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Bisphosphonates in osteoporosis

Received: 13 August 2003
Accepted: 13 August 2003
Published online: 16 September 2003
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Abstract Bisphosphonates are compounds characterized by a P-C-P structure. They act essentially on bone, inhibiting bone resorption. Through this mechanism they decrease bone loss, increase bone mineral density, and decrease bone turnover. They are therefore administered in diseases with elevated bone destruction, such as Paget's disease, metastatic bone disease, and osteoporosis. In the latter they diminish both vertebral and nonvertebral frac-

tures. The adverse events are few, mostly gastrointestinal, and can be avoided to a large extent by correct administration. Since there are no other compounds available which have a similar profile, they represent today the drugs of choice in the treatment and the secondary prevention of osteoporosis.

Keywords Bisphosphonates · Etidronate · Alendronate · Risedronate · Osteoporosis

Preclinical characteristics

Chemistry

The bisphosphonates used in clinical practice are compounds characterized by a P-C-P structure. This structure allows a great number of possible variations, especially by changing the two lateral chains in the carbon atom. These compounds have been known for a long time, the first bisphosphonates having been synthesized by German chemists as early as 1865. The bisphosphonates were first used only for a variety of industrial applications, among them as antiscaling agents. It was only in 1968–1969 that we showed these compounds also to have biological effects, more specifically on the calcified tissues [7, 8]. Each bisphosphonate has its own physicochemical and biological characteristics, and therefore each compound must be considered on its own, with respect to its action and behavior.

Biological actions

The bisphosphonates have been shown to have various physicochemical effects on bone salt crystals and biological effects on bone mineralization and bone resorption.

Physicochemical effects

Bisphosphonates inhibit the formation and aggregation and slow down the dissolution of calcium phosphate crystals. These effects are related to the marked affinity of these compounds for solid-phase calcium phosphate, on the surface of which they bind strongly. This property is the basis for the use of these compounds as skeletal markers in nuclear medicine and the basis for their selective pharmacological effects.

Inhibition of bone resorption

The main effect of the pharmacologically active bisphosphonates is to inhibit bone resorption [7]. This effect has been shown both in vitro culture and in intact animals. In growing rats bisphosphonates can block the degradation of both primary and secondary trabeculae, thus arresting the modeling and remodeling of the metaphysis. The latter therefore becomes club shaped and radiologically more dense than normal. This effect is often used as an experimental assay to determine the potency of new compounds (Schenk test) [22]. The inhibition of bone resorption by bisphosphonates has also been documented using ^{45}Ca ki-

netic studies, markers of bone resorption, and by other means. The effect occurs within 24–48 h and is therefore slower than that of calcitonin. The decrease in resorption is accompanied, at least in the growing animal, by a positive calcium balance, and an increase in the mineral content of bone and in bone mass. This is possible because of an increase in intestinal calcium absorption.

Bisphosphonates can also prevent an experimentally induced increase in bone resorption. Thus they impair resorption induced by many bone resorbing agents such as parathyroid hormone, $1,25(\text{OH})_2\text{D}$ and retinoids, the latter effect having been used to develop a powerful and rapid screening assay for new compounds. They also inhibit bone loss induced by different procedures to induce experimental osteoporosis such as immobilization, the first model used [15], ovariectomy, corticosteroids, or lactation combined with a low calcium diet. When not given in excess, bisphosphonates have also a positive effect on mechanical characteristics both in normal animals and in various experimental osteoporosis models [25]. This effect seems to be due to alterations in bone mass, architecture and quality.

The activity of bisphosphonates on bone resorption varies greatly from compound to compound. For etidronate the dose required to inhibit resorption is relatively high, very near that which impairs normal mineralization. One of the aims of bisphosphonate research has therefore been to develop compounds with a more powerful antiresorptive activity, without a stronger inhibition of mineralization. This has proven to be possible. Compounds have been developed that are up to 10,000 times more powerful than etidronate in the inhibition of bone resorption in experimental animals without being more active in inhibiting mineralization.

Inhibition of mineralization

When given in larger amounts, bisphosphonates can inhibit normal mineralization of bone and cartilage as well as ectopic mineralization [22].

Mechanisms of action

While the effect on mineralization is due to the physicochemical inhibition of crystal growth, the action on bone resorption is mediated through mechanisms other than the physicochemical inhibition of crystal dissolution, as was initially postulated, namely by acting on the osteoclast. Four mechanisms appear to be probably involved: inhibition of osteoclast recruitment, inhibition of osteoclastic adhesion, shortening of the life span of osteoclasts due to earlier apoptosis, and inhibition of osteoclast activity. Very recently the cellular mechanism has been partially unraveled. It was found that nitrogen containing bisphosphonates can, by inhibiting farnesyl pyrophosphate synthase,

decrease the formation of some compounds important for many cell functions, including cytoskeletal assembly and intracellular signaling, which leads eventually to apoptosis and death. In contrast, some non-nitrogen-containing bisphosphonates, such as clodronate, and etidronate, can be incorporated into the phosphate chain of ATP-containing compounds, which also impair cell function, leading to apoptosis and cell death. Thus the bisphosphonates can be classified into two major groups with different modes of action but the same final effect [19].

Pharmacokinetics

The bisphosphonates appear to be absorbed, stored, and excreted unaltered in the body. Therefore the bisphosphonates seem to be nonbiodegradable, at least with respect to their P-C-P bond. The bioavailability of an oral dose of a bisphosphonate both in animals and in humans lies between less than 1% and 10%. Absorption is substantially diminished when the drug is given with meals, especially in the presence of calcium and iron. Therefore bisphosphonates should never be given at mealtimes and never together with milk or dairy products. Between 20% and 80% of the absorbed bisphosphonate is taken up very rapidly by bone, the remainder being rapidly excreted in the urine. This rapid uptake by bone means that the soft tissues are exposed to bisphosphonates for only short periods, explaining why practically only bone is affected *in vivo*. The areas of deposition are mostly those of bone formation and destruction. Once deposited in the skeleton and covered under new layers of bone, the bisphosphonates are released to a large extent only when the bone in which they were deposited is resorbed. The half-life in bone bisphosphonates is therefore very long, for humans it can be over 10 years. The renal clearance of bisphosphonates is high, at least in animals higher than that of inulin, indicating active secretion.

Clinical use in osteoporosis

Bisphosphonates are today the most frequently used drug in metabolic bone disease. About ten are commercially available in the world, the conditions treated most frequently with these compounds being osteoporosis, Paget's disease and metastatic bone disease. This review deals only with osteoporosis. A more extended clinical and clinical information can be found in a book written for the practicing physician [6].

Definition and pathophysiology of osteoporosis

Osteoporosis is a disease characterized by a decrease in bone mass and a deterioration in the architecture of the

bones, which leads to an enhanced fragility of the skeleton and therefore to a greater risk of fracture. It is defined as present in women when the bone mass is more than 2.5 SD below that of the young woman (*t* score). It is a very common disorder which will become even more common with the increase in life expectancy. It is also frequent in men, although less so than in women. Its main cause is the continuous loss during life of both cancellous and cortical bone, which is exacerbated in women after the menopause. The second contributory factor is failure to achieve adequate peak bone mass during adolescence. The causes of these changes are not yet clear, although genetic factors are involved, at least for the latter.

The clinical manifestations of osteoporosis are fractures, occurring often spontaneously or after minimal trauma, and their consequences. Osteoporosis is diagnosed and assessed quantitatively by techniques that measure bone mineral density (BMD), most commonly dual X-ray absorptiometry. Chemical analyses cannot be used to diagnose osteoporosis. Markers of bone turnover, however, are useful to determine bone turnover and consequently to identify those patients who are likely to be losing bone rapidly and to follow the effect of treatment.

Treatment of osteoporosis

Until recently the only mechanism by which to prevent or treat osteoporosis was to influence bone mass. It was also thought that the latter was reflected with fidelity by BMD. Both of these assumptions have proven to be wrong. Thus we do know today that bone mass is not the only parameter responsible for bone strength, but that bone architecture and bone turnover are also very important in the determination of fracture risk. Furthermore, BMD, although a good indicator of bone mass is not a perfect one since it is also influenced by the degree of mineralization of bone tissue [13]. This is especially true when inhibitors of bone resorption, such as bisphosphonates, are administered, in which case BMD as assessed by densitometry can increase without any change in the amount of bone [2].

The main future aim for therapy is still to try to increase bone mass by increasing bone formation. Unfortunately there was no way to do this until very recently. Fluoride does increase bone formation, but has not been shown to decrease the occurrence of fractures. However, it was shown recently that parathyroid hormone administered daily dramatically increases bone formation and bone mass and reduces the occurrence of fractures [16]. This therapy has just been commercialized in the United States and is now given in very advanced cases of osteoporosis. However, this treatment is not yet advocated for less disabling cases and for prevention. For these patients the decrease in bone resorption is still the pharmacological mechanism used.

For many years the most commonly used treatment acting through a decrease in bone resorption, apart of bisphosphonates,

was estrogen replacement after the menopause. However, it has recently been shown that estrogens increase the risk of breast cancer, and increase instead of decrease cardiovascular insults [20]. Calcitonin is sometimes used, but parenteral administration can have unpleasant side effects, and the nasal form is relatively weak in its effect on BMD and fracture incidence. Calcium can also decrease bone turnover and diminish bone loss in certain conditions. It was found to diminish hip fractures when given with vitamin D in the elderly institutionalized patients [3]. This is why calcium, although it is not effective enough to affect strongly fractures in most patients with osteoporosis, is recommended at a dose of about 1 g daily in the elderly. Calcium is, however, an obligatory adjunction in all patients who receive an antiresorptive treatment. Vitamin D should be present in sufficient amounts, and the addition of 400–800 U are generally recommended in the elderly.

Treatment of osteoporosis with bisphosphonate

Although many bisphosphonates have been investigated in human osteoporosis, most of the studies have been carried out with alendronate, etidronate, and risedronate. These are the compounds which are commercialized in the greatest number of countries. Many well controlled studies have confirmed the efficacy of bisphosphonates in preventing the decrease in BMD, as assessed by dual X-ray absorptiometry first in not-menopausal osteoporosis and then in various other types of osteoporosis. Actually BMD was most often even increased. The first compound thoroughly investigated was etidronate [26]. This was then followed by alendronate [11] and later risedronate [14]. Bisphosphonates are active in whites, Asians, and black osteoporotic women. They are also effective in elderly women without osteoporosis [12] and in healthy women, as well as in men. They prevent and partially even reverse the bone loss in glucocorticoid-treated patients [4, 21] and are therefore a standard therapy in patients receiving this drug over longer time.

All the bisphosphonates induce a marked decrease in bone turnover when given in doses effective on BMD. Both bone formation and resorption are decreased. The important question to answer was whether bisphosphonates were also be able to decrease the fracture risk. Indeed an efficacious drug in osteoporosis should not be tested on BMD but on fracture risk, fractures, both vertebral and appendicular, being the key clinical problem. Both alendronate [1, 17] and risedronate [10, 18] decrease by about one-half the occurrence of vertebral and nonvertebral fractures in osteoporotic patients. Etidronate could not be proven to be efficacious on these parameters. This effect on fractures is probably due both to the increase in BMD and the decrease in bone turnover. It is not yet known which is the relative part played by each of them. However, the fact that the fractures decrease even after 6 months, when the

effect on BMD is still very small, suggests that turnover is important. Lastly, bisphosphonates do reduce fractures also in children with osteogenesis imperfecta [9].

Only few studies have addressed what happens after the discontinuation of the drug. It seems that this depends of the duration of the previous treatment. After a short-term treatment of 1–2 years, turnover and bone loss pick up again to some extent, the latter less so than the former one. After long-term treatment such as 7 years bone turnover goes up only very slowly and BMD stay constant for at least 1–2 years [24].

The treatment regimens for the three main commercialized compounds are the following:

- Alendronate: The dose recommended by the producers is 10 mg orally daily, 5 mg in Japan. Since this compound has a similar effect on BMD when given once weekly at 70 mg [23], the weekly regimen is used today in the countries where this regimen is commercialized.
- Etidronate: The regimen recommended by the producer is 400 mg daily orally for 2 weeks every 3 months.
- Risedronate: The recommended regimen is 5 mg daily orally or 35 mg once weekly.

Adverse events

As is the case in animals, studies in humans have revealed only a few important adverse events. Oral administration of bisphosphonates, especially those containing a nitrogen

atom, can be accompanied by digestive tract disturbances [5]. The latter can be substantially reduced by taking the drug with enough fluid, and by not reclining after the intake. It also seems that these disturbances are decreased when the compounds are administered once a week instead of daily, at the same total dose. The intravenous administration of N-containing compounds can induce a transient pyrexia of usually 1–2°C, accompanied by flulike symptoms, which resembles an acute-phase response. Until now no negative consequences of these episodes have been described. Lastly, compounds with little efficiency and which must administered in higher doses, such as etidronate, can inhibit normal skeletal mineralization. This can happen at doses of etidronate above 800 mg daily. Fracture healing or new orthopedic implants are no contraindication to the use of bisphosphonates provided they are not given in doses that inhibit mineralization. Lastly, bisphosphonates should not be given during pregnancy and lactation.

An important question is what happens after long-term treatment. A study of 7-years administration of alendronate did not show any adverse events. Actually the turnover stays at a constant level, the BMD still goes up, and the fracture rate remains low [24]. This course appears to continue up to 10 years of treatment. Similar results are seen with risedronate. Therefore there is until now no indication that one would have to stop the treatment because of an increase in osseous fragility. However, this issue has to be followed closely. Whether it would be of advantage to interrupt treatment for a certain time is not known.

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