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# *Ascorbic Acid Therapy for the Relief of Bone Pain in Paget's Disease*

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Paget's disease of the bone is a metabolic disorder characterized clinically by bone deformity and pain. In addition, there may be nerve compression, cardiac failure and in some patients there may be a sarcomatous change. Histologically there is evidence of excessive and disorderly resorption and formation of bone (11), and biochemically there is an increase in the plasma alkaline phosphatase activity, an enzyme derived from osteoblasts, and an increase in total daily urinary excretion of hydroxyproline (HOP), which is derived from bone collagen (8). In the past, Paget's disease has been treated by a variety of means, such as aspirin (10), cortisone (1) and sodium fluoride (5); these treatments have often produced relief of pain but have had little specific effect on the underlying pathology. Recently, research has centered on the study of other drugs which are able to suppress increased bone activity, such as diphosphonates (13), calcitonin (15) and glucagon (3). The effects of these drugs, however, ceases rapidly as soon as therapy is stopped. Furthermore, a course of calcitonin is very expensive and diphosphonates are not yet commercially available; the use of these drugs, therefore, is very limited.

In recent years there has been a large number of reports claiming that patients with bone pain due to various causes, such as bone metastases (2), osteogenesis imperfecta (9) and disc lesions (4) are relieved by administration of large doses of ascorbic acid. It was thought, therefore, that ascorbic acid might also be of benefit in Paget's disease.

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The purpose of the present trial was to monitor the clinical and biochemical response of patients with Paget's disease to treatment with ascorbic acid. The criterion for admission to the trial was pain in a patient with radiologically established Paget's disease.

## PATIENTS AND METHODS

Two groups of patients were studied. In the first group of 16 patients (Table I), 3 g of ascorbic acid were given orally daily for 2 weeks, following which the treatment was changed to 160 MRC units of porcine calcitonin per day intramuscularly, unless there had been complete relief of pain with the vitamin therapy. Treatment with calcitonin was continued as long as was clinically necessary. Twentyfour hour urine samples were collected weekly with the patients having a diet low in HOP for the 24 hours before and the 24 hours during collection. Total HOP was measured in urine following the method described by Stegemann and Stalder (14). Blood samples were also taken weekly and plasma alkaline phosphatase measured by the method of King and Armstrong (7). The second group of 5 patients were treated with calcitonin alone (160 MRC units per day) and the urinary levels of HOP and ascorbic acid were measured weekly. Ascorbic acid was measured by a method based on the

**Table I - Details of 16 patients with Paget's disease showing initial levels of plasma alkaline phosphatase (PAP) activity and urinary hydroxyproline (HOP) levels; also pain relief following 2 weeks therapy with ascorbic acid and then after further therapy with calcitonin.**

| Case n. | Age (yr) and Sex | Site of Pain | Duration of pain (yr) | PAP (KAU/100 ml) | HOP (mg/24 hr) | Relief of Pain | |
|---|---|---|---|---|---|---|---|
| | | | | | | Ascorbic acid | Calcitonin |
| 1 | 85 M | R. knee; Legs; L. spine | 5 | 60.5 | 119.0 | 2 | — |
| 2 | 81 M | Lower back | 15 | 98.0 | 120.0 | 2 | — |
| 16 | 75 M | R. knee; Back | 9 | 71.0 | 98.4 | 2 | — |
| 3 | 78 F | Back; Knees; Hips | 4 | 27.9 | 26.7 | 1 | 1 |
| 9 | 76 F | L. knee; L. leg | 5 | 39.6 | 37.0 | 1 | 1 |
| 11 | 69 F | L. leg | 1 | 15.3 | 65.2 | 1 | 1 |
| 8 | 62 M | Back; R. leg | 5 | 25.2 | 21.0 | 1 | 2 |
| 15 | 75 M | L. leg; L. knee | 11 | 58.5 | 72.8 | 1 | 2 |
| 4 | 81 M | Neck; back | 4 | 37.5 | 38.7 | 0 | 2 |
| 6 | 61 M | Back; R. groin | 8 | 14.6 | 53.4 | 0 | 2 |
| 7 | 64 M | Back; R. groin | 10 | 14.0 | 46.2 | 0 | 1 |
| 10 | 78 F | Back | 10 | 29.1 | 21.5 | 0 | 1 |
| 13 | 85 M | L. buttock; L. leg | 2 | 10.7 | 31.4 | 0 | 1 |
| 14 | 81 F | Legs; R. ankle | 6 | 46.8 | 25.4 | 0 | 1 |
| 15 | 74 F | L. leg; L. knee | 11 | 58.5 | 72.8 | 0 | 0 |
| 12 | 72 F | R. knee; R. hip | 5 | 30.9 | 46.7 | 0 | 0 |

Relief of pain was classified as 0, 1 and 2 corresponding to no change, partial relief and full relief of pain, respectively. The 3 patients who obtained maximum pain relief with ascorbic acid were not treated with calcitonin.

coupling reaction of ascorbic acid with 2:4-dinitrophenylhydrazine to form a chromogenic compound (12).

All patients were in hospital for the first 4 weeks of the trial, but were nevertheless encouraged to be actively up and about in order to avoid the possibility of developing immobilization osteoporosis.

## RESULTS

*Clinical.* Assessment of diminution of pain is subjective, and each patient's response to ascorbic acid and calcitonin respectively has been classified as 0, 1 or 2, corresponding to nil, some or marked response (Table I). Of the 16 patients in the first group, 3 claimed complete relief of pain when receiving ascorbic acid alone. These 3 patients did not go on to the second part of the trial in which calcitonin was given. All 3 continued to be free of pain, including 1 patient who gave a history of pain for 15 years. Five patients claimed partial relief of pain on ascorbic acid therapy, but a further 8 patients had no relief.

Of the 13 patients who went on to the calcitonin stage, 4 had total and 7 partial relief of pain, whilst 2 received no benefit at all. In the 2 patients who obtained no relief of pain by either treatment, it was thought that the pain was not entirely due to Paget's disease but also to secondary arthritis.

*Biochemical.* The excretory levels of HOP were elevated by ascorbic acid intake at one week in the 8 who responded to the vitamin therapy with either complete or partial relief of pain. The vitamin administration did not result in any marked change in the HOP excretion of the 8 patients who did not experience any pain relief from the therapy (Table II). The alkaline phosphatase activity, however, remained unaffected by the vitamin therapy in all 16 patients (Table II). In the 3 patients who were pain free following ascorbic acid therapy, the elevation of urinary HOP excretion during the first week of treatment with ascorbic acid was followed by a fall to near « pre-vitamin » values following therapy with the vitamin for a further two or three weeks. This up and down pattern was repeated two to three times by each patient during nine weeks of therapy.

In the 5 patients treated with calcitonin alone, there was a typical reduction in the excretion of HOP. The urinary excretion of

**Table II - Effect of ascorbic acid administration for one week on the urinary excretory levels of hydroxyproline and the plasma levels of alkaline phosphatase activity in patients with Paget's disease of bone.**

| Groups (N. of patients) | Urinary hydroxyproline (mg/24 hr) | | Plasma alkaline phosphatase (KAU/100 ml) | |
|---|---|---|---|---|
| | Pre-ascorbate | Post-ascorbate | Pre-ascorbate | Post-ascorbate |
| 0 (8) | 36 (21-53) | 36 (12-52) | 25 (11-47) | 26 (10-48) |
| 1 (5) | 44 (21-72) | 74 (45-102) | 33 (15-58) | 32 (16-55) |
| 2 (3) | 112 (98-119) | 168 (158-188) | 76 (60-98) | 69 (60-81) |

Patients were classified as Groups 0, 1 and 2, corresponding to nil, partial and complete relief of pain respectively, in response to ascorbic acid therapy.

ascorbic acid was also reduced and fell in parallel to HOP. As far as could be determined, all patients were having a similar diet throughout the experimental period, and hence it is unlikely that variations in excretory levels of the vitamin could be associated with changes in diet.

## DISCUSSION

The results of this investigation indicate that the treatment of Paget's disease with ascorbic acid can be associated with total or partial relief of pain. The relief of pain by the vitamin is accompanied by an elevated excretion of HOP and no change in plasma alkaline phosphatase activity. Relief of pain by calcitonin is typically associated with a reduction in both of these parameters (15). It appears, therefore, that the mechanisms by which ascorbic acid and calcitonin act to cause pain relief are not identical. However, we also find that the decrease in HOP excretion with calcitonin is accompanied by a parallel drop in ascorbic acid excretion and this indicates that calcitonin and ascorbic acid may be linked at some point in their actions.

The cyclic increase in HOP excretion by the patients who experienced complete pain relief with ascorbic acid is difficult to explain, but may arise from changes in bone metabolism following the stimulation of collagen synthesis by ascorbic acid (6). An increased synthesis of bone matrix proteins may provide conditions which lead to a more favourable remodelling of the bone clusters which are repeatedly formed due to the high osteoblastic and osteolytic activity in these patients, and hence result in a decrease in pain. It is of interest, therefore, that maximum pain relief following vitamin therapy was achieved only in those patients who had extensive bone resorption as indicated by the very high urinary levels of HOP and plasma alkaline phosphatase activity (Table I).

Finally, it must be emphasized that this was a short term trial. The long term effects of treatment with ascorbic acid await clinical, radiological and biochemical review at a later date. From the patient's point of view, the relief of pain is an important factor for it is this that causes him to visit his doctor. If pain can be alleviated or even abolished by cheap easily produced drugs which can be taken orally, like ascorbic acid, this is to be preferred to embarking immediately on an expensive course of injections. However, the use of ascorbic acid should not prevent subsequent therapy with calcitonin if this leads to the greater radiological and biochemical improvement of Paget's disease.


## *SUMMARY*

Sixteen patients with painful Paget's disease of the bone were treated with high doses of ascorbic acid. Of these patients, 8 experienced lessening of pain within a period of 5 to 7 days after commencing the vitamin therapy. In 3 of these patients pain was completely abolished. Subsequent treatment with calcitonin caused improvement in most cases. There was little change in plasma alkaline phosphatase levels but the excretion of hydroxyproline was elevated following administration of the vitamin. The highest excretions were found in those patients who experienced complete relief of pain. In patients treated with calcitonin alone, the excretion of hydroxyproline was reduced and urinary levels of ascorbic acid dropped in parallel. It seems clear that ascorbic acid and calcitonin have different effects upon bone metabolism.

## *RIASSUNTO*

*Terapia con acido ascorbico per alleviare il dolore nel morbo di Paget.*

Sono stati trattati con alte dosi di acido ascorbico 16 pazienti sofferenti di dolori per un morbo di Paget delle ossa. Di questi pazienti otto hanno visto diminuire il dolore fra cinque-sette giorni dall'inizio della terapia vitaminica; in tre di essi il dolore era completamente scomparso. Piccole variazioni si

ebbero nei livelli plasmatici di fosfatasi alcalina, ma l'escrezione di idrossiprolina risultò molto alta dopo la somministrazione della vitamina, con livelli più elevati nei soggetti in cui il dolore era del tutto abolito. Nei pazienti trattati solo con calcitonina la escrezione di idrossiprolina era ridotta e parallelamente si erano abbassate le concentrazioni urinarie di acido ascorbico. Sembra evidente che questa vitamina e la calcitonina hanno effetti differenti sul metabolismo dell'osso.

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