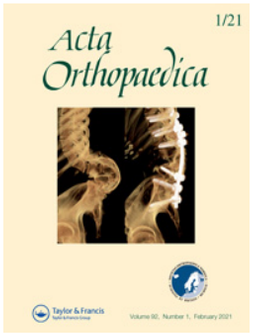

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Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures

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We examined the analgesic effect of nasal salmon calcitonin in patients with acute pain due to recent, nontraumatic osteoporotic vertebral crush fractures. 32 men and 68 postmenopausal women were studied using a prospective, double-blind, placebo-controlled clinical design. Men and women taking 200 IU of nasal salmon calcitonin daily for a period of 28 days had a dramatic decrease of spinal pain. This analgesic effect was accompanied by early mobilization and gradual restoration of the locomotor functions, such as sitting, standing and walking. Patients receiving the placebo nasal spray remained in bed for almost the entire period of observation. The consumption of high doses of paracetamol did not help placebo patients to get out of bed during the 4 weeks of hospitalization. Nasal salmon calcitonin and early mobilization also reduced hydroxyproline excretion, thus preventing massive bone loss during the period of bedrest.

Laboratory for the Research of Musculoskeletal System, University of Athens, KAT Hospital, Athens Greece. Correspondence: Dr. G Lyritis, Laboratory for the Research of Musculoskeletal System, University of Athens, KAT Hospital, Kifissia, Athens 145 61 Greece. Tel +30-1-808 7617. Fax -801 8122

Osteoporosis is characterized by a reduction in bone mass that may result in fracture, particularly of the vertebral bodies and the proximal end of the femur (Avioli 1987). This bone mass loss is accelerated during the early postmenopausal period and coincides with the gradual failure of ovarian function. It is now well-known that men also lose a considerable amount of bone mass after the sixth decade of life (Kanis and McCloskey 1992).

One of the earliest manifestations of osteoporosis is fracture of the vertebral bodies (Lyritis et al. 1989) with severe, acute pain, that gradually resolves spontaneously over the ensuing weeks (Lyritis et al. 1991, Pun and Chan 1989). Patients obtain pain relief by resting, which, however, temporarily increases bone resorption (Lyritis et al. 1991).

Calcitonin inhibits osteoclast function and therefore, prevents bone resorption (Azria 1989, Chambers and Dunn 1983). Furthermore, calcitonin has an analgesic effect in painful osteoporotic crush fractures (Lyritis et al. 1991, Pun and Chan 1989, Azria 1989), but also in, for example, headache. This analgesic activity may be caused by increase in plasma endorphin levels (Laurian et al. 1986).

This clinical, double-blind controlled study evaluates the efficacy of nasal salmon calcitonin in relieving post-fracture pain for early mobilization.

Patients and methods

32 men and 68 postmenopausal women with a mean age of 76 and 71 years, respectively, who had sustained a nontraumatic vertebral fracture within the previous 5 days, were included in the trial. The patients were hospitalized for a period of 28 days. The presence of a recent vertebral fracture was confirmed in all cases radiographically and clinically. In all cases, radiographs revealed a vertebral fracture with a more than 25% decrease in the anterior, middle or posterior height. Clinically, all patients presented with intolerable pain at the site of the collapsed vertebra. The combination of the radiograph picture and pain was considered evidence of a recent fracture. In 41 patients, the recent lateral radiograph of the spine could be compared with a previous radiograph and suggested a fresh fracture. Most patients reported a recent mild accident, usually a fall indoors on their buttocks or backwards, while only 14 reported no history of injury. Patients with high energy injuries, such as road traffic accidents were not included in the study. In addition, patients with other recent fractures (hip, wrist, etc.) were also excluded, as most of these cases had restriction of their mobility. Patients suffering other diseases, such as insulin-dependent diabetes, sever liver dysfunction, intestinal malabsorption,

rheumatoid arthritis, malignancy, hemiplegia or other disabilities of the locomotor system and patients receiving drugs affecting bone metabolism during the past 6 months, particularly corticosteroids, were also excluded from the study.

Patients were randomly assigned to receive either salmon calcitonin nasal spray 200 IU (Miacalcic, Sandoz) or a matching placebo nasal spray. The nasal spray was administered at the same time each day, preferably in the evening. In addition, patients were permitted to take paracetamol (0.5 g tablets) as a rescue analgesic up to 6 tablets daily. Treatment was initiated after baseline measurements on day 0. Pain evaluation was performed on day 0 and daily until the end of the study (day 28) using a visual analogue scale (VAS), where patients marked the degree of pain they felt on a 10-cm long vertical line with vertical ticks representing degrees of pain ranging from "no pain" rated 0 to "agonizing pain" rated 10. Pain was evaluated during different locomotor functions, e.g. bed rest, sitting, standing and walking functions. For a better assessment of the clinical relevance of the response to calcitonin, VAS estimation was initially done in the bedridden position, and afterward the patient was encouraged to sit, stand and walk for reevaluation of the VAS estimation. If a patient was unable to carry out these functions, the pain induced by attempting to do so was estimated as severe (over 8 in VAS). In our experience (Lyritis et al. 1991), if a patient's pain is rated less than 7 they are capable of attempting locomotor functions. In turn, a rating of pain less than 7 during walking, usually suggests that the patient does not require nursing and bed rest and the patient can begin physiotherapy.

Bone resorption was assessed at baseline (day 0), day 7 and 28, using the measures of total plasma calcium, albumin, phosphate, alkaline phosphatase, creatinine, urea, electrolytes and protein electrophoresis. In addition, fasting urine calcium/creatinine and hydroxyproline/creatinine ratios on the second void urine of the morning after ingestion of 0.2 L water was determined. Other hematological parameters, such as RBC, hemoglobin, hematocrit, WBC, platelets, ESR, total bilirubin, SGOT, SGPT were done at baseline and day 28. Side-effects were recorded daily, with the tolerability of the calcitonin or placebo treatment evaluated as: 3) very good, 2) good, 1) poor, 0) not tolerated.

Results were expressed as the mean ± SEM and statistical analysis was performed using the Student's t-test for unpaired data. A significance level of $p \leq 0.05$ was used.

Table 1. Mean VAS (SD) pain assessment

Group	Baseline	1	2	3	4 weeks
Bedridden position					
Calcitonin	9.0 (0.8)	4.9 (2.3)	3.5 (0.9)	2.1 (1.1)	1.0 (0.9)
Placebo	8.8 (1.6)	8.8 (1.7)	8.0 (2.1)	7.1 (2.9)	5.9 (1.9)
p-value	NS	<0.05	<0.001	<0.001	<0.0001
Sitting position					
Calcitonin	9.8 (0.1)	7.0 (1.2)	4.3 (1.3)	3.1 (0.8)	1.8 (0.6)
Placebo	9.6 (0.2)	9.5 (0.3)	8.2 (1.1)	7.1 (1.3)	6.8 (2.0)
p-value	NS	<0.1	<0.001	<0.001	<0.001
Standing position					
Calcitonin	9.9 (0.1)	7.5 (0.7)	4.9 (1.6)	4.0 (1.2	2.2 (1.1)
Placebo	9.9 (0.1	9.9 (0.1)	9.3 (0.3)	9.1 (0.8)	8.7 (1.2)
p-value	NS	<0.01	<0.001	<0.001	<0.0001
Walking position					
Calcitonin	10 (0)	9.1 (0.3)	6.1 (1.0)	5.3 (1.1	3.1 (1.5)
Placebo	10 (0	9.9 (0.1)	9.9 (0.1)	9.8 (0.2)	9.5 (0.3)
p-value	NS	NS	<0.05	<0.01	<0.0001

Table 2. Number of bedridden patients

Group	Baseline	1	2	3	4 weeks
Calcitonin	50	3	0	0	0
Placebo	50	50	50	38	26
p-value	–	<0.0001	<0.0001	<0.0001	<0.0001

Results

Pain was reduced dramatically in the group receiving calcitonin ($p \leq 0.001$). The analgesic effect of nasal calcitonin was negatively associated to the number of paracetamol tablets requested by the patients ($p \leq 0.001$). Pain rating on the VAS, showed that the most patients were gradually able to gain full mobility after the first week of calcitonin treatment (Table 1). The number of patients who remained bedridden was significantly greater in the placebo group at all time points than in the calcitonin group (Table 2)

In the placebo group, the hydroxyproline/creatinine ratio increased ($p \leq 0.01$) between days 0 and 28, whereas in the calcitonin group, it fell ($p \leq 0.001$) between days 0 and 7 and remained low during the entire period of observation (Figure 1). The difference between serum calcium levels between the two groups was not statistically significant, suggesting that a hypocalcemic effect produced by nasal calcitonin treatment was not present. Urinary fasting calcium/creatinine ratio levels increased in the placebo group, probably as an effect of fracture immobilization. In contrast, calcitonin reduced levels at 28 days ($p \leq 0.01$). All other biochemical values were normal and no significant differences were found between the 2 groups.

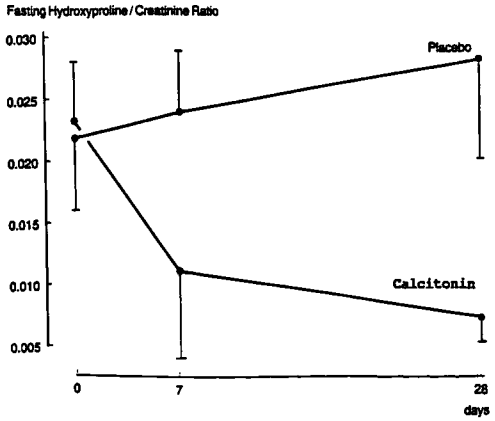

Figure 1. Fasting hydroxyproline/creatinine (HPr/Cr) ratio is an index of bone resorption. Patients in the placebo group showed a gradual increase of HPr/Cr during the bedrest period. On the other hand, nasal salmon calcitonin decreased dramatically the HPr/Cr ratio after the first week of treatment and remained low.

Nasal salmon calcitonin was well-tolerated by all patients. Mild symptoms, mainly headache, were reported in only 6 cases. No interruption of treatment was necessary.

Discussion

Analgesic treatment of patients with osteoporotic vertebral treatment should relieve pain to permit early mobilization. The effect of calcitonin on bone pain has been demonstrated by many investigators (Lyritis et al. 1991, Pun and Chan 1989, Azria 1989, Gennari and Agnusdei 1988, Szanto and Sandor 1983). Other studies report a beneficial effect of calcitonin on vertebral pain after a crush fracture (Lyritis et al. 1991, Pun and Chan 1989, Szanto and Sandor 1983). Intranasal administration of salmon calcitonin has been reported to relieve post-fracture vertebral pain (Pun and Chan 1989)

Our study confirmed these findings and focused on the importance of early mobilization of these patients. The analgesic effect of calcitonin facilitated mobilization when pain was rated below 7 on the VAS scale (Lyritis et al. 1991). A rating of 7 appears to be the pain threshold below which the patient can tolerate movement, which is important to avoid prolonged bedrest. We found that more than half of the placebo-treated patients required bed rest at the end of the 28th day of observation.

Apart from exerting an analgesic effect, nasal salmon calcitonin reduced hydroxyproline excretion, an effect which has been shown to prevent the worsening of osteoporosis. Massive bone loss which can occur during acute immobilization, is exaggerated in the so called "fracture disease". Calcitonin was found to prevent increased hydroxyproline and calcium excretion in cases of immobilized elderly osteoporotic patients with a hip fracture and internal fixation of the fracture (Tsakalakos et al. 1993).

In conclusion, nasal salmon calcitonin in a daily dose of 200 IU had an adequate analgesic effect and facilitated mobilization of patients suffering from a recent osteoporotic vertebral fracture. Nasal salmon calcitonin and early mobilization also reduced hydroxyproline excretion, thus preventing massive bone loss during the period of bed rest.

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