irrespective of the MPA (Group I and II) were pooled together. Groups receiving 1 mg of E_2V throughout the study irrespective of the MPA dose (Group V and VI) were pooled together. Also groups receiving 2 mg of E_2V throughout the study irrespective of the MPA dose (Group III and IV) were pooled together. Pooling was considered justified since MPA is not expected to affect the response of estrogen on bone mineral density (BMD).

The bone mineral densities at the vertebrae and the hip were measured using dual-energy X-ray absorptiometry (DPX) at baseline, 6-, 12-, 24-, 36- and 48-month follow-up visits, and at premature discontinuation. The BMD from the hip was measured by three separate measurements at the femur neck, Ward's triangle, major trochanter and BMD from the vertebrae was measured at L2-L4. In addition, the area and bone mineral content (BMC) of vertebrae L2-L4 were determined.

Bone mineral density at 48 months

Both vertebral and femoral bone mineral densities increased in all three groups. The increases were more pronounced at the vertebrae, but significant improvement was also observed at all indices at the hip (femoral neck, trochanter and Ward's triangle).

Pooled results of all subjects

In the vertebrae there was a statistically significant difference in favor of the 2 mg estrogen dose. The mean percentage change was 7.4% in the group receiving 2 mg of E_2V compared to 6.2% in the group receiving 1 mg of E_2V ($p=0.0079$). Similarly, BMD response in group switching from 1 mg to 2 mg E_2V differed statistically significantly from 1 mg E_2V group 8.9%, ($p<0.001$).

In the femoral neck no significant difference could be seen between lower and higher estrogen dose groups, but the group switching from 1 mg to 2 mg had statistically significantly larger BMD response compared to 1 mg of E_2V group (4.3% vs. 2.9%, $p=0.0361$).

Osteopenic/osteoporotic vs normal bones in pooled groups

Results were further analysed to compare the effect varying dosages on BMD in groups that had either normal, osteopenic or osteoporotic BMD value at baseline. Subjects were classified as osteopenic if the BMD was 0.90 to1.08 g/cm^2 in vertebrae (L2-L4) and 0.68 to 0.86 g/cm^2 in femoral neck (corresponds to T score between -1 and -2.5 in Finnish population). BMD was regarded as normal if the values were above 1.08 g/cm^2 in vertebrae and above 0.86 g/cm^2 in femoral neck. Values below 0.90 g/cm^2 in vertebrae and below 0.68 g/cm^2 in femoral neck were considered as osteoporotic.

In vertebrae, the mean change from baseline in osteopenic/osteoporotic subjects (BMD T score below –1) was 7.3% in 2 mg of E_2V group, 7.7% in 1 mg E_2V and 9.4% in 1 mg/2 mg E_2V group, no significant differences were seen. For the group with normal BMD, corresponding changes were 7.5%, 4.7% and 8.3%. Both the 1 mg/2 mg E_2V group and 2 mg of E_2V group differed statistically significantly from the 1 mg E_2V group ($p<0.001$).

Vertebral BMD and change (%) in BMD from baseline can be seen in Figure 1.

In femoral neck, the BMD changes ranged from 2.1% to 2.5% in the group that had normal BMD values at baseline. For osteopenic/osteoporotic subjects, the percentage changes were 6.4% for the 1 mg/2 mg E_2V group, 3.5% for 2 mg E_2V group and 3.8% for 1 mg of E_2V group. The differences between 1 mg/ 2 mg of E_2V group and the two other groups were statistically significant (1 mg/ 2 mg vs. 2 mg p=0.0258 and 1 mg /2 mg vs. 1 mg p=0.0086).

Femoral BMD and change (%) in BMD from baseline can be seen in Figure 2.

The most prominent increase for all incides measured was seen in women who had first been taken 1 mg E_2V for 6 months before switching over to the 2 mg regimen. The baseline bone mineral density values were somewhat, but not significantly, lower in this group, which may explain the obvious superiority of this group in gaining bone mineral density after six months. However, there were no differences in baseline bone mineral

density of women with low bone mass between the groups, and nevertheless greater vertebral and particularly femoral bone mineral density increases were seen in these women. Furthermore, about half of women in each group had used some kind of HRT previously. Thus, there was no unbalanced distribution of previous HRT users in the three groups which could have been resulted in slower bone mineral density gain in group with a higher number of previous users. Morever, there were no other differences in the baseline characteristics between the groups that could have affected the results.

Although the invention has been illustrated by the preceding example, it is not to be construed as being limited to the materials employed therein; rather, the invention is directed to the generic area as herein disclosed. Various modifications and embodiments thereof can be made without departing from the spirit or scope thereof.

CLAIMS:

1. Use of an estrogenic compound in the manufacture of a medicament for the prevention or treatment of postmenopausal osteoporosis wherein the treatment is initiated with a low dose of an estrogenic compound for about 4 to about 8 months and after the initiation period the dose of the estrogenic compound is increased.

2. The use according to claim 1, wherein the initiation period lasts about 6 months.

3. The use according to claim 1 or claim 2, wherein the amount of the estrogenic compound is doubled after the initiation period.

4. The use according to any one of claims 1 to 3, wherein the dose of the estrogenic compound in the initiation period is a dose equivalent in estrogenic activity to approximately 0.5 to 1.5 mg of estradiol valerate.

5. The use according to claim 4, wherein the dose of the estrogenic compound in the initiation period is a dose equivalent in estrogenic activity to 1mg of estradiol valerate.

6. The use according to claim 1, wherein the initiation period lasts from about 4 to about 6 months.

7. The use according to claim 1, wherein the initiation period lasts from about 6 to about 8 months.

8. The use according to claim 1, wherein the estrogenic compound is estradiol valerate.

9. The use according to claim 1, wherein the estrogenic compound is estrone, estrone sulphate, and estrone sulphate piperazine salt, or an ester thereof, or a synthetic estrogen.

10. The use according to claim 1, wherein the amount of the estrogenic compound is increased by about 33% to about 100% after the initiation period.

11. Use of an estrogenic compound in the manufacture of a medicament for the prevention or treatment of postmenopausal osteoporosis wherein the treatment is initiated with a low dose of an estrogenic compound and after the initiation period the dose of the estrogenic compound is increased and maintained at the increased amount for at least 6 months.

12. Use of an estrogenic compound in the manufacture of a medicament for the prevention or treatment of postmenopausal osteoporosis wherein the treatment is initiated with a daily dose 1 mg of estradiol valerate for an initiation period of about 6 months and the daily dose of estradiol valerate is increased to 2 mg after the initiation period.