Bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis

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ABSTRACT

Bisphosphonates are effective for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP). Their mechanism of action in this secondary osteoporosis is similar to the mechanism in postmenopausal osteoporosis. Patients with GIOP treated with bisphosphonates have a higher bone mineral density than placebo-treated patients (4% and 2% at the lumbar spine and femur, respectively). In addition, there is a trend for a reduction in vertebral fracture incidence in postmenopausal women. In parallel with general bone health measures, bisphosphonate therapy must be considered both in patients initiating and in those on chronic glucocorticoid therapy.

Introduction

There are several studies in the literature regarding the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP) with different bone-sparing agents, but the best evidence of efficacy have been provided by bisphosphonates.

Bisphosphonates are widely used as anti-resorptive drugs for the treatment of metabolic bone diseases. They are non-hydrolyzable analogs of pyrophosphate characterized by two C-P bonds (Fig. 1). From the basic P-C-P structure, a great number of variations are allowed by changing the side chains R_1 and R_2. The anti-resorptive potency of the drug is dependent upon the side chain, and the activity of the different bisphosphonates on bone resorption varies markedly.

At the tissue level, bisphosphonates decrease bone turnover, decreasing the birth of new remodeling units, while allowing normal filling in the remodeling space. This results in a decrease in bone remodeling, and an increase in bone mineral density. These two mechanisms can explain the effect of the drugs on bone strength: a decrease in the thinning of trabeculae, a decrease in the probability of perforation of the thinner trabeculae, and improvement of both the primary and secondary mineralization of bone.

Bisphosphonates decrease both the function of mature osteoclasts, and the recruitment and differentiation of osteoclast precursors.

Various mechanisms of action have been described, including changes in the ruffled border, shortening of the osteoclast lifespan by apoptosis, etc. They also may act through the secretion by osteoblasts of an inhibitor of osteoclast-mediated resorption (1-4). The molecular mechanism of action probably differs among the compounds depending upon their struc-

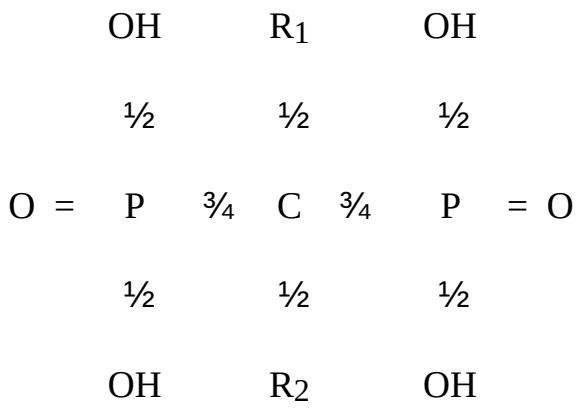

Fig. 1. Chemical structure of bisphosphonate. The anti-resorptive potency of the drug is dependent upon the side chains R_1R_2.

ture. Clodronate can be metabolized to a cytotoxic, non-hydrolyzable analog of ATP by macrophages, and probably osteoclasts (5). In contrast, the nitrogen-containing bisphosphonates (pamidronate, alendronate, risedronate, ibandronate) are not metabolized; it is likely that they act by preventing protein prenylation in osteoclasts, and that their molecular targets are enzymes of the mevalonate pathway or prenyl-protein transferases (6).

Bisphosphonates have shown efficacy in postmenopausal osteoporosis: they decrease the risk of vertebral and peripheral fractures in osteoporotic postmenopausal women (7-10). Surrogate markers of their efficacy are the decrease in biochemical markers of bone remodeling and the increase in bone mineral density (BMD).

In contrast with postmenopausal osteoporosis, the main pathophysiologic mechanism in GIOP is a decrease in both the number and the activity of osteoblasts, with a reduced trabecular wall thickness and bone mineralizing surface (11, 12). Glucocorticoids may promote osteoblast apoptosis (12). Changes in bone microarchitecture are different: in GIOP a thinning of the trabeculae is primarily observed, perforated only for a large decrease in trabecular volume (13). The effects of glucocorticoid on osteoclast activity are less clear; an increase in bone resorption has been proposed. Using bone histomorphometry, contradictory results have been obtained on resorption parameters, perhaps because of the effect of the underlying disease. However, the mechanism of action of the bisphosphonates is similar in GIOP and postmenopausal osteoporosis. In a histomorphometric analysis of transiliac biopsies performed in a large study of patients receiving high doses of glucocorticoids (11), it has been shown that the amino-bisphosphonate alendronate has no effect on bone resorption parameters (osteoclasts and eroded surfaces), in contrast with a decrease in biochemical markers of bone resorption (14), indicating a decrease in osteoclast function rather than in osteoclast number. Alendronate markedly decreases the rate of bone turnover, with a large decrease in the activation frequency; the magnitude of this effect is similar to that reported in postmenopausal osteoporosis treatment. This mechanism is the rationale for the use of an anti-osteoclastic drug in GIOP.

Prospective studies have been conducted on both the prevention and treatment of GIOP, with four bisphosphonates: etidronate, alendronate, pamidronate and risedronate.

Etidronate

Prospective studies have been conducted with etidronate, using cyclical intermittent use, 400mg/d for 14 days, following by calcium supplementation for 76 days, and repeated every 3 months for either 1 or 2 years.

Both controlled open studies and placebo-controlled studies (15-25) suggest that intermittent cyclic etidronate is able to reverse the loss of bone mineral density in patients with GIOP. BMD increases at both the spine (5% - 7%) and total hip (2.5% - 6.8%), compared to controls. Three prospective placebo controlled studies of one year duration have been conducted in patients initiating high dose glucocorticoid treatment for various medical conditions, including polymyalgia rheumatica, rheumatoid arthritis and vasculitis (22-24). Glucocorticoid treatment was started within 3 months prior to study entry, at a mean daily dose equal to or greater than 7.5 mg/day. In the European study (24), there was a statistically significant difference between etidronate and placebo groups at the lumbar spine (+0.3% versus -2.8%). At the femoral neck, the bone loss was decreased by a half, although the difference was not statistically different (effect of treatment: 1.3%). In the Canadian study (23), the same result was observed at the spine (+0.6% versus -3.2%) and a significant difference was observed at the great trochanter (+1.5% versus -2.7%). The changes in the femoral neck were not different between the groups. In these studies there was no difference in the incidence of adverse events (including problems involving the gastrointestinal tract) between the placebo and treated groups.

Because these studies were conducted using the same protocol, data were pooled, allowing analysis between subgroups (25). Similar treatment effects were seen in the diseases subgroups. The benefit of the treatment at the lumbar spine was 2.9%, 3.3% and 4.4% for men, premenopausal and postmenopausal women respectively. At the femoral neck and great trochanter differences between the placebo and etidronate groups were observed for postmenopausal women only. In the pooled prevention studies, 7 and 14 patients in the etidronate and placebo groups experienced a total of 8 and 34 vertebral fractures, respectively. Five patients had 5 non-vertebral fractures in the treated group, whereas 8 patients had 12 non-vertebral fractures in the placebo group (25).

In recent studies of etidronate for the treatment of GIOP (20, 21), there was a significant difference between the etidronate and placebo groups at the lumbar spine of 4.1% and 5.4% after 1 and 2 years, respectively (25). In these patients on long-term steroid therapy, who were also receiving calcium, lumbar spine BMD was unchanged during follow-up.

Alendronate

Alendronate is a potent amino-bisphosphonate which has a positive effect on BMD in patients receiving glucocorticoids (26) and in patients with Cushing's disease (27).

A large prospective study by Saag *et al.* (14) was performed on patients taking a median dose of 10 mg of prednisone daily at baseline. In this one-year study, 477 men and women were randomized to receive either alendronate 5 mg/d or alendronate 10 mg/d or placebo. All of the patients received 800 to 1000 mg of elemental calcium and 250 to 500 IU vitamin D daily. Patients with different diseases were comprised in the cohort, including 30% with rheumatoid arthritis and 20% with polymyalgia rheumatica. BMD increased at the spine (2.1% and 2.9% in the alendronate 5 and 10 mg groups) at the trochanter (1.1% and 2.7%), at the femoral neck (1.2% and 1.0%) and at the total body (0.4% and 0.7%). In women, BMD changes in the 10 mg alendronate treated group were dependent on the hormonal status: +2.0% in premenopausal women, +1.5% in postmenopausal women on hormonal replacement, and +4.0% in postmenopausal women without estrogen therapy, respectively. It is noteworthy that the

change in spine BMD in the placebo group was related to the duration of glucocorticoid therapy: -1% in the 34% of patients treated for less than 4 months, -0.6% for those treated for 4 to 12 months, and +0.2% in patients treated for more than 12 months. In contrast, neither the duration of glucocorticoid therapy nor the underlying disease influenced the response to alendronate.

Urinary excretion of N-telopeptides of type I collagen (a marker of bone resorption) decreased by 60% and serum bone-specific alkaline phosphatase concentrations decreased by 27% in the alendronate group (14). New vertebral fractures during the study were uncommon: 2.3% of the patients in the 2 alendronate treatment groups (pooled) versus 3.7% in the placebo group. A trend for a treatment effect was observed in post-menopausal women. The treatment with alendronate was safe. However, abdominal pain was more frequent in patients receiving alendronate 10 mg/d than in the other two groups. There was no increase in side effects involving the esophagus in the alendronate groups, compared to the placebo group.

Pamidronate

Pamidronate is another potent aminobisphosphonate, that is widely used for the treatment of malignant hypercalcemia and Paget's disease.

Pamidronate 150 mg/d was proposed in 1988 for the treatment of GIOP, and a benefit on vertebral mineral density over two years, as measured by quantitative computed tomography, was seen (28, 29). However, the effects of oral pamidronate on the upper gastrointestinal tract preclude its long-term use, and intravenous administration has been studied (30).

In a randomised open trial, 32 patients with inflammatory rheumatic diseases who required first-time corticosteroid therapy received either calcium alone or calcium and pamidronate (90 mg at the first injection, followed by 30 mg every 3 months) (31). A positive change was measured at the spine (+3.6%) and the hip (+2.2%) in contrast with a decrease in the calcium group (-5.3% at both sites). No acute phase reaction was observed, although this may be obliterated by glucocorticoid treatment.

Optimal compliance and convenience is ensured by the intravenous administration of bisphosphonate. This type of treatment certainly deserves further study.

Risedronate

Risedronate is a new pyridinyl bisphosphonate, which has been studied in 224 men and women who were initiating long-term corticosteroid treatment (32). Patients received either placebo or 2.5 or 5 mg/d of risedronate. After 12 months, there was no change in BMD compared to baseline at the spine in the 2 treated groups, but a 2.8% decrease in the placebo group. The mean difference in BMD between the 5 mg risedronate and the placebo groups was 3.8%, 4.1%, and 4.6% at the lumbar spine, the femoral neck and the great trochanter respectively ($p < 0.001$ for both). Urinary deoxypyridinoline/creatinine excretion decreased by 16.5% and 24.3% as early as 1 and 3 months, respectively, in the risedronate 5 mg group. Serum levels of bone-specific alkaline phosphatase did not change at 1 month and decreased by 15% at 3 months. No significant changes in these markers were observed in the placebo group. A trend toward a decrease in the incidence of vertebral fracture was observed in the 5 mg risedronate group, compared with the placebo group: 5.7% versus 17.3% ($p = 0.07$).

A randomized trial of treatment of GIOP by daily risedronate was conducted by Reid *et al.* (33). Patients were receiving high dose oral corticosteroid for more than 6 months, and all of them received calcium 1 g and vitamin D 400 IU daily during the trial. Risedronate 5 mg increased BMD at 12 months, by 2.9%, 1.8% and 2.4% at the lumbar spine, the femoral neck and the trochanter, while no change was observed in the placebo group ($p < 0.001$, $p = 0.004$ and $p = 0.01$, respectively). Nine out of 60 (15%) patients in the placebo group and 3 out of 60 (5%) patients in each treatment group experienced incident vertebral fractures by month 12, indicating a trend for a reduction in fracture risk (significance was reached when the risedronate-treated groups were combined). Treatment with risedronate was not associated with adverse gastrointestinal events.

Recently, this bisphosphonate was studied in a placebo-controlled trial on 120 women with rheumatoid arthritis requiring long-term glucocorticoid therapy. The administration over 2 years of 2.5 mg risedronate daily prevented bone loss at the lumbar spine and femoral trochanter, while significant bone loss was observed in the placebo patients. There was no difference between the 2 groups at the femoral neck, although bone density was maintained by the treatment at this site. Interestingly, most of the patients received NSAIDs and risedronate had a similar upper gastrointestinal profile to that observed in the placebo group (34).

Conclusion

When analyzing the different treatments proposed for GIOP, bisphosphonates certainly have the best effectiveness score. According to a meta-analysis, the mean difference in BMD between bisphosphonate-treated patients and controls in GIOP is 4.0% at the lumbar spine, and 2.1% at the femoral neck (34).

Bone loss is more prominent during the first months of medium to high-dose glucocorticoid therapy, with a slower rate of bone loss thereafter. The extent of change in bone density is mainly related to the duration of the treatment. In patients on chronic glucocorticoid treatment, bisphosphonates increase BMD; they stop bone loss in patients initiating glucocorticoid treatment.

None of the studies were able to assess the anti-fracture effect of bisphosphonates. There are no data on peripheral fractures. On the other hand, a trend has been seen for a reduction in vertebral fracture risk, especially in post-menopausal women.

In parallel with general preventive measures for bone health, including calcium and vitamin D supplementation, and hormone replacement therapy in hypogonadic subjects, bisphosphonates should be considered, both in patients with GIOP and in patients initiating high-dose, long-term, glucocorticoid treatment.

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