Effect of Different Doses of Nasal Salmon Calcitonin on Bone Mass

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Summary. Forty postmenopausal women with a former Colles' fracture were enrolled in a 1-year study to determine the dose-effect relationship of nasal salmon calcitonin (SCT) on bone mass. They were randomized to receive either placebo, 50, 100, or 200 IU per day of SCT given as a nasal spray. The rate of change in the bone mineral content of the lumbar spine was 0.7, 0.2, 1.1, and 2.0 g HA per year, respectively, and the rate of change in the bone mineral content in the forearm was −0.4, −0.1, 0.0, and −0.1 AU per year, respectively. The rate of change in the bone mineral content of the lumbar spine in patients receiving 200 IU of SCT per day differed significantly from zero (P < 0.01). Except for one patient, who experienced intolerable nausea, no systemic side effects were observed. Seven patients withdrew, two patients from nasal intolerance to the spray. These preliminary data suggest that SCT given by the nasal route has a positive and dose-dependent effect on spinal bone mass, but affects forearm bone mass only minimally.

Key words: Postmenopausal women — Nasal salmon calcitonin — Dose-finding — Bone mass — Tolerance.

Calcitonin (CT) has been evaluated in therapeutic trials of osteoporosis for more than a decade. Although the results have not been uniform, recent studies suggest that CT is able to reduce subsequent bone loss in patients with established osteoporosis [1–3]. As treatment with CT is bereft of serious complications, it may also be considered an attractive candidate in the primary prevention of osteoporosis. However, the necessity of parenteral administration and a high incidence of side effects are major obstacles to a more widespread use of CT.

Recently, the feasibility of administration of CT through the nasal route has been documented. Human CT given as nasal drops produced a significant hypocalcemic response in normal subjects [4], and in Pagetic patients salmon calcitonin (SCT) administered as a nasal spray was able to improve both clinical and biochemical parameters [5]. In the latter study, except for minor facial flushing in one patient, no side effects were observed.

These encouraging results have led us to investigate the effect of SCT given as a nasal spray on skeletal bone mass in postmenopausal women. The trial was designed as a dose-finding study.

Experimental Subjects

For over half a year 40 postmenopausal women aged 51 to 75 (mean 66.5 years) were enrolled in the study. All had had a Colles’ fracture 1 to 5 years prior to inclusion. Presence of malignant disease, liver disease, and generalized bone diseases other than osteoporosis, and treatment with glucocorticoids, estrogens, vitamin D metabolites, bisphosphonates, or fluoride within the previous 6 months resulted in exclusion. Informed consent was obtained from each individual according to the Helsinki Declaration II, and the protocol was approved by the local Ethics Committee.

The participants were randomized to four groups and treated in a double-blind and parallel design for 1 year. All took two squirts—one in each nostril—every morning of a nasal spray corresponding to a total daily dose of either placebo, 50, 100, or 200 IU of SCT (Miacalcic®, nasal spray, Sandoz). A daily supplement of 0.5 g elemental calcium (Calcium Sandoz®) to be taken in the evening was given to all subjects in a 4-week run-in period and subsequently throughout the entire study period.
Table 1. Number of side effects and dropouts among 40 postmenopausal women with a former Colles’ fracture randomized to 1 year of treatment with either placebo, 50, 100, or 200 IU of salmon calcitonin per day as a nasal spray

<table>
<thead>
<tr>
<th>Group</th>
<th>Included</th>
<th>Side effects</th>
<th>Dropouts from personal reasons</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>1, rhinitis(^b)</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>50 IU</td>
<td>10</td>
<td>1, nausea(^b), 1, epistaxis</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>100 IU</td>
<td>10</td>
<td>1, rhinitis(^b), 1, nasal dryness</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>200 IU</td>
<td>10</td>
<td>1, rhinitis, 1, epistaxis</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) No. of patients with this feature, description of side effect
\(^b\) Dropout due to side effect

Methods and Materials

Bone Mineral Content Measurements

Bone mineral content (BMC) measurements were done every 3rd month. The BMC of the lumbar spine was measured with dual photon absorptiometry using a \(^{153}\)gadolinium source (BMC-LAB 22\(^a\)TM, Novo Diagnostic Systems, Denmark). The result is expressed as the sum of the BMC readings for the 1nd, 3rd, and 4th lumbar vertebrae (L-BMC \(^g\) hydroxyapatite, gHA). The coefficient of variation of this technique is 4.5% (serial measurements in osteoporotic patient within 2 weeks, \(n = 10\), mean = 26.3 gHA). Long-term precision and accuracy were ensured by calibrating with five standards (0, 15, 30, 45, and 60 gHA) on a regular basis. The BMC in the distal forearms was measured with single photon absorptiometry using a \(^{125}\)iodine source (Novo GT 35\(^a\), Novo Diagnostic Systems, Denmark) and expressed as the sum of the BMC readings from the 8 mm separation point of radius and ulna and further 24 mm proximally. The coefficient of variation with this technique is 2.2% (serial measurements in osteoporotic patient within 2 weeks, \(n = 10\), mean = 31.5 arbitrary units (AU)). Long-term precision and accuracy were ensured by calibrating with three standards (20, 40, and 80 AU) on a regular basis. The results are from the nondominant distal forearm (A-BMC AU). The same pattern of changes in the BMC of the distal forearms was found whether estimated from the nonfractured, the fractured, or the dominant distal forearm. For each subject, the change in L-BMC and A-BMC is presented in two ways. First, as the actual change from baseline and, second as the rate of change with time. For each subject, the rate of change with time in L-BMC and A-BMC was calculated as the slope estimate from simple linear regression between L-BMC or A-BMC and the actual times between measurements.

Serum and Urine Chemistries

Blood and urine was collected the morning after an overnight fast every 3rd month. Serum ionized calcium was determined with an ion-selective electrode (ICA 1\(^a\)TM, Radiometer, Denmark). Serum phosphate and alkaline phosphatase were determined by spectrophotometry (Cobas-Mira\(^a\)TM, Roche, Switzerland). Urine creatinine was analyzed using Jaffes chromogen reaction (Astra\(^a\), Beckmann, USA). Urine hydroxyproline was analyzed as described by Prockop and Kivirikko [6] employing spectrophotometry (Pye Unicam 8600\(^a\), Philips, The Netherlands). Serum osteocalcin (bone-gla protein) was measured by a radioimmunoassay [7].

Statistics

Parametric tests were used, one-factor ANOVA for comparisons between groups, and two-factor ANOVA with repeated measures for time-group interactions. Significant findings from ANOVA were analyzed with paired and unpaired Student’s \(t\) tests. A two-sided \(P\)-level \(<0.05\) was considered significant. Percent changes are mean percent changes from baseline.

Results

Seven patients left the study before completion leaving a total of 33 patients for evaluation (Table 1). The demographics and baseline clinical features of the completed patients are presented in Table 2. There were no statistically significant differences between the groups, but L-BMC and weight differed slightly. The mean L-BMC and mean A-BMC for all patients in the study were lower than in age-matched normal controls (14% and 11%, respectively).

Bone Mass

The time course of the changes in L-BMC from baseline is shown in Fig. 1. L-BMC rose by 1.0 gHA (\(P = 0.21\); 2.4%) in the placebo group in the first 9 months, but fell subsequently to 0.6 gHA above baseline (\(P = 0.16\); 1.9%). L-BMC was largely unchanged in the 50 IU group. There was a marked increase in L-BMC of 2.2 gHA (\(P < 0.01\); 8.6%) in the 200 IU group in the first 9 months followed by a minor decrease during the last 3 months of treatment to 1.8 gHA (\(P < 0.01\); 7.6%). The change in