THE USE OF BISPHOSPHONATES IN OSTEOPOROSIS: A REVIEW

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ABSTRACT: **Bisphosphonates are synthetic analogues of pyrophosphate. Their main pharmacological effect is to inhibit bone resorption by a variety of mechanisms, not all of which are clearly understood. The activity of the bisphosphonates varies depending on the compound. In clinical trials, they have been shown to stop postmenopausal bone loss and increase bone density, with a concomitant reduction in fracture rate with some agents. This article reviews the currently known mechanisms of action of the bisphosphonates and the evidence that they are useful in the treatment of osteoporosis.** *(JUMMEC 1998 1&2: 13-17)*

Introduction

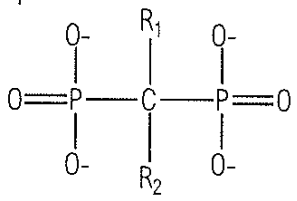
The bisphosphonate class of drugs have been developed over the last 20 years following the discovery in blood and urine of pyrophosphate, a naturally occurring inhibitor of calcification (1). Pyrophosphate consists of a P-0-P back bone which is easily hydrolysed and therefore does not allow for therapeutic use. Analogues of pyrophosphate, with the oxygen atom in the P-0-P backbone being replaced by a carbon atom to form a P-C-P backbone, were developed which are resistant to hydrolysis (2) and are called bisphosphonates (previously diphosphonates) (Figure 1).

Modification of the side chains of the carbon atom has led to the development of a variety of compounds with different properties. The aim of these modifications has been to increase anti-resorptive activity without a similar effect on inhibition of mineralization, since the latter has little clinical potential (2). The addition of amino groups (pamidronate, alendronate and risedronate), increasing the length of the side chains on the carbon atom (alendronate) and more recently adding methyl and pentyl groups (ibandronate) have led to high anti-resorptive properties without the concern of inducing defective mineralization (Table 1).

Mechanism of Action

All bisphosphonates bind strongly to hydroxyapatite, inhibit calcium phosphate formation and ectopic mineralization through a physicochemical inhibition of crystal growth. Bisphosphonates have similar effects on calcium carbonate, which is why they were originally developed as washing powders. Apart from this, they also inhibit bone resorption by inhibiting osteoclastic activity. The bisphosphonates are deposited onto bone because of their strong affinity for the mineral, and the ostcoclasts are then inhibited when they start to

Basic bisphosphonate



Pyrophosphate

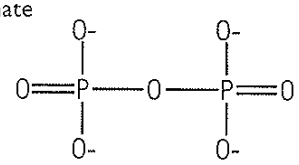


Figure 1. Chemical structure of a bisphosphonate and pyrophosphate

Table 1. Relative anti-resorptive properties of bisphosphonate compounds (4)

Compound	Anti-resorptive Potency *(in vivo)*
Etidronate	1
Clodronate	10
Tiludronate	10
Pamidronate	100
Alendronate	700
Ibandronate	4000
Risedronate	5000
Zolendronate	10,000

engulf the bisphosphonate containing bone. They seem to be preferentially deposited under the osteoclasts (3). Experiments with bisphosphonates on osteoclast cells show a reduction in acid production, reduction in lysosomal enzyme activity, reduction in prostagiandin secretion and increased membrane permeability (4). In addition, bisphosphonates also reduce the formation of osteoclasts from their mononuclear haematopoietic precursors in marrow cultures (5) and there is evidence that they can cause osteoclast apoptosis *in vitro* and *in vivo* (6). However, bisphosphonates will inhibit *in vitro* resorption of mineralized substrate even if they are added directly to the cells only, which suggests that they will also act in ways apart from binding onto bone mineral. This was found by Sahni and colleagues (7) who showed *in vitro* that inhibition of bone resorption is dependent on the presence of osteoblasts. Recently, it has been shown that in the presence of bisphosphonate, osteoblasts are stimulated to produce an inhibitor of osteoclast resorption which is heat and proteinase labile and has a molecular mass between 1 - 10 kDa (8).

The current evidence suggests that the mechanism by which bisphosphonates inhibit bone resorption is complex and involves a combination of a direct effect on osteoclasts and precursors and an indirect effect on osteoclasts via osteoblasts. The relative importance of these two mechanisms remains unclear.

Most of the pharmacokinetic data for the bisphosphonates come from animal studies with limited data on humans. Gastrointestinal absorption is poor with only 1 - 10 % of the ingested dose absorbed (2). Absorption occurs in the small intestine (in rats) and is markedly decreased by the presence of food, especially those which contain calcium. Therefore when these compounds are administered orally they need to be taken on an empty stomach (2). Metabolism does not occur, at least of the P-C-P bond, and approximately 20-50% of a given dose (depending on the compound) is taken up by bone, the remainder undergoing renal excretion (9). The half-life in the blood is therefore short - between 30 minutes and 2 hours. However, the half-life in bone is very long, as the compounds are buried within the skeleton. Although skeletal blood flow partly determines uptake of bisphosphonate into bone, the other important factor is that there is preferential uptake to bones that have high turnover rates, especially at sites undergoing resorption, probably due to the larger exposure of hydroxyapatite in these areas, onto which bisphosphonates are adsorbed. Once in bone, they are liberated again only when the bone in which it was deposited is resorbed and thus the bisphosphonate half-life in bone is related to the rate of local bone turnover (2).

Clinical Uses

Etidronate

Etidronate was the first bisphosphonate compound used clinically to treat Paget's disease of bone. At higher doses, it had the disadvantage of impairing mineralization of newly formed bone matrix as well as inhibiting resorption (10). However, when used at low doses (400 mg daily) in an intermittent cyclical regimen, it has been shown to improve bone mineral density (BMD) and reduce fracture rates in women with spinal osteoporosis compared to placebo-treated controls who lost BMD and had an increased risk of fracture. It was the first bisphosphonate used for the treatment of postmenopausal osteoporosis (11- 13).

Treatment with etidronate for 3 years led to an increase in lumbar spine BMD of between 5-8% (11,13) and, to an increase in proximal hip BMD of 1.44 % (13). Further treatment for another year maintained the gain in BMD obtained over the first 3 years (13). In 17 patients that took etidronate for 5 years, there was an additional 1.4% increase during the fourth and fifth years on top of the 5.5% gain in vertebral BMD after the first 3 years (14).

Looking at the more important clinical end-point of fractures, in the 2 year study with etidronate, there were 29.5 in the treated group compared to 62.9 new vertebral fractures per 1000 patient years in the placebo group (12). In contrast, Storm and colleagues (11) found no overall significant difference in the rate of new vertebral fractures in their 3 year study with etidronate (18 in the treated compared to 43 in the placebo group per 100 patient years) but the difference was significant between weeks 60 to 150 (6 in the treatment group compared to 54 new fractures in the placebo group per 100 patient years). After 5 years of etidronate therapy, there was no further reduction in the rate of new vertebral fractures (14). Harris and colleagues (13) found no overall significant differences between the fracture rate in their bisphosphonate-treated group compared to placebo. However, there was a significant reduction in the new vertebral fracture rate in etidronate-treated patients at high risk for fracture (that is, those with low spinal bone density and 3 or more vertebral fractures at study entry), compared with non-etidronate-treated patients (228 compared to 412 fractures per 1000 patient years respectively). There is no data with etidronate on non-vertebral fracture rates.

Alendronate

Alendronate, an amino-bisphosphonate, has recently become available in Malaysia for the treatment of osteoporosis. It has been shown to be useful in the treatment of postmenopausal women with osteoporosis (15-18). After 2 years of alendronate therapy, there

was an increase in lumbar spine BMD of 7.2 %, an increase in femoral neck BMD of 5.0 % and an increase in total body BMD of 2.5% (16). After 3 years of therapy, there was an increase in lumbar spine BMD of 6.2-8.8%, an increase in femoral neck BMD of 4.1-5.9% and an increase in total body BMD of 1.8-2.5%, compared to placebo (17, 19).

The rate of new vertebral fractures was reduced by approximately 50%; the incidence of new vertebral fractures in the alendronate-treated group was reduced to 3.2% compared to 6.2% in the placebo group overall (17). In addition, alendronate has been shown to reduce the incidence of new hip and wrist fractures, as well as new vertebral fractures, by approximately 50% after 3 years treatment (19). However, the numbers that needed to be treated to prevent a fracture were large; the 1022 women in the study that took alendronate for 3 years had 11 hip fractures (1. 1%) compared to the 1005 women on placebo who suffered 22 hip fractures (2.2%). For wrist fractures, 2.2% of women taking alendronate suffered a fracture compared to 4. 1 % of those on placebo (19).

Alendronate has also been shown to prevent postmenopausal bone loss (20). In a study of 1174 healthy postmenopausal women, 5 mg of alendronate increased lumbar spine BMD by 3.5% and increased femoral neck BMD by 1.3% after 2 years treatment, compared to the placebo groups which lost 1.8% and 1.6% at the lumbar spine and femoral neck respectively. The gains in BMD with alendronate were only slightly less than those obtained with a oestrogen-progestin regime given to an additional 110 women in the same study (20). This suggests that alendronate can be used to prevent postmenopausal bone loss with a similar efficacy to hormonal regimes, which makes it a useful alternative to women unable or unwilling to take hormone replacement therapy.

Other Bisphosphonates

Other bisphosphonates that have been shown to improve BMD in postmenopausal women are pamidronate, both intravenously (21) and orally (22,23), clodronate, both intravenously (24) and orally (25), tiludronate (26), risedronate (27), and ibandronate, both intravenously (28) and orally (29). However, only the first 3 compounds are currently licensed overseas, and, apart from pamidronate (22) and clodronate (24), there is no fracture data with these other bisphosphonates.

Intravenous pamidronate infusion of 30 mg every month over 2 years have been shown to increase lumbar spine BMD by 10. 1% and femoral neck BMD by 4.8% (21). Oral pamidronate at a dose of 300 mg daily will improve lumbar spine BMD by 3. 1% and femoral neck BMD by 3.2% after 1 year of treatment (23). At a lower dose of 150 mg oral pamidronate daily over 2 years, there was an increase in lumbar spine BMD of 7% and femoral neck BMD was maintained, compared to a fall in the placebo group (22). In this study, there was also a non-significant reduction in vertebral fracture rates in the pamidronate group of 13/ 100 patient years compared to 24/ 100 patient years in the placebo group (22).

Cyclical oral clodronate 400 mg daily for 1 month, followed by 2 months without any treatment, will increase lumbar spine BMD by 3.88% compared to a loss of BMD of 2.34% in the placebo group after 1 year (25). Giving oral clodronate continuously daily does not result in a better gain in BMD (30). In a 6-year trial, 200 mg intravenous clodronate given every 3 weeks lead to a 5.69% increase in lumbar spine BMD compared to controls and reduced the incidence of new vertebral fractures after the third year of treatment (24).

Tiludronate has been shown to maintain lumbar spine BMD in postmenopausal women compared to a 2. 1% loss in the placebo group after a 6 month course of oral tiludronate 100 mg daily (26).

Oral risedronate can be taken either cyclically, 5 mg daily for 2 weeks followed by no treatment for 2 weeks, or 5 mg daily. When taken cyclically for 2 years, it will prevent postmenopausal bone loss at the lumbar spine compared to a 4.3% reduction in the placebo group. Daily treatment with risedronate will increase lumbar spine BMD by 1.4% after 2 years, an increase of 5.7% compared to placebo. At the femoral neck, BMD is maintained with either cyclical or daily risedronate compared to a decrease of 2.4% in the placebo group after 2 years (27).

Ibandronate is another of the bisphosphonates that can be given orally or intravenously. Oral therapy at a dose of 2.5 mg daily will lead to a 4.6% increase in lumbar spine BMD after 1 year (29). Cyclical bolus injection of 2 mg of ibandronate every 3 months increased lumbar spine BMD by 5.2% after 1 year and maintained femoral neck BMD (28).

Side-Effects

The most common side-effects of the oral bisphosphonates are gastro-intestinal, most frequently nausea, but also abdominal pain and dyspepsia. However, in most of the clinical trials, the frequency of adverse events have been similar in the placebo and treatment groups. Alendronate has been associated with severe oesophagitis and oesophageal ulceration (31) although the actual incidence is very low. It is reversible on stopping therapy with alendronate and its occurrence prevented by careful instructions on taking the drug, i.e. the tablet should be taken with at least 180 ml of water and the patient should maintain an upright position for 30 minutes after swallowing the tablet. Concomitant use of acid-suppression drugs together

with, alendronate do not seem to heal the oesophageal lesions(31).

Response to Therapy

The majority of patients seem to respond to bisphosphonate therapy with a gain in bone mass. Of the limited data that is available, over 96% of women treated with alendronate 10 mg daily showed increases in lumbar spine BMD (17) and between 60-80% of patients will respond to oral pamidronate 300 mg daily (23). However, although the bisphosphonates have a long half-life in bone, it is disappointing that once treatment is stopped, the bone loss resumes, similar to the patients on placebo (27,32). But, reassuringly, there is no evidence that bone loss is accelerated once these agents are stopped.

Conclusion

Bisphosphonates have potent inhibitory effects on bone resorption due a variety of mechanisms. They have been shown to stop postmenopausal bone loss and increase BMD. In addition, some agents have been shown to reduce the incidence of fracture, the end result of low bone mass. The currently available bisphosphonates are taken orally, which can create problems because of poor/variable absorption and the potential for gastro-intestinal side-effects. A more promising approach would be the use of intermittent intravenous infusions/injections of potent bisphosphonates which would avoid the above problems with similar improvements in BMD.

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