

CLINICAL REVIEW ARTICLE

Bisphosphonates in the Pediatric Rheumatic Diseases

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Treatment and prevention of osteopenia associated with pediatric rheumatic diseases is important in order to avoid bone fragility fractures, but also to obtain an optimal peak bone mass. Treatment options have been so far relatively unsuccessful.

Bisphosphonates (BPs), which are analogues of pyrophosphate characterized by P-C-P bonds, were first studied in humans about thirty years ago. Several chemical features contribute to their biological action: the P-C-P moiety gives to the compounds the ability to adsorb to hydroxyapatite and therefore to target to bone, while variations in the side chains determine the potency and spectrum of action of each individual compound. BPs are selectively concentrated in bone, and inhibit bone resorption by interfering with the action of osteoclasts. Some of the biochemical mechanisms that underly this effects have recently been elucidated.

Bisphosphonates (BPs) have been successfully used in adults for conditions such as Paget's disease, osteoporosis and hypercalcemia. Until recent years the use of BPs in the pediatric age has been limited, mainly due to concerns of possible adverse effects of these drugs that may persist in bone for many years, on a growing skeleton. More recently, BPs have been shown to be quite safe, at least on the short term, even in the pediatric age, and their use has been expanding (1,2). The conditions for which BPs have been used in children can be mainly divided in four categories: primary defects in bone mineralization (juvenile idiopathic osteoporosis); bone matrix abnormalities (osteogenesis imperfecta); bone abnormalities secondary to systemic diseases or iatrogenic; and soft tissue calcifications. The use of BPs in childhood has been so far mainly limited to the treatment of osteogenesis imperfecta, a group of genetic disorders principally affecting type I collagen and characterized by recurrent fractures and skeletal deformities. Intravenous pamidronate has been shown in several studies to be beneficial and safe in these patients, even when administered at a very young age (3-6).

Adverse effects in children have not been reported with increased frequency compared to adults, but the main concern remains possible interference with bone remodelling in a growing skeleton. Observed adverse effects include increase in body temperature following intravenous infusion, flu-like symptoms, nausea, abdominal pain, esophagitis, and mineralization defects (with

etidronate). Reversible radiological alterations, including bandlike metaphyseal sclerosis and concentric epi- and apophyseal sclerosis, have been described in prepubertal patients (7). Feared, but not observed, adverse effects include irreversible and permanent effect on bone remodelling, impaired healing and non-union of fractures, and damage to growth plates with impairment in linear growth. Indeed, bone biopsies of treated patients have shown no signs of mineralization defects, with normal bone structure (8).

This report will focus on the use of BPs in the treatment of low bone mass in patients with pediatric rheumatic diseases. Initially, Lepore et al. (9) treated seven patients with juvenile chronic arthritis with disodium clodronate for one year. Spinal bone density was measured with computed tomography: after one year of treatment there was an 8% mean increase, compared to a 7% decrease in a control group. One patient stopped treatment because of gastrointestinal side effects. Subsequently, Falcini et al. successfully treated 4 girls with intravenous alendronate (one with vasculitis, two with systemic lupus erythematosus, and one with juvenile dermatomyositis) who had received corticosteroids and who had suffered from vertebral fractures (10). Improvement of back pain and bone density increase (measured by dual X-ray absorptiometry, DXA) were observed.

More recently, we have performed an open multicenter prospective study, in order to assess safety and efficacy of oral alendronate in children with rheumatic diseases and low bone mass (11). Thirty-eight children were treated with alendronate for one year; 38 children who had the same primary disorders as the study patients but in a less severe form served as untreated controls. Mean bone mineral density (BMD), measured by DXA, increased by $14.9 \pm 9.8\%$ ($P < 0.002$ vs baseline) in the treated patients (reaching the normal range in 13 patients), and by only 2.6% in the control group (in which 15 patients had a decrease). Also, there was an increase in BMD ($15.3 \pm 9.9\%$) after alendronate therapy in 16 children who in the year before the study had shown almost no increase in BMD (mean, 1%). No new fractures were observed in the treated group.

After the first year, 10 patients (out of 30 who could be evaluated) continued treatment for another year, while 20 stopped treatment (12). During the second year the treated group had an additional BMD increase of $9.6 \pm 3.8\%$, while in the untreated group BMD increase was only $3.6 \pm 4.9\%$. Seven patients of this latter group had an actual BMD decrease.

In a follow-up study, we have evaluated the changes in bone metabolism and disease activity markers in 45 patients (31 F, 14 M) with rheumatic diseases treated with alendronate for 12 months (13). Relevant variables analyzed included demographic and anthropometric data, biochemical parameters of bone metabolism, disease activity indexes, and BMD values. For all variables, the differences between levels at baseline and at 12 months were calculated; the correlations between the variables studied, and between the BMD variation over 12 months and baseline levels of the different variables were also evaluated. There was a statistically significant decrease of both bone resorption and bone formation markers over the 12-month treatment period. On the contrary, none of the disease activity indexes changed significantly over one year. BMD Z-score change over one year did not correlate with variations of erythrocyte sedimentation rate, interleukin-6 levels, or C-reactive protein over the same period. These results support the conclusion that alendronate treatment is accompanied by a reduction of bone turnover also in the

pediatric age, and that the observed BMD increase is not secondary to a reduction of inflammatory activity.

Other studies followed our experience. Lang et al. (14) treated seven patients aged 6-18 years with connective tissue diseases (juvenile dermatomyositis 3, systemic lupus erythematosus 2, vasculitis 2) and previous fractures with pamidronate or clodronate. Despite continuous corticosteroid treatment, BMD Z-score significantly increased after one year. No significant side effects were noted.

Gattinara et al. (15) have evaluated the efficacy of cyclic etidronate in children with rheumatic diseases on chronic corticosteroid treatment. Twenty-five patients with a mean age of 15.6 years were enrolled. Most (22/25) of them were affected by juvenile idiopathic arthritis; all of them were supplemented with vitamin D. Etidronate was given orally for 15 days, followed by calcium citrate for 75 days on a cyclic course. Results were excellent, since DXA scans showed a substantial improvement of BMD over time. The mean yearly percentages of BMD changes were in fact – 6.5% in the year preceding onset of treatment, + 3.5% after 1 year, and + 13.8% after 2 years. No significant variation in steroid dose was observed during this period. A worldwide survey on the use of BPs among pediatric rheumatologists was performed in July 2002; fifteen centers (10 North America, 5 Europe) answered that they have used BPs for pediatric rheumatic diseases, for a total of 64 patients. Their diagnoses were: juvenile idiopathic arthritis 31 (systemic-onset for the vast majority), juvenile dermatomyositis 10, systemic lupus 10, vasculitis 2, steroid-induced (not specified) 3, other 8 (chronic recurrent multifocal osteomyelitis 3, calcinosis 2, CINCA/NOMID 1, infantile sarcoidosis 1, systemic sclerosis 1).

Apart from osteoporosis, other potential uses of BPs include the treatment of dystrophic calcinosis and of chronic recurrent multifocal osteomyelitis (CRMO). Encouraging results have been obtained in these settings, although mostly anecdotal case reports or small series have been described. Juvenile dermatomyositis is frequently complicated by calcinosis, that can be debilitating and for which there is no known effective treatment. BPs could induce a reduction of calcium turnover and deposition, and could also inhibit calcium accretion to the already formed calcifications (16). Moreover, their action on macrophages may reduce inflammation in the calcified areas. These effects could also be beneficial in other rare diseases characterized by pathological calcifications such as fibrodysplasia ossificans progressiva and myositis ossificans progressiva. CRMO is characterized by sterile inflammatory bone lesions. The analogy of this disorder to other diseases with localized areas of abnormal bone turnover and that are known to respond to therapy with BPs, such as Paget's disease and fibrous dysplasia of bone, has suggested their use in this condition as well.

In conclusion, bisphosphonates can also be administered in the pediatric age; however, since their long-term effects are still unknown, their use in clinical practice (i.e. outside research settings) should be restricted to selected cases.

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