Rehabilitation

TREATMENT OF INVOLUTIONAL OSTEOPOROSIS USING CALCITONIN AND BISPHOSPHANATES

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SUMMARY: Osteoporosis is a process, throughout which the mineral and matrix content of bone steadily decreases in equal ratios below the normal ranges and chance for spontaneous fractures gradually increases. There is sizeable amount of clinical trials indicating the use of calcitonin or bisphosphanates in the treatment of osteoporosis. Bisphosphanates, with avid adherence to the hydroxyapatite crystals of bone, inhibit osteoclastic bone resorption. On the other hand, calcitonin prevents further bone loss by suppressing the activity of osteoclasts. In the present study, we compared the efficacy of the two treatments in the rectification of bone loss in postmenopausal osteoporosis. Our results revealed that either of the drugs are equally effective in the restoration of bone resorption with regard to dual-photon absorptiometry test, but on the basis of hemochemical laboratory data, calcitonin provides greater increments in alkaline phosphatase, calcium, ionized calcium than those of etidronate.

Key Words: Calcitonin, Bisphosphanates, Osteoporosis.

INTRODUCTION

Osteoporosis is a disease characterized by reduced bone strength. It occurs most frequently in elderly women during the periods of estrogen depletion. It's hallmark is low bone mass with an increased risk for low traumatic fractures of the hip and vertebra (1).

Following the recognition that osteoporosis is a major health problem for the aging population in developed countries, considerable attention has been focused on devising methods to measure bone loss and asses the risk for osteoporotic fracture (2).

The bisphosphanates (etidronate) are analogs of inorganic phosphate. These compounds have a high affinity for hydroxyapatite and inhibit osteoclastic resorption of bone (3).

Calcitonin is a polypeptid hormone and mainly produced by parafollicular or C cells of the thyroid gland. Osteoclasts possess specific receptors that bind calcitonin. Administration of calcitonin causes the brush borders of the osteoclasts to disappear and the osteoclasts to move away from the bone resorption surface (4-5).

However, it became clear that, in the early menopausal period, the aim of treatment is to stabilize bone tissue, to reduce the rate of bone resorption with slowing down the overall turnover. In women with

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established osteoporosis at late postmenopausal years, the main goal of treatment is to increase bone mass.

In our study we compared the efficacy of cal-citonin and etidronate therapy during 1 year of period in post-menopausal women.

MATERIALS AND METHODS

130 female patients with a mean age of 61 ± 7.19 years with involutional osteoporosis, were included in this study. The mean postmenopausal age was 15 ± 9.75 years. Patients with any disorder known to effect bone mass or receiving any treatment that could interfere with calcium metabolism were excluded from the study. For the determination of hemochemical laboratory parameters for the routine observation of essential organ functions, the following parameters were analyzed by the clinical laboratory of Ankara Numune Hospital: sodium, potassium, total ionised calcium, phosphate, magnesium, urea, creatinine, uric acid, cholesterol, triglycerids, alkaline phosphates, creatinephosphokinase, bilirubin, total calcium level in 24 hour urine. Radiographs of the thoracic and lomber spine in two views were performed.

Dual-photon absorptiometry was used to determine the bone mineral density of lomber spine (L1-4) and proximal femur.

Z scores for bone mineral density of the spine were calculated for each patient. Patients with one standard deviation (sd) below the mean range of young normals were conducted for the study.

Later we comprised two homogenous groups of 15 patients at each (Table 1). All patients received daily supplements of 1 gr. elemental calcium and 400 IU vitamin D throughout the study. First group assigned to receive cyclical etidronate treatment. Etidronate was given orally 400 mg/day for two weeks and the patient rested for the following ten weeks. These cycles continued for one year. The second group received 100 IU/day intramuscular calcitonin for 15 days, continued with 50 IU intramuscular injections on alternate days.

Dual photon-absorptiometry was performed to evaluate the efficacy of the treatment in the sixth and twelfth months of the study. Two-tailed t test, Levene's test, Mann-Whitney-U and Wilcoxon tests were used for statistical analysis.

RESULTS

55 patients were given etidronate and 75 patients were given calcitonin treatment at the beginning of the study, but 100 patients were excluded because of several reasons. Of the 130 patients who begun the study regimen, 30 of them completed the study. There were no significant intergroup differences in the T and Z scores in the bone mineral density of the spine and proximal femur or other characteristics like age, height, weight, mean duration of menopause, and hemochemical laboratory parameters like calcium, phosphate, alkaline phosphates (Table 1).

Table 1

	ETIDRONATE	CALCITONIN	P
Age	59.53 ± 8.245	62.60 ± 5.841	P>0.05
Height	1.5487 ± 0.71	1.5927 ± 0.75	P>0.05
Weight	71.933 ± 13.43	68.00 ± 10.00	P>0.05
Menap. Survey	14.7507 ± 11.1239	15.8667 ± 12.5262	P>0.05

After one year of treatment, in group one treated with etidronate, the mineral content evaluated by dual-photon absorptiometry was significantly increased when we compared the data with the pre-treatment values (p<0.05). In the 2nd group, treated with calcitonin, the mineral content was increased too (p<0.05). When we compared Z_2-T_2 scores of two groups, there was statistically no significant difference (p>0.05).

Serum total Ca and ionized Ca levels and alkaline phosphates levels were slightly increased in patients treated with calcitonin compared to patients treated with etidronate (Table 2).

Table 2

	ETIDRONATE	CALCITONIN	P
TOTAL Ca	2.4290 ± 0.1880	2.3487 ± 0.1823	P<0.05
ICA	1.1393 ± 0.2103	1.2673 ± 0.1823	P<0.01
ALP	81.00 ± 13.1582	62.60 ± 11.0699	P<0.05
P	12.50	1850	P>0.05
BMD (L2-L4)	0.7402 ± 0.84	0.7216 ± 0.136	P>0.05
T2	-2.4273 ± 0.801	-2.9600 ± 0.971	P>0.05
Z2	-1.0540 ± 0.7095	-1.3133 ± 0.8938	P>0.05

DISCUSSION

Osteoporosis is characterized by an imbalance of the cell-biological linkage between bone formation and resorption, resulting in a reduction of bone mass (7). The primary goal of any therapy is to rebuild new bone mass.

Organic bisphosphanate compounds inhibit osteoclast-mediated bone resorption (8). These compounds have been used in clinical trials in osteoporosis as continuous therapy, as intermittent cyclical therapy or in combination with other agents in a therapeutic approach known as coherence therapy or ADFR (activate-depress-free and repeat) or in combination with short-term activators (less than 12 months in duration). Because of these trials, the roles of etidronate and bisphosphanates in general and coherence therapy for osteoporosis remain undefined. Watts and collegues performed a prospective, two-year placebo-controlled study in 429 women with postmenopausal osteoporosis to determine the effects of intermittent cyclical etidronate therapy on bone mass of the spine. Two years of therapy resulted in significant increases in the bone mineral density of the spine and reduction in vertebral fracture rates. Serum alkaline phosphatase levels declined steadily during the study (1). The effects of etidronate on bone mass were most pronounced in the spine, a site rich in trabecular bone. The increase in spinal bone density did not occur as a result of loses of bone mass of the hip or wrist. The response to treatment with eridronate as other skeletal sites were heterogeneous (8).

Storm *et al.* performed cyclic etidronate therapy 400 mg/day for 2 weeks and the patients were kept free from the drug for the following 13 weeks. They concluded that at the end of nearly three years, etidronate therapy for postmenopausal osteoporosis resulted in significant increases in vertebral bone mineral content and a significant decrease in the rate of new vertebral fractures (9).

Watts *et al.* conducted a multicentral study and examined a large number of patients with mild osteoporosis for 2 years. They examined the rates of new vertebral fractures and compared placebo-treated patients with etidronate treated patients. The study revealed no significant difference.

Harris *et al.* performed 3 years of blinded treatment with administration open-label intermittent cyclic etidronate therapy. During the third year of the study, the number and rate of vertebral fractures were highest in the patients who received etidronate alone.

Neverthless, the increase raised concern regarding the effects of etidronate on the quality of bone. Some authors suggested that long term etidronate treatment might actually increase the risk for osteoporotic fractures similar to the experiences with sodium floride treatment (10). In our study after 1 year of cyclic etidronate treatment, with the dual-photon absorptiometry, we observed a significant increase in the vertebral bone content at Z2 scores.

In an overall review we can say that, intermittent cyclical therapy with oral etidronate results in small but significant increase in the bone mineral content of vertebral column (9). Although etidronate is not approved for the treatment of postmenopausal osteoporosis by US Food and Drug Administration, it appears to be effective and well tolerated for 2-3 years.

Calcitonin has been evaluated for it's utility in postmenopausal osteoporosis for almost 20 years, reports on its therapeutic effects are variable and difficult to interpret as they vary in the dose of calcitonin applied, duration of treatment, methods used to asses the efficacy of treatment (6).

Gennari *et al.* studied the effects of a one year course of 200 IU intranasal salmon calcitonin spray administered on alternate days. The study indicated that the dose of 200 IU on alternate days is adequate to stop axial bone loss in early postmenopausal women (11).

Reginster *et al.* conducted a long term study. Randomised controlled group comparison was made of 287 healthy women with 6-36 months of natural menopause. Nasal salmon calcitonin was given 5 days a week with 500 mg of calcium to healthy women for at least 3 years. The average changes in the bone mineral density after 36 months showed a positive outcome in the group treated with calcitonin (12).

Mazzvoli *et al.* presented the results of 12 months double blind multicenter study. Treated patients were given 100 IU synthetic salmon calcitonin injected intramuscular in the morning every other day and received 500 mg of elementary Ca. The mean bone mineral content evaluated by dual photon absorptiometry increased strikingly in the treated group over the first 6 months and reached an overall increment of 13 % of pre-treatment values after 12 months (13).

Chiristiansen *et al.* investigated the dose res-ponse effect of intranasal salmon calcitonin on bone mass. 208 participants were allocated to daily intranasal treatment with either 50 IU, 100 IU, 200 IU salmon calcitonin and placebo for 2 years. The number of patients with either vertebral or peripheral fractures during the 2 years were lower in all three groups than in placebo group (14).

The nasal administration of 200 IU salmon calcitonin modified calcium metabolism in osteoporotic women with a decrease in biochemical parameters of both bone resorption and bone formation. This results in decreased further bone loss both at trabecular and cortical sites.

As a result, after one year period of treatment the mean mineral content evaluated by dual photon absorptiometry was increased in both of the patient groups, but there was no statistical difference between the two groups.

In conclusion we confirmed that the use of intermittent etidronate and calcitonin during one year in low bone mass osteoporotic patients emphasized the effects of each in the reduction of bone resorption. However, one year duration of treatment is ineffective in osteoporotic patients. Many other studies with longer duration of follow up and with different treatment regimes are needed to asses the effective dose and to appreciate the clinical effects.

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