Clodronate in Hypercalcaemia and Osteolytic Bone Disease due to Breast Cancer

J. A. Kanis, E. V. McCloskey, N. O’Rourke, S. Khan, D. Fern, K. Eyres, P. Sirtori, T. Taube, T. Powles, A. Paterson


Clodronate is one of the geminal bisphosphonates which are analogues of pyrophosphate (Fig. 1). Like pyrophosphate and other bisphosphonates it is adsorbed onto bone mineral, a property which is exploited in skeletal scintigraphy. Unlike pyrophosphate, the bisphosphonates are resistant to enzymatic hydrolysis. In tissue culture they inhibit normal and stimulated bone resorption, and prevent osteolysis due to parathyroid hormone, calcitriol, prostaglandins and the cytokines. The wide spectrum of inhibitory activity suggests that all the bisphosphonates act at a distal step in the cellular events which effect bone resorption.

The precise mechanism of action of clodronate on bone cells is uncertain since, for example, the inhibitory activity of bisphosphonates on bone resorption in vitro bears little relationship to their activity in vivo. It is likely that the bisphosphonate structure itself permits its targeting to skeletal sites, and that the structural modifications of the side-chains determine potency and range of activity. The aminobisphosphonates are particularly potent inhibitors of bone resorption, and their potency varies according to the length of the side-chain. Some bisphosphonates also inhibit the mineralization of bone. The relative potency to inhibit mineralization and resorption differs between compounds, and of those tested in man, etidronate has the more marked effects on mineralization. This makes etidronate less suitable for long-term use than clodronate or pamidronate.

Progressive osteolysis is a significant cause for morbidity in patients with neoplasia affecting the skeleton. It gives rise to fractures, bone pain and hypercalcaemia. The mechanism for osteolysis is principally mediated by the activation of bone resorbing cells. The bisphosphonates are specific inhibitors of osteoclast mediated bone resorption and have been widely used in the management of osteolysis. Clodronate is one of the bisphosphonates that may be given by mouth or by parenteral injections. Both formulations lower serum calcium in the vast majority of affected patients due to the inhibition of bone resorption. Moreover, the agent also has significant effects on bone pain. There is increasing evidence that the long-term use of clodronate decreases the incidence of intercurrent hypercalcaemia, bone pain and fracture and thereby improves the quality of life of affected patients.
Figure 1. Structure of pyrophosphate and of three bisphosphonates which are available for the treatment of hypercalcaemia in breast cancer.

Hypercalcaemia and osteolysis in malignant disorders are both mediated by accelerated rates of osteoclastic bone destruction. In healthy adults, bone resorption occurs in discrete foci on bone surfaces, but is followed by a subsequent in-filling of resorption cavities by new bone formation and mineralization governed by the activity of bone forming cells or osteoblasts. The osteolysis of malignant disease is associated with increased osteoclast activity followed by an inadequate osteoblastic response giving rise to progressive destruction of bone. Focal skeletal lesions are induced by paracrine activators of osteoclasts (e.g. lymphotoxin, prostaglandins, procathepsin D), whereas generalized osteolysis is induced by stimulation by systemic endocrine factors produced by the tumour (e.g. parathyroid hormone related protein; PTHrP), or by the effect of tumour on host tissues (e.g. some cytokines). Since hypercalcaemia and increased bone destruction are both mediated by the activation of authentic osteoclasts, and because the bisphosphonates inhibit the activity and numbers of osteoclasts, there has been much interest in their use in these disorders.

### Table 1

<table>
<thead>
<tr>
<th>Metastases</th>
<th>n</th>
<th>% Hypercalcaemic</th>
<th>% Hypocalcaemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoblastic</td>
<td>25</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Mixed</td>
<td>15</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Osteolytic</td>
<td>31</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>22</td>
<td>18</td>
<td>5</td>
</tr>
</tbody>
</table>

Serum calcium and the nature of skeletal metastases in breast cancer. Note that hypercalcaemia is most frequently associated with osteolytic metastases

cancer is nearly always associated with osteolytic metastases (Table 1). However, several other factors are important both for the induction and maintenance of hypercalcaemia. In the induction of hypercalcaemia, the production of endocrine factors such as PTHrP secreted by many solid tumours, not only results in a generalized increase in bone resorption, but also increases renal tubular reabsorption of calcium. Increased renal tubular reabsorption contributes to hypercalcaemia in about one-third of patients with breast cancer and this aggravates hypercalcaemia. In some patients without skeletal metastases, increased renal reabsorption of calcium may be the principal mechanism for the induction of hypercalcaemia (the humoral hypercalcaemia of malignancy).

In addition, hypercalcaemia may be maintained by the secondary effects of the hypercalcaemic state. These secondary effects include nephrogenic diabetes insipidus resulting in polyuria, sodium depletion and a secondary increase in renal tubular...
reabsorption of calcium. Intravascular volume depletion may impair renal function, and so too may hypercalcaemia by inducing structural damage. Both factors decrease the ability of patients to withstand a hypercalcaemic challenge.

These variable mechanisms for the induction and maintenance of hypercalcaemia are important to consider when evaluating the activity of bisphosphonates in hypercalcaemia. Thus, most hypercalcaemic patients are volume depleted, and the administration of saline alone will improve hypercalcaemia. The apparent efficacy of agents given with saline or other concurrent medications may be incorrectly attributed to the trial agent. For example, the use of saline and corticosteroids is well established in the management of hypercalcaemia due to solid tumours. It is clear, however, that the principal effect of this regimen is due to saline, and corticosteroids, contrary to popular belief, have little if any added effect.

In assessing the effects of clodronate in hypercalcaemia, these problems have been overcome either by the use of controlled trials, or by the pre-treatment of hypercalcaemic patients with intravascular volume expansion until a new steady state of serum calcium has occurred. Under these conditions, and in the absence of concomitant therapy, further changes in serum calcium can be attributed to the bisphosphonate. Much clinical experience indicates that the administration of clodronate either by mouth or by intravenous infusion improves hypercalcaemia due to malignancy and that the principal mechanism of action is the inhibition of bone resorption. But the ultimate effect of clodronate (or other bisphosphonates) on serum calcium depends critically upon the factors responsible for its maintenance. In the case of breast cancer with skeletal metastases, normocalcaemia is usually attained (Fig. 2). In contrast, in the humoral hypercalcaemia of malignancy, serum calcium is less frequently normalized since clodronate does not decrease renal tubular reabsorption of calcium.

Optimal effects are observed with an intravenous regimen of 300 mg daily for 5 days. A comparable response is observed with a single infusion of 1500 mg over a single day. Lower doses have less complete effects (Table 2). When used intravenously clodronate must be given by slow infusion over 2–4 h, since a rapid bolus injection may induce renal damage.

Studies with the use of oral clodronate (generally 1600–3200 mg daily) have shown that serum calcium is reduced to normal in the majority of hypercalcaemic patients. When clodronate is given by mouth it is important that it is taken well away from food and from calcium-containing liquids, both of which decrease absorption, which is in any case very low (in the order of 1–4%).

The action of clodronate to inhibit tumour mediated bone resorption appears to last for the duration of treatment, both in myelomatosis and in solid tumours associated with skeletal metastases. Thus, the bisphosphonates have been used not only to treat hypercalcaemia, but also to prevent its recurrence. In a few cases an initially favourable response to treatment has been followed by a relative resistance to further treatment. It is not certain whether this represents true resistance of osteoclasts to bisphosphonates, or the emergence of non-osteoclast mediated bone resorption in the late stages of neoplastic disease.

### Treatment of Accelerated Osteolysis

Advanced breast cancer is a common cause of skeletal disease. Bone pain, pathological fracture and hypercalcaemia account for significant morbidity and some of the mortality associated with this disease. It is important to be able to recognize those patients who are at risk of skeletal complications and to institute appropriate therapy to prevent or delay the development of these complications.
Table 3
Incidence of complications in 34 patients with breast cancer and skeletal metastases given clodronate or placebo for 1 year and followed up for a further year

<table>
<thead>
<tr>
<th></th>
<th>Clodronate 1 year</th>
<th>2 years</th>
<th>Total</th>
<th>Placebo 1 year</th>
<th>2 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>New bone metastases</td>
<td>3</td>
<td>11</td>
<td>14</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Skeletal fractures</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Episodes of hypercalcaemia</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Survival</td>
<td>4</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

with this tumour. Focal and generalized skeletal disease often responds to chemotherapy and local radiotherapy. It is clear, however, that in many patients skeletal disease is slowly progressive, despite the induction of otherwise stable remission. Several studies have now shown that clodronate is capable of inhibiting bone resorption in normocalcaemic patients for prolonged periods, either with continuous treatment or with intermittent intravenous administration.11-15

Histomorphometric measurements from bone have shown that long-term treatment is associated with a reduction in osteoclast numbers at the site of metastases from breast cancer, and no adverse effects on bone formation or mineralization have been observed.16 In a double-blind study,11,12 clodronate (1600 mg daily) decreased the morbidity of skeletal complications as judged by the incidence of hypercalcaemia, pathological fractures and severe bone pain. In this study there was also an apparent survival advantage in the treatment wing. It should be noted, however, that the number of patients studied in this trial was not sufficient to eliminate type II statistical errors. It is of interest, however, that the apparent survival advantage was largely due to a decrease in hypercalcaemia and orthopaedic complications. It is also of interest that new bone metastases were observed in 3 of 17 clodronate treated patients, but 11 of 17 placebo treated patients, suggesting that clodronate might inhibit the growth of micrometastases (Table 3).16

Our own studies in breast cancer have examined the effects of clodronate 1600 mg daily or placebo on the incidence of hypercalcaemia and vertebral fractures. Both were significantly decreased by treatment. Bone pain as assessed indirectly by the requirements for radiotherapy to bone and these also decreased.17 These studies, undertaken under double-blind conditions indicate a substantial improvement in the quality of life in clodronate treated patients.

Side-Effects

Very few side-effects from treatment with intravenous bisphosphonates have been reported. The rapid bolus injection of clodronate may precipitate acute renal failure,1 but this type of nephrotoxicity can be avoided by slow intravenous infusion over 1 or 2 h.18 Intravenous etidronate may be associated with an unpleasant metallic taste in the mouth, which is transient and disappears several hours after the cessation of the infusion.19 This effect is not seen with clodronate. Pami-

dronate, like other amino bisphosphonates, causes transient leukopenia and, in some instances, a fever 24-48 h after the first infusion.20 Again, such effects are not observed with clodronate.

Very few side-effects from treatment with oral clodronate have been reported. The most frequently reported side-effect is mild intestinal intolerance, which occurs in about 10% of patients after oral treatment with 1600 mg daily or more. This can be avoided by splitting the daily dose. Unlike etidronate, clodronate may be used after its intravenous infusion to maintain normocalcaemia in hypercalcaemic patients since it has no adverse effects on the mineralization of bone.21

References


