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Use of bisphosphonates in bone pathology – benefits and risks

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ABSTRACT

This article aims to establish, on the basis of medical literature and of the authors' experience, whether bisphosphonates still have a role in treating skeletal diseases, with increased bone resorption. The effects of bisphosphonates on the bone tissue, as well as the diseases in which they are recommended and the benefits obtained are reviewed. Possible side effects are emphasized, both the immediate ones, which are better known and the late ones, occurring after a long-term administration. It is shown that the benefit/risk ratio remains favorable. The conclusions highlight the fact that nowadays bisphosphonates still have an important place in the treatment of skeletal diseases.

Keywords: bisphosphonates, osteoporosis, Paget's disease, bone metastases, osteogenesis imperfecta, atypical femural fractures, aseptic necrosis of the jaw

INTRODUCTION

Bisphosphonates (BFs) were introduced into the therapy of skeletal diseases in 1970, hoping to effectively prevent fragility fractures in elderly persons, as initial studies have confirmed. Since 2003, various publications have been issued, frequently explaining severe complications as a result of a long-term administration of BFs. This determined many patients to decline the BFs treatment and the physicians became more reticent in prescribing them. Based on recent literature and on personal experience, this article aims to answer the following question: are Bisphosphonates still of interest today?

Bref History. Synthesized in the mid 19-th century and used as anticorrosive agents in the textile industry [1-3], BFs have also conquered, since 1960, the pharmaceutical industry. Neuman and Fleisch noted that the body fluids are supersaturated with calcium phosphate, containing calcification inhibitors, whereof the inorganic pyrophosphate is present in urine [4,5] (Figure1). Starting from the pyrophosphate core (P – O – P), the BFs core (P – C – P) was reached by synthesis (Figure 2).

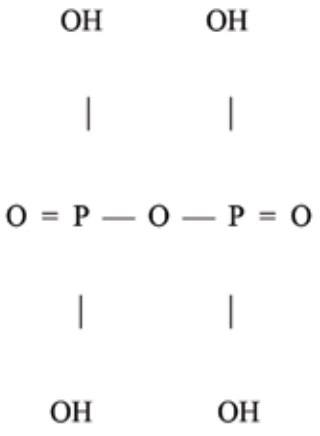

FIGURE 1. - Formula of pyrophosphate

Over three decades of research have resulted in the synthesis of more than 1,000 molecules, which differ from one another in the substituents of chains R^1 and R^2 (Figure 2). The BFs of first generation - Etidronate, Tiludronate, Clodronate – contain no nitrogen in their composition. The second generation – Alendronate, Pamidronate, Neridronate, Olpadronate – as well as the third one – Risedronate, Ibandronate, Zoledronate – contain an amino group in R^2. The an-

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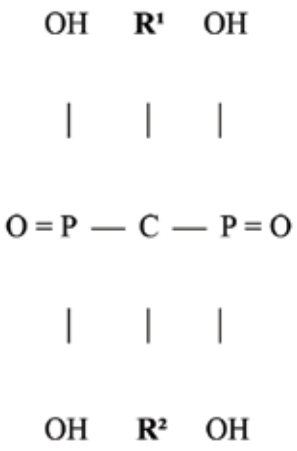

FIGURE 2. - Formula of bisphosphonates

tiresorptive efficiency is increased in the second generation and especially in the third one. As against Etidronate, Alendronate is 1,000 times and Zoledronate is 10,000 times more active. The first two articles describing the biological effects of BFs were published in 1969, in *Science* magazine [6,7]. BFs have the capacity to prevent bone resorption and to increase bone density, to prevent experimentally induced calcification, to inhibit ectopic bone mineralization, to inhibit the dissolution of hydroxyapatite crystals. By increasing the bone resistance, the fracture incidence is decreased [8-12]. But in animals, high doses result in the worsening of microfractures and even in the occurrence of fractures [13,14].

MECHANISM OF ACTION

BFs prevent recruitment, differentiation and resorptive activity of mature osteoclasts and they even may cause the apoptosis thereof. BFs also prevent the fusion of mononuclear cells, precursors of osteoclasts [15-20], and prevent osteoblast and osteocyte apoptosis [21].

CLINICAL APPLICATIONS OF BISPHOSPHONATES IN BONE PATHOLOGY

Their first use was aimed at *inhibiting heterotopic calcification and ossification* in progressive myositis ossificans as well as inhibiting the same processes occurring after cranial or spinal traumas. Etidronate is the only bisphosphonate used, in doses of 20 mg/kg body weight per day, administered for 3 months at most. A long-term treatment may cause osteomalacia. Its effectiveness is uncertain, especially in myositis ossificans [3,22,24].

Osteoporosis therapy with BFs is the most effective and most frequent recommendation. Its results are absolutely superior to the use of Calcitonine, to the hormone replacement therapy or to Raloxifene. Osteoporosis is characterized by a significant loss of bone mass {after menopause, women lose about 50% of the cancellous bone mass and 30% of the cortical bone [15]}, changes in the bone architecture, associated with a decreased bone mechanical strength and an increased risk of spine and non-spine fractures. About 40% of postmenopausal women have osteoporosis and 40% of them undergo a fracture during their lifetime. The quality of life decreases, morbidity and mortality increase (an osteoporotic spine or hip fracture increases the mortality risk by 20%) [24,25]. Alendronate, Risedronate, Ibandronate and Zoledroate are counted among the used BFs. Alendronate, orally administered, 10 mg daily or 70 mg weekly, for 3 years, induces an increase by 7% in BMD (Bone Mineral Density) on the spine and hip level (in comparison with 1% loss in the placebo group). Spinal fractures occur in 8% of treated women and non-spinal fractures occur in 2.3%, as against 15% respectively 5% in the placebo group [22,26,27]. Risedronate, 5 mg administered daily, 35 mg weekly or 75 mg monthly, for 2 consecutive days, ensure an effective protection against vertebral and non-vertebral fractures, starting after 6 months of treatment. In the first year, the incidence of vertebral fractures was reduced by 65% and their cumulative decrease after 3 years reached 41%. The incidence of non-vertebral fractures decreased by 39% after 3 years of treatment. At the same time, BMD increased significantly in comparison with the placebo group, both on lumbar spine level (5.4% versus 1.1%) and on femoral neck level (1.6% versus -1.2%) [28,29]. The "HORIZON" study (Health Outcomes and Reduced Incidence with Zoledronic Acid) kept a close watch on the efficacy of annual infusions of Zoledronate, highlighting a significant decrease in vertebral and non-vertebral fractures, as well as in the associated mortality [30,31]. The BFs therapy was also extended to osteoporosis in men {the treatment results are similar to the outcomes of postmenopausal osteoporosis [32-34]} and to the one occurring after corticotherapy (≥7.5 mg prednisone daily, for over 1 year). Risedronate is particularly used, as it decreases the incidence of vertebral fractures by 70% [27,35].

Paget's disease is characterized by a localized, accelerated bone resorption, followed by a chaotic deposition of the mineralized bone matrix. It occurs with an incidence of 3.3%, in people aged over 40 [36]. The use of 40 mg/day Alendronate, for a time of 6 months results in a bone turnover decrease by 70% - 80% in 40% - 65% of the patients. Risedronate is administered in doses of 30 mg/day, for 3 months. Over 90% of the patients respond to this therapy, with a decrease of the alkaline phosphatase of at least 50%. Pamidronate, by perfusion of 60 mg in mild forms of the disease and of 60 mg once a week or every two

weeks, up to a dose of 400 mg in moderate and severe forms, determines a remission of the disease. Zoledronate, by a single perfusion of 5 mg, determines a normalization of alkaline phosphatase in 88.6% of patients and their response is maintained in 95% of cases, after a period of 6 months. Zoledronate is considered to be the elective bisphosphonate for Paget's disease [22,37-40].

Bone metastases. After lungs and liver, the skeleton is the third location, as far as frequency is concerned, for carcinoma metastases. The incidence varies between 40% and 90%, depending on the neoplasm type [41]. The most common locations are on the level of the spine (particularly lumbar), in the sacrum, pelvis, upper femoral extremity. The skeletal complications of metastases are hypercalcemia, bone pains, pathological bone fractures, spinal cord compression (in spinal fractures). The invasion of malignant cells into bones destroys the normal balance of bone remodeling, causing the occurrence of an excessive osteoclastic activity. Among BFs, Zoledronate 4 mg, Ibandronate 6 mg or Pamidronate 90 mg are used by perfusion, every 3-4 weeks. In breast cancer, BFs reduce bone complications of metastases by 15% as against the control group and they ensure a longer skeletal event-free period. Survival and the quality of life are improved [35,42-44]. Besides the inhibition of osteoclast function, BFs reduce the local release of tumor growth stimulating factors, they have a direct antitumor activity, acting synergistically with other antitumor agents [24,45-47].

Hypercalcemia affects over 20% of patients with multiple myeloma, lung, breast or kidney cancer. BFs represent the most effective therapy. Perfusions with Pamidronate (90 mg) or Zoledronate (4 or 8 mg) are used in the treatment. Zoledronate is more active in this case, 87% of patients having a complete response to this therapy [48].

In total hip and knee arthroplasty, BMD of the periprosthetic bone decreases up to 6 months after surgery. Experimental and clinical investigations (Alendronate 10 mg/day for 6-12 months, Risedronate 2.5 mg/day or 35 mg/week for 6 months, Pamidronate 90 mg in a single dose on the 5-th day after surgery) prove that BFs inhibit bone resorption and increase BMD in postoperative acute phase [49-51]. Late periprosthetic osteolysis, which results in the prosthesis mobilization, is mainly determined by the osteoclast activation, induced by the macrophages that engulfed the wear products of the frictional torque of metal (ceramic)-on-polyethylene. It was positively influenced by BFs in experiments on animals (canine arthroplasty), but the benefits are not obvious in clinical applications. As a matter of fact, FDA has not approved the use of BFs for osteolysis treatment, associated with arthroplasty complications [24,52,53].

The use of BFs in children remains controversial. The long-term inhibition of bone remodeling might result in a decrease in skeletal strength. The long period of half-decay in bone determines the continuation of the inhibitory effect even after the administration interruption. It has been described the occurrence of a "osteopetrosis" [54]. BFs have been used, most frequently, in the treatment of Osteogenesis. Imperfecta.

Osteogenesis imperfecta is a genetic disorder, whose symptoms are osteopenia, frequent fractures, progressive deformities, decreased mobility and chronic bone pains. Pamidronate is used by perfusion (0.5 mg/kg for children aged under 2 and 1 mg/kg - 1.5 mg/kg for children aged over 2) for 3 consecutive days, every 2-4 months. The treatment duration is 2-9 years [19]. Post-therapy, a decrease in the incidence of fractures, a pain relief and a walking gait improvement can be noticed. BMD increases and bone turnover markers decrease. The cortical of long bones thickens and the spans of cancellous bones multiply. The most visible changes occur in the first 2-4 years of treatment [55,56].

Fibrous displasia is a genetic disorder related to the tuning of interaction between the proliferation and differentiation of osteoblasts and osteoclasts. As a result, abnormal, thin bone trabeculae are formed, associated with a population of preosteogenic cells and with a proliferation of fibrous tissue. Along the peripheral lesions, there are hyperactivated osteoclasts. The most commonly used is intravenous Pamidronate, administered by perfusions of 0.5 mg/kg/day for children or of 60 mg/day for adults, for 3 consecutive days, every 4-6 months. As a result of the treatment, pain is reduced significantly and the incidence of fractures is decreased. In terms of X-rays, a cortical thickening and a progressive ossification occur in some adult patients [24,35,57-59].

In *Legg-Calvé-Perthes disease* (aseptic necrosis of the femoral head in children), the bisphosphonate treatment is justified by the role of bone resorption, unbalanced by reconstruction, in the deformation of the femoral head. Experimental studies on rats and pigs have shown the positive effect of the bisphosphonate treatment on maintaining the spherical shape of the femoral head. At this time, there still are no clinical studies to confirm the usefulness of BFs [60,61].

The use of BFs may lead to ***the occurrence of side effects.*** The oral administration might cause *irritations of the digestive tract,* especially of the esophagus. Intravenous administration may cause fever and *"flu-like" symptoms*, predominant in the first perfusion [62,63]. *Hypocalcemia* is usually mild, asymptomatic and transient. *The increase in PTH* (parathormone) is modest, being caused by hipocalcemia. Latest studies have revealed the occurrence of *atrial*

fibrillations after administration of Zoledronate and Alendronate, favored by heart failure, coronary artery disease, diabetes. Fluctuations in serum calcium might be decisive. [64-66]. Some other studies have not confirmed the existence of a causal relationship between BFs and atrial fibrillations [67].

A long-term administration of BFs may cause, in women undergoing osteoporosis treatment, *atypical femoral fractures*, subtrochanteric or diaphyseal, frequently bilateral (simultaneously or sequentially), transverse or slightly oblique, with a unicortical beak, in a femur with cortical thickening. They occur spontaneously or are caused by low-energy traumas. They may be preceded by pains in the thigh. If the X-ray does not show the fracture line, a magnetic resonance examination is recommended. The incidence varies between 3.2 and 50 cases in 100,000 persons per year. It may reach ≈ 100 cases in 100,000 persons per year for very long periods of administration [68-70]. Schilcher and Aspenberg [71] surveyed 900,000 patients undergoing bisphosphonate treatment for osteoporosis and they noticed the occurrence of 13,500 osteoporotic fractures, as against 900 atypical fractures. The decreased bone turnover, associated with the increased bone mineralization, due to BFs, causes bones to become brittle. This alteration of bone strength, combined with the lack of microfracture repair, due to a late bone remodeling, leads, in the long run, to an increased fracture risk [72,73]. Over 26% of the cases of atypical fractures have a late consolidation or they do not heal at all. Despite the severity of atypical fractures, the benefit offered by BFs is 100 times higher than the fracture risk [74]. Another late and serious complication is the *aseptic necrosis of the jaw*. It occurs especially after the treatment with Pamidronate or Zoledronate, in patients treated with high doses, for various neoplasms (multiple myeloma, breast cancer, prostate cancer etc.). A series of risk factors (concomitant corticotherapy, dental procedures, poor oral hygiene, treatment duration, dose and type of Bfs) enhance its occurrence. It is presumed that it would happen due to mechanical microfractures, occurring during mastication, which do not heal because of bone remodeling inhibition or because of the antiangiogenic properties of BFs. The incidence varies between 0.03% and 10.5%, being very low in case of osteoporosis treatment and much higher after the exposure to 10-12 times higher doses, as part of neoplasm therapy [75-78].

Our experience in using BFs is not important, but it enabled us to get acquainted with this field, from a practical point of view as well. It includes 53 cases of postmenopausal osteoporosis, treated with Alendronate for 3-5 years, 16 cases of Paget's disease, treated by perfusions with Zoledronate, 11cases of fibrous dysplasia in teenagers and adults, where we used perfusions with Pamidronate, as in a case of Osteogenesis Imperfecta, treated for a period of 7 years, starting from the age of 4. In osteoporosis cases, we obtained an increased BMD and we prevented the occurrence of fractures, in Paget's disease we obtained decreased bone turnover markers, with a significant improvement of the clinical symptoms, as in the case of fibrous dysplasia as well, where the radiological changes were discrete. Osteogenesis Imperfecta had the most spectacular evolution, resulting in a BMD improvement and, particularly, in an almost normal life, with a daily attendance of school classes, in comparison to the severe walking deficiencies at the beginning of the treatment. Besides the immediate side effects we have not registered any atypical fractures or any jaw necrosis. In the few cases treated and surveyed, the bisphosphonate treatment proved to be effective, having a high benefit/risk ratio.

After this exploration of the rich medical literature, as well as relying on our limited experience, we can assert that BFs have not lost their validity. Their therapeutic effect is important in all skeletal diseases with a more pronounced bone resorption and their benefit/risk ratio is positive. It is estimated that, even under a 10 year-treatment with BFs, the incidence of atypical fractures is of 1.1 per 1,000 patients/year [79-81]. In exchange, the incidence of the total non-vertebral fractures is of 37 per 1,000 patients/year and the incidence of vertebral fractures reaches 62.7 per 1,000 patients/year [81]. Given that the incidence of atypical femoral fractures increases together with the extension of treatment, it is considered that, after 5 years of bisphosphonate administration, if the fracture risk is not high (T-Score >-2.5, without a history of osteoporotic fractures), this treatment may be interrupted (drug holiday) for 2–3 years. The resumption of treatment is recommended if an osteoporotic fracture occurs, if BMD is decreased and/or if the values of the bone turnover markers are increased [81]. Considering these precautions for use, BFs must keep their important place in the treatment of bone resorption disorder.

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