Bisphosphonates and Oral Pathology I. General and preventive aspects

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ABSTRACT
Bisphosphonates constitute a group of drugs capable of modulating bone turnover, and reduce its remodelling when an excessive resorption occurs. This is why they are indicated in a large group of bone diseases like postmenopausal osteoporosis or osteolysis associated with breast cancer or multiple myeloma. Over the last years and due to their extensive use, many cases of complications associated with their use have been published. Among the most important possible adverse effects are the oral ones, with the appearance of ulcerations and, especially, osteonecrosis of the jaws associated with this therapy. In this paper, we have analyzed the general characteristics of these drugs and their mechanisms of action as well as the described adverse effects, especially oral and maxillofacial has been made special reference regarding the prevention of osteonecrosis of the jaws, heightened by cases described in medical and odontological literature. The preventive protocol backs up the fundamental role of the odontologist in the effective prevention of this process before, during and after the treatment.

Key words: Bisphosphonates, adverse effects, osteonecrosis, jaws, prevention.

RESUMEN
Los bisfosfonatos constituyen un grupo de fármacos capaces de modular el recambio óseo y disminuir su remodelado cuando existe una reabsorción excesiva. Por ello están indicados en numerosas patologías óseas como la osteoporosis postmenopáusica o la osteolisis asociada al cáncer de mama o al mieloma multiple. En los últimos años y a raíz de su utilización masiva se han ido publicando numerosos casos de complicaciones asociadas a su uso. Entre los posibles efectos adversos más importantes se encuentran los orales, con la aparición de ulceraciones y sobre todo los casos de osteonecrosis de los maxilares asociados a esta terapéutica. En esta revisión analizamos las características generales de estos medicamentos y su mecanismo de actuación, así como los efectos adversos descritos, especialmente los orales y maxilofaciales, haciendo una referencia especial sobre la prevención de la osteonecrosis de los maxilares, a la luz de los casos descritos en la literatura médica y odontológica. El protocolo preventivo refuerza el papel fundamental del odontólogo en la prevención efectiva de este proceso antes, durante y después del tratamiento.

Palabras clave: Bisfosfonatos, efectos adversos, osteonecrosis, maxilar, prevención.
GENERAL ASPECTS
Bisphosphonates (BPP) are non metabolized analogues of pyrophosphate, capable of binding to the bone and inhibit the osteoclast function reducing bone turnover and the active remodelation in places where excessive bone reabsorption occurs (1). They have been used in toothpaste as antiplaque and in diagnostic tests as a conveyor of Tc 99 (2).

The first BPP introduced was etidronate with low power and with a tendency to produce osteomalacia (3). Searching for more powerful compounds and without adverse effects, the second (alendronate, pamidronate, ibandronate, tiludronate) and the third generation BPP risedronate, zoledronic acid, minodronate) have been developed.

Few changes in the structure of BPP modify their physicochemical, biological, therapeutic and toxicological properties (4).

The structure of BPP (Figure 1), shows two phosphate groups binding to a carbon atom (P-C-P), that to a certain extent is responsible for their low bioavailability. Like pyrophosphates, BPP bind strongly to hydroxapatite, explaining their pharmacological actions in the bone (5). R1 radicals influence in their affinity, therefore, OH groups increase the fixation, while CI groups decrease it. This would explain why BPP with OH groups (alendronate, pamidronate…) bind more than clodronate (6).

BPP are released when there is bone reabsorption that would explain their long half-life (7). This release is multiphasic, and in the case of alendronate is 10.5 years. This fact would explain their persistent long term effect in the bone (8).

Fig. 1. Basic structure of the Bisphophonates.

MECHANISM OF ACTION
BPP inhibit bone reabsorption by reducing osteoclast reasorptive activity (9), promoting their apoptosis (10), avoiding their formation from hematopoyetic precursors (11) or affecting osteoblasts (12).

Once inside the osteoclast, R2 chain determines the power and efficacy of the drug. In the case of clodronate (Cl in R2) and etidronate (CH3 in R2), they act through the metabolization to toxic analogues of ATP that induce osteoclastic apoptosis (13).

Different studies (14,15), have proved the role of FPP-synthase like molecular target of nitrogen-containing BPP.

These drugs induce osteoclast apoptosis by the inhibition of cholesterol biosynthesis and the mevalonate pathway, due to the inhibition of the synthesis of farnesiliprophosphate (16-19). These disturbances affect the organization of cytoskeleton, vesicle traffic and the formation of the osteoclast brush border. BPP also have some effect on the osteoblasts, which is still not totally clear, reducing apoptosis and stimulating the secretion of inhibitors in the recruitment of osteoclasts (20).

It has also been said to have an antiangiogenic effect on BPP by the inhibition of endothelial cells, reducing their proliferation and inducing apoptosis (21).

THERAPEUTIC INDICATIONS
The indications of BPP have undergone a large evolution since they were introduced in the treatment of some bone and calcium metabolic disorders (22, 23). Nowadays, the main indications of BPP are:

1. In postmenopausal and corticosteroid induced osteoporosis. In these cases the most used BPP is alendronate, which precludes the appearance of pathological fractures (24).
2. In Paget’s disease, it is used to improve bone morphology and reduce pain (25).
3. In hypercalcaemia of malignancy, its role is in trying to check hypercalcaemia, reducing pain and preventing the development of osteolitic lesions and fractures (26).
4. In patients with breast and prostate cancer with bone metastasis, it is used to relieve pain, reduce fractures and hypercalcaemia (27, 28).
5. In multiple myeloma, it is indicated to reduce associated bone pathologies such as vertebral collapse, fractures and pain (29, 30).

Oral BPP are potent inhibitors of osteoclasts, but less efficient in the treatment of bone processes associated with malignant diseases. Therefore, they were principally indicated in the treatment of osteoporosis. On the other hand, systemic BPP are indicated in patients with metastatic breast cancer, multiple myeloma, hypercalcaemia of malignancy, Paget’s disease and bone metastasis of solid tumours (prostate, lung…)

GENERAL ADVERSE EFFECTS
BPP are well tolerated in general if they are correctly administrated. Nevertheless, various adverse effects and complications associated with their use have been described.

In the case of oral BPP, the digestive effects are the most frequently described: gastric ulcerations, oesophagitis and oesophageal stenosis.

Isolated cases of uveitis in patients treated with alendronate (31, 32), pamidronate (33, 34) and recently with zoledronic acid (35) have been described.

The continuous administration of etidronate can produce a picture of osteomalacia that regresses after discontinuation of therapy (36, 37). Nevertheless, the most modern BPP do not present this adverse effect.

Some experimental models have contemplated the possibi-
lity that the inhibition of bone remodelation may lead to a reduction of bone resistance although there is no clinical evidence, at least concerning the administration of oral BPP. In fact, even with the most powerful BPP, the remodeling process is completely annulled (38).

The general adverse effects of intravenous BPP are similar to the oral ones, and some cases of flebitis (18%) have been described. There are also accounts of transitory febril, shivers (10-41%) and a pseudogrippal syndrome (20%) in the first two days (39).

There are references of hypocalcaemia, usually asymptomatic, after high doses of BPP (40, 41). Nevertheless, most of the patients are unaffected thanks to the compensatory increase of parathyroid hormone (42).

One has to be careful when high doses of intravenous BPP are administrated because its rapid administration can cause renal failure, due to the formation of a solid phase in the blood, which is retained in the kidney.

**ORAL ADVERSE EFFECTS**

There are some cases of chronic ulcerations in the oral mucosa associated with the administration of aldosterone in osteoporotic patients (44). These cases belonged to postmenopausal osteoporotic women in treatment with alendronate. They presented oral ulcerations in the mucosa secondary to an inappropriate administration, which disappeared with topic corticoids. There are other cases of oral ulcerations generally associated with an inappropriate administration (45, 46). Figure 2 presents a recent case of a 55 year woman with ulcerations in the floor of the mouth associated with the alendronate administration.

In the past 4 years there have been publications describing numerous cases of a special form of osteonecrosis of the jaws (ONJ) in patients affected with myeloma or breast cancer and in treatment with high effectiveness BPP, especially pamidronate and zoledronic acid and more rarely with alendronate (47-50).

![Fig. 2. Ulcerations in the floor of the mouth following alendronate administration.](image)

Two theories have been proposed to explain the appearance of ONJ. One related to the action of the BPP in bone turnover, and the other to their antiangiogenic action (51). The main theory suggests that ONJ is caused by the cessation of bone remodelling and the osteoclast-inhibiting effect. BPP is highly concentrated in the jaws because there is a greater blood supply than in other bones and a faster bone turnover, related to their high activity and the presence of the teeth. This circumstance, together with the frequent appearance of dental pathologies, odontological treatment and the thin mucosa over the maxilar bone; explains why osteonecrosis is especially patent in these bones.

The bone turnover maintenance is crucial to maintain bone viability. If osteoclast function decreases severely, osteocytes are not replaced and bone capillary network is not maintained, permitting the appearance of avascular bone necrosis (52). The breakdown of the oral mucosa, caused by a traumatic ulceration or surgery, causes local bone necrosis which progresses when healing fails. The risk of ONJ increases with dental manipulation and poor hygiene, because bone is exposed to the oral microbiota, later causing infection with pain, tumefaction, suppuration and progressive bone necrosis, which is difficult to control (53).

The other etiopatogenic theory is based on experimental evidence showing that most potent BPP also inhibit capillary neoangiogenesis, decreasing capillary formation and inhibiting endothelial growth factors (21), leading to avascular necrosis. However, this is not the only cause as it is not associated with the administration of more potent antiangiogenic drugs (54, 55).

There are accounts of ONJ cases associated with BPP in patients who have been on medication for years, and even for a few weeks (53). However, a study of multiple myeloma patients showed that ONJ risk is time-dependent and is significant only after 12 or 36 months after (56).

**PREVENTION OF BPP ASSOCIATED OSTEO- NECROSIS OF THE JAWS**

As in any prophylactic approach, the preventative measures of osteonecrosis of the jaws is introduced before initiating BPP therapy.

*a.- Measures before initiating BPP therapy*

As soon as the oncologist or other specialists consider the administration of BPP necessary, the patient should be referred to a dentist for an urgent oral examination (57), consisting of a complete clinical and radiographic exploration.

Oral treatment is aimed at eliminating infections and the need for invasive dental procedures in the near future; so preventive therapy should be aggressive and should include: tooth removal, periodontal surgery, root canal treatment, tooth decay control, dental restorations and prosthesis if needed. These patients are not candidates for dental implants because of the risk elements involved (51). A month before initiating BPP therapy, removal of large mandibular tori or palatal tori with thin overlying mucosa, is recommended to avoid the risk of ulcerations.
Patients with no cardiac disease do not require prophylactic antibiotic coverage for non invasive procedures but there is a need for an invasive procedure; in this case, the chosen drug is penicillin and its derivatives. For individuals with penicillin allergy, a combination therapy using quinolones and metronidazole have proven efficient. Clindamycin alone is not recommended because it is ineffective against actinomycetes, Eikenella corrordens, and similar species that frequently colonize the exposed bone in the oral cavity (51).

If the patient requires only non invasive dental care BPP therapy is not delayed. But if the patient requires invasive procedures, BPP therapy should be deferred for a month to allow bone recovery and good healing. A surveillance schedule every 4 months with plaque control and strict hygienic measures is recommended.

b.- Measures during BPP therapy

The dentist should carefully examine the oral cavity in the search for the presence of bone exposures in the most commonly affected areas, such as the posterior and lingual area of the mandible. A complete radiographic examination should be carried out to look for signs of osteolysis, osteosclerosis, widened periodontal spaces and furcation affection.

A careful dental cleaning and preventive use of fluor and chlorhexidine should be considered as well as strict hygienic measures (51).

All the needed procedures to conserve the teeth and avoid the appearance of infections should be done as soon as possible. If the tooth is not restorable, root canal treatment and amputation of the crown are preferable to extraction. Root canal treatment should be carried out with minimum trauma to the marginal and apical periodontal tissues (58).

In relation to periodontal disease, teeth will only be removed when they have 3 or more mobility grade or an associated periodontal abscess. In these situations, adequate antibiotic treatment is imperative, as previously indicated (51). Surgery procedures are contraindicated. Nevertheless, in patients that need surgery, BPP withdrawal is recommended in the case of a bad recovery. However, it is not certain that BPP withdrawal will prevent the appearance of ONJ, due to their half-life (59).

When oral surgery procedure is needed in a patient with BPP therapy, some special precautions should be taken as for instance, absolutely aseptic procedures, atraumatic surgery and achieving a first intention closing if possible (60). If prosthesis is needed, it should be preferably fixed and well carried out, to avoid if possible the appearance of secondary traumatic ulcerations.

In patients in treatment with BPP it is recommended to engage in a continuous surveillance schedule every 3 or 4 months with plaque control and strict hygienic measures.

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