Intranasal calcitonin for the prevention of bone erosion and bone loss in rheumatoid arthritis

A Sileghem, P Geusens, J Dequeker

Abstract

The effect of intranasal salmon calcitonin on pain, erosion progression, and bone loss in 40 women with rheumatoid arthritis was investigated. The study design was double blind, placebo controlled for the first four months and open for the next 36 months, allowing for cross over to active drug treatment or to the control group.

Morning stiffness was reduced in the group treated with salmon calcitonin after two and four months. After an average follow up of 28 months no significant effect on erosion progression was observed using the Larsen score. The mean (SD) monthly progressions in the Larsen score in the calcitonin and control groups were 0.21 (0.22) and 0.23 (0.28) respectively.

The bone mineral density was evaluated in the forearm and spine. During the 12 months of follow up the control group lost bone at a rate of 2%/year at the spine and 4.8%/year at the radius distal third. In contrast, the group receiving nasal calcitonin gained 1% in bone mineral density at the lumbar spine and no loss at the radius distal third. The increase in bone density at the spine in the calcitonin group was not sustained and a loss of 1.8%/year was observed in the second year. The difference with the placebo group remained significant.

Destruction of cartilage and juxta-articular bone occurs in most patients with rheumatoid arthritis (RA), resulting in deformity and impairment of daily activities. Bone loss has been recognised as a complication of RA for more than a century.¹⁻⁵ Loss is accelerated in the peripheral skeleton⁶ and bone turnover indices are increased.⁶⁻⁸

Calcitonin inhibits not only spontaneous bone resorption during phases of increased bone turnover, but also parathormone induced osteolysis.⁹ It has thus been proposed for the primary prevention of bone erosion and osteoporosis in RA, especially as it also has analgesic activity.¹⁰ Intranasal calcitonin has been shown to be effective in postmenopausal women¹¹ and to be associated with fewer side effects than parenteral treatment.¹²

We investigated the effect of intranasal salmon calcitonin on pain, bone erosion, and bone loss in women with RA. The study was double blind versus placebo for the first four months, and then open over the next 36 months, during which patients from the placebo group could transfer to active drug treatment.

Subjects and methods

SUBJECTS

The population consisted of 40 women with RA aged 31-64 years treated with non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying drugs for at least six months, except one patient in the calcitonin group who was only receiving NSAIDs. None of the patients was receiving corticosteroids. Doses remained stable during the study period. The patients were randomised to two groups: group I received salmon calcitonin (Sandoz, Basle) 200 IU/day as one 100 IU spray in each nostril in the morning for the first month, followed by 100 IU/day (one spray in one nostril) thereafter; group II received 2.5 ml bottles identical in appearance but containing a pharmacologically inactive solution, given according to the same schedule. The functional status of the two groups was comparable. In the calcitonin group 90% of the patients were in functional class II, 5% in class I, and 5% in class III. In the placebo group 85% were in class II and 15% in class III. After four months, patients in groups I and II were allowed to switch over from placebo to active treatment or vice versa. Five switched from active to placebo and 13 from placebo to active treatment.

For comparison purposes in the bone erosion study, we increased the numbers in the control group by including the results from a parallel group of 13 women with RA, matched for age and disease duration, who received neither calcitonin nor placebo spray.

The protocol was approved by the local ethical committee before the study began, and informed consent was obtained in all instances.

METHODS

Bone densitometry

Bone mineral density was estimated on starting treatment and at six month intervals thereafter using single photon absorptiometry at the radius distal third, 8 cm from the styloid process, and dual photon absorptiometry at the lumbar spine (L₂-L₄). The two techniques have been described previously.¹³ Reproducibility is 1.8% with the two methods in postmenopausal women.

Radiographic analysis Larsen score

Hand radiographs were assessed blind by one of us (AS) using the Larsen grading.¹⁴ The overall appearance of individual joints was graded on a scale from 0 to 5 by comparison with standard radiographs from patients with RA.

Arthritis and Metabolic
Bone Disease
Research Unit,
KU Leuven,
UZ Pellenberg,
B-3212 Pellenberg,
Belgium

A Sileghem
P Geusens
J Dequeker

Correspondence to:
Professor Dequeker.

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Figure 1 Individual Larsen scores before treatment and at end of follow up in (A) 18 controls and (B) 21 patients treated with calcitonin spray.

Figure 2 Individual bone mineral density changes in (A, B) the radius distal third and (C, D) the lumbar spine in treated patients and controls.

STATISTICS
Non-parametric analysis was used for the bone mineral density data. The percentage changes in bone mineral density from baseline after 6, 12, and 24 months were compared using Student's *t* test. Results were compared to the control group using the Mann-Whitney *U* test. Student's *t* test was used in the bone erosion study.

Results
The two groups were matched at the start of the study for demographic and RA characteristics, bone density, and Larsen score (table).
At the end of the four month double blind phase, there were no significant differences from baseline in biochemistry, bone mineral density, and Larsen score in the treated patients or control subjects. In the calcitonin group, however, morning stiffness was significantly reduced from 38.3 (40) to 25.2 (30) minutes ($p<0.05$) after two and four months.
Continuous radiographic follow up over at least 12 months was performed for 21 patients from the calcitonin group and 18 control subjects (five in the initial placebo group and 13 in the added patient group with RA run in parallel).

EFFECT OF INTRANASAL CALCITONIN ON BONE EROSION
Figure 1 shows the time courses of individual Larsen scores in treated patients and control subjects. Duration of follow up was similar in the two groups: 28 (8) months in the calcitonin group and 27 (12) months in control subjects. The increase in the mean score was similar and not significant in each group, with monthly increments of 0.21 (0.22) and 0.23 (0.28) in the calcitonin and control groups respectively.

PREVENTIVE EFFECT OF INTRANASAL CALCITONIN ON BONE LOSS IN RHEUMATOID ARTHRITIS
Figure 2 shows individual bone mineral density changes at the radius distal third and lumbar spine in 19 treated and 10 placebo patients followed up for at least 12 months. Bone loss occurred at the radius distal third in 60% of placebo patients versus 47% of treated patients ($p<0.002$), and in the lumbar spine in 70% versus 31.5%, respectively ($p<0.002$).
Figure 3 shows the mean bone mineral density changes in the forearm (radius distal

third) and spine at 6, 12, and 24 months. For the first 12 months the control group lost bone at a rate of 2%/year in the spine and 4.8%/year in the forearm ($p<0.025$ in both instances). Conversely, in treated patients, the lumbar bone mineral density increased by 1% and forearm bone mineral density remained stable. There were insufficient forearm data after 12 months, particularly in the control group, for statistical evaluation, owing to a change of instrumentation midway through the study.
At 12 months, the calcitonin and control groups differed significantly with respect to vertebral and forearm bone loss ($p<0.03$ and 0.05 respectively). The increased vertebral bone density in the calcitonin group was not sustained and a loss of 1.8%/year was observed in the second year, though the difference from the placebo group remained significant. An analysis of responders and non-responders in the calcitonin group according to disease activity parameters at the start, in particular erythrocyte sedimentation rate, did not reveal any differences. The mean erythrocyte sedimentation rates of the responders and non-responders were 16.1 (10.8) and 17.5 (16.5) mm in the first hour (Westergren) for the radius and 15.7 (11.6) and 25.9 (17.0) mm in the first hour (Westergren) for the lumbar spine.

Pretreatment characteristics of patients. Results given as mean (SD)

	Group 1: calcitonin spray (n=20)	Group 2: placebo (n=20)
Age (years)	50.1 (8.3)	54.2 (7.7)
Height (cm)	159.9 (5.6)	158.6 (5.3)
Weight (kg)	63.9 (9.2)	64.0 (8.3)
Duration disease (months)	98 (78)	122 (80)
Morning stiffness (min)	38.3 (40)	63.6 (80)
Grip strength mean R-L (mmHg)	139 (64)	200 (178)
Postmenopausal (n)	17	11
Bone mineral density		
Radius 8 cm (g/cm ²)	0.59 (0.10)	0.63 (0.06)
Lumbar spine L ₂ -L ₄ (g HA*/cm ²)	0.85 (0.02)	0.96 (0.21)
Larsen score	21 (14)	28 (21)

*HA=hydroxyapatite.

Figure 3 Mean changes in bone mineral density in (A) the radius distal third and (B) the lumbar spine.

Discussion

As far as we are aware, this is the first time that calcitonin, and specifically intranasal salmon calcitonin, has been tested under controlled conditions for its effect on morning stiffness, bone erosion, and bone loss in RA. Calcitonin significantly improved morning stiffness after two and four months, possibly via the increased endorphin secretion shown in other diseases with pain.¹⁰ At the end of the four month double blind phase, no significant effect on bone erosion and bone loss was seen. At 6 and 12 months, however, intranasal calcitonin actually increased the vertebral bone mineral density and maintained a stable forearm bone mineral density. This finding confirms reports that intranasal calcitonin prevents vertebral bone loss, as in osteoporosis and immediately postmenopausal women, and modulates peripheral bone loss.¹¹⁻¹⁵ The fact that inhibition of cortical bone loss in the forearm was only partial in our study does not exclude total inhibition occurring in normal postmenopausal women.

Peripheral bone loss in RA is faster and more marked than in the spine⁶ owing to local inflammation, which induces local bone resorption factors such as interleukin 1 and prostaglandin E₂, and to pain induced disuse.

As other long term calcitonin studies have shown,¹⁶ tolerance develops after one to two years of continuous treatment. The increased bone mineral density, which is probably due to osteoclast inhibition and the temporary continuation of bone formation, is not sustained and bone loss starts again. The increase over the placebo group achieved in the first year remained, however. Despite the relatively long follow up, calcitonin had no protective effect against juxta-articular bone erosion in this study. A larger number of subjects is necessary to make a definite statement about the progression of erosions. This aspect needs to be addressed in a larger patient population in a disease with such a variable course. Almost all our subjects were in a steady disease state.

Bone erosion is the radiological hallmark of RA and is probably as important in joint destruction as breakdown of cartilage and soft ligament tissue. If bone erosion could be prevented, the long term progression of RA

could be substantially delayed. There has been no unequivocal demonstration to date of long term radiological progress in RA due to disease modifying drugs. Given that outcome in RA is the result of a multifactorial process, inhibition of local bone disease could be of major importance. Until now there has been no unequivocal demonstration of the prevention of long term radiological progression in RA. Further trials are required to study the bone response to inflammation associated bone resorbing factors.

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