Effects of Calcitonin in Metastatic Bone Carcinoma, Osteoporosis, Polyostotic Fibrous Dysplasia and Hypercalcemia

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Synopsis

Porcine calcitonin was administered intramuscularly at doses of 4.5–10 MRC u. per day to patients with metastatic bone carcinoma, osteoporosis and polyostotic fibrous dysplasia during 22–50 days period. Transient effects of calcitonin were also investigated in hypercalcemia of primary hyperparathyroidism, multiple myeloma and vitamin D intoxication.

Serum calcium and/or magnesium showed gradual decrease during the period of administration in metastatic bone carcinoma, senile osteoporosis and polyostotic fibrous dysplasia. Urinary calcium and/or magnesium also decreased in metastatic bone carcinoma and osteoporosis. Alkaline phosphatase did not change during the period of calcitonin treatment but was lowered in the posttreatment period in polyostotic fibrous dysplasia. Serum hydroxyproline showed a transient decrease in metastatic bone carcinoma.

Hypercalcemia of multiple myeloma and vitamin D intoxication was improved temporarily by calcitonin. These results suggest a beneficial effect of calcitonin in the treatment of some of the bone diseases and hypercalcemia.

Effects of calcitonin have been described in patients with hypercalcemia and bone diseases (Bell et al., 1970; Bijvoet et al., 1968; Haas and Dambacher, 1968; Kammerman and Canfield, 1970; Pak et al., 1968). It was shown that calcitonin is effective in lowering serum calcium in primary hyperthyroidism, metastatic cancer and idiopathic hypercalciuria (Haas and Dambacher, 1968). In addition the prolonged effect was also observed in Paget's disease (Bell et al., 1970), and primary hyperparathyroidism (Pak et al., 1968).

Dose of calcitonin administered usually varied from 4 to 8 MRC u./kg/day. However, the smaller dose was also effective in lowering serum calcium level (Foster et al., 1966; Haas et al., 1968). In this report the transient and prolonged effects of small dose of porcine calcitonin were investigated in metastatic bone carcinoma, osteoporosis, fibrous dysplasia and hypercalcemia.

Materials and Methods

Nine patients were studied either at the Third Department of Internal Medicine, University of Tokyo Hospital, Yokufuen Hospital, Suginami, Tokyo or National Children's Hospital in Tokyo. Three of them were women and 6 were men. Age ranged from 5 to 73 years. One of them had metastatic bone tumors of hypernephroma, 3 had senile osteoporosis, one had steroid induced osteoporosis and one had polyostotic fibrous dysplasia. Other 3 had hypercalcemia causes of which were primary hyperparathyroidism, multiple myeloma and vitamin D intoxication.

Fasting serum and 24 hr urinary calcium was analyzed by atomic absorption spectrophotometry or Webster's method (1962). Serum and urinary magnesium was also determined by atomic absorption spectrophotometry. Serum alkaline phosphatase was determined by the method of King-Armstrong (normal
adult range: 3–10 u./100 ml. Serum and urinary hydroxyproline was analyzed by the method of Kivirikko et al. (1967) in a patient.

Since patients were usually given normal diet and water, daily intakes of calcium ranged from 240 to 660 mg.

Porcine calcitonin (Teikoku Hormone Manufacturing Company, Tokyo, Lot No. ZJ-15 and AB-22) was administered intramuscularly daily at a dose of 4.5–10 MRC u. in 5 ml volume of saline.

**Case Abstract**

1. S. F., a 73 year-old man, was admitted with the chief complaints of tumors and pains on the left shoulder and the right iliac bone. Angiography of the renal artery showed a tumor shadow at the hilar part of the right kidney. Roentgenological examination of bones revealed destruction of bony structures on the left scapula, the right iliac bone and the 7th chest vertebra. Cobalt irradiation at a dose of 3000 r to the 7th chest vertebra resulted in an ameriolation of the back pain. However, pains on the left shoulder and the right iliac bone still persisted. The serum calcium was 8.2–8.3 mg/100ml, the phosphorus was 3.1–3.5 mg/100ml. Serum alkaline phosphatase activity was normal. Diagnosis was hypernephroma with bone metastasis. Calcitonin was administered intramuscularly at a dose of 4.5 MRC u. once daily for 24 days.

2. Y. K., a 68-year-old woman, with senile osteoporosis and spondylosis deformans complained of a back pain. The serum calcium was 8.4 mg/100ml and the serum magnesium was 2.2 mg/100ml. Calcitonin was administered intramuscularly at a dose of 4.5 MRC u. once daily for 24 days.

3. E. T., a 64-year-old man, with senile osteoporosis complained of the gait disturbance due to pains on the back and lower extremities. Serum calcium was 8.2 mg/100ml and serum magnesium was 2.4 mg/100ml. Calcitonin was administered intramuscularly at a dose of 1.5 MRC u. once and 4.5 MRC u. once daily for 22 days.

4. S. O., a 60-year-old woman with senile osteoporosis complained of kyphosis and lumbago. Calcitonin was administered at a dose of 10 MRC u. once a week for 100 weeks.

5. T. A., a 36-year-old man, with osteoporosis after steroid treatment to hyper gammaglobulinemia complained of pathological fractures of vertebrae and ribs. He had been orally administered methyl prednisolone daily at doses of 10–20 mg for 8 months before initiation of dehydroepiandrosterone sulfate (DHEA-S) and calcitonin administration. DHEA-S was orally administered daily at a dose of 20 mg with or without calcitonin which was injected intramuscularly twice a week at a dose of 10 MRC u. for a period of 50 days. Total dose of calcitonin was 150 MRC u.

6. I. M., a 35-year-old man, was diagnosed to have polyostotic fibrous dysplasia. Abnormal skin pigmentation were noted at the age of 11 years. He had experienced abnormal bone fractures, deformities and pains since the age of 13 years. Hyperthyroidism was also found at the age of 27 years. Since then he had been treated with 6-methyl-2-thiouracil and methimazole. Serum calcium was low normal and serum alkaline phosphatase was 22.0–34.0 u. Analysis of isoenzymes for alkaline phosphatase revealed that the large part was originated from bone. Calcitonin was administered intramuscularly daily at a dose of 4.5 MRC u. for 27 days.

7. M. K., a 55-year-old woman with multiple myeloma showed hypercalcemia as high as 14.0 mg/100ml. Punched out lesions were observed on the roentgenological study of the skull. Calcitonin was administered intramuscularly once at a dose of 10 MRC u.

8. K. K. H., a 5-year and 10-month-old boy with vitamin D resistant rickets had been treated with massive doses of vitamin D3. He developed hypercalcemia 2 months after
initiation of vitamin D$_2$ treatment. Serum calcium was 13.3 mg/100ml and serum phosphate was 1.9 mg/100ml before administration of calcitonin. Calcitonin was administered intramuscularly at a dose of 1.7 MRC u.

9. K. I., a 24-year-old man with primary hyperparathyroidism complained of pathologic bone fractures and kidney stones. Serum calcium was 10.9 mg/100ml before administration of calcitonin. Serum calcium was 10.9 mg/100ml before administration of calcitonin. Calcitonin was administered intramuscularly at a dose of 10 MRC u.

### Table 1. Transient effects of calcitonin

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Dose of calcitonin (MRC u.)</th>
<th>before injection</th>
<th>hr after intramuscular injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. F.</td>
<td>73</td>
<td>M</td>
<td>Hypernephroma with bone metastasis</td>
<td>4.5</td>
<td>8.25</td>
<td>7.78 7.94 7.78</td>
</tr>
<tr>
<td>S. O.</td>
<td>60</td>
<td>F</td>
<td>Senile osteoporosis</td>
<td>10</td>
<td>9.3</td>
<td>9.1 9.2 —</td>
</tr>
<tr>
<td>T. A.</td>
<td>36</td>
<td>M</td>
<td>Steroid osteoporosis</td>
<td>10</td>
<td>9.5</td>
<td>9.2 9.3 —</td>
</tr>
<tr>
<td>K. M.</td>
<td>35</td>
<td>M</td>
<td>Fibrous dysplasia</td>
<td>4.5</td>
<td>9.1</td>
<td>8.7 8.7 8.4</td>
</tr>
<tr>
<td>K. I.</td>
<td>24</td>
<td>M</td>
<td>Primary hyperparathyroidism</td>
<td>10</td>
<td>10.9</td>
<td>10.8 10.7 10.6</td>
</tr>
<tr>
<td>M. K.</td>
<td>55</td>
<td>M</td>
<td>Multiple myeloma</td>
<td>4.5</td>
<td>14.0</td>
<td>12.8 12.0 13.0</td>
</tr>
<tr>
<td>K. K. H.</td>
<td>5</td>
<td>M</td>
<td>Vitamin D intoxication</td>
<td>1.5</td>
<td>13.3</td>
<td>12.3 12.8 13.3</td>
</tr>
</tbody>
</table>

### Table 2. Acute effect of calcitonin on serum magnesium and hydroxyproline

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Dose of calcitonin (MRC u.)</th>
<th>before injection</th>
<th>hr after injection of calcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. F.</td>
<td>73</td>
<td>M</td>
<td></td>
<td></td>
<td>2.45</td>
<td>2.42 2.43 2.43</td>
</tr>
<tr>
<td>S. O.</td>
<td>60</td>
<td>F</td>
<td></td>
<td></td>
<td>13.1</td>
<td>13.4 12.8 11.1</td>
</tr>
</tbody>
</table>

Calcitonin was administered intramuscularly at a dose of 4.5 MRC u.

mg/100ml at 1 hr and this lowered level persisted at least until 5 hr after administration of calcitonin (Table 1). Serum magnesium did not show significant changes until 5 hr after administration of calcitonin. Serum hydroxyproline was reduced 0.3 µg/ml at 3 hr and 2.0 µg/ml at 5 hr after administration of calcitonin (Table 2).

When calcitonin was administered daily, serum calcium showed a progressive decrease until the 16th day of calcitonin administration (Fig. 1 & Table 3). Urinary calcium did not show significant changes during the period of administration of calcitonin. Serum magnesium showed a gradual and steady decrease even after cessation of calcitonin administration (Fig. 1). Urinary magnesium began to decrease from the 4th day of administration of calcitonin and this lowered level persisted for
Fig. 1. Effect of calcitonin on serum and urinary Ca, Mg and hydroxyproline in metastatic bone carcinoma. Calcitonin was administered intramuscularly at a dose of 4.5 MRC u. daily for 24 days. Difference between the mean value of urinary magnesium before treatment, $118 \pm 23$ mg, and that during the period from the 4th to 12th day of treatment, $82 \pm 4$ mg, was significant ($p<0.025$).
Table 3. Maximum decrease in serum calcium after initiation of calcitonin administration

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Daily dose (MRC u.)</th>
<th>Period (days)</th>
<th>Serum Ca (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before (B)</td>
</tr>
<tr>
<td>S. F.</td>
<td>73</td>
<td>M</td>
<td>Metastatic bone carcinoma</td>
<td>4.5</td>
<td>16</td>
<td>8.3</td>
</tr>
<tr>
<td>K. M.</td>
<td>35</td>
<td>M</td>
<td>Fibrous dysplasia</td>
<td>4.5</td>
<td>22</td>
<td>9.1</td>
</tr>
<tr>
<td>Y. K.</td>
<td>68</td>
<td>F</td>
<td>Senile osteoporosis</td>
<td>4.5</td>
<td>8</td>
<td>8.4</td>
</tr>
<tr>
<td>E. T.</td>
<td>64</td>
<td>M</td>
<td>Senile osteoporosis</td>
<td>4.5</td>
<td>8</td>
<td>8.7</td>
</tr>
</tbody>
</table>

9 days (Fig. 1).

Although serum hydroxyproline was lowest on the 3rd day of administration of calcitonin, it returned to the preinjection level on the 5th day and never changed thereafter (Fig. 1). Urinary hydroxyproline did not show significant changes throughout the period of investigation (Fig. 1).

2. Effect of calcitonin in osteoporosis

Serum calcium decreased slightly at 1 and 3 hr after administration of 10 MRC u. of calcitonin in a 60-year-old woman, S. O., with senile osteoporosis and a 36-year-old man, T.A., with steroid-induced osteoporosis (Table 1). After prolonged administration of 4.5 MRC u. of calcitonin to 2 patients (Y. K. and E. T.) with senile osteoporosis, serum calcium and serum magnesium decreased slightly (Fig. 2, 3 and Table 3).

While 24 hr urinary calcium showed significant decrease during the period from the first to 7th day of administration of calcitonin compared to the pretreatment period in patient Y. K., 24 hr urinary magnesium also decreased significantly during the same period as above (Fig. 2). However, both urinary calcium and magnesium showed an even slight but non-significant increase from the period beginning on the 8th day of administration of calcitonin (Fig. 2).

Similar results were obtained in the patient E.T. with senile osteoporosis. In this patient even dose of 1.5 MRC u. of calcitonin had a prolonged effect on serum and urinary calcium and magnesium (Fig. 3). Bone pains seemed to be improved in both patients of senile osteoporosis.

In the patient T. A. pathologic fractures had began to appear repeatedly after daily administration of 20 mg of methyl prednisolone for 6 months for the treatment of interstitial plasma cell pneumonitis and hypergammaglobulinemia. After oral administration of 20 mg of DHEA-S hypercalcemia was improved and 24 hr urinary calcium decreased significantly during the period of administration (Table 4). After addition of calcitonin treatment a gradual and steady decrease in 24 hr urinary excretion of calcium was observed and the bone pain was markedly improved (Table 4).

3. Effect of calcitonin in polyostotic fibrous dysplasia

Calcitonin was administered intramuscularly at a dose of 4.5 MRC u. for 27 days. Serum calcium decreased 0.7 mg/100ml at 5 hr after administration of calcitonin. The maximum response in serum calcium to prolonged administration of calcitonin was observed on the 22nd day after initiation of calcitonin treatment (Table 3). Tetany was provoked easily during the period of administration. Although the elevated level of serum alkaline phosphatase persisted during the period of calcitonin administration, it decreased after cessation of calcitonin administration temporarily. The lowered level of serum alkaline phoshatase persisted at least 10 days, but it was again raised to the pretreatment level 53 days after cessation of calcitonin.
4.5 MRC u. Calcitonin

Fig. 2. Effect of calcitonin on serum and urinary Ca and Mg in senile osteoporosis. Calcitonin was administered intramuscularly at a dose of 4.5 MRC u. daily for 24 days. Difference between the mean value of 24 hr urinary calcium, 117 ± 5 mg, during the 7 day period before treatment and that, 82 ± 2 mg, during the 7 day period immediately after initiation of treatment was highly significant (p<0.001).

Comparison of 24 hr urinary magnesium between the same periods as above (91 ± 6 mg for the pretreatment period and 57 ± 3 mg for the period after initiation of treatment showed significant difference also (p<0.001).

administration (Fig. 4). Cranial bone pain seemed to be improved by calcitonin treatment.

4. Effect of calcitonin on hypercalcemia
A slight decrease in serum calcium level was observed in primary hyperparathyroidism after calcitonin was administered at a dose of 10 MRC u. Calcitonin was also effective in lowering the elevated level of serum calcium in multiple myeloma and vitamin D intoxication (Table 1).
Fig. 3. Effect of calcitonin on serum and urinary Ca and Mg in senile osteoporosis. Calcitonin was administered intramuscularly at a dose of 1.5 MRC u. one day and with a 3-day interval 4.5 MRC u. daily for 22 days. Difference between the mean value of urinary calcium before treatment, 27 ± 7.0 mg, and that during the initial 7 days of treatment, 9 ± 1.5 mg, was significant (p<0.01). Comparison of mean value of urinary magnesium before treatment, 186 ± 29 mg and that during the initial 7 days of treatment, 84 ± 14 mg, showed a statistically significant difference also (p<0.01).

Discussion

The present investigations showed that prolonged administration of calcitonin to metastatic bone carcinoma or senile osteoporosis induced gradual lowering in serum calcium in both of the diseases and a transient decrease in urinary calcium in the latter. Long term effects of calcitonin on serum and urinary calcium have been proved in primary hyperparathyroidism (Pak et al., 1968), Paget's
Table 4. Synergistic effect of calcitonin and dehydroepiandrosterone sulfate in lowering urinary excretion of calcium in steroid induced osteoporosis

<table>
<thead>
<tr>
<th>Period</th>
<th>Days</th>
<th>DHEA-S mg/day</th>
<th>Calcitonin MRC u./week</th>
<th>Methyl prednisolone mg/day</th>
<th>Serum Ca mg/100 ml</th>
<th>mean ± SE of urinary calcium in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>16</td>
<td>11.0—11.6</td>
<td>135±22</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>20</td>
<td>—</td>
<td>16</td>
<td>9.8—9.9</td>
<td>118±14</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>20</td>
<td>—</td>
<td>16</td>
<td>8.8</td>
<td>75±6</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>20</td>
<td>—</td>
<td>16</td>
<td>9.5</td>
<td>76±5</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>20</td>
<td>—</td>
<td>16</td>
<td>91±5</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>5</td>
<td>9</td>
<td>20</td>
<td>16</td>
<td>9.7</td>
<td>112±6</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>16</td>
<td>9.5—9.7</td>
<td>79±5</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>12—16</td>
<td>9.3</td>
<td>75±4</td>
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<tr>
<td>8</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>12</td>
<td>66±7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>12</td>
<td>69±5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>12</td>
<td>9.0—9.8</td>
<td>50±6</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>I</td>
<td>10</td>
<td>—</td>
<td>8—10</td>
<td>9.1—9.5</td>
<td>43±6</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>10</td>
<td>—</td>
<td>6—8</td>
<td>15±1</td>
<td></td>
</tr>
</tbody>
</table>

Significance of difference
p<0.025 between the period 1 and 2 and between the period 1 and 3.
p<0.001 between the intermediate period and the period 5.
p<0.01 between the period 6 and 9.

Fig. 4. Effect of calcitonin on serum Ca and alkaline phosphatase in polyostotic fibrous dysplasia.
disease (Kammerman and Canfield, 1970) and senile osteoporosis (Caniggia, 1969). Retention of calcium occurred in these patients as a result of calcitonin administration. The maximum decrease in serum calcium is usually obtained at 60 min after calcitonin administration in rats and serum calcium level returns to preinjection level in 240 min (Morii and DeLuca 1967) and it takes 6 to 18 hr in humans that serum calcium returns to preinjection levels (Foster et al., 1968). Therefore, it is difficult to explain the reason for the prolonged effect of calcitonin on serum calcium level in some patients with bone diseases, in which the maximum response in serum calcium was observed on the 8th-22nd day after initiation of calcitonin treatment (Table 3), although no consistent effect of calcitonin on serum calcium was observed in adrenocorticosteroids induced osteoporosis. Functional states of parathyroids would be a factor which influences the response of serum calcium to calcitonin. Bordier et al. (1970) suggested that both serum calcium and urinary hydroxyproline are decreased by calcitonin in patients with bone diseases associated with increased numbers of osteoclasts.

An additional effect of DHEA-S to calcitonin in decreasing urinary excretion of calcium was observed in our patient with adrenocorticosteroids induced osteoporosis (Table 4). Ogata et al. (1970) reported that androgens enhanced the hypocalcemic effect of calcitonin in rats. An anabolic or androgenic effect of steroids may play a role in enhancing the effect of calcitonin.

In acute experiments and in some of prolonged observations calcitonin causes increased excretion of calcium, probably by decreasing the reabsorption of calcium (Bijvoet et al., 1970). However, Bijvoet et al., (1970) also suggested that a positive calcium balance with decreased excretion of calcium may be produced by calcitonin in patients with increased bone turnover.

Calcitonin also lowered serum hydroxyproline in Paget’s disease (MacIntyre et al., 1963). The maximum response was observed at 60-120 min after intravenous administration of calcitonin. The lowest level of serum hydroxyproline was obtained at 5 hr after intramuscular administration of calcitonin in metastatic bone carcinoma (Table 2). Urinary excretion of hydroxyproline was also lowered in senile osteoporosis (Caniggia, 1969) and Paget’s disease (Bell et al., 1970). While it was difficult to restrict proline content of the diet in our patient with metastatic bone carcinoma, we could not observe such an effect in urinary excretion of hydroxyproline. Bell (1970) showed that calcitonin did not change serum alkaline phosphatase level in Paget’s disease, but it was reduced in post-treatment period in polyostotic fibrous dysplasia. Our results in polyostotic fibrous dysplasia similarly indicated that serum alkaline phosphatase was decreased during 10 days period after cessation of calcitonin administration (Fig. 5).

The fall of serum magnesium after calcitonin administration was reported smaller than that of serum calcium (Foster et al., 1966). Our investigation also demonstrated that serum magnesium level did not change at least 5 hr after intramuscular administration of calcitonin in metastatic bone carcinoma (Table 2). However, the prolonged observation showed gradual lowering in serum magnesium and also a transient decrease in urinary magnesium in metastatic bone carcinoma and senile osteoporosis (Fig. 1–3). Since the turnover of magnesium in the body is slow in tissues other than plasma, liver, kidney and heart muscle in which exchange occurs in 3 hours or less (Rogers and Mahn, 1959), time lag may be needed before magnesium metabolism in bone is affected by calcitonin. While the negative feed back mechanism was suggested in the relationship between serum magnesium level and parathyroid function (MacIntyre et al., 1963), it is a problem of interest to investigate the magnesium metabolism in relation to calcitonin in view of the fact that calcitonin secretion is accelerated by magnesium loading.
Dosage of calcitonin has not been established in various diseases. Although the dose of 4–8 MRC u./kg/day was proposed for Paget’s disease (Bell et al., 1970), smaller dose was also effective in hypercalcemia (Foster et al., 1966; Haas and Dambacher, 1968). Haas (1968) demonstrated that generally speaking the smaller was the dose of calcitonin, the smaller the fall of serum calcium level, although the dose of 2–10 MRC u. showed the similar response as 50–100 MRC u. in some of the patients. While our patients was administered 4.5–10 MRC u. of calcitonin daily, other schedules of administration should be investigated.

It was reported that bone pain was ameliorated in Paget’s disease by calcitonin (Bijvoet and Jansen, 1967). In the present study bone pain seemed to be improved in some of the patients.

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References