Calcitonin in the Treatment of Paget's Disease of Bone

a retrospective study

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This study was undertakent at the request of Pharmacy & Therapeutics Committee, St. Luke's Hospital.

INTRODUCTION

A retrospective survey was undertaken to evaluate prescribing habits of calcitonin in Paget's disease of bone, as well as to assess its effectiveness.

MATERIALS AND METHODS

The material presented is based on a review of the case histories and radiographs of 33 patients suffering from Paget's disease and receiving calcitonin therapy. The diagnosis of Paget's disease was made on the basis of an elevated level of serum alkaline phosphatase (S.A.P.) in association with typical radiological abnormalities (areas of osteolysis alternating with osteosclerosis, loss of normal trabecular bone pattern, with or without bone distortion). (Fig. 1, 2) The patients involved were 28 males, age range 41 to 81 (mean 60) years and 5 females, age range 47-68 (mean 62.4) years at the time of diagnosis. 5 of the male patients were below 50 years of age. Except for one, all patients were symptomatic, 9 having low back pain, 8 hip pain, 5 knee pain, 4 diminished hearing. Other complaints included lower limb weakness, paraesthesiae and cramps in the legs, swelling in the forearm, swelling in the leg and pain in one shoulder (one patient each). From the radiological data available, the parts of the skeleton involved were as follows: pelvis (27 patients), femur (22 patients), skull (13 patients), lumbar spine (17 patients), dorsal spine (7 patients), radius (1 patient), humerus (1 patient). Other x-ray changes noted included degenerative joint disease (in hips, knees, spine) as well as diffuse idiopathic skeletal hyperostosis (D.I.S.H.) in 4 patients.

All patients received calcitonin therapy. No single dosage schedule was followed. Some patients were started on daily injections (50-200 U) and the maintenance dose varied from one injection (50-200 U) monthly to 3 injections (50-100) per week. Three patients experienced side effects — flushing, nausea, vomiting; in one patient they became severe enough that treatment had to be stopped. Duration of treatment varied from a few months (5 of the 33 patients were started on treatment in the second half of 1988, so there was not enough time for a full evaluation) up to 7 years. Several patients had other forms of treatment — 9 had calcium supplements, 11 had nonsteroidal anti-inflammatory drugs and/or other analgesics and 16 had anabolic steroids (Primobolan injections).

Of the 33 patients 6 felt better in so for as the pain was concerned: one felt significantly better within 4 weeks of starting calcitonin injections; 2 had a moderate improvement, while 3 had slight improvement. The other patients did not seem to benefit: in particular none of the patients with reduced hearing showed any improvement.

The only biochemical parameter examined was serum alkaline phosphatase: there was not enough time for follow-up levels of alkaline phosphatase to be measured on the five patients started on calcitonin after the middle of 1988. Of the remaining 28 patients there was no drop in serum alkaline phosphatase levels in 19 patients. In the other 9 a significant drop of the enzyme was noted, arbitrarily taken to mean a drop of 40% or more from initial levels. Of these 9 patients, 1 was receiving both calcitonin and disodium editronate (Didronel), 3 had a transient drop of serum alkaline phosphatase within 6-9 months of starting treatment which then returned to the initial high levels, whereas 5 patients had a sustained drop in serum alkaline phosphatase level. 4 patients were treated with disodium editronate after no effect had been noted with calcitonin: they all experienced a significant drop in serum alkaline phosphatase levels. *Only two of the patients with a reduction in the level of alkaline phosphatase had symptomatic improvement;* in the remaining 11 patients, despite a drop in the enzyme level, no change in symptomatology was noted. Conversely, 4 patients who felt better did not show any drop in alkaline phosphatase level.

COMMENTS

Several problems were encountered in carrying out this survey, the main one being poor clinical documentation, e.g. lack of characterisation of pain as to whether it was primarily bone pain or pain due to coincidentally associated osteoarthritic changes (and these are particularly common in the age group under consideration) as well as poor follow-up information regarding changes in symptomatology. The only biochemical parameter that can be measured locally is the serum alkaline phosphatase: this only measures one aspect of the disease (osteoblastic activity). The other facet of the disease, osteoclastic activity — now considered to be the initial pathology of the disease — can be measured by urinary hydroxyproline estimation. Besides, the true extent of the disease can only be properly assessed by nuclear bone scanning; this technique can also be used in the follow-up of patients to assess disease activity. Conventional radiography is not sensitive enough for this, as radiologically abnormal bone is not necessarily the site of active pagetic bone.

In general, calcitonin seemed relatively *ineffective in the majority of patients with Paget's disease in whom it was used.* This may have been due partly to poor patient selection — e.g. ascribing pain to be due to bone involvement by Paget's disease rather than to associated, or secondary, degenerative joint disease or nerve compression. None of the 4 patients with hearing impairment showed any improvement on calcitonin therapy — quite possible because treatment was started too late. The small number of patients showing a significant drop in serum alkaline phosphatase levels while on calcitonin, however, speaks out for the relative lack of efficacy of the drug in this group of patients. An estimate of the cost involved was calculated in 23 patients — where the average consumption was known: this worked out at LM11,000 (average LM484 per patient). *This is a very high price to pay for the comparatively little benefit obtained.* The fact that 4 patients showed a significant drop in serum alkaline phosphatase levels when treated with disodium editronate after having shown no effect with calcitonin is in keeping with the current view that *diphosphonates are more effective than calcitonin in controlling activity in Paget's disease.*

The disparity between clinical and biochemical improvement noted in several of the patients could have been due to various causes:

a. poor patient selection — i.e. the pain not being due to Paget's disease itself but due to, for example, associated osteoarthritis. Concomitant nonsteroidal anti-

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inflammatory therapy may relieve pain with having any effect on the underlying disease. Alternatively, pagetic activity may be reduced, but symptoms due to mechanical problems (such as degenerative joint disease, nerve compression) persist.

b. a nonspecific analgesic effect from calcitonin itself may operate: calcitonin is also recommended for other painful bone conditions, such as acute painful crises in osteoporosis as well as in metastatic bone disease.
c. one patient who showed a significant improvement in back pain after 4 weeks of calcitonin therapy would have probably shown a drop in alkaline phosphatase level had he been followed up for a longer period. Most pagetic patients who respond to calcitonin, in fact, show a clinical response much before a biochemical one.
d. a placebo effect cannot be entirely ruled out.

CONCLUSIONS

Certain broad guidelines should be followed by physicians and orthopaedic surgeons who are involved in the management of patients with Paget's disease of bone. In several instances the disease is entirely asymptomatic, and discovered only as an incidental finding: in most such patients no specific therapy is generally indicated. *Abnormal biochemistry is NOT in itself an indication for treatment.*

Major indications for treatment should include:

1. bone pain
2. prior to orthopaedic surgery, to reduce bone vascularity
3. neurologic involvement
4. high output congestive cardiac failure — a situation most likely to be found in patients with extensive Paget's disease and with preexisting heart disease
5. bone fractures
6. treatment or prevention of hypercalcaemia resulting from immobilisation.

Specific therapy may be indicated as a prophylactic measure especially in young individuals in certain situations, such as:

1. involvement of the base of the skull
2. involvement of the spine — especially above L2
3. asymptomatic involvement in a weight-bearing bone.

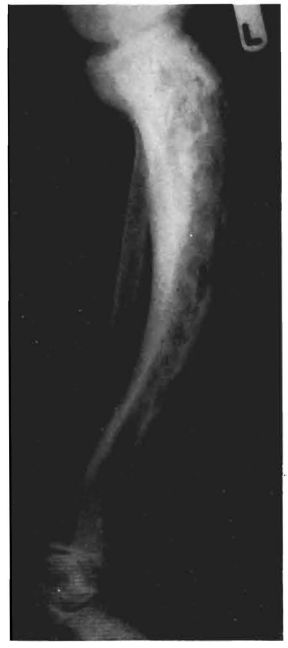
In general, calcitonin should no longer be considered as the first line specific agent for Paget's disease of bone. If it is used, and no pain relief is apparent within 8 weeks, then it should be stopped. If pain is relieved, it can be continued for a year and then stopped. Rebound is inevitable with time, but another course can be successful. Recurrent and prolonged use of calcitonin will result in the production of antibodies which further reduced its effectiveness.

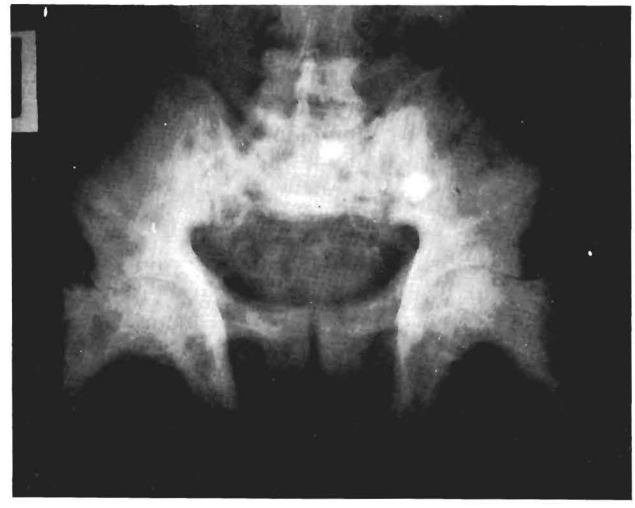
Diphosphonates are considered more effective than calcitonin. They are certainly not the final answer, and disodium editronate (Didronel), the only diphosphonate currently available locally, suffers from several major disadvantages — it is poorly absorbed; it may cause on increase in bone pain at the start of treatment; and — most important of all — it can produce osteomalacia when used for prolonged periods of time. For this reason, it is generally recommended for the drug to be given in a dose of 5 mg/kg body weight for a period of 6 months. A favourable response is reported in over 65% of patients, and the benefit often lasts several years after the drug is stopped. Following a relapse, control can be regained by a further 6 month course. It is not a cheap drug, and an average course (400 mg/day for 6 months) would cost just over LM100.

New diphosphonates have been developed which do not cause osteomalacia. One particular preparation, disodium amino-hydroxy-propylidene biphosphonate — AHPrBP — (Aredia, Ciba-Geigy) has been shown to exert a significant effect in patients with Paget's disease of bone after one single intravenous injection, with a significant benefit still being demonstrable one year after treatment.[1]

Patients with severe and unresponsive disease may occasionally benefit from combined therapy with calcitonin and a diphosphonate.

Severe Paget's Disease of
1. TIBIA
2. PELVIS





Except for a single report that a combination of oral calcium and a thiazide diuretic (in an attempt to stimulate endogenous calcitonin secretion) caused a modest drop in alkaline phosphatase activity and urinary hydroxyproline excretion,[2] there is *no evidence that other forms of therapy such as anabolic steroids confer any benefit to patients with Paget's disease of bone,* and their use ought to be actively discouraged. Pain due to osteoarthritis can very often be managed by analgesia, anti-inflammatory drugs and physiotherapy.

Surgery may be needed in certain situations — e.g. orthopaedic surgery for patients who develop severe degenerative arthritis of the hip, where a hip replacement can result in pain-free normal ambulation, or tibial osteotomy for severe bowing of the tibia which may correct the deformity and allow much improved ambulation; neurosurgery for patients with nerve compression from vertebral involvement or for patients with severe basilar impression and neurologic deficit. All such surgery should be done after treatment with a drug which suppresses the activity of the disease to prevent excessive haemorrhage and postoperative hypercalcaemia.

ACKNOWLEDGEMENT

I would like to thank Ms Maryse Gatt of the Pharmacy Department, St. Luke's Hospital, without whose invaluable help this survey would not have been possible.

REFERENCES

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