

# Bisphosphonates and jaw osteonecrosis

## Bisfosfonatos e osteonecrose dos maxilares

### Abstract

Bisphosphonates have been widely prescribed for treatment of diseases characterized by intense bone resorption. These drugs have also been associated with a serious side effect, avascular osteonecrosis of the jaws. The authors present a literature review on bisphosphonates, focusing on their pharmacological features and their reported association with jaw osteonecrosis. The morbidity and lack of treatment response of this condition are serious facts to be considered when prescribing bisphosphonate therapy. The risk-benefit relationship needs to be seriously analyzed, and the treatment pros and cons should be explained to the patient. If the therapy with bisphosphonate is indicated, rigorous oral health adequacy must be performed and periodic evaluation of oral conditions is mandatory. At this moment, caution in treatment seems to be the best way to approach bisphosphonate users.

**Key words:** Bisphosphonates; osteonecrosis; jaw

### Resumo

Os bisfosfonatos têm sido amplamente empregados no tratamento de enfermidades cuja característica principal é a intensa reabsorção óssea. Tais drogas também têm sido associadas a um importante efeito colateral – a osteonecrose avascular dos maxilares. Os autores apresentam uma revisão da literatura sobre bisfosfonatos, enfocando aspectos farmacológicos e a osteonecrose dos maxilares. A morbidade e a falta de resposta ao tratamento desta condição são fatores importantes a serem considerados na prescrição de terapia com bisfosfonatos. A relação risco-benefício precisa ser seriamente analisada, e os prós e contras do tratamento devem ser explicados ao paciente. Se a terapia for indicada, uma rigorosa adequação bucal deve ser realizada e o paciente necessita ser periodicamente avaliado. No presente momento, a precaução parece ser o melhor modo de abordar os usuários de bisfosfonatos.

**Palavras-chave:** Bisfosfonatos; osteonecrose; maxila; mandíbula

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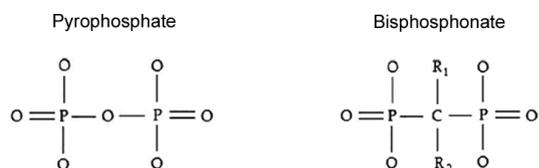
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## Introduction

Bisphosphonates represent a group of chemicals characterized by a geminal bisphosphonate bond (P-C-P). Bisphosphonates are synthetic analogs of pyrophosphate (Fig. 1), a natural inhibitor of bone resorption. Pyrophosphate cannot be used as a therapeutic agent in bone diseases because it easily undergoes enzymatic hydrolysis. Bisphosphonates, on the other hand, are more resistant to enzymatic degradation and have longer half-lives, allowing them to affect bone metabolism (1). The substitution of different groups in the R1 and R2 radical positions bonded to the central carbon confers specific properties on each bisphosphonate (Fig. 1). The R1 group affects the compound's affinity for bone crystals, while the R2 group is responsible for its potency and pharmacological activity (2). The presence of a hydroxyl radical group (OH) in R1 confers stronger binding to bone; this characteristic is found in alendronate, etidronate, ibandronate, pamidronate, risedronate and zoledronate. Moreover, the presence of chloride (Cl) in R1, as occurs in chlodronate, leads to reduced binding to bone (3).

The first generation of bisphosphonates comprises non-nitrogenated compounds and includes the ATP analogs etidronate, chlodronate (3,4) and tiludronate (5). The latter has antiresorptive action similar to that of chlodronate (6). The second and third generations are represented by the nitrogenated bisphosphonates. Alendronate, pamidronate (7) and ibandronate (8) belong to the second generation and are 10 to 1000 times more potent than compounds of the first generation (9). The third generation is represented by risedronate and zoledronate (7) and is characterized by the presence of a cyclic hydrocarbon chain (6). Zoledronate, which is 100 to 850 times more potent than pamidronate, is the most potent bisphosphonate tested *in vitro* and *in vivo* (10).



**Fig. 1.** Chemical structures of pyrophosphate and bisphosphonate.

## Pharmacokinetics

Orally administered bisphosphonates are poorly absorbed by the human body (11-13), with an absorption rate corresponding to 1% or less of the dose administered. The absorption is almost completely prevented by food containing calcium or other divalent ions that chelate the drug (12,13). Intravenously administered bisphosphonates are rapidly removed from plasma, showing a renal excretion rate of 40% in the first 24 hours. They are not metabolized by bone (14), and renal excretion is the unique route of elimination. On

the other hand, the fraction bound to bone is liberated during resorption (9). The cumulative effect is characteristic, and data suggest that not all of the accumulated fraction is active, only the portion that is on the bone surface, which requires repeated doses (15). In humans the intestinal absorption is low, with bioavailability of about 0.7% for alendronate, for example (9).

## Mechanism of action

Besides determining their affinity for bone and their potency, the chemical structure of bisphosphonates is responsible for the specific intracellular effects of these compounds (4). The two fundamental effects of the bisphosphonates are inhibition of bone resorption and, at high dosages, inhibition of calcification (16). Their mechanism of action is based on their high affinity for bone calcium and on their prevention of dissolution of bone crystals (1). As bisphosphonate metabolism does not occur in bone (17), administered bisphosphonates remain at high concentrations in bone tissue over a long period of time (17), strongly bound to hydroxyapatite crystals (1,18). During bone resorption, bisphosphonates are taken up by osteoclasts (1,18) leading to perturbation of the resorption process (17).

Though the distinct groups of bisphosphonates act through different pathways, they all result in both lowering of osteoclast performance and induction of osteoclast apoptosis. Early reduction of resorption followed by late reduction of bone formation is also observed. *In vitro*, osteoclastic bone resorption, which is stimulated by parathyroid hormone (PTH), calcitriol, prostaglandins and cytokines, is inhibited. The inhibition of resorption leads to low levels of serum calcium and consequently to elevated levels of PTH (19). Research on biochemical markers showed that bisphosphonates inhibit resorption and decrease bone turnover (20,21). Their effects on osteoclasts occur in several stages: recruitment inhibition (22,23), lifespan reduction (24), inhibition of osteoclast activity on the bone surface (25), and apoptosis activation (23,26).

Osteoblasts control recruitment and activity of osteoclasts in both physiological and pathological conditions (27). It has been postulated that bisphosphonates induce osteoblasts to secrete an inhibitor of osteoclastic resorption (28) known as osteoprotegerin (OPG) (29). Reinholz et al. (30) demonstrated that human embryonic osteoblasts treated with pamidronate or zoledronate exhibit enhanced bone formation. It was also reported that bone neof ormation induced by risedronate can be detected on radiographic images (31).

Bisphosphonates have distinct mechanisms of action depending on whether they are nitrogenated or non-nitrogenated. Evidence suggests that nitrogenated bisphosphonates, which include zoledronate and alendronate, have effects on osteoclast activity and on tumor cells (32). Nitrogenated bisphosphonates inhibit a key enzyme of the mevalonate pathway, farnesyl pyrophosphate synthase (FPP-synthase); as a result, prenylation and activation of intracellular signaling proteins are suppressed (3,32,33).

These events lead to GTPase inactivation and interference in some cytokine signal transmission pathways, causing the osteoclast apoptosis and inhibition (3,33). Mutations that inactivate Ras and Rho GTPases suppress bone resorption and cause changes in osteoclast morphology and motility (3) as well as in cytoskeletal organization (3,33).

Non-nitrogenated bisphosphonates are metabolized into cytotoxic analogs of ATP, which inhibit osteoclast mitochondrial function and cause apoptosis (6). The activation of proteases called caspases is important in apoptosis induction. Caspases 3, 8 and 9 can be activated by bisphosphonates in osteoclasts, causing hydrolysis of several proteins within the DEVD amino acid sequence (3).

Although the mechanism of action of bisphosphonates is still poorly understood (34,35), there are reports that they have antiangiogenic effects (36-38). Angiogenesis is a response to an increase in tissue mass or to changes in oxygen tension or both; the endothelial vascular growth factor (VEGF) elevates with hypoxia. In adults under physiological conditions, angiogenesis occurs only in specific situations such as fracture consolidation. In rheumatoid arthritis, malignancies and cardiovascular disease, it assumes a pathological profile (39). Low proliferation and high apoptosis rates were observed in rat endothelial cells under bisphosphonate therapy, suggesting that these agents inhibit angiogenesis (36). The antiangiogenic effect of zoledronate demonstrated in rats supports its therapeutic use in bone malignancies and other bone diseases with an angiogenic component (38). It was reported that pamidronate causes a significant reduction in bone blood supply in rats (37) and in VEGF serum levels in patients with malignancies (40).

## Indications

Bisphosphonates are indicated to treat diseases characterized by bone metabolism disturbances. The prescription of these drugs to children is restricted to local or general osteoporosis (imperfect osteogenesis, juvenile idiopathic osteoporosis, osteoporosis secondary to corticosteroids, hyper- and hypophosphatasia), diseases of bone metabolism (polyostotic fibrous dysplasia, ossifying myositis), soft tissue calcifications and hypercalcemic conditions such as those occurring in malignancies or with immobilization (children with brain injury who develop heterotopic calcifications in joints) and primary hyperparathyroidism (18). As bisphosphonates reduce osteoclast lifespan, they are also used for treating fibrous dysplasia and for improving imperfect osteogenesis symptoms (33). In adults, these drugs are indicated in calcium and bone metabolism disturbances (41) associated with excessive osteoclast activity, such as primary and secondary hyperparathyroidism and osteoporosis (16). With increasing life expectancy of populations, osteoporosis has become an important public health problem (42). Bisphosphonates have been widely used with the aim of preventing osteoporosis and thereby reducing the incidence of fractures (19).

In conjunction with chemotherapeutic agents, bisphosphonates are indicated to treat both moderate and severe hypercalcemia

of malignancies and metastatic osteolytic lesions in breast cancer and multiple myeloma (43,44). Bisphosphonates that are used intravenously are the most efficient for this purpose (11,45,46). They are also used in Paget's disease and in lung (47) and prostate cancer bone metastases (46). Zoledronate has been prescribed most frequently for hypercalcemia and bone pain associated with malignancies (45) and in prostate cancer metastasis treatment (48). Oral bisphosphonates are better indicated for the treatment of osteoporosis, as they are not efficient in the treatment of osteolytic lesions associated with malignancies (35).

Until 2001, etidronate, chlodronate, pamidronate, alendronate, risedronate, ibandronate and tiludronate were the primary bisphosphonates in clinical use (19). In 2002, zoledronate became the most widely used (49). Altundal and Gursoy (50) reported that alendronate stimulates bone formation in autogen grafts and that it represents a therapeutic alternative for stimulation of bone neof ormation. Its role in reducing tooth resorption and alveolar bone loss has also been investigated (51,52).

The effectiveness of bisphosphonates in reinforcing tooth anchorage and minimizing recurrences in patients under orthodontic treatment has been studied. It was demonstrated that both bone and root resorption were significantly inhibited during orthodontic movement in rats under daily systemic bisphosphonate administration (53). Liu et al. (54) injected chlodronate into the sub-periosteum adjacent to the upper first molar in Wistar rats under orthodontic movement and observed dose-dependent movement reduction, inhibition of root resorption and, on histological examination, significant reduction in the number of osteoclasts on the chlodronate-injected side.

Zoledronate can have a direct antitumor effect on hematopoietic cell lineages. The drug induces apoptosis of malignant B-lymphocytes whether or not patients have received chemotherapy or show a functional phenotype of multiple drug resistance. Hence, zoledronate plays an important complementary role in the treatment of these neoplasias (55).

## Adverse effects

Although well tolerated after both oral and intravenous administration, bisphosphonates have some adverse effects. When they are given by the oral route, the most common side effects are headaches, dyspepsia, diarrhea and constipation. Less commonly, corrosive esophagitis can occur, contraindicating oral administration. The most frequent side effects of intravenous administration of bisphosphonates are corporal temperature increase and flu-like syndrome, both of which can be controlled with analgesics and antipyretics. Transient hypocalcemia and hypophosphatasia can also occur, often without clinical repercussion (18). Gastric ulcer and esophageal stenosis have also been reported (8). Bone mineralization inhibition can occur, leading to clinical and histological features of osteomalacia (56). Among the oral adverse effects, ulceration of the floor of the mouth

after alendronate use (8,57) and osteonecrosis of the jaws (5,35,58-72) have been reported.

## Osteonecrosis of the jaws

Osteonecrosis is defined as an avascular necrosis of bone (73), which occurs in cancer patients who have undergone radio- or chemotherapy or have taken drugs such as corticosteroids (74,75). It results from transient or permanent loss of blood supply, which leads to necrosis and bone collapse (67). Bisphosphonate users can also develop alveolar bone necrosis. Although most cases of bisphosphonate-associated osteonecrosis are secondary to intravenous administration, there are reports of cases associated with oral administration (76,77). Many of these patients had recently been subjected to tooth extractions (78).

Bisphosphonate-associated osteonecrosis is characterized by destruction of the vascular complex of the jaws and secondary infection of the bone matrix. Its definition includes the criterion of absence of head and neck radiotherapy. The first terminology proposed was *avascular necrosis of the jaws* (63). Subsequently, other terms such as *oral cavity avascular bone necrosis* (79), *osteonecrosis of the jaws* (ONJ) (35), *bisphosphonate-associated osteonecrosis* (BON) (78), *bisphosphonate-associated osteonecrosis of the jaws* (BONJ) (80) and *bisphosphonate-related osteonecrosis of the jaws* (BRONJ) were suggested (81).

Clinical examination detects infected and necrotic bone exposed to the oral environment (79) with edema and erythema of the soft tissues (82). The site of the lesion is painful, which disturbs patients' feeding, speaking and oral hygiene. Ulceration of the oral mucosa is frequent and exposed bone shows a white-yellowish color. The adjacent soft tissue is often swollen due to secondary infection, while exploration of the exposed bone is painless and does not result in bleeding. At the first stage, exposed bone is smooth, but with time, it becomes rough and susceptible to fractures induced by chewing. Pain results from secondary infection of soft tissues or trauma caused by rough bone edges. The osteonecrosis often is progressive and may lead to extensive areas of bony exposure and dehiscence (78), which disturb oral hygiene, predispose to local infection and increase necrosis even more, leading to tooth mobility and loss. Oroantral communication, suppurating cutaneous fistulas (66), chronic inflammation and halitosis can also be present (76).

The mandibular posterior region is the area most often affected (8,83), followed by the posterior region of the maxilla (83), especially in cases of tooth extraction. Even without a history of recent dento-alveolar procedures, signs of osteolysis (35) as well as of avascular necrosis with spontaneous bone exposure (63,79) can occur. Spontaneous cases can be attributed to anatomical and physiological characteristics of the affected area, as the mandibular posterior region has a thin mucosa (84). There are also reports of patients under bisphosphonate therapy who developed osteonecrosis from trauma caused by removable partial dentures (58,61). Spontaneous cases in the mandible

can be associated with particularities of the blood supply in this region, where arteries are terminal, which is one of the reasons that chemotherapy is also associated with osteonecrosis (34).

Suppression of osteoclasts changes bone quality and, in association with other factors such as local trauma, favors osteonecrosis (67) and infection by commensal flora (34,70). Orthodontic treatment can also elevate the risk of bisphosphonate-associated osteonecrosis (53) because the lessening of osteoclastic activity (54) makes the orthodontic treatment last longer (53). Caution is necessary when such patients are evaluated and invasive laser therapies, mini-implant anchorage and tooth extraction should be avoided (85).

Although tooth extraction and oral surgery are considered trigger factors, there is evidence that in some cases, alveolar bone was previously affected. Cancer patients often have chemotherapy and steroids (75,86) as risk factors predisposing them to oral infection after minor oral traumas (77). Anemia, bleeding disturbances, infection, pre-existing oral diseases (87), family history, life style, alcohol and tobacco use are also predisposing factors (78). Taking into account the relationship of the syndrome to patients' history, clinical features, surgery and antibiotic therapy response, it seems that the pathogenesis of bisphosphonate-associated osteonecrosis is related to local vascular damage. As the blood supply is often disturbed by radiotherapy and drugs, necrosis and osteomyelitis can occur (35).

Bisphosphonate-associated osteonecrosis is restricted to the jaws; there are no reports in the literature of its occurrence in other bones. According to Marx et al. (83), this specificity results because the jaws are exposed to the external environment via the gingival crevice; as we have seen, a high percentage of cases of osteonecrosis are triggered by tooth extractions (35,63). Moreover, as the jaws may be affected by periodontal disease, abscesses and endodontic lesions (83), they require bone metabolism and good blood supply for balanced maintenance. Therefore, after treatment with bisphosphonates, bone turnover, which is modified by inhibition of osteoclastic resorption, is incapable of responding adequately to metabolic needs, and osteonecrosis takes place (35). Because they are constantly subjected to impact forces, jaws have a high bone-remodeling index (78). When bisphosphonates inhibit the remodeling process under conditions of high metabolic demands for vitality maintenance, they also make bone tissue susceptible to osteonecrosis (88).

Reviewing 119 case reports of bisphosphonate-associated osteonecrosis, it was observed that 45 cases (37%) were triggered by tooth extraction; in 34 (28.6%) there was previous periodontal disease; in five (11.2%) there was history of previous periodontal surgery; in four (3.4%), dental implant; and in one case, there was previous apicoectomy. Nevertheless, 30 cases (25.2%) had spontaneous osteonecrosis with absence of evident dental problems or trauma (83). A six-month evaluation showed 5.48 events of jaw osteonecrosis in 100 cancer patients using bisphosphonates and only 0.30 events in 100 cancer patients without bisphosphonate use (89).

Histological features of bisphosphonate-associated osteonecrosis include necrotic bone with bacterial colonies and granulation tissue (66) as well as non-prominent blood supply and osteoblasts (78). According to Bertè et al. (82) biopsy specimens show fungal and bacterial colonies. These lesions occur in cancer patients regardless of the existence of jaw metastases (66,76,78).

Although on physical examination bisphosphonate-associated osteonecrosis is similar to osteoradionecrosis, they can be distinguished on histological examination. In osteoradionecrosis, there are extensive homogenous areas of completely necrotic bone, whereas bisphosphonate lesions consist of multiple, partially confluent areas of necrotic bone honeycombed with residual nests of vital bone. *Actinomyces* sp. colonies and inflammatory infiltrate are seen in both osteoradionecrosis and in bisphosphonate-associated osteonecrosis (90).

Mortensen et al. (66) performed culture exams and verified that patients with bisphosphonate-associated osteonecrosis have normal oral flora. Badros et al. (91) studied cases of osteonecrosis in myeloma multiple patients. Histological examination showed inflammation similar to that in osteomyelitis and areas of acellular necrotic bone. Microbiological exam showed the presence of *Actinomyces* sp. in seven out of 20 patients. Other species including *Peptostreptococcus* sp., *Streptococcus* sp., *Eikenella* sp., *Prevotella* sp., *Porphyromonas* sp. and *Fusobacterium* sp. were also observed in nine patients, but their role in the soft tissue infection and osteomyelitis in these patients is not known.

Nase and Suzuki (67) reported a case of a patient taking alendronate for five years who developed alveolar bone osteonecrosis. The patient had been subjected to crown-lengthening surgery. Brooks et al. (58) reported two cases of osteonecrosis in patients using risedronate, one in a mandible torus associated with a partial removable denture, the other after a bone graft and dental implant in the posterior region of the mandible. Reviewing 22 case reports, Wyngaert et al. (70) observed 225 cases of bisphosphonate-associated osteonecrosis, corresponding to 1.5% prevalence. The nitrogenated bisphosphonates involved were pamidronate, zoledronate, alendronate and risedronate. Although pain was the main symptom (81.7%), 12.2% of the cases were asymptomatic. There was previous tooth extraction in 69.3% of the cases. At the moment of diagnosis, 74.5% of the patients reported chemotherapy and 38.2% steroid therapy. Although several conservative surgical treatments had been attempted, residual osteonecrosis persisted in 72.5% of the cases.

Early diagnosis of bone lesions in patients undergoing bisphosphonate therapy is essential to prevent and control morbidity associated with advanced destructive lesions (35). Interruption of bisphosphonate use prior to tooth extractions does not guarantee the prevention of osteonecrosis because the drug remains in bone tissue for many years (77,83).

Lesions tend to enlarge after attempts at surgical treatment (79,82). Removing the adjacent bone is contra-indicated because it may cause higher bone exposure. Tooth extractions can relieve pain momentarily, but they can also lead to higher bone exposure and pain. Surgical flaps are not effective, as they can fistulize and intensify bone exposure (63). Many other proposed treatments, such as mouthwashes, systemic antibiotics, hyperbaric oxygen therapy and surgery, have been shown to be ineffective (77,78). Thus, despite the stabilization of their cancers, patients with bisphosphonate-associated osteonecrosis have poor quality of life (79).

Lesion prevention requires careful evaluation and adequate oral health (77). Clinical and radiographic examination of the oral cavity and any necessary invasive procedures should be performed prior to bisphosphonate therapy. If a patient undergoes an invasive oral procedure, it is recommended that bisphosphonate therapy be postponed for one month until complete wound healing. While therapy is ongoing, clinical examination of the oral cavity should be performed every four months, with dental plaque control orientation and instruction in effective oral hygiene procedures. At each appointment, the dentist must examine the oral cavity carefully to detect any bone-exposed sites. A complete radiographic examination to detect osteolysis, osteosclerosis, widening of the periodontal space and furca lesions should also be required. In case of dental prosthetic needs, the prosthodontic appliance should be preferentially fixed and well adapted, avoiding traumatic ulcers (8). The increasing number of bisphosphonate-associated osteonecrosis cases, the poor response of this condition to surgical treatment and the involvement of dental factors demand prophylactic dental care in high-risk patients (92), as prevention is still the best approach (81,93).

## Final considerations

Bisphosphonates have been widely prescribed for treatment of diseases in which bone resorption is the main feature. Although these drugs are very effective for this purpose, bisphosphonate-associated osteonecrosis is an important adverse effect. The morbidity and lack of response to treatment of this condition are facts that must be considered when prescribing bisphosphonate therapy. The risk-benefit relationship must be seriously analyzed, and the pros and cons of the treatment must be explained to the patient. In cases in which therapy is indicated, rigorous oral hygiene measures must be performed, and the patient should undergo periodic dental evaluation. Dentists must be aware of the oral risks involved in bisphosphonate therapy and be prepared to evaluate and treat these patients in the correct manner. Considering the seriousness of the potential occurrence of bisphosphonate-associated osteonecrosis, caution in prescribing these drugs and careful observation of patients being treated with them seems to be indicated.

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