Biphosphonates

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Background
The bisphosphonates (previously referred to as biphosphonates or diphosphonates) are a group of agents which are analogues of pyrophosphate. When administered either orally or parenterally they are adsorbed onto hydroxyapatite crystals in bone mineral and, because their structure renders them resistant to enzyme degradation, they act principally by inhibiting bone resorption, although some effect on bone formation probably also occurs.1

The net effect is to promote bone mineral accretion while at the same time considerably reducing bone turnover. Because of this latter effect, there have been concerns about the use of bisphosphonates in children in whom bone turnover is normally much greater than in adults. As a result, there have been fears that interference with the rapid remodelling process, which is necessary in growing bones, might result in bone deformity or serious disruption of the normal mineralisation process. The limited experience of their use has, so far, largely proved these fears to be groundless.

Wide experience of the use of bisphosphonates has been gained in adults, principally for the treatment of involutional osteoporosis, Paget’s osteitis deformans, and the hypercalcaemia and bone pain of malignancy. Several hundred papers have been published on these topics, many of them as a result of properly controlled trials. In contrast, very few studies in children have been published.2–4 These are all anecdotal and only one study included any control subjects.5 Nevertheless, the limited experience of the use of bisphosphonates in children and adolescents which has so far been gained does suggest that, for some conditions such as osteogenesis imperfecta and perhaps juvenile osteoporosis, wider use is indicated and may provide a useful additional therapeutic measure.

Pharmacology
The bisphosphonates are pharmacologically simple compounds that all have a phosphorus-carbon-phosphorus structure (compare with the phosphorus-oxygen-phosphorus structure of pyrophosphate). The presence of carbon rather than oxygen allows the addition of side chains to the carbon atom that determine the specific properties of any individual compound. Thus nitrogen is present in pamidronate, alendronate and neridronate, chlorine in clodronate and tiludronate, and sulphur in tiludronate. These alter the pharmacological profiles and influence the extent to which bone formation as well as bone resorption is inhibited. They may also determine side effects. Some bisphosphonate preparations are used after technetium labelling as bone scanning agents.

Little is known of the pharmacology of the bisphosphonates in children as no specific studies have been undertaken and all the information that is available has been obtained in adult subjects. They can be administered either intravenously or orally. If given orally, only a small proportion (about 2%) is absorbed, the rest remaining within the bowel lumen. The amount absorbed is dependent on the time of administration in relation to food and it is usually recommended that food is avoided for at least two hours before or after administration. However, bisphosphonates are readily soluble in water and can be made up in different strengths for paediatric use.

Only four agents, etidronate, pamidronate, clodronate, and alendronate have been given product licences in the UK. None of these is recommended for use in children and therefore no dosage schedules are available. In the published paediatric studies intravenous administration has been given daily for between one and 18 days in doses ranging between approximately 0.2 and 1.0 mg/kg/day. In some reports these doses have been repeated after three or six months, depending on the condition being treated. In others, the initial intravenous treatment has been followed by oral administration and oral treatment alone has also been used. The duration of oral treatment has varied from one to 83 months, but has mostly been for between six and 24 months either continuously or intermittently in doses approximately 20 to 40 times that of intravenous use (reflecting the poor bioavailability via the oral route).

Clinical usage
The conditions for which bisphosphonates have been used in children are more diverse than those of adults and can broadly be divided into four groups: those in which (1) there is a primary defect in bone mineralisation (for example juvenile osteoporosis); (2) bone matrix abnormalities are seen (for example osteogenesis imperfecta); (3) bone abnormalities result from systemic disease or the effects of treatment of systemic disease (for example...
Bone abnormalities secondary to systemic disease

This forms the largest group of children (20) who have been treated with bisphosphonates. In most cases this resulted either from immobilisation (with or without hypercalcaemia) after tetraplegia, 12, 13 or cerebral palsy, 14 or from steroid treatment of juvenile chronic arthritis. 3, 15 One further child was treated for hypercalcaemia associated with acute leukaemia, 16 another had hypercalcaemia after immobilisation after a liver transplant, 17 a third had severe osteoporosis associated with congenital neutropenia, 18 a fourth girl with primary oxalosis was treated for hypercalcaemia after transplantation with either liver and/or kidney, 19 and a fifth child with malignant osteopetrosis was treated for hypercalcaemia after bone marrow transplantation. 20 In all cases hypercalcaemia, where present, was corrected and in many the osteoporosis improved.

Adverse effects

The use of bisphosphonates in children appears to be relatively safe even when used for quite long periods. All of the preparations used have an influence on bone turnover and in those conditions in which increased turnover is present, this effect is desirable and is reflected in a reduction in plasma alkaline phosphatase. However, an increase in translucent areas in bone, 21 and widening of the growth plate, 22 have been reported and, in one instance of juvenile osteoporosis, there was an initial deterioration in spinal fractures before overall improvement occurred. 23 Transient hypocalcemia, which may be symptomatic, can also be a problem, although this is only temporary. 10–12 Both of these effects are more likely to occur with intravenous than with oral treatment. It should also be noted that long term use of some bisphosphonates, particularly etidronate, can cause marked osteomalacia in adults, although this effect is less likely to occur with other compounds.

In rapidly growing bones, interference with bone remodelling may occur while treatment is being continued. This effect has been described as ‘undertubulation’, and consists of a failure of remodelling of the wide growth plate into the narrower metaphysis as the growth plate itself advances. When treatment is discontinued, remodelling does then occur leaving a normally shaped bone with a dense line of mineralisation at the point where the growth plate was being formed during the time.
of treatment. The increased density of bone which occurs during bisphosphonate treatment is largely seen at the points where bone mineralisation is occurring most rapidly, but does not seem to lead to bone deformity. The one young patient described who had severe osteogenesis imperfecta type III did show quite a marked disruption of bone architecture, but this was identical to the appearances seen in untreated osteogenesis imperfecta type III and has been described as ‘popcorn bone’ (F Glorieux, personal communication) and is unlikely to be a bisphosphonate effect.

Transient fever is recognised as a side effect of bisphosphonate treatment in adults and also occurs in children. However, it is an effect that is confined to the use of nitrogen containing compounds and has only been described with pamidronate.10 12 Anterior uveitis, episcleritis, and transitory conjunctivitis have all been reported with the use of pamidronate, but only when used intravenously.26 Transient myalgia, leucopenia, lymphopenia, and gastrointestinal disturbance may occasionally occur.27 All of these effects are self-limiting, although the ocular problems did recur if the patients were rechallenged.

Conclusions

Only very limited experience with bisphosphonates in children has been gained and most of the reports are either single or small numbers of case reports. The approach to treatment has been somewhat serendipitous and often in situations where a child is extremely ill. Nevertheless, the data which are available do suggest that bisphosphonates may be of value under certain circumstances, but the very real concerns about adverse effects will need to be addressed particularly as children may live for several decades after treatment has been instituted and it is necessary to ensure that long-term problems do not arise as a consequence. This is best done by ensuring that proper monitoring of plasma and urine biochemistry, markers of bone turnover, bone density measurements and the results of treatment on growth are undertaken and are best done where these patients can be gathered together so that larger numbers of these rare conditions can be studied under more controlled circumstances than previously. It may also be appropriate to extend the studies to children where problems of bone mineralisation are milder than those in whom bisphosphonates have hitherto been used. When treatment is being considered, informed consent from the parents and, if appropriate, the child needs to be obtained and an explanation given that none of the bisphosphonates is licensed for use in children and that knowledge of the long-term safety is very limited.

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