Low dose intravenous 3-amino-1-hydroxypropylylidene-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-hydroxypropylylidene-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, requirement for further courses, and merits relative to other second generation bisphosphonates remain to be established.

Key words: diphosphonates, metabolic bone disease, alkaline phosphatase.
Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Bone scan score</th>
<th>Treatment regimen</th>
<th>Alkaline phosphatase (IU/l)</th>
<th>Serum phosphate (mmol/l)</th>
<th>% of pre-treatment value</th>
<th>Weeks after start of APD</th>
<th>Pre-treatment value</th>
<th>Lowest value during treatment</th>
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<td>M</td>
<td>58</td>
<td>1</td>
<td>1</td>
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<td>28%</td>
<td>50</td>
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<td>44%</td>
<td>27</td>
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<tr>
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<td>82</td>
<td>3</td>
<td>1</td>
<td>1911</td>
<td>0.96</td>
<td>17%</td>
<td>48</td>
<td>1.05</td>
<td>0.71</td>
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<tr>
<td>4</td>
<td>F</td>
<td>81</td>
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<td>1</td>
<td>222</td>
<td>0.96</td>
<td>48%</td>
<td>48</td>
<td>1.03</td>
<td>0.57</td>
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<td>M</td>
<td>57</td>
<td>5</td>
<td>1</td>
<td>411</td>
<td>0.96</td>
<td>74%</td>
<td>28</td>
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<td>76%</td>
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<td>11</td>
<td>2</td>
<td>955</td>
<td>0.92</td>
<td>62%</td>
<td>6*</td>
<td>0.95</td>
<td>1.04</td>
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<td>8</td>
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<td>&gt;3800</td>
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<td>1</td>
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<td>24%</td>
<td>10</td>
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<td>71%</td>
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<td>12</td>
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<td>42%</td>
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<td>2</td>
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<td>57%</td>
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<tr>
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<td>F</td>
<td>55</td>
<td>12</td>
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<td>56%</td>
<td>26</td>
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<td>57%</td>
<td>38</td>
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<tr>
<td>18</td>
<td>F</td>
<td>69</td>
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<td>62%</td>
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<td>78%</td>
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<tr>
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<td>77</td>
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<td>1.17</td>
<td>85%</td>
<td>15</td>
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<td>1.02</td>
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</tbody>
</table>

*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-dimethylaminoazobenzenadehyde.

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.
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, 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. 3  Response to intravenous APD (regimen 2) in patient No 14 who had osteoporosis circumscripta of the skull (see Fig. 4 for radiological evidence of healing). ●●● alkaline phosphatase (IU/l); × --- hydroxyproline (HOP)/creatinine (Cr) ratio.

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, 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...
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.\(^\text{17}\) This contrasts with discontinuation of prolonged calcitonin treatment, which results in a rapid return to pretreatment alkaline phosphatase levels.\(^\text{18}\)

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 hyperphosphataemia after APD confirms the results of Heynen et al.\(^\text{10}\) 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,\(^\text{19}\) 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

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