Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: a two year follow up study

Maite Luengo, Francesca Pons, Marià J Martinez de Osaba, César Picado

Abstract

**Background** - Injectable calcitonin is effective in reducing spinal bone loss in steroid-dependent asthma but side effects are frequent. In contrast, a nasal spray presentation has been shown to be effective and well tolerated in involutional osteoporosis. To test the efficacy of nasal calcitonin a two year prospective trial was conducted in 44 steroid-dependent asthmatic patients.

**Methods** - All patients received a calcium supplement of 1000 mg and were allocated randomly into two groups treated with either salmon calcitonin nasal spray (200 IU every other day, n = 22) or calcium alone (n = 22) for two years. All patients completed the first year of the study. Five patients in each group dropped out during the second year. In the calcitonin group one patient developed generalised pruritus and four lost steroid dependence, and in the calcium alone group five were no longer dependent on steroids. The efficacy of treatment was evaluated as follows: bone turnover assessed by biochemical markers, bone loss assessed by serial measurement of lumbar spine density, and rates of bone fractures.

**Results** - The bone mass in the calcitonin group decreased by 7-8% in the first year while in the group receiving calcium alone it decreased by 2-8%; this difference was significant. Calcitonin prevented more bone loss during the second year while the calcium alone group continued losing bone mass (-7-8%). The difference between means was 0-1077 (95% CI 0-0381 to 0-1773). Three new fractures occurred in both groups. No changes in biochemical parameters were detected in either group.

**Conclusions** - Calcitonin given intranasally increased spinal bone mass during the first year of treatment and maintained bone mass in a steady state during the second year. These results suggest that calcitonin may be a useful agent to prevent steroid-induced osteoporosis. However, the lack of effect of calcitonin on the rate of vertebral fractures does not permit its recommendation for routine use in preventing steroid-induced osteoporosis.

Osteoporosis is the most disabling side effect of prolonged, oral glucocorticoid therapy. Corticosteroids increase bone resorption and also depress bone formation, perhaps through a decrease in osteoblast activity associated with a decrease of vitamin D receptors. Different strategies are currently being investigated to prevent the development of steroid-induced osteoporosis including inhibitors of bone resorption and stimulators of bone formation. Bone formation may be stimulated by anabolic steroids while resorption can be inhibited by bisphosphonates or calcitonin. In a previous study we have shown that injectable calcitonin can be effective in reducing spinal bone loss in chronic steroid-dependent asthma. With this formulation, however, side effects were frequent and represented a serious inconvenience for prolonged treatment. In contrast to the parenteral route, a nasal spray presentation has been shown to be well tolerated and effective in involutional osteoporosis. To test the efficacy and tolerability of nasal calcitonin in steroid-dependent asthma we conducted a 24-month prospective trial in a group of adult asthmatic patients receiving long term oral glucocorticoid treatment.

**Methods**

**Patients**

Forty four consecutive glucocorticoid-dependent asthmatic patients were recruited from outpatients. Those receiving drugs (hormones, diuretics, vitamin D, and anticonvulsants) or suffering from diseases known to affect bone metabolism were excluded. The patients had all received oral glucocorticoids for at least one year. All patients were non-smokers, led a sedentary life, and none drank more than 20 g ethanol/day. Patients eligible for the study who gave informed consent were grouped according to sex and age (a difference within two years was accepted) and randomly assigned to receive either salmon calcitonin nasal spray (200 IU every day) (Sandoz, Barcelona, Spain) and 1 g of elemental calcium daily (calcium lactate gluconate, Sandoz), or calcium alone.

Twenty two patients were allocated to each treatment group. The patients visited the outpatient clinic every four weeks. Periodically, if the patient was clinically stable according to clinical symptoms and spirometric results, the dose of prednisone was tapered down by 2.5 mg. When clinical deterioration occurred oral corticosteroid treatment was intensified.
Table 1  Mean (SD) patient data

<table>
<thead>
<tr>
<th></th>
<th>12 months follow up</th>
<th>24 months follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sCT-NS group (n = 22)</td>
<td>Calcium group (n = 22)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58:9 (7:6)</td>
<td>58:8 (6:3)</td>
</tr>
<tr>
<td>Average glucocorticoid dose (mg prednisone/day)</td>
<td>10 (4:2)</td>
<td>10:5 (4:5)</td>
</tr>
<tr>
<td>Duration of steroid treatment (years)</td>
<td>9:7 (6:7)</td>
<td>11:6 (8:4)</td>
</tr>
<tr>
<td>Aerosol steroid dose (µg/day)</td>
<td>1472 (596)</td>
<td>1193 (764)</td>
</tr>
</tbody>
</table>

sCT-NS = salmon calcitonin nasal spray.

(prednisone 30 mg/day tapered down by 5 mg/day every three days). Inhaled steroids (budesonide or beclomethasone) were given to all patients.

All patients gave informed consent to participate in the study which was approved by the hospital research committee.

BONE MINERAL MASS
The bone mineral density (BMD) was determined by means of dual photon absorption measurement on L2 to L4 at the beginning of the study and at one and two years (Lunar Radiation Corporation Scanner DP3, Madison, Wisconsin, USA) and expressed in terms of g/cm². The coefficient of variation in vitro, calculated with daily phantom studies (n = 300) collected over one year, was 0.51%. The coefficient of variation in vivo was 1.37% in healthy young subjects and 2.7% in patients with osteoporosis. These data were obtained from 10 normal volunteers and five osteoporotic patients measured weekly for five weeks. Predicted BMD values were obtained from 547 healthy women and 328 healthy men (unpublished data).

RADIOLOGICAL STUDY
Radiographs of the thoracic and lumbar spine in two projections were obtained before entry to the study and at the end of the follow up period. Deformities of vertebral bodies were divided into two groups: wedge and crush fractures. Wedge fractures were defined as a reduction of 25% or more in the anterior height of the vertebrae; a crush fracture was diagnosed when the posterior height of the vertebra was less than 25% of the posterior height of an adjacent vertebra. Radiological evaluation was performed by a blinded experienced observer. Symptomatic fractures from other bones (ribs, femurs) were also recorded.

LABORATORY STUDIES
Serum and urine biochemical measurements were performed at baseline, one year, and two years. Serum and urine levels of calcium, phosphate and creatinine levels were measured by routine methods using an autoanalyzer. Serum osteocalcin levels (bone Gla-protein) were measured by radioimmunoassay. Urine hydroxyproline levels were measured colorimetrically after fractioning by high pressure liquid chromatography.

DATA ANALYSIS
Changes in BMD and biochemical indices during the follow up period were analysed by one way analysis of variance (ANOVA) and Sheffe’s contrasts. Differences in these parameters between the calcitonin group and the control group were analysed by a non-parametric test (Mann-Whitney U test). A probability value of 0.05 was considered significant. Bonferroni’s adjustment (0.05/n tests) for multiple testing was used to prevent a type I error.

Results
The first year of follow up was completed by all participants. During the second year of the study there were five dropouts in the calcitonin group and five in the calcium alone group. One patient was withdrawn from the calcitonin group due to the development of a generalised pruritus. Four and five patients from the calcitonin and calcium alone groups respectively were withdrawn because, due to a progressive stabilisation of asthma, they could be removed from oral glucocorticoid treatment. Table 1 summarises the characteristics of the subjects and their glucocorticoid treatment upon entry into the study. Four patients in each group had suffered bone fractures before entering the clinical trial.

Tables 2 and 3 show the average changes in anti-asthmatic treatment (oral and inhaled steroids) in the patients who completed one and two years of treatment. There was a similar and significant decrease in oral steroid doses in both groups during the study. Before the study the calcium alone group was on significantly lower doses of inhaled steroids. However, inhaled steroid dosage rose during the study and both groups received similar doses of these drugs throughout the two years.

Table 4 gives the biochemical parameter values at one year of follow up. Similar results were seen at two years. No significant changes were detected in the biochemical parameters over the two year treatment period.

The mean (SD) baseline value of BMD expressed as percentage predicted was 87:8(12) for the calcitonin group and 91(11) for the calcium alone group; this difference was not statistically significant. The serial measurements of the bone mineral mass of the lumbar spine over the two years are shown in the figure. The bone mass in the calcitonin group increased by 2.7% during the first year while in the group receiving calcium alone it decreased by 2.8% (p<0.005) Calcitonin prevented more bone loss during the second
Table 2 Mean (SD) changes in steroid doses at entry to the study and at 12 months

<table>
<thead>
<tr>
<th></th>
<th>sCT-NS group</th>
<th>Calcium group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
</tr>
<tr>
<td>Average glucocorticoid</td>
<td>10 (4-3)*</td>
<td>7.9 (3-9)*</td>
</tr>
<tr>
<td>doses (mg prednisone/day)</td>
<td>9.9 (0-5)</td>
<td>9.5 (0-5)</td>
</tr>
<tr>
<td>Aerosol glucocorticoid</td>
<td>1472 (590)</td>
<td>1647 (586)</td>
</tr>
<tr>
<td>doses (μg/day)</td>
<td>24 months</td>
<td></td>
</tr>
<tr>
<td>Average glucocorticoid</td>
<td>10.6 (4-6)</td>
<td>7.7 (5-5)</td>
</tr>
<tr>
<td>doses (mg prednisone/day)</td>
<td>7.4 (0-5)</td>
<td>9.6 (3-5)</td>
</tr>
<tr>
<td>Aerosol glucocorticoid</td>
<td>1411 (597)</td>
<td>1729 (604)</td>
</tr>
<tr>
<td>doses (μg/day)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

sCT-NS = salmon calcitonin nasal spray. *p < 0.05; **p < 0.01.

Table 3 Mean (SD) changes in steroid doses at entry to the study and at 24 months

<table>
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<tr>
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<td>Baseline</td>
<td>24 months</td>
</tr>
<tr>
<td>Average glucocorticoid</td>
<td>10.6 (4-6)</td>
<td>7.7 (5-5)</td>
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<tr>
<td>doses (mg prednisone/day)</td>
<td>7.4 (0-5)</td>
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<tr>
<td>doses (μg/day)</td>
<td></td>
<td></td>
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sCT-NS = salmon calcitonin nasal spray. *p < 0.05.

Table 4 Mean (SD) biochemical parameters at entry to the study and at 12 months

<table>
<thead>
<tr>
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<th>Calcium group</th>
<th>sCT-NS group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.7 (0-4)</td>
<td>9.3 (0-5)</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>3.4 (0-5)</td>
<td>3.4 (0-4)</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>1.9 (0.2)</td>
<td>2.0 (0.1)</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>7.3 (2)</td>
<td>9.6 (3-5)</td>
</tr>
<tr>
<td>AP (IU/l)</td>
<td>151 (54)</td>
<td>174 (64)</td>
</tr>
<tr>
<td>Ca/Cr ratio</td>
<td>0.168 (0-11)</td>
<td>0.187 (0-11)</td>
</tr>
<tr>
<td>HA/HPr ratio</td>
<td>107 (35)</td>
<td>116 (52)</td>
</tr>
</tbody>
</table>

sCT-NS = salmon calcitonin nasal spray; AP = alkaline phosphatase; Ca/Cr = calcium creatinine ratio; HA/HPr = hydroxyproline creatinine ratio.

Evolution of lumbar bone mineral density (BMD) during a two year course of salmon calcitonin nasal spray (sCT-NS) 200 IU every other day + 1000 mg calcium versus calcium alone. BMD increased in the first year of treatment with calcitonin and remained almost stable during the second. The control group lost bone mass in the first year and this continued and became statistically significant at the end of the second year. The evolution of bone mass was statistically different between both groups at one and two years.

Table 5 New bone fractures

<table>
<thead>
<tr>
<th>Patient</th>
<th>Previous fractures</th>
<th>New fractures</th>
<th>Months of treatment</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>4</td>
<td>Yes</td>
<td>T5</td>
<td>18</td>
<td>sCT-NS + Ca</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>12</td>
<td>sCT-NS + Ca</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>No</td>
<td>12</td>
<td>sCT-NS + Ca</td>
</tr>
<tr>
<td>20</td>
<td>Yes</td>
<td>No</td>
<td>12</td>
<td>sCT-NS + Ca</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>Sternal</td>
<td>20</td>
<td>sCT-NS + Ca</td>
</tr>
<tr>
<td>19</td>
<td>No</td>
<td>T7, T10, L1</td>
<td>2</td>
<td>sCT-NS + Ca</td>
</tr>
<tr>
<td>15</td>
<td>Yes</td>
<td>L1, L2</td>
<td>8</td>
<td>Ca</td>
</tr>
<tr>
<td>26</td>
<td>Yes</td>
<td>T9, T10, T12</td>
<td>12</td>
<td>Ca</td>
</tr>
<tr>
<td>53</td>
<td>Yes</td>
<td>No</td>
<td>12</td>
<td>Ca</td>
</tr>
<tr>
<td>40</td>
<td>No</td>
<td>Femoral</td>
<td>13</td>
<td>Ca</td>
</tr>
</tbody>
</table>

sCT-NS + Ca = salmon calcitonin nasal spray plus calcium; Ca = calcium only.

Discussion

Nasal calcitonin treatment had beneficial effects on bone mineral density in glucocorticoid-dependent asthmatic patients. In the lumbar spine bone mineral density increased after one year of treatment and remained stable during the second year of treatment. These changes represent a reversal of the progressive decrease of bone mineral density in patients on placebo treatment. This result suggests that the gain in bone mass after administration of calcitonin is transient, prob-
ably because a new steady state is reached after
the initial period of treatment characterised by
a decrease in bone resorption coupled by a
decrease in bone formation.

Four patients from the calcitonin group and
five patients from the control group were with-
drawn during the second year of follow up
because they lost their dependence on steroid
treatment. This is not surprising since it has
been shown in many studies that steroid-de-
dpendent asthmatics who regularly attended
the outpatient clinic are able to be completely re-
moved from oral steroids. A better compliance
with the treatment, especially with inhaled
corticosteroids, probably accounts for this
finding.

The effects of prolonged treatment with cal-
citonin are not known. Since the slower turn-
over associated with antiresorptive treatment
may lengthen the time expended in replacing
bone tissue, the possibility that prolonged anti-
resorptive treatment can decrease the strength
of bones must not be overlooked.7

No serious side effects attributable to cal-
citonin treatment occurred during the trial and
only one patient dropped out of the study as a
consequence of a generalised pruritus. Since
this symptom did not completely disappear
after discontinuing the treatment it is not clear
whether the skin reaction was actually caused
by calcitonin.

The effects on bone mass obtained with the
nasal formulation at one year were less than
those observed with the injectable presentation
in our previous study (2.7% increase in the
BMD with the spray v 4% with the injection).5
Although it is considered that the dose of 200 IU
calcitonin administered by the nasal route is equivalent to 100 IU given by the parenteral
route, the bioavailability of the nasal for-
mulation is probably less than with the in-
jectable preparation. This might explain the
minor effect of the nasal spray on bone mineral
density. This lower dose might at least in part
also account for the better tolerability of the
nasal preparation. Since most of the asthmatic
patients suffered from rhinitis of variable se-
vverity, it is possible that the presence of a
chronic inflammatory process in the nose might
have interfered with calcitonin absorption
thereby affecting the biodegradability of the
drug.

Although calcitonin treatment prevents bone
mass loss, no differences in the incidence of
bone fractures could be detected. Most of the
asthmatic patients included in the study had
been on steroid treatment for several years.
Since corticosteroid-induced bone loss appears
to be most marked during the first 12 months
of treatment, it could be argued that preventive
treatment should start at the same time as the
steroid treatment. This approach has been used
by Sambrook et al8 in a recent study including
patients with different rheumatic and immu-
no logical diseases. In these patients pre-
ventive treatment was initiated at the same
time as steroids. This approach can hardly be applied
to bronchial asthma, however, because it is
almost impossible to predict which patient will
require prolonged oral treatment when initially
seen. Many asthmatic patients must be treated
with oral steroids for varying periods of time
before becoming clinically stabilised with the
use of other drugs such as inhaled steroids.

More than six months are usually needed to
decide that the patient is definitely dependent
on the oral steroid therapy, by which time the
period of rapid effect of steroids on bone mass
has already taken place. Moreover, for the prac-
tising physician the most common dilemma is
how to slow down the progression of bone loss
and prevent fractures in patients who have been
on steroid treatment for many years and suffer
a moderate or marked osteopenia, sometimes
accompanied by bone fractures. In a group of
such patients we have shown that intranasal
salmon calcitonin at a dose of 200 IU on alternate
days for two years is able to sig-
ificantly decrease the magnitude of bone loss
in the spine in glucocorticoid-dependent
asthma. The lack of side effects of the nasal
spray of calcitonin should permit the use of the
hormone in prolonged treatment. However, the
lack of effect on the rate of fractures precludes
considering nasal calcitonin as a routine treat-
ment to prevent steroid-induced osteoporosis.
More patients followed for a longer period of
time would be needed to determine whether
calcitonin decreases the rate of bone fractures
in addition to increasing BMD.

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