Bisphosphonates in Bone Diseases Treatment

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Bisphosphonates are the most frequently used drugs in the treatment of various bone and cancer diseases. They are complex chemical compounds, having a structure similar to that of pyrophosphates, but with certain differences: i.e., bisphosphonates have P-C-P in their composition; instead of an oxygen atom, a carbon atom is present. The R1 and R2 chains bind to the carbon atom and thus, the antiresorptive capacity of bisphosphonates on the one hand, and their bone-binding capacity on the other hand are stimulated. Through their action, they favor the treatment of diseases for which they have been prescribed, but they can also favor a number of undesired side effects.

Keywords: bisphosphonates, nitrogen atoms, ATP, osteoporosis, treatment

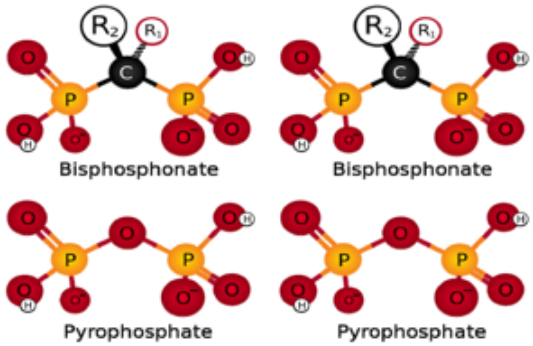
The first types of bisphosphonates were developed in the 1970-1980s, being successfully used in diseases with bone mineral imbalance (marked activity of osteocytes in relation to osteoblasts) and low absorption of bone hydroxyapatite calcium (osteoporosis). These included etidronate, clodronate, and pamidronate. Over the years, research in this area has evolved, and neridronate, risedronate, zoledronate, minodronate, alendronate and ibandronate were included in the same pharmacological category [1].

They were initially used in the process of production of industrial oils, textile manufacturing and even fertilization [2]. According to the first scientific data on these drugs, it was known that pyrophosphates inhibit tissue calcification by inhibiting hydroxyapatite activity. Pyrophosphates could be administered orally, being hydrolyzed in the stomach. Thus, bisphosphonates, being resistant to hydrolysis, can be administered per os [3].

Bisphosphonates represent the category of drugs that are the most frequently used in the treatment of osteoporosis in postmenopausal women having this disease [4], as well as in the treatment of bone metastases in prostate carcinomas [5], bone metastases in solid myeloma (Berenson,1996; Hortobagyi et al., 1996; Major, 2002) [6], in patients treated with high corticoid doses for various disorders [7], and according to recent studies, they can also be administered to children with osteogenesis imperfecta [8].

Chemical structure

Bisphosphonates are structural analogues of pyrophosphates. From a chemical point of view (fig. 1), pyrophosphates have a P-O-P molecular structure, two phosphate groups binding an oxygen atom. Bisphosphonates have a similar chemical structure to that of pyrophosphates, but with certain differences, i.e., they have P-C-P in their composition; instead of an oxygen atom, a carbon atom is present. The R1 and R2 chains bind to the carbon atom and thus, the antiresorptive capacity of bisphosphonate on the one hand, and its bone-binding capacity on the other hand are stimulated.



Fig, 1. Molecular structure of bisphosphonates atoms compared to pyrophosphate atoms

Bisphosphonates that include nitrogen atoms in their structure(fig. 2) (primary NH2 in the R2 lateral chain), i.e., alendronate, risedronate, etc., have much more expressed properties than those without nitrogen atoms in their composition. If the R1 chain is represented by the OH group, bisphosphonate binding to hydroxyapatite is significantly increased. At the same time, the R2 chain is also important in the antiresorptive process of bisphosphonates. If NH2 is combined with a tertiary amine in the R2 chain (ibandronic acid), the bisphosphonates of this category are much more active. Currently, bisphosphonates containing NH2 in their structure are the most potent and, as such, the most effective [9].

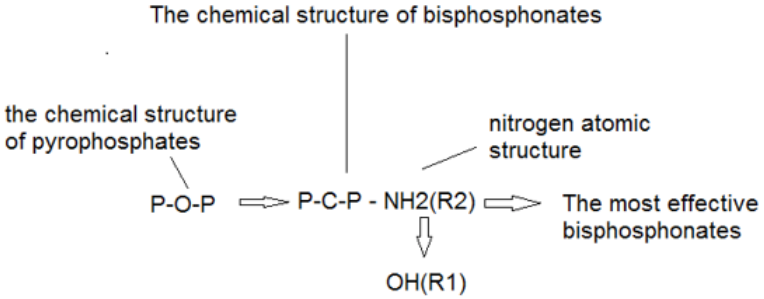


Fig. 2. Schematic representation of the structure of pyrophosphates and bisphosphonates; binding of nitrogen atoms to bisphosphonate chains and final results

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Mode of action

The cellular action mechanism of bisphosphonates

Bisphosphonates with nitrogen in their composition inhibit the enzymatic synthesis process of farnesyl diphosphate at metabolic cellular level [10]. This aspect is responsible for the production of isoprenoid lipids and cholesterol. Of isoprenoid lipids, two are important and necessary in the normal formation of GTPases (Ras, Rho, Rac) for the normal functioning of these enzymes – farnesyl diphosphate, geranyl diphosphate [11]. The role of GTPases is to control osteoclast morphology, apoptosis, skeletal architecture and vesicular circulation [12]. Bisphosphonates containing nitrogen in their structure inhibit osteoclast function by a direct action on GTPases, thus inhibiting their action [13].

Bisphosphonates, which are structurally similar to pyrophosphates, are incorporated into non-hydrolyzable ATP analogues [14]. As they accumulate in osteoclasts, they cause their insufficiency. ATP analogues accumulated inside the cytoplasm interfere with biological process, thus leading to osteoclast and macrophage apoptosis [15].

Bone resorption

The main function of bisphosphonates is direct inhibition of mineralization, stopping in this way bone resorption [16]. In this respect, new generation bisphosphonates had considerably diminished levels in bone resorption. From a physical point of view, they largely change bone resorption and thus alter bone cellular metabolism. Their binding to the calcified bone matrix is essential, so that they can become fixed in bone.

Essentially, bisphosphonates attach to each osteoclast cell, leading to increased apoptosis and altered metabolic activity [17]. Thus, osteoclasts demineralize the extracellular bone matrix, which results in bone resorption. During treatment with bisphosphonates and other drugs, their molecules are captured and thus, the connection between osteoclasts and bone surface is lost, which leads to the rupture of the cytoskeleton and finally, to the loss of their functions [18]. The main action of bisphosphonates consists of inhibiting the action and activity of osteoclasts, stimulating the development of mature osteoclast cells. Through all these processes, bone resorption is prevented.

Regarding absorption in the entire body, bisphosphonates are rapidly absorbed by bone, their circulating level being very low. Thus, single bisphosphonate doses administered to postmenopausal patients can have an important effect in the bone resorption process. Oral administration may also have undesired consequences at gastrointestinal and other levels; a number of studies on injectable bisphosphonate administration in a single monthly or quarterly dose have been conducted [19].

Bisphosphonate therapy

Bisphosphonate therapy administered in the case of osteoporosis, bone metastases, Paget's disease, etc. has beneficial effects on patient quality of life, in stopping localized or generalized bone damage. In addition to these benefits, like any other treatment, it involves potential risks and side effects. It is extremely important for the general dental practitioner to know in detail these types of drugs and permanently monitor patients during treatment, and to know how to identify possible changes in the jaw bones.

Benefits of bisphosphonate therapy

Oral bisphosphonates

These types of bisphosphonates are recommended for the treatment of osteoporosis and osteopenia. In addition to these bone diseases, they are administered for osteogenesis imperfecta in children, Paget's disease, etc. However, the highest prevalence of prescription and administration of oral bisphosphonates is in the case of osteoporosis most frequently developed in the postmenopausal period [20]. In this case, bisphosphonates play an important role in the function of vitamin D and calcium, potentiating their beneficial action.

Injectable bisphosphonates

These types of bisphosphonates were the first administered types, being indicated in malignant hypercalcemia, breast cancer, lung cancer, prostate cancer, and multiple myeloma[21, 22].

Their efficiency is focused on reduction and prevention of hypercalcemia, stabilization of already existing bone lesions, and even prevention of fractures located in the skeleton. It has been scientifically demonstrated that bisphosphonate administration in advanced and terminal cancer stages has improved patient quality of life. Before the 2000s, in USA, pamidronate was the only drug approved for the treatment of bone metastases. In the early 2000s, zoledronate (Zometa) made a strong entrance on the market and was subsequently approved by FDA as the best bisphosphonate at that time [23].

Risks of bisphosphonate therapy

In addition to the considerable benefits of these types of drugs, there is also the possibility of risks. At the beginning of the 2000s, when zoledronate was introduced on the market and was frequently administered to patients with bone diseases, cases of exposed necrotic bone in the oral cavity of patients during intravenous bisphosphonate treatment were reported [24]. The Novartis company, a manufacturer of injectable bisphosphonates, i.e., zoledronate and pamidronate, admitted and subsequently introduced in the drug information leaflet the possibility of development of necrosis of the jaw. In this regard, professional care and close monitoring of these groups of patients receiving both oral and injectable bisphosphonates were indicated [25].

General side effects of bisphosphonates

The most frequently found general side effects of bisphosphonate treatment are: necrosis of the jaw, facial erythema, gastrointestinal and renal toxicity. The risk of these phenomena depends on the type of bisphosphonates administered. In the case of zoledronic acid, facial erythema and renal toxicity may occur, which is why well conducted anamnesis is imperative to know the patient's medical history, and potential risks should be explained to the patient when starting bisphosphonate therapy.

The administration of oral bisphosphonates (ibandronic acid) may cause very unpleasant gastrointestinal side effects for the patient. These occur by an impairment of local cellular metabolism and an increase of apoptosis. Clinically, symptoms of nausea, vomiting, dyspepsia, diarrhea, etc. are reported. Alendronate administered per os causes ulcerations and esophageal erosions. In addition to all these symptoms, in the oral and maxillofacial area, cases of osteonecrosis of the jaw have been reported, as another consequence of bisphosphonate therapy (table 1) [26].

It can be easily seen that osteonecrosis of the jaw is a frequently found adverse effect, regardless of the type of bisphosphonate administered. Avascular necrosis of the jaw is predominantly due to osteoclast activity [27]. Physiologically, bone undergoes a continuous resorption

Bisphosphonate type	Pathology	NH2 content	Adverse effects
Alendronate (Fosamax)	Osteoporosis	YES	-Osteonecrosis of the jaw -Esophageal erosions -Ulcerations
Ibandronate (Boniva)	Osteoporosis	YES	Gastrointestinal toxicity (dyspepsia, nausea, vomiting, diarrhea)
Zoledronate (ZOMETA)	Bone metastases	YES	-Osteonecrosis of the jaw -Facial erythema -Renal toxicity -Anemia -Fatigue

Table 1
ADVERSE EFFECTS OF DIFFERENT TYPES OF BISPHOSPHONATES AND THE DISEASES FOR WHICH THEY ARE ADMINISTERED

Fig. 3. Local side effects of bisphosphonates in the oral cavity

process, caused by the action of osteoclasts, but when a disturbance of this process and implicitly, an inhibition occurs, this results in the presence of non-vital bone over large areas. The lack of bone proteins and cytokines will decrease new mineral binding, and thus, fragile bone with microfractures in the bone matrix and extensive non-vital osteoclast areas will result [28].

Local side effects of bisphosphonates in the oral cavity

Osteoporosis in postmenopausal women is associated, in addition to other effects, to estrogen deficiency. This manifests in the oral cavity by tooth and even bone loss. At a routine check-up performed by the general dental practitioner, bone resorption of edentulous alveolar ridges is detected, and in the absence of adequate prosthetic treatment, the presence of generalized periodontal disease and even its aggravation is observed (fig. 3) [29]. This is why, before starting short- or long-term bisphosphonate therapy, it is recommended to treat the existing dental foci and periodontal disease, to perform adequate prosthetic treatments and to continuously monitor the patient in collaboration with the treating oncologist [30].

Conclusions

The treatment of osteoporosis is represented by bisphosphonate drugs, which through their action at cellular level stop the action of osteoclasts and even improve bone architecture.

Bisphosphonates represent the most frequently used drug category for the treatment of osteoporosis in postmenopausal women, as well as for the treatment of bone metastases in prostate carcinomas, bone metastases in solid myeloma, patients treated with high corticoid doses for various disorders, and according to recent studies, they can also be administered to children with osteogenesis imperfecta.

The main function of bisphosphonates is direct inhibition of mineralization, thus inhibiting the action and activity of osteoclasts, and they stimulate the development of mature osteoclast cells. Through all these processes, bone resorption is prevented.

Regarding absorption in the entire human body, bisphosphonates are rapidly absorbed by bone, their circulating level being very low. Thus, single bisphosphonate doses administered to postmenopausal patients can have an important effect in the bone resorption process. Oral administration may also have undesired consequences at gastrointestinal and other levels; a number of studies on injectable bisphosphonate administration in a single monthly or quarterly dose have been conducted.

Bisphosphonate therapy administered in the case of osteoporosis, bone metastases, Paget's disease, etc. has beneficial effects on patient quality of life, in stopping localized or generalized bone damage. In addition to the considerable benefits of these types of drugs, there is also the possibility of risks. At the beginning of the 2000s, when zoledronate was introduced on the market and was frequently administered to patients with bone diseases, cases of exposed necrotic bone in the oral cavity of patients during intravenous bisphosphonate treatment were reported.

The general side effects of bisphosphonate treatment are: necrosis of the jaw, facial erythema, gastrointestinal and renal toxicity. The risk of these phenomena depends on the type of bisphosphonates administered. In the case of zoledronic acid, facial erythema and renal toxicity can develop; administration of oral bisphosphonates (ibandronic acid) may cause gastrointestinal side effects: symptoms of nausa, vomiting, dyspepsia, diarrhea, etc.; alendronate administered per os can induce ulcerations and esophageal erosions. The local side effects of bisphosphonates in the oral cavity are associated with tooth and even bone loss. At a routine check-up performed by the general dental practitioner, bone resorption of the edentulous alveolar ridges is detected, and in the absence of adequate prosthetic treatment, the presence of generalized periodontal disease and even its aggravation, as well as the presence of osteonecrosis of the jaw are observed.

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