Low dose intravenous 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) for the treatment of Paget's disease of bone

J A CANTRILL,² H M BUCKLER,¹ AND D C ANDERSON¹

From the University Departments of ¹Medicine and ²Pharmacy, Hope Hospital, Eccles Old Road, Salford

SUMMARY Twenty patients with severe symptomatic Paget's disease were treated with a series of 15 mg intravenous infusions of 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD). A regimen of either five consecutive days of treatment (regimen 1) or a course of 12 weekly infusions was administered (regimen 2). In five cases regimen 2 followed regimen 1 after a three month interval. Alkaline phosphatase levels fell in all patients and returned to the normal range in 12. All but one of the patients obtained symptomatic improvement. There was a median fall in alkaline phosphatase activity of 63%. Eight patients observed a transient increase in bone pain starting about 24 hours after the first infusion. Intravenous APD was well tolerated, and we conclude that it is an effective treatment for Paget's disease; this route of administration avoids the problem of poor and unpredictable gastrointestinal absorption seen when a bisphosphonate is given orally. The optimal dose and duration of APD therapy, frequency of relapse, requirements for further courses, and merits relative to other second generation bisphosphonates remain to be established.

Key words: diphosphonates, metabolic bone disease, alkaline phosphatase.

For over 15 years the principal treatment for Paget's disease of bone has been synthetic salmon or porcine calcitonin. This therapy, which has to be given by injection two or three times a week, may produce unacceptable side effects, including nausea, flushing, and febrile reactions, in up to 12% of patients.¹ Another potential problem is the development of resistance, which is at least partly related to the development of antibodies.² The cytotoxic antibiotic, mithramycin, has also been used^{3,4} but is not licensed for this purpose in Britain. Several bisphosphonate (diphosphonate) compounds have also been developed, of which the only one commercially available is disodium 1-hydroxyethylidene-1,1-bisphosphonate (disodium etidronate, EHDP, Didronel). Although EHDP therapy has been found to be effective in Paget's disease,⁵ its long term use has been associated with the development of focal osteomalacia.⁶ Dichloromethylene bisphosphonate (clodronate sodium, Cl₂MDP) has also been found

to be an effective treatment,⁷ but the suspicion of other, unconfirmed side effects has slowed the evaluation of this drug. Yates *et al* have recently shown that a short course of intravenous clodronate may result in a biochemical remission of Paget's disease, which is sustained for at least six months.⁸ Another bisphosphonate compound, 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD), has also been shown to be effective⁹⁻¹¹ and has not been shown to produce any mineralisation defect. When administered orally APD, like other bisphosphonates, has a very low and variable bioavailability¹² and may produce gastrointestinal side effects.¹³ Intravenous APD has been successfully used in the treatment of malignant hypercalcaemia.¹⁴ The use of the intravenous route permits the administration of a small dose of the drug and eliminates those bioavailability problems which are due to variable absorption of the drug. In view of the known efficacy, but the variable response to oral APD that we have confirmed,¹⁵ we have carried out an open study of low dose intravenous APD in 20 patients with severe symptomatic Paget's disease.

Accepted for publication 5 June 1986.

Correspondence to Professor D C Anderson, University Department of Medicine, Hope Hospital, Eccles Old Road, Salford M6 8HD.

Table 1 Patient characteristics

Patient No	Sex	Age (years)	Bone scan score	Treatment regimen	Alkaline phosphatase (IU/l)			Serum phosphate (mmol/l)			
					Highest ever value	Pre-treatment value	Post-treatment value	Maximum fall % of pre-treatment value	Weeks after start of APD	Pre-treatment value	Lowest value during treatment
1	M	58	1	1	314	314	84	73	60	0.88	0.64
2	M	77	3	1	688	688	446	35	5	1.01	0.86
3	M	82	3	1	191	161	117	27	8	0.96	0.87
4	F	81	1	1	222	172	89	48	15	0.96	0.71
5	M	57	5	1	411	341	90	74	28	1.05	0.69
6	F	75	8	1	1520	815	199	76	26	1.03	0.57
7	M	58	11	1	955	955	499	48	61	1.01	0.84
8	F	72	13	1	—	499	367	62*	6†	1.02	0.93
9	M	76	10	2	>3800	3775	2710	28	16	1.05	1.04
10	F	70	12	2	—	2710	2350	38*	17†	1.18	1.02
11	F	74	5	1	420	236	179	24	22	—	—
12	F	77	9	2	1435	1070	870	57*	18†	1.41	1.24
13	F	84	12	2	—	870	315	19	12	—	0.75
14	F	54	2	2	—	590	395	71*	14†	0.90	0.72
15	F	55	12	2	1820	395	395	33	17	—	—
16	F	73	3	2	—	395	130	78*	11†	0.96	0.89
17	F	79	2	2	1665	528	107	80	21	0.94	0.86
18	F	84	12	2	805	805	459	31	42	1.03	0.92
19	F	54	2	2	232	204	74	64	38	0.80	0.64
20	F	55	12	2	1195	995	188	81	26	1.05	0.85
21	F	73	3	2	592	592	57	90	17	0.98	0.85
22	F	79	2	2	414	272	101	63	14	0.84	0.84
23	F	69	2	2	312	282	65	77	14	1.18	1.04
24	F	81	10	2	860	845	134	84	26	0.91	0.67
25	F	77	2	2	172	170	43	15	15	1.17	1.02

*Overall percentage decrease in AP after two courses of intravenous APD.
†Time (weeks) to maximum percentage fall in AP after the start of the second course of intravenous APD.

Patients and methods

Patients with severe, symptomatic Paget's disease which was judged to require treatment were included in the study. Patients either had contraindications to other therapies, e.g., lytic disease, or had been shown to be resistant to or had experienced unacceptable side effects with other treatment. The last six patients were the first in a formal open trial approved by the Salford Area Ethical Committee. Each patient was assigned a bone scan score as a crude measure of the extent of their disease. This was calculated from a baseline total skeletal bone scan, assigning one point for each bone involved. The bone scan scores showed a median value of 5 (range 1-13).

All patients received 15 mg of APD administered in 250 ml of normal saline over two hours. Initially, a course of five consecutive daily infusions (regimen 1) was given, but the APD was later administered as a course of 12 weekly infusions (regimen 2). Biochemical assessment was performed by serial estimations of serum alkaline phosphatase levels in all patients, and of fasting urinary hydroxyproline/creatinine ratios in 12. Full biochemical profiles and full blood counts were obtained at regular intervals. Alkaline phosphatase and creatinine were measured by sequential multichannel analyser with computer (Technicon) and the hydroxyproline by colorimetry after coupling with *p*-dimethylaminobenzaldehyde.

Twenty patients, six male and 14 female, aged 54–84 years (mean 71), received intravenous APD. Their characteristics are shown in Table 1. All were symptomatic before treatment, 19 with severe bone pain or headaches, four with some degree of hearing impairment, and one with loosening of the teeth due to monostotic Paget's disease of the maxilla. Thirteen patients had previously been treated with calcitonin; of these, 11 had developed side effects and two resistance. Eleven had received EHDP (20 mg/kg/day for three months), of whom six had experienced gastrointestinal side effects. Eight had received oral APD (4.5 mg/kg/day for three months); of these, two had experienced gastrointestinal side effects. Seven had received no previous therapy for Paget's disease.

Eleven patients received regimen 1; five of these later received a further course of up to 12 weekly infusions (regimen 2). Nine patients received a course of 12 weekly infusions, and one patient (No 6) was withdrawn from the study after only two infusions owing to an apparently unrelated exacerbation of an existing illness (angina). Nevertheless, she showed marked symptomatic improvement

and her alkaline phosphatase declined from 815 to 199 IU/l. She is currently receiving a further course of intravenous APD. One further elderly patient with extensive Paget's disease received two doses of intravenous APD a week apart without apparent adverse effects. One week later she was admitted elsewhere with a stroke; she was subsequently found to have an undifferentiated hypopharyngeal carcinoma. This patient has been excluded from analysis.

Fig. 1 Serum alkaline phosphatase (IU/l) before and after treatment with intravenous APD. Levels shown are those immediately before treatment (pre-APD) and the lowest levels attained after the end of treatment (post-APD).
 □ = regimen 1 followed by 2; △ = regimen 1 alone;
 ○ = regimen 2 alone.

Fig. 2 Change in serum alkaline phosphatase (AP; IU/l) after treatment with intravenous APD in four patients. Response to previous therapy is also shown. E=oral EHDP; C=calcitonin; A₀=oral APD; A₁=intravenous APD regimen 1; A₂=intravenous APD regimen 2.

Results

The fall in alkaline phosphatase levels is detailed in Table 1, the mean pretreatment level was 690 IU/l (range 161–3775) and mean post-treatment level 276 IU/l (range 43–2710). These results are shown in Fig. 1. As expected,^{10 15} changes in alkaline phosphatase were preceded by a fall in the hydroxyproline/creatinine ratio (data not shown). Individual charts are shown for four patients in Fig. 2, which also show changes in alkaline phosphatase

during and after previous treatments. Fig. 3 shows the response in the only patient treated who had osteoporosis circumscripta. As early as three months after the end of the course of therapy with regimen 2 there was a dramatic degree of remineralisation and marked reduction in activity on the bone scan (Fig. 4).

The treatment was well tolerated by all patients, but eight complained of a transient exacerbation of pain after the first injection. One claimed to experience headaches both during and after each

Fig. 4a

Fig. 4b

infusion but complained of the same symptoms after an infusion of normal saline. No haematological or biochemical abnormalities were noted except a transient hypophosphataemia (<0.8 mmol/l), which occurred in seven patients (Table 1).

Although no objective assessment was made of symptomatic response in the first 14 patients, 12 of the 13 patients with pain reported a marked improvement. All six of the patients in the formal study showed an improvement in pain, which was assessed with a visual analogue scale. All patients have been followed up, and six have remained in remission for a mean of 11 months (range 9–14). Twelve patients have been retreated, three with a single 30 mg infusion and nine with a further course of intravenous APD, and another patient is currently awaiting retreatment. One patient (No 10), with partial fractures and severe bone pain, had a tibial osteotomy five months after a second course of APD. A further course of treatment, delayed for three months after surgery, has not led to a further decline in alkaline phosphatase.

One patient (No 9) developed severe pain with increased size of a longstanding fissure fracture of the femoral shaft six months after stopping treatment.

Discussion

Our findings indicate that even a short course of low dose intravenous APD can produce a marked biochemical and clinical response in Paget's disease

of bone. In 12 of the patients alkaline phosphatase concentrations returned to within the normal range (30–130 IU/l) after treatment with intravenous APD. These patients all had less than 11 bones affected (bone scan score <11), and all had an initial alkaline phosphatase level of less than 600 IU/l. A further three patients had bone scan scores of less than 11 but also had initial alkaline phosphatase levels of 688, 845, and 815 IU/l respectively, which fell, but not to within the normal range, after treatment. In the present study we administered the same dose of APD to all patients irrespective of weight and extent of Paget's disease. APD is rapidly cleared from the blood and taken up into bone, especially at sites of resorption,¹⁶ and the half life of bone retention will probably depend on the bone turnover rate. It may well be that patients with very extensive disease require a larger dose to achieve the same degree of uptake into affected bones. This is currently the subject of further study.

Fig 2 shows the alkaline phosphatase profiles of four representative patients who had received previous forms of therapy. In all except two cases the level of alkaline phosphatase after intravenous APD was the lowest recorded. Evidently, patients resistant to calcitonin may be successfully treated with bisphosphonates, and some patients who only achieved a partial response to oral APD show a more marked response to intravenous APD.

It is not possible to conclude from the current data whether the use of daily or weekly infusions is more effective, but the use of a weekly regimen enables

Fig. 4 x Rays of anterior half of the skull (a) before and (b) five months after the end of treatment with intravenous APD, regimen 2, in patient No 14 with severe osteoporosis circumscripta. Radiological evidence of healing, initially evident by three months, was seen in an increase in density in the lucent areas, and a dramatic loss of the clear line of demarcation between affected and unaffected bone; it was matched by an improvement in headache, loss of bone tenderness, and a marked reduction in activity on the bone scan (scans shown are those (c) immediately before and (d) three months after the end of treatment).

outpatient treatment. With the current regimen all patients started to show a fall in serum alkaline phosphatase level either before or after the fourth infusion. Regardless of which treatment regimen was used, most patients showed a progressive fall in alkaline phosphatase, which continued for some time after the discontinuation of therapy. It remains to be seen for how long this fall will be sustained. Khairi *et al* showed that many patients treated with EHDP remain in remission for several months after stopping treatment.¹⁷ This contrasts with discontinuation of prolonged calcitonin treatment, which results in a rapid return to pretreatment alkaline phosphatase levels.¹⁸

Earlier studies in rats showed that EHDP led to hyperphosphataemia, which was postulated to result from competitive inhibition of renal tubular secretion of phosphate by the diphosphonate. In contrast, our finding of mild hypophosphataemia after APD confirms the results of Heynen *et al*.¹⁰ Although we did not detect any significant reduction in plasma calcium concentration, it is likely that this occurred transiently due to the inhibitory effect of the diphosphonate on bone resorption. This would lead to an increase in plasma parathyroid hormone concentration and hence account for the subsequent hypophosphataemia. In all six subjects in whom the phosphate concentrations fell to <0.8 mmol/l the values returned to within the normal range, either during or after discontinuation of treatment.

We believe that the intravenous route of administration of bisphosphonates has two potential advantages over the oral route. Firstly, for reasons that are not clear, absorption of oral diphosphonate varies as much as 10-fold between individuals,¹⁹ and is of course totally inhibited by food. Secondly, it should be possible to distinguish between genuine resistance to bisphosphonates and apparent resistance due to failure of absorption, and to make adjustments to the dose with less risk of toxic effects.

We are grateful to Professor L M Bijvoet for providing supplies of APD powder; to Mr G Norman and Dr M Jones of Manchester Royal Infirmary Pharmacy Department for preparing the APD for intravenous administration; to the nursing staff of the Medical Investigation Unit, Hope Hospital for their help; to Dr S Willets, District and General Hospital, Ormskirk, for the hydroxyproline assays; and to the Department of Chemical Pathology, Hope Hospital, for the other biochemical determinations.

References

- 1 Grunstein H S, Clifton P, Bligh M, Posen S. Paget's disease of bone: experience with 100 patients treated with salmon calcitonin. *Med J Aust* 1981; **2**: 278-80.
- 2 Woodhouse N J Y, Mohamedally S M, Saed-Nejad F, Martin T J. Development and significance of antibodies to salmon calcitonin in patients with Paget's disease on long-term treatment. *Br Med J* 1977; **ii**: 928-9.
- 3 Ryan W G. Treatment of Paget's disease of bone with mithramycin. *Clin Orthop* 1977; **127**: 106-10.
- 4 Russell R G G. Treatment of Paget's disease of bone. *Clin Rheum Dis* 1979; **5**: 673-95.
- 5 Canfield R, Rosner W, Skinner J, *et al*. Diphosphonate therapy of Paget's disease. *J Clin Endocrinol Metab* 1977; **44**: 96-106.
- 6 Boyce B F, Fogelman I, Ralston S, Smith L, Johnston E, Boyle I T. Focal osteomalacia due to low dose diphosphonate therapy in Paget's disease. *Lancet* 1984; **i**: 821-4.
- 7 Meunier P J, Chapuy M C, Alexandre C, *et al*. Effects of disodium dichloromethylene diphosphonate on Paget's disease of bone. *Lancet* 1979; **ii**: 489-92.
- 8 Yates A J P, Percival R C, Gray R E S, *et al*. Intravenous clodronate in the treatment and retreatment of Paget's disease of the bone. *Lancet* 1985; **i**: 1474-7.
- 9 Frijlink W B, Tevelde J, Bijvoet O L M, Heynen G. Treatment of Paget's disease with 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD). *Lancet* 1979; **i**: 799-803.
- 10 Heynen G, Delwaide P, Bijvoet O L M, Franchimont P. Clinical and biological effects of low dose 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) in Paget's disease of the bone. *Eur J Clin Invest* 1982; **11**: 29-35.
- 11 Vellenga C J L R, Mudler J D, Bijvoet O L M. Radiological demonstration of healing in Paget's disease of bone treated with APD. *Br J Radiol* 1985; **58**: 831-7.
- 12 Recker R R, Saville P D. Intestinal absorption of disodium ethane-1-hydroxy-1,1-diphosphonate using a devolution technique. *Toxicol Appl Pharmacol* 1973; **24**: 580-9.
- 13 Mautalen C A, Casco C A, Gonzalez D, *et al*. Side effects of disodium aminohydroxypropylidene diphosphonate (APD) during treatment of bone disorders. *Br Med J* 1984; **288**: 828-9.
- 14 Sleeboom H P, Bijvoet O L M, van Oosterom A T, Gleed J H, O'Riordan J L H. Comparison of intravenous (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate and volume repletion in tumour induced hypercalcaemia. *Lancet* 1983; **iii**: 239-43.
- 15 Dewis P, Prasad B K, Anderson D C, Willets S. Clinical experience with the use of two diphosphonates in the treatment of Paget's disease. *Ann Rheum Dis* 1985; **44**: 34-8.
- 16 Michael W R, King W R, Wakim J M. Metabolism of disodium ethane-1-hydroxy-1,1-diphosphonate (disodium etidronate) in the rat, rabbit, dog and monkey. *Toxicol Appl Pharmacol* 1972; **21**: 503-15.
- 17 Khairi M R A, Altman R D, De Rosa G P, Zimmerman J, Shenk R K, Johnston C C. Sodium etidronate in the treatment of Paget's disease of bone. *Ann Intern Med* 1977; **87**: 856-63.
- 18 Aramides A, Flores A, DeRose J, Wallach S. Paget's disease of bone: observations after cessation of long term synthetic calcitonin treatment. *J Clin Endocrinol Metab* 1976; **42**: 459-63.
- 19 Fogelman I, Smith L, Mazess R, Wilson M A, Bevan J A. Absorption of oral diphosphonates in normal subjects. *Clin Endocrinol (Oxf)* 1986; **24**: 57-62.