



## EFFICACY AND SAFETY OF BISPHOSPHONATES IN OSTEOPOROSIS

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### ABSTRACT

The aim of this study was to conduct a literature review to evaluate the efficacy and safety of bisphosphonates in osteoporosis. Bisphosphonates are a group of drugs that decrease bone resorption by different mechanisms of action. They are widely used, especially in patients with osteoporosis postmenopausal. Your risk-benefit balance has been questioned because there are no clear evidence regarding their benefits and because various adverse effects associated with long term use have been detected in recent years. Among them we can mention, osteonecrosis of the jaw, atypical fractures, musculoskeletal pain, esophageal cancer, atrial fibrillation and inflammatory eye disorders. It is important to remain alert to these adverse effects of late onset and evaluate their effectiveness in clinical practice to determine definitively the risk-benefit balance in the osteoporosis.

**Keywords: Bisphosphonates, Safety, Adverse Reactions, Efficacy, Pharmacovigilance**

### INTRODUCTION

Since the risks associated with hormone replacement therapy were known, used in the prevention of menopausal osteoporosis, a considerable increase in the use of oral bisphosphonates has been recorded in recent years [1]. The marketing of new agents and dosage forms, the expansion of indications, and the excessive medicalization have also contributed to this increase. Prolonged exposure of numerous patients to bisphosphonates, has permitted detect new adverse effects associated with their use [2].

The authors of a systematic review have estimated that there are no significant clinically

proven benefits to the use of bisphosphonates in postmenopausal women with and without prior fracture or vertebral compression [3]. In another review, the authors concluded that in secondary prevention, the small benefits of bisphosphonates may outweigh the damage for the first three years of therapy, but the damage are likely to outweigh the benefits for durations of more than three years [4].

The older and less powerful bisphosphonates are captured by osteoclasts, accumulating inside and interfering with the activation and differentiation of osteoclastic precursor cells into mature osteoblasts, modifying their

adhesion to the bone and causing apoptosis. These bisphosphonates act as prodrugs, being intracellularly converted in active metabolites after uptake by osteoblasts [5]. The most potent bisphosphonates, act by inhibiting synthetase farnesildifosfato, an enzyme of the cholesterol synthesis pathway from mevalonate. These nitrogen-containing bisphosphonates indirectly suppress the process of geranylgeranylation of proteins, which in turn inhibits osteoclastic activity [6, 7].

The bone metabolism at the tissue, at cellular and molecular level, is altered by the bisphosphonates. A tissue level, these drugs decrease bone turnover and reduce bone resorption. At the cellular level, the recruitment, adhesion, apoptosis and activity of osteoblasts are altered by the bisphosphonates. At the molecular level, the osteoclast function is altered by interacting with surface receptors or intracellular enzymes [8]. They can also act indirectly stimulating the formation of osteoblast precursors, increasing its number and differentiation, so that promotes release of osteoclast inhibitory substances [9].

The bioavailability of orally bisphosphonates is 1-2%. Their absorption is hindered by food. To avoid reflux and the consequential esophageal lesions, it should avoid taking other liquids or foods and lying. Their half-lives are between 30 min - 2 h, in bone persist more than 10 years. The 50-60% of the dose is incorporated into bone; the rest is excreted by the kidney [7].

The aim of this study was to conduct a literature review to evaluate the efficacy and safety of bisphosphonates in osteoporosis.

## MATERIAL AND METHODS

For this review, the following search and selection criteria we used: Cochrane systematic reviews, PubMed, and Pharmacology Bulletin of the International Society of Independent Bulletins. Terms used to find related studies were the following: bisphosphonates, osteoporosis, safety, adverse events, adverse reactions, pharmacovigilance, alendronate, risedronate, ibandronate, etidronate, clodronate, tiludronate, pamidronate, zoledronate.

## RESULTS

Gastrointestinal effects, including nausea, dyspepsia, abdominal pain and esophageal erosion, orally; and the fever, flu-like symptoms, reactions at the site of administration and renal disorders, intravenously, are the most common adverse effects of bisphosphonates. Among the serious adverse reactions, are osteonecrosis of the jaw, atypical fractures, atrial fibrillation, and ocular inflammatory disorders [10].

In patients treated with bisphosphonates, the risks of severe pain of bone, joint, and muscle, sometimes widespread or disabling, can occur from days to years after starting treatment; these risks were alerted in 2008 [11]. This pain is usually kept with the treatment, unlike the flu-like symptoms associated with the initial administration of bisphosphonates intravenously, or weekly or monthly doses of oral bisphosphonates, which usually resolve within a few days with the continued use. Although some patients have experienced complete improvement after discontinuation of treatment, in other, resolution has been slow and

incomplete. Risk factors and their impact are not known [2, 12].

In the HORIZON clinical trial (2007), a higher incidence of serious atrial fibrillation among patients who received an annual dose of intravenous zoledronic acid, compared to the control group that received placebo, was found. The authors of a review showed that risk of atrial fibrillation is increased by alendronate in 0.5% in absolute terms. A significant increase in the risk of serious atrial fibrillation, with an incidence of 0.69% and 1% among untreated and treated with bisphosphonates is showed in a meta-analysis [2, 13].

The first cases of spontaneous femur fracture with delayed resolution were described in 2005 in nine patients treated with alendronate for more than three years, and since then similar cases are still running [14, 15]. Most are elderly women treated for years with alendronate for osteoporosis or osteopenia, having a shaft fracture of femur or proximal subtrochanteric, and these fractures occur spontaneously or after minimal trauma [16-18]. Some patients have had fractures of both femurs [19, 20]. Fractures are usually preceded by pain in the affected thigh [21], have a typical radiographic pattern of horizontal fracture of the femur with hypertrophy of diaphysis cortical, and that slow to heal. Unexplained femoral shaft fractures were also presented in patients treated with alendronate for years [2, 22-25].

Prolonged treatment with alendronate was associated with a dose-proportional increase in the number of osteoclasts accumulated, among which are differentiated osteoclasts giant

hypernucleated and delayed apoptosis. There are no known clinical implications of this finding [26, 27]. Some data suggest that to continue to take alendronate after fracture involves a risk of delay or absence of consolidation [2].

In some patients, prolonged treatment with bisphosphonates can cause excessive suppression of bone turnover, resulting in fragile and brittle bone, despite the increase in bone mineral density. Some authors recommend stopping treatment with bisphosphonates after 5 years [28]. Patients treated with bisphosphonates for a prolonged period should be considered at risk. Furthermore, bisphosphonates should not be considered as a therapeutic option in patients recovering from recent fracture, because they can interfere with the resolution of the fracture [2].

In a study carried out for Park-Wyllie *et al.* 2011, [11] was found that women treated for 5 years or more had a higher risk of atypical femur fracture, and a lower risk for fractures typical than those treated for less than 100 days. The optimal duration of treatment with bisphosphonates and the benefit-risk of prolonged treatment are still uncertain [29]. This confirms that prolonged treatment with bisphosphonates is associated with an increased risk of atypical femoral fractures [2] and it highlights the need to carefully assess the individual risk of fracture [12, 29].

Osteonecrosis of the jaw is an area of exposed bone that persists for longer than 8 weeks in the absence of prior radiation and / or metastasis in the mandible [30]. It is a rare bone injury, secondary to bone ischemia. The first cases were

published in 2003 and 2004 and have increased the described cases related to taking these medications [7]. The pathogenesis of osteonecrosis of the jaw is unknown, but appears to be based on the action of bisphosphonates on the metabolism of Ca/P and osteoblasts, which inhibit indirectly the neoangiogenesis of bone, and injures the endothelium of small vessels. The jaws are under constant stress, microfractures occur, and the bone becomes brittle and unable to repair these microfractures [7].

If the jaws also are exposed to the oral environment, as in a tooth extraction, are infected with the flora, evolving towards that destroys bone osteomyelitis [7]. The risk factors are the diagnosis of cancer (especially breast cancer) [31], concomitant treatment with chemotherapy, radiotherapy and steroids, pre-existing infection or oral pathology, and the presence of anemia or coagulation disorders [32]. The risk of osteonecrosis of the jaw, associated with the intake of oral bisphosphonates therapy for osteoporosis, has been estimated between 1:10,000 and 1:100,000 patients / treatment and year [7]. The intravenous nitrogen bisphosphonates (pamidronate and zoledronate) have a complication rate much higher; lesions appear earlier and are much more aggressive and difficult to solve [30-35].

The osteonecrosis of the jaw by bisphosphonates usually appears between 4 months and 6 years of starting treatment. The average time of consumption is 5.6 years, for oral bisphosphonates; and less than one year, for

intravenous. Lesions develop more frequently where the patients had surgery, like tooth extraction, apicoectomy, periodontal surgery and dental implants. It is more common in the lower jaw and molar area. It appears as a lack of healing after tooth extraction, or bone exposure with pain, swelling, infection, tooth mobility, that is difficult to cure [7].

A treatment algorithm for patients treated with bisphosphonates has been created, and the authors mostly are agree that the risk of osteonecrosis of the jaw with bisphosphonates, used at the doses used in the osteoporosis, is very low. The recommendations focus on to individualize the bisphosphonates prescription, based on fracture risk presented by the patient, and in the prevention of these risks through dental hygienic measures and the review by the dentist [7, 36].

Moreover, Chamizo Carmona *et al.*, 2012, [12] conducted a systematic review and found insufficient evidence to say that the bisphosphonates, used exclusively for the treatment of osteoporosis leads to a significant risk of osteonecrosis of the jaw [37].

Andrici *et al.*, 2012, [14] found that bisphosphonates may be associated with increased risk of esophageal cancer, and believe that this relationship should be confirmed [38].

## CONCLUSIONS

- The effectiveness of bisphosphonates to prevent the incidence of fractures and its benefit-risk are very small and uncertain.
- The prevention of falls in people at high risk is more beneficial that increase bone mineral density with bisphosphonates.

- The bisphosphonates produce serious adverse effects such as osteonecrosis of the jaw, generalized pain, atypical fractures, and atrial fibrillation.
- The incidence of osteonecrosis of the jaw is much higher in cancer patients and is related to the power of the bisphosphonates, the treatment time, and tooth extractions.
- There are many controversies about if the bisphosphonates induce atypical femoral fractures. It is necessary to evaluate the individual risk of fractures.
- With regard to the association between the use of bisphosphonates and the onset of bone pain joint or muscle, there is no evidence yet clear, but it is advisable not to delay diagnosis, because in most cases resolve after discontinuation of therapy.
- It is very important to identify subgroups of elderly patients treated with bisphosphonates with increased risk of atypical fractures, and assess whether discontinuation of treatment reduces the risk of fractures in the long term.
- With continuous exposure to bisphosphonates no there is clear benefit or harm to the overall risk of osteoporotic fracture. Patients with well recognized risk of fracture, despite continuous treatment with bisphosphonates, are more prone to fracture.
- The suspension or continuation of treatment with bisphosphonates gives similar fracture rates, and remains stable in those patients treated for 3-5 years. The continuing drug therapy beyond 5 years would represent no significant advantage.

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