Influence of disodium etidronate on Paget's disease of bone

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Summary

The use of agents that decrease bone resorption, notably the calcitonins, diphosphonates and mithramycin, has been shown to result in symptomatic and/or biochemical improvement in patients with Paget's disease of bone (osteitis deformans). The effects of short-term (6 months), low-dose (5 mg/kg body mass/d) etidronate disodium, a diphosphonate compound at present subject to registration in this country, on the clinical and laboratory manifestations of this disorder were examined. Marked symptomatic improvement was noted in 70% of patients, while biochemical parameters of bone turnover, namely serum alkaline phosphatase level (44%) and urine hydroxyproline excretion (56%), decreased significantly ($P < 0,001$). A technetium-99m bone scan revealed an impressive reduction in uptake of isotope in 50% of patients. The drug was well tolerated and no adverse reactions (clinical, biochemical or haematological) were evident. It is concluded that short-term low-dose etidronate disodium affords a convenient and effective therapeutic alternative in patients with symptomatic Paget's disease.

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Paget's disease of bone affects some 4 - 10% of patients over the age of 45 years.[1-3] The disease is highly prevalent in South Africa and often presents in the asymptomatic patient as a coincidental radiological finding. Usual symptoms include localised bone pain, deformities, fractures and sensorineural deafness; rarely high output cardiac failure, neurological complications, immobilisation hypercalcaemia, hyperuricaemia or sarcomatous degeneration of Pagetic lesions are observed.[1-3] The radiological diagnosis of the disorder is usually apparent — initial osteolytic disease secondary to increased bone resorption progresses to a mixed lytic-sclerotic phase which culminates in the typical sclerotic, expansive bone lesions that characterise the disease. Although the condition is readily diagnosed radiologically, biochemical parameters (serum alkaline phosphatase, serum osteocalcin and urinary hydroxyproline excretion) and/or radio-isotope bone scanning are required to assess activity of the disease.

Specific treatment is usually reserved for the symptomatic patient. Therapeutic indications are, however, controversial and clinical distinction between active disease and pain secondary to nerve entrapment or degenerative arthritis in joints adjacent to involved bones, is often difficult. In South Africa the hormone calcitonin still comprises the mainstay of specific therapy. The calcitonins (porcine, salmon, eel, human) have been shown to decrease the biochemical activity of the disease, improve symptoms and induce healing of lytic bone lesions.[3-5] However, they require administration by injection and not too infrequently cause intolerable nausea.[3-5] The diphosphonates, a group of compounds related to inorganic pyrophosphate, can be taken orally and have also been shown to beneficially affect the symptomatic and biochemical features of the disease.[6-9]

This report summarises experience in the short-term use of etidronate disodium (EHDP), a diphosphonate compound at present subject to registration in this country.

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Patients and methods

Ten patients (4 men) aged 39 - 70 years with severe symptomatic Paget's disease were randomly selected for inclusion in the study. A history of proven Paget's disease ranged from less than 3 months in 5 patients to many years in others (Table I). Monostotic disease was present in 4 cases, with polyostotic involvement in the rest. Four patients had a history of previous treatment with salmon calcitonin, with little or no symptomatic improvement, while the rest were either untreated or had received non-steroidal anti-inflammatory agents only (Table I).

Patients were admitted to the Endocrine Unit of Tygerberg Hospital, underwent a full clinical evaluation, which included a detailed dietary history, and followed a standard diet (800 mg calcium, 1 000 mg phosphate, gelatin-free) for 3 days before biochemical testing. Serum total calcium, phosphate, alkaline phosphatase (AP), urea, creatinine, electrolytes and liver enzyme levels were measured by routine Beckman auto-analytical techniques, a full blood count was obtained, and 24-hour urinary hydroxyproline excretion[10] determined in each patient. All measurements were done in duplicate on samples obtained on 2 consecutive days. A radiological skeletal survey and technetium-99m bone scan concluded the initial work-up.

Treatment with EHDP 5 mg/kg body mass/d, was initiated and this regimen was maintained for 6 months. Patients were followed up monthly to evaluate (*i*) clinical response (pain); (*ii*) adverse reactions; (*iii*) serum biochemistry; and (*iv*) haematology. After 6 months of therapy patients were readmitted to the unit and the initial work-up was repeated.

Results

Of the 10 subjects treated with EHDP 7 had a very satisfactory symptomatic response and were virtually pain-free after 6 months of therapy. Three patients experienced minimal to no improvement (Table I). No adverse reactions were experienced by any of the patients and no subject reported an exacerbation of bone pain.

A decrease in serum total AP level was apparent in all patients studied. The mean serum AP level for the group decreased by an average 44% after 6 months of therapy; this was most noticeable within the first 3 months after which serum levels tended to stabilise (Fig. 1). Moreover, a good correlation between clinical improvement and biochemical response was noted. Similarly, urinary hydroxyproline excretion decreased by an average 56% after 6 months of therapy (Table II). The isotope bone scan was

TABLE I. STUDY POPULATION

Patient No.	Age (yrs)	Sex	Duration (mo.)	Skeletal involvement	Previous therapy	Response to EHDP
1	70	M	1	P	None	Good
2	66	M	15	P	SCT	Good
3	70	F	16	M	SCT	Good
4	69	F	72	P	None	Good
5	59	F	1	P	None	Good
6	63	F	1	P	None	Good
7	70	M	3	P	None	Good
8	70	F	20	M	SCT	Poor
9	39	M	2	M	None	Poor
10	54	F	41	M	SCT	Poor

P = polyostotic; M = monostotic; SCT = salmon calcitonin.

TABLE II. INFLUENCE OF EHDP ON SERUM AND URINE PARAMETERS (MEAN ± SEM)

Parameter	Before EHDP	After EHDP
Serum		
Alkaline phosphatase (IU/l)	412,00 ± 20,00	230,00 ± 26,00**
Total calcium (mmol/l)	2,36 ± 0,05	2,35 ± 0,05
Phosphate (mmol/l)	0,91 ± 0,10	1,21 ± 0,10*
Creatinine (umol/l)	82,00 ± 5,00	87,00 ± 6,00
Urea (mmol/l)	4,70 ± 0,60	5,40 ± 0,70
Total bilirubin (μmol/l)	8,00 ± 1,20	10,00 ± 1,40
AST (U/l)	25,00 ± 4,00	20,00 ± 4,00
ALT (U/l)	19,00 ± 5,00	19,00 ± 6,00
GGT (U/l)	19,00 ± 6,00	19,00 ± 9,00
Haemoglobin (g/l)	138,00 ± 4,00	135,00 ± 5,00
Leucocytes ($10^3/\mu l$)	6,30 ± 0,60	6,10 ± 0,50
Platelets (10^9/l)	301,00 ± 38,00	267,00 ± 21,00
Urine		
Hydroxyproline (μmol/m²/d)	502 ± 69,00	221,00 ± 59,00**

*$P < 0,05$ comparing values before and after EHDP.
**$P < 0,001$ comparing values before and after EHDP.

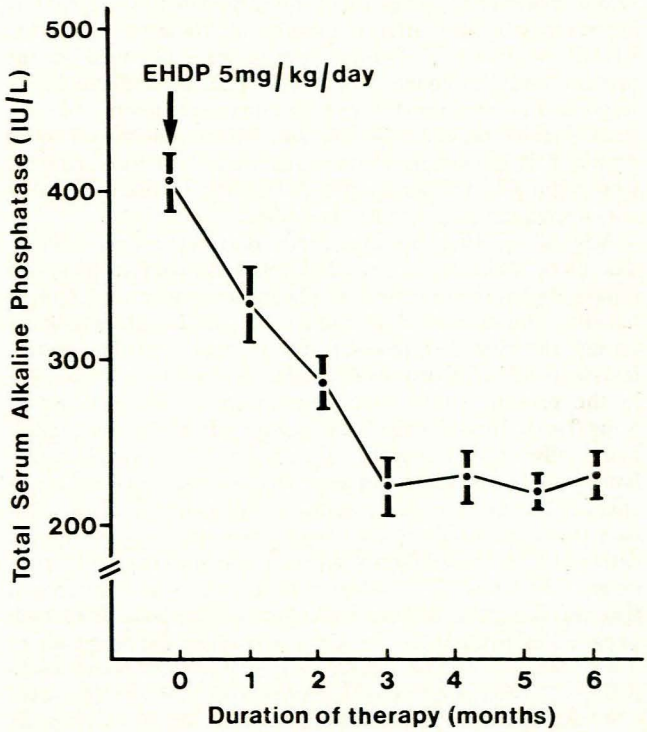

Fig. 1. Effect of EHDP on serum alkaline phosphatase levels in 10 patients with Paget's disease. Values (mean ± SEM) are shown at monthly intervals after the start of EHDP therapy.

unchanged in the 3 clinical non-responders, improved marginally in 2 subjects, and revealed a marked reduction in uptake in the remaining 5 patients.

The radiological survey, blood count, serum urea and creatinine levels and liver function profile were unchanged after 6 months of EHDP treatment (Table II). Similarly, the serum total calcium was unaltered, but the serum phosphate increased marginally, albeit significantly, on therapy (Table II).

Discussion

Before 1970, no safe and effective drug therapy for Paget's disease was available. Today at least three main medical treatments — the calcitonins, the diphosphonates and mithramycin — have been shown to cause symptomatic, biochemical, histological and/or radiological improvement. All these drugs are primarily inhibitors of bone resorption and their ingestion results in a rapid decrease in urinary hydroxyproline excretion (a parameter of bone resorption), followed by a decrease in serum AP levels (an index of bone formation).[1-3] Bone pain is the main indication for drug therapy. However, the presence of local (e.g. nerve entrapment syndromes) or systemic (e.g. immobilisation hypercalcaemia, cardiac failure) complications or severe progressive disease especially in young patients, even if asymptomatic, should also be considered as possible indications for treatment.[1-8,11,12] Since drug therapy is known to diminish bone turnover and blood flow, and appears to prevent excessive haemorrhage and postoperative hypercalcaemia, preparation for major orthopaedic surgery should be regarded as yet another potential indication.[13]

The calcitonins are very effective in alleviating symptoms and improving the biochemical and histological parameters of the disease.[1-5,11] These drugs are, however, expensive, require administration by injection, and commonly cause nausea, flushing, gastro-intestinal intolerance and a metallic taste sensation.[3-5] In some patients antibody-mediated resistance to the drug develops although responsiveness is usually restored by use of a calcitonin derived from another species. The major problem with calcitonin therapy is, however, a biochemical/symptomatic relapse shortly after stopping treatment, suggesting incomplete suppression of disease and implying that long-term therapy with this agent may be needed in some patients.[4,5,11] Weekly infusions of mithramycin, a cytotoxic

antibiotic, is very effective in rapidly improving bone pain, and markedly decreases bone turnover in patients with severe Paget's disease.[11] Renal, bone marrow and hepatic toxicity, however, makes this drug less than ideal as first choice in the treatment of Paget's disease.[12]

Several diphosphonates have proved useful in the treatment of Paget's disease.[6-9] EHDP is administered orally, although absorption from the gut is only 1 - 10% of an oral dose, being highest when the drug is not taken with food.[6] The effect of EHDP on biochemical and histological parameters of the disease is evident at doses of 2,5 - 20 mg/kg body mass/d.[6-8] At doses of 10 - 20 mg/kg/d greater suppression of bone turnover is usually achieved with EHDP than with calcitonin.[6] Also, acquired resistance to treatment is absent and maintenance of suppression after stopping treatment is prolonged, often for several years.[8,9,14] The nature and length of remission is partly related to the severity of the disease, to drug dosage and to treatment duration.[9] On average, some 60% of patients exhibit symptomatic relief, while biochemical parameters decrease by approximately 50% after 6 months of low-dose (5 mg/kg) EHDP treatment.[6-9] Similar results were obtained in the present study, although 4 of our 10 patients had previously responded poorly to treatment with salmon calcitonin. Although small patient numbers do not allow firm conclusions to be drawn, it is interesting to note that while 6 of the 7 patients who responded to therapy had polyostotic involvement, all 3 non-responders had monostotic disease.

Adverse reactions are also partly dose-related and include diarrhoea, a rise in serum AP levels secondary to increased renal tubular reabsorption of phosphate, and in 1 - 10% of patients, the *de novo* development of pain in affected bones during the first few months of treatment.[1-3,6-9] No gastrointestinal side-effects or exacerbation of bone pain were noted in the present study which employed an EHDP dose of 5 mg/kg/d, although the mean serum AP levels did increase marginally after 6 months of therapy. This change in AP homeostasis is, however, not associated with any known adverse effects.[2] The most serious potential complication of diphosphonate therapy comprises the development of a mineralisation defect and the possibility of an increased propensity to spontaneous fractures.[6-9,15-17] Most clinical studies have confirmed that the 5 mg/kg/d dose is seldom if ever associated with impaired mineralisation,[6-9,15] although a recent report by Boyce *et al.*[17] documented histological evidence of focal osteomalacia in 9 of 13 patients receiving 5 - 8 mg EHDP/kg/d. The agent dichloromethylene diphosphonate (Cl_2 MDP) is also an extremely potent inhibitor of bone resorption, but unlike EHDP has a much weaker effect on inhibiting bone mineralisation.[2] Although the evidence for radiological healing of osteolytic lesions with EHDP is less compelling than reports of clear regression of bone lesions after treatment with calcitonin,[18] large controlled clinical trials have provided no objective evidence of an increased fracture rate if treatment with EHDP does not exceed 6 months.[6-9,15]

We conclude that the diphosphonate EHDP affords a convenient and most effective therapeutic alternative to the calcitonins in patients with symptomatic Paget's disease of bone. It is suggested that the drug be administered in a dose of 5 mg/kg/d for 4 - 6 months. Regular follow-up and close biochemical monitoring, preferably by physicians versed in the management of patients with metabolic bone disease, are necessary. Because of the potential development of mineralisation defects, it is probably not justified to advocate the use of higher dose regimens and/or longer treatment periods, particularly for patients with lytic lesions in weight-bearing bones, until the optimum dose and duration of therapy have been established.

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