Bisphosphonate treatment of bone disease

N J Shaw, N J Bishop

The purpose of this review is to identify what new information has been gained over the past seven years and to provide our opinions for the future use of such drugs in children and what further research needs to be undertaken.

MECHANISM OF ACTION AND RELATIVE POTENCY

Bisphosphonates are chemical analogues of pyrophosphate. The presence of a carbon rather than oxygen atom at the centre of the molecule prevents its breakdown. The two phosphate groups are attached directly to the carbon atom from which also extend the R1 and R2 side chains (fig 1). The R1 side chain is usually a hydroxyl group and is often referred to as the “bone hook” in association with the phosphonic groups. It is the R2 side chain that confers the differential potency of the different molecules. The older bisphosphonates, etidronate and clodronate, form cytotoxic acyclic ATP analogues which accumulate in osteoclasts (following endocytosis from bone surfaces), leading to apoptosis (programmed cell death). This inhibition leads to failure of prenylation (transfer of fatty acid chains) of a variety of intracellular proteins, particularly small GTP binding proteins such as Ras, Rab, Rho, and Rac. Failure of prenylation leads to the inability of these small proteins to translocate into cell membranes. The resulting interference with cellular processes leads to earlier apoptosis of several cell types including osteoclasts. At the cellular level, the loss of osteoclast function leads to a reduction in bone resorption and, hence, a cascade of events (fig 2).

The commonly used nitrogen containing bisphosphonates comprise pamidronate, olpadronate, ibandronate, alendronate, risedronate, and zoledronate. Their relative potency which has been assessed in in-vitro assays for osteoclast inhibition and the effect on pit formation of osteoclasts seeded onto dentine slices, are shown in table 1, taking etidronate as having a potency of 1.

In 1997 a review article on bisphosphonates in this journal identified 24 published articles relating to children at that time. Since then there has been a considerable increase in their use in clinical paediatric practice and research with there being nearly a further one hundred articles published at the time of writing.
of 1 mg/kg of pamidronate, one study which examined the use of intravenous pamidronate (dose range 2–15 mg/kg/y) given every three to six months and include glucocorticoid in-
terpretation. The lack of beneficial effect on functional outcome is in contrast to the previously reported uncontrolled studies using intravenous pamidronate. No child who received active treatment reported gastrointestinal upset or had evidence of renal or hepatic dysfunction.

One study of 38 children with connective tissue disease, 30 of whom were receiving continuous glucocorticoid therapy for at least six months, evaluated the use of alendronate over a period of one year. Subjects weighing less than 20 kg received a dose of 5 mg daily and those greater than 20 kg received 10 mg daily. Lumbar spine BMD increased by a mean of 14.9%, in comparison to an increment of 2.6% in an untreated control group containing patients with less severe disease. There were insufficient duration and numbers to comment on effects on fracture incidence. Apart from some reports of gastrointestinal irritation the drug was well tolerated. There are currently few studies of oral bisphosphonate usage in children containing a significant number of children with the same condition to enable decisions to be made regarding their efficacy, and there are no studies comparing oral to intravenous bisphosphonates in the same condition.

**Hypercalkaemia**

Bisphosphonates have been used in children with hypercalcaemia due to a variety of causes including immobilisation, leukaemia, hyperparathyroidism, and subcutaneous fat necrosis. A retrospective review of the use of intravenous pamidronate in five children with hypercalcaemia associated with malignancy showed successful resolution within 48 hours with single infusions of 1–2 mg/kg. One patient developed symptomatic hypocalkaemia and two developed transient hypophosphataemia. Intravenous pamidronate in doses of 35–60 mg/m² also proved successful in children with advanced liver disease and hypercalcaemia prior to liver transplantation. Another report documents responses to intravenous pamidronate in doses ranging from 0.5 to 1.0 mg/kg in three children with hypercalcaemia of differing aetiology. Oral etidronate in a dose of 3.7 mg/kg/day proved effective in normalising plasma calcium within two weeks in a child with immobilisation induced hypercalcaemia secondary to Guillain–Barré syndrome. Etidronate was also used in a dose of 5 mg/kg twice daily in a 1 month old infant with hypercalcaemia secondary to subcutaneous fat necrosis who had failed to respond to intravenous saline, frusemide, and prednisone, with the plasma calcium normalising within 24 hours. We are also aware of the use of intravenous

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**Table 1 Relative potency of bisphosphonates to inhibit bone resorption**

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Relative potency</th>
</tr>
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<tbody>
<tr>
<td>Etidronate</td>
<td>1</td>
</tr>
<tr>
<td>Clodronate</td>
<td>10</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>100</td>
</tr>
<tr>
<td>Olpadronate</td>
<td>200–500</td>
</tr>
<tr>
<td>Risedronate</td>
<td>500–1000</td>
</tr>
<tr>
<td>Alendronate</td>
<td>2000</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>10000</td>
</tr>
</tbody>
</table>

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**Figure 1 Structure of pyrophosphate and bisphosphonate.**

- **Pyrophosphate**
  - O
  - O
  - O
  - O
  - O

- **Bisphosphonate**
  - O
  - O
  - R1
  - O
  - R2
  - O

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Pamidronate in the treatment of hypercalcaemia due to neonatal severe hyperparathyroidism and immobilisation hypercalcaemia following spinal cord injury.

**Calciosis**

In contrast to their use in osteopathy and hypercalcaemia, there have been few further reports of the use of bisphosphonates in conditions associated with calciosis in paediatric practice such as dermatomyositis, fibrodysplasia ossificans progressiva, and scleroderma. One report of a 6 year old child with extensive subcutaneous calcification secondary to dermatomyositis documents the use of oral alendronate in a dose of 10 mg daily for one year. During this time the bouts of fever and cellulitis related to the calciosis ceased and the range of joint movements improved within six months, with radiological resolution of calcified deposits in the axilla and extrusion of several calcified deposits through the skin.

**Miscellaneous conditions**

Fibrous dysplasia is a condition in which bone marrow cells are affected by somatic activating mutations of the gene encoding the α subunit of the stimulatory G protein Gsα. In this condition dysplastic lesions within the skeleton can cause bone pain, cranial nerve compression, bone deformity, and fractures. It may occur in isolation or more commonly as part of the McCune-Albright syndrome. Intravenous pamidronate has been used in several small studies with reports of improvement in bone pain and a reduction in markers of bone turnover. Although a study in adults reported refilling of the dysplastic bone lesions in approximately 50% of patients, a detailed radiological and histological study in 18 children and adolescents treated with pamidronate for at least one year did not confirm this effect. Iliac crest bone biopsies containing dysplastic bone lesions showed no effect of treatment on parameters of bone resorption and a progression in the bone deformity necessitated orthopaedic surgery in seven patients. Thus it would appear that in this particular patient group the only indication for such treatment would be uncontrollable bone pain.

Idiopathic hyperphosphatasia is a rare autosomal recessive bone disorder characterised by excessive bone resorption and bone formation which may present in infancy or later childhood. Most cases are due to inactivating mutations in the gene coding for osteoprotegerin. Progressive bone deformity and fractures often lead to loss of ambulation by the teenage years. An 11 year old girl with this condition, who had failed to respond to conventional monthly doses of pamidronate, was then treated with intravenous ibandronate; 5 mg infusions were given every month until suppression of alkaline phosphatase levels was achieved. She received 45 mg over three years, during which biochemical markers of bone turnover were suppressed into the normal range; she had no further fractures and she remained mobile.

**Figure 2** Cascade of events triggered by administration of a bisphosphonate.
ADVERSE EFFECTS

The most common side-effect of oral bisphosphonate is gastrointestinal upset, which occurs in approximately 30% of patients. It is usually self-limiting, and patients should be advised to take the medication with food or milk to reduce the risk of esophageal irritation. Other common side effects include nausea, vomiting, and abdominal pain. Infusion-related reactions are also common, with symptoms typically occurring within 30 minutes of the start of the infusion. These reactions are usually transient and can be managed with supportive care. Potentially more serious problems have arisen from the use of bisphosphonates, including severe symptomatic hypocalcaemia, which can lead to symptomatic hypercalcemia and osteonecrosis of the jaw. These complications are rare, but they can be severe and are usually associated with high doses of oral bisphosphonates or prolonged infusion therapy. There have been several reports of severe symptomatic hypocalcaemia occurring in patients with chronic renal failure, who may be at increased risk of bisphosphonate-associated hypercalcemia.

Although there has been a considerable addition to the published literature on the use of bisphosphonates in children since 1997, there remain a number of unanswered questions which would benefit from future research. These include:

- The role of oral bisphosphonates in the treatment of children with OI
- The optimum dose and frequency of administration
- The impact on bone density and fracture frequency
- The role of biochemical markers in monitoring treatment
- The effect of bisphosphonate treatment on the risk of osteonecrosis of the jaw
- The potential long-term effects of bisphosphonate treatment on bone and mineral metabolism
- The role of bisphosphonates in the treatment of other bone diseases in children

There is currently little information on the use of bisphosphonates in children, and further studies are indicated. It is important to continue to evaluate the efficacy and safety of bisphosphonates in children, particularly in those with severe bone disease, to ensure that the benefits outweigh any potential risks.

Although bisphosphonates have been shown to be effective in the treatment of bone disease in children, there are still questions which need to be addressed. These include:

- The optimum dose and frequency of administration
- The impact on bone density and fracture frequency
- The role of biochemical markers in monitoring treatment
- The effect of bisphosphonate treatment on the risk of osteonecrosis of the jaw
- The potential long-term effects of bisphosphonate treatment on bone and mineral metabolism
- The role of bisphosphonates in the treatment of other bone diseases in children

There is currently little information on the use of bisphosphonates in children, and further studies are indicated. It is important to continue to evaluate the efficacy and safety of bisphosphonates in children, particularly in those with severe bone disease, to ensure that the benefits outweigh any potential risks.
Use as prophylaxis. The majority of current usage in children is for conditions with significant clinical effects, for example, fractures inOI and bone pain in fibrovascular dysplasia. We are aware of them being administered prophylactically in conditions where a child has been identified as having a low bone density in the absence of fractures, and it has been felt important by the clinician responsible to offer treatment. However, in many of these conditions there is currently a lack of good evidence that the low bone density leads to an increased fracture frequency in the short or long term, and such studies are necessary to justify the use of prophylactic treatment. One condition where there is a high prevalence of abnormal bone density and fractures is juvenile idiopathic arthritis. A multicentre study in the UK is due to commence, which will examine the prophylactic use of a bisphosphonate. In many conditions where abnormal bone density has been identified, there is a need to understand the aetiology, as such knowledge may lead to alternative methods of prevention and treatment; for example, the role of hypogonadism in thalassaemia and the importance of appropriate sex steroid replacement in this group.24

WHO SHOULD BE TREATING AND MONITORING PATIENTS?
The availability of bisphosphonates is undoubtedly a significant advance in the therapeutic armamentarium for bone disease in children. However, the case report of bisphosphonate-induced osteopetrosis17 illustrates the potential risks of misinterpretation of clinical information and the inappropriate use of a bisphosphonate. Such a case is unlikely to be isolated. The availability of bone densitometry for children leads to the identification of many children with chronic disease who have abnormal results, leading to a temptation for the clinician to administer treatment with a bisphosphonate. The potential pitfalls in the use of bone densitometry in children are not widely appreciated,33 and incorrect interpretation may lead to misdiagnosis of abnormal bone density. The management of osteoporosis and related bone disorders in children is an evolving discipline with few clear guidelines to date. In view of these issues we would support the view that bisphosphonate therapy should be used only in the context of a well-run clinical programme with specialist knowledge in the management of bone disease in children.34

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REFERENCES
For young people with chronic disease the process of transfer from paediatric to adult care may be stressful, and prolonged and careful preparation may be needed. Paediatric rheumatologists in Birmingham (KM Bailey and colleagues. Annals of Rheumatic Diseases 2004;63:1544–8) refer to the event of transfer and the process of transition. During transition many factors need to be considered that affect the medical, psychosocial, and educational and career needs of the young person. In too many cases transfer is a sudden event with little or no apparent prior consideration.

The Birmingham team take as an example the case of a young man with juvenile idiopathic arthritis (JIA) who was recently transferred to adult care at the age of 19 years. He had developed systemic JIA at the age of 2 years and had suffered many of the complications of severe disease including small stature, delayed puberty, osteoporosis, and joint destruction. He had had many drug treatments (steroids, nonsteroidal antiinflammatory drugs, penicillamine, methotrexate, ciclosporin, intravenous immunoglobulin, rifampicin, isoniazid, and etanercept) and many operations (synovectomy, supracondylar osteotomies, replacement of one hip at age 12, the other hip at age 19, knees at ages 15 and 17, and cervical fusion and odontoidectomy). He has an electric wheelchair and is about to learn to drive a modified car. In spite of all his troubles he is now at university.

This young man has been prepared gradually for transfer to adult care since the age of 11 when the suggestion that he should be seen alone in clinic, or choose who should attend, was introduced. The eventual transfer to adult care was discussed from the age of 15. When the transfer occurred he was seen initially in a young adult clinic with his paediatric rheumatologist present. An individualised transition plan was worked out that referred to transitions in health, home activities, and educational and career plans. Control of disease activity needs to be as good as possible at the time of transfer and parental anxiety needs to be anticipated. Adolescents with chronic disease often know surprisingly little about their disease (for instance, two thirds of adolescents with JIA in a recent study were unaware of what the letters JIA stood for).

Disease education should be reviewed before transfer. Young people with chronic disease need careful preparation for transfer to adult care and professionals who care for young people, both paediatricians and specialists in the medicine of adults, should be trained in adolescent health.