Effect of Calcitonin and Hexestrol on Urinary Excretion of Hydroxyproline in a Patient with Prostatic Cancer and Bone Metastases

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Synopsis

Salmon calcitonin was administered intravenously at a dose of 5 MRC units per day to a patient with prostatic cancer and bone metastases during 20 days period. Serum calcium maintained pretreatment level during the period of administration with a slight decrease after cessation of the treatment. Urinary total hydroxyproline showed a gradual decrease during the treatment. Serum alkaline phosphatase increased gradually, and the elevated level continued even after cessation of the administration. Urinary phosphorus increased transiently after the initiation of the administration.

When hexestrol was administered intramuscularly at a total dose of 765 mg, enlarged cervical lymph nodes and metastatic lung infiltration disappeared completely at the end of the treatment. Urinary hydroxyproline began to increase at the initiation of administration, and the high value was maintained during and after the hexestrol therapy.

It is generally accepted that calcitonin inhibits bone resorption, decreases serum calcium and antagonizes the action of parathyroid hormone on bone (Raisz et al., 1967; O'Riordan and Aurbach, 1968). Calcitonin may, therefore, be useful in the management of patients with hypercalcemia or an enhanced resorption of bone. Effects of calcitonin have been described in hypercalcemia of various etiologies including metastatic bone disease (Bell et al., 1970; Bijvoet et al., 1968), Paget's disease (Bell et al., 1970), and senile osteoporosis (Cohn et al., 1971).

Huggins (1941) had proved that estrogens were effective in preventing the progression of prostatic cancer and metastatic bone disease.

In this report the effects of salmon calcitonin (SCT) and of large dose of hexestrol were investigated in a patient with prostatic cancer and bone metastases.

Method and Patient

a) Method

Serum and urinary calcium was determined by the method of atomic absorption spectrophotometry, serum and urinary phosphorus by the method of Fiske-SubbaRow (1925), and urinary hydroxyproline by the method of Prockop and Udenfriend (1960). Control value of urinary hydroxyproline in 5 subjects with ages 49-67 was 10.0±1.9 mg/24 hr (mean±S.E.). Serum alkaline phosphatase and acid phosphatase were determined by the method of Kind and King (1954).

b) Case report

A 61-year-old male was referred to the Shirokita Municipal Hospital, Osaka, with chief complaints of general lymphadenopathies, lumbago and gait disturbance. He also complained of moderate neuralgic pain on the left upper arm. In April, 1972, he noticed many enlarged lymph nodes on both sides of cervical
region. In September, 1972, he was admitted to another hospital because of gait disturbance due to severe lumbago and cervical lymphadenopathies. Because biopsy of a lymph node disclosed metastatic adenocarcinoma, he was admitted to our hospital. He had lost 10 kg of body weight during 10 months before admission. During a week before admission he also noticed moderate peripheral edema. There was no history of hemosputum, chest pain, cough or sputum, dysuria, macroscopic hematuria or exposure to tuberculosis.

The temperature was 36.0°C, pulse rate 80 per min and regular, respiration normal, and blood pressure 116/60 mmHg. On physical examination the patient appeared moderately well nourished but chronically ill. Generalized lymphadenopathies were found; the cervical lymph nodes were 1.5 to 2 cm in diameter and showed hard smooth surface. Thyroid gland was not palpable. Coarse rales were heard over the both lung fields, more prominently on the lower lobe. The heart was not enlarged; there was no murmur. The edge of the liver was felt 3 cm below the right costal margin, and no splenomegaly was found. There was one plus edema on the pretibial region. Neurologic examination was negative. There was a knock pain and a pain by pressure on the left upper arm and the lower lumbar region. Digital examination of the prostate revealed moderately enlarged hard prostate with irregular surface.

The laboratory data showed that the urine was normal, red blood cell count 391 x 10⁴, hematocrit 37.7%, white blood cell count 6700, with 55% neutrophils, 35% lymphocytes, 5% monocytes, 5% eosinocytes. A stool specimen gave a negative test for occult blood. Serum chemistry; uric acid 3.95 mg/dl, calcium 8.0 mg/dl, phosphorus 4.15 mg/dl, and the protein 5.4 g/dl (albumin 2.9 g/dl, and globulin 2.5 g/dl). Sodium was 138 mEq/L, potassium 4.4 mEq/L, and chloride 109 mEq/L. Glutamic oxalacetic transaminase was 21 u, lactic dehydrogenase 160 u, leucine aminopeptidase 280 u, alkaline phosphatase 42.5 K.A.u. and total acid phosphatase 25.8 K.A.u. with prostatic acid phosphatase 13.4 K.A.u. Serum electrophoresis showed albumin 55.6%, alpha1 globulin 3.7%, alpha2 globulin 14.1%, beta globulin 8.4%, and gamma globulin 18.2%. Electrocardiogram showed low voltage in the extremity leads.

X-ray films of the chest revealed diffuse reticulo-nodular metastatic infiltrates that involved the entire field of both lungs; the contours of the heart and mediastinum were normal, but atherosclerosis of aorta was noted. Roentgen films of bones showed extensive sclerosing metastases in the spine and pelvis and osteolytic metastases in both humerus. No tumor cells were found in smear specimens of sputum.

![SCT 5 MRC units](image)

**Fig. 1** Effect of salmon calcitonin on serum alkaline phosphatase, urinary excretion of hydroxyproline, serum and urinary calcium, and serum and urinary phosphorus.
Result

1) Effect of calcitonin

SCT (supplied by Teikoku Pharmaceutical Company) was administered intravenously daily at a dose of 5 MRC u. for 20 days. At the end of the period of calcitonin treatment, he felt much less pain over the regions of left arm and the lumbar region. Urinary total hydroxyproline gradually decreased after initiation of administration of calcitonin with a gradual return toward initial levels thereafter (Fig. 1). Throughout the period of the treatment serum calcium showed values of subnormal range with a furthermore decrease after cessation of the treatment; serum phosphorus declined to subnormal levels, and then returned to normal after calcitonin administration (Fig. 1). Urinary excretion of phosphorus ranged from 60 to 80 mg per day before the treatment and increased to 100-140 mg per day during 5 days after initiation of calcitonin treatment. However, urinary phosphorus excretion returned to the initial level thereafter (Fig. 1). Urinary calcium did not show significant changes during the period of calcitonin treatment. Serum alkaline phosphatase activity gradually increased. This tendency of increase in the activity of this enzyme continued even after cessation of calcitonin treatment.

2) Effect of hexestrol

Hexestrol was administered intramuscularly at a dose of 30 mg daily for 14 days, and 15 mg daily for 23 days thereafter with an interval of 22 days. By the 13th day of hexestrol therapy, when he had received 390 mg, there was a definite reduction in size and number of his cervical lymph nodes. Metastatic lung infiltration subsided completely at the end of the hexestrol treatment and bone pain was very much improved. Although serum calcium and phosphorus were unchanged throughout the period of therapy, alkaline phosphatase activity increased up to 150 K.A.u. and decreased slightly after cessation of the treatment (Table 1). Total and prostatic acid phosphatase activities decreased prominently while hexestrol had been administered (Table 1). On the 10th day of the treatment, he complained of moderate ankle edema on both sides. Elevation of glutamic oxalacetic transaminase was noticed transiently. Total tri-

Table 1. Effect of hexestrol on serum calcium, phosphorus and alkaline and acid phosphatases, and urinary excretion of hydroxyproline.

<table>
<thead>
<tr>
<th></th>
<th>Period in relation to hexestrol treatment</th>
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<tbody>
<tr>
<td></td>
<td>before (11)</td>
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<tr>
<td>Calcium</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Phosphorus</td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>K.A.u.</td>
</tr>
<tr>
<td>Total acid phosphatase</td>
<td>K.A.u.</td>
</tr>
<tr>
<td>Prostatic acid phosphatase</td>
<td>K.A.u.</td>
</tr>
<tr>
<td>Urine Hydroxyproline</td>
<td>mg/24 hr</td>
</tr>
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Numbers in parentheses indicate the period in days.

* Mean ± S.E. of 11 days
** Mean ± S.E. of 7 days
*** Mean ± S.E. of 12 days

Difference between the mean of urinary excretion of hydroxyproline for the period before and that for the period during hexestrol therapy was significant (p > 0.001).
glyceride in the post-treatment period was 183 mg/dl and decreased to 86 mg/dl thereafter. Urinary hydroxyproline increased prominently during and even after hexestrol administration (Table 1).

Discussion

The present investigations showed that administration of SCT to a patient with prostatic cancer and bone metastases induced a gradual decrease in urinary excretion of hydroxyproline, a transient increase in urinary phosphorus, and a slight decrease in serum calcium after cessation of treatment. Calcitonin therapy was also effective in ameliorating bone pain. However, alkaline phosphatase activity progressively increased during the period of the treatment.

Cohn et al., (1971) proved that the administration of porcine calcitonin (PCT) to patients with osteoporosis induced positive calcium balance and marked decrease in urinary hydroxyproline. Milhaud et al. (1969), Baud et al., (1969) and Hioco et al., (1970) reported clinical improvement in osteoporotic patients treated with PCT. Calcitonin also has been shown to be therapeutically effective in treating Paget's disease (Bijvoet et al., 1968; Haddad et al., 1970). Several workers have shown a lowering of serum calcium upon administration of calcitonin to patients with hypercalcemia which was idiopathic (Milhaud and Job, 1966) or secondary to malignancy (Bijvoet et al., 1968; Pak et al., 1968). Pak et al., (1968) reported a case with parathyroid carcinoma and hyperparathyroidism who responded to calcitonin therapy with a fall in serum and urinary calcium, with a change in calcium balance from negative toward positive. Morii et al., (1971) proposed that calcitonin therapy was effective in lowering serum calcium in a case of hypernephroma with bone metastases.

By the 14th day, urinary hydroxyproline decreased gradually after initiation of administration of calcitonin, and returned toward initial levels thereafter in the present case. Both osteoblastic and osteolytic types of bone metastases from prostatic cancer were reported. Spencer et al., (1967) proposed that urinary excretion of calcium was in the normal range in some patients with carcinoma of the prostate with or without metastatic bone disease, but in rare cases it was elevated. Although both osteoblastic and osteolytic changes were noted roentgenologically in the present case, it was probable that osteoblastic process was more prominent than osteoclastic from the findings of serum calcium and urinary calcium and hydroxyproline levels. However, it may not be concluded whether osteoclastic or osteoblastic process was inhibited by administration of SCT. Since it was demonstrated that osteoclasts appear at the site of resorption where bone is invaded by tumor cells (Baker, 1956), calcitonin may have affected this resorptive process in addition to that operating at the normal part of bone. The resistance which appeared during the treatment to the effect of calcitonin may be due to secondary hyperparathyroidism or appearance of calcitonin binding substances and or neutralizing material in serum. However, the latter possibility is very improbable because it was only the 14th day when calcitonin became ineffective.

Alkaline phosphatase activity increased gradually to the high level and maintained this level even after cessation of calcitonin administration. Since liver function was normal and no metastatic nodules were found on liver scintigram, the increase of serum alkaline phosphatase activity may be due to secondary hyperparathyroidism induced by calcitonin.

It was demonstrated that estrogen was effective in increasing urinary excretion of hydroxyproline and that acid phosphatase decreased and alkaline phosphatase increased markedly by estrogen treatment in the present study. The mechanism of estrogen on the prostatic cancer has not precisely been
known. However, the antiandrogenic action and the inhibition of gonadotropin secretion would be beneficial in suppressing tumor growth (Huggins and Hodges, 1941). Since estrogen may also have a direct inhibitory effect on cancer cells, not only the invasion of bone by tumor cells was alleviated but also the process of bone formation may have been accelerated by estrogen. Spencer et al., (1967) proposed alkaline phosphatase is a good prognostic indicator of the effect of estrogen therapy. A marked elevation of urinary excretion of hydroxyproline would be a reflection of the increased activity of osteoblastic process in our patient.

References