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Narrative Review

Knowing Bisphosphonates and the Potential Use in Dentistry

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Abstract

Bisphosphonates (BPs) are compounds which reduce the rate of bone turnover and affect the activity of several bone cells like the osteoclasts, osteoblasts and osteocytes. BPs have been used for the treatment of bone diseases characterised by high turnover (Paget's disease of bone, hypercalcemia of malignancy) and osteoporosis by reducing the turnover rate and increasing the bone density. BPs are avidly absorbed by the bone and, on a special way, by the area subjected to remodeling either for physiological needings or as consequence of inflammatory conditions. Bisphosphonates bind to the bone mineral and are retained buried in the bone for extended period of time which vary from weeks, months up to years. The capability to prevent the bone loss has also stimulated investigations on the potential use in the field of dentistry where the BPs can be used systemically or by local application.

Keywords: *Bisphosphonates; Dentistry; Bone Remodeling; Periodontal Disease; Implantology*

Introduction

Bisphosphonates (BPs), previously called Diphosphonates, are well known since long time [1,2] for their effects on bone metabolism and the capability of reducing the rate of bone turnover. These compounds exert a peculiar pharmacological action on the bone as a consequence of the strong affinity for the major inorganic component of the bone, the hydroxyapatite, and for the antiresorption effect on the same bone. These biological effects are the core of their use in all pathological conditions characterised by increased bone resorption. The skeleton is a metabolically active organ that undergoes continuous remodelling throughout life to maintain structural integrity and to provide for calcium homeostasis. It is known that once reached maturity, the bone switches from a modelling phase, when the bone's final physiological shape is reached, to a remodelling phase, a process that is responsible for the preservation of the bone structure with an almost complete renewal, in approximately ten years, and for the repair of microfractures.

The cells in the mature bone that are involved in the remodelling, i.e. osteoblasts (OBs), osteoclasts (OCs) and osteocytes (Oct), belong to functional units called BMU (bone multicellular units), whose dimension is 1 - 2 mm (length) 0.2 - 0.4 mm (width) and are active as 4 - 5 million per year. Every moment roughly 1 million BMU is active and each one is functional for a period of 6 - 9 months. As this period of time exceeds the cell lifespan there is a continuous renewal of OCs and OBs [3,4].

Bone histomorphometry has indicated that the rate of OCs activity in a single BMU is 10 - 25 μm/day, the pit volume is roughly 0.025 mm^3, whereas the OCs lifespan is roughly 2 - 3, or more, weeks and the OBs is roughly 3 months. The time lapse between two remodelling phases in the same area, although largely variable, can be between 2 and 5 years. It is interesting to note that the pit depth is around 60 μm [5,6]. Once entered in to the circulation BPs are adsorbed to the bone subjected to a remodeling phase where the hydroxyapatite is exposed, at this specific site the BPs may inhibit osteoclasts attachment or maturation, interfere with the osteoblasts signals to the osteoclastic cells and, once desorbed in the resorption pits, interfere with the OCs function.

Modes of action of Bisphosphonates

Due to the effect on bone metabolism, BPs have been developed for a wide range of bone diseases characterised by abnormally high turnover and increased bone resorption as in Paget's disease of bone, hypercalcemia of malignancy and osteoporosis where BPs reduce the turnover and increase bone density [7,8]. In spite of the predominant use in the above mentioned indications, several BPs have also been shown to exert significant antiarthritic effect in rat adjuvant-induced polyarthritis and in a model of granulomatous inflammation [9,10]. The anti-inflammatory activity has also been confirmed by clinical data on several conditions like osteoarthritis [11,12], rheumatoid arthritis [13-15], ankylosing spondylitis [16,17] and others where the chronic inflammation induces release of cytokines, especially IL-1, IL-6, IL-17 and TNF-α as well as prostaglandins and leukotrienes, involved, together with the activation of gamma/delta T-lymphocytes and the release of RANK-L (receptor activator NFkB ligand) as activator of the OCs [18].

Matrix metalloproteinases have also been implicated in the excessive matrix degradation that characterises bone degeneration in several inflammatory conditions [19].

There is extensive evidence for the association between proteinases and a large number of disease processes. Microbial proteinases can act in concert with host proteinases in the promotion of tissue destruction as seen in periodontium [20].

The clinical application of the BPs is justified by their biological activity at cell and molecular level which involve not only the inhibition of the OCs recruitment and activity but also the inhibition of macrophages [21,22] and prostaglandins synthesis [18,23,24], while also several MMPs are inhibited. All together these properties have stimulated the research to the field of dental diseases where a bone loss may happen after a tooth extraction, or around an implant or, even more, as consequence of periodontitis.

It is known that at the moment of dental implant some particles are formed which attract macrophages. Similarly, it is known that synovial like pseudomembrane containing abundant macrophages and fibroblasts, together with large numbers of particles, form around the implant. Several cytokines are released in the interspace: TNFα, IL-1, IL-6 (but also IL-4, IL-10 and INF-α) which stimulate the attraction of the OC precursors and the inhibition of the mature OCs apoptosis.

Periodontitis represents a specific inflammatory response to microbial residents of the subgingival biofilm. Emerging evidence strongly suggests that the inflammatory response of the host induces tissue destruction. Nevertheless, although bacteria are necessary for disease appearance, periodontitis does not develop unless it is associated with inflammatory response and host susceptibility [25]. The inflammatory reaction induced by the large bacterial bioburden, brings to the activation of the monocyte/macrophagic system and T-lymphocytes with release of MMPs and RANKL, while gingival fibroblasts release M-CSF [26] and modulate negatively Osteoprotegerin (OPG) synthesis with the imbalance on RANKL/OPG axis towards the bone resorption [27,28]. Periodontitis associated osteoclastogenesis depends also on up regulation of cyclooxygenase-2 (COX-2), enzyme responsible for the expression of PGs by periodontal fibroblasts, cementoblast and osteoblast with the increased production of PGE2 [29].

It is also common evidence that following a tooth extraction the mandible is affected by internal and external changes due to an intense phase of remodeling, as response to an inflammatory reaction, which result in an extensive loss of bone, the crest of the residual ridge

become narrow and the alveolar processes are reduced. The validated efficacy of the BPs in the treatment of other bone disease prompted many scientist to evaluate the efficacy of these compounds in periodontal and other mandible diseases. The interest for the dental field is, actually, quite old due to the discovery of relevant concentration of Pyrophosphate (PPi) in saliva and its interference on the deposition of dental calculus [30].

Although endogenous PPi in saliva might be a factor in the prevention of calculus deposition, the fast enzymatic hydrolysis due to the pyrophosphatase present in saliva and salivary bacteria, have suggested the use of the BPs which show a similar activity but a resistance to the hydrolysis.

In a double blind clinical study [31,32] a toothpaste containing 1% etidronate (EHBP) was able to reduce the calculus formation by 34.1% or 41.1% as well as the degree of mineralization of the same.

Some animal studies have also shown that BPs may be able to reduce the incidence of caries in rats.

Periodontal diseases

The efficacy of BPs as inhibitors of the bone resorption as well as the capability to inhibit degradative enzymes and the synthesis of inflammatory factors, has promoted a large amount of data on the potential application of BPs in the treatment of periodontal diseases after local application or systemic treatment.

It is generally understood that a successful management of periodontal disease is focused on the elimination of etiologic factors, as the pathogenic bacteria, by the use of scaling and root planing or administration of systemic, as well as topical, antimicrobial medication together with a reduction of some risk factors. Despite of all these approaches, even when the periodontal disease is controlled or cured, the patients have often evidence of the disease with loss of alveolar bone and deficiency of periodontal support. This last problem have originated the research of different approaches including the modulation of the host inflammatory reaction, the inhibition of destructive enzymes and the use of inhibitors of bone resorption [33].

In a preliminary study in an animal model of experimental periodontitis in monkeys [34] it was demonstrated that a bisphosphonate, sodium Alendronate, injected at 0.05 mg/kg i.v. biweekly was able to prevent the bone loss, while an higher dose, 0.25 mg/kg induced local cytotoxic effect to other stromal cells by an upregulation of inflammatory processes.

Another study in monkeys [35] in which periodontitis was induced by ligating mandibular molar teeth and inoculating the ligature with Porphyromonas gingivalis, intravenous injection of 0.05 mg/kg of Alendronate confirmed the previous study by reducing the bone loss.

A further demonstration of the efficacy of the BPs in this pathological condition was obtained in dogs with naturally occurred periodontitis, a model that mimes the human disease. After weekly oral treatment with 3.0 mg/kg of Alendronate [36] a statistically significant difference in bone mass ($P < 0.001$) was observed in comparison with the placebo, even if the results were not as robust as in previous experiences. The reason was considered due to the different dose of Alendronate and to the magnified disease activity induced also by the use of a ligature.

Other studies have demonstrated the efficacy of BPs, other than Alendronate, in preventing the bone loss in animals models of inflammatory periodontitis [37]. Similar results have been obtained after topical application of Clodronate injected at 20, 40 or 60 mM solution into the subperiosteal palatal area, adjacent to the interdental area of rat with experimental periodontitis [38].

The biological properties of BPs and the published animal data have also stimulated several preliminary clinical investigations: a controlled clinical trial has demonstrated the efficacy of the local delivery of 1% Alendronate gel into the periodontal pocket of patient affected by chronic periodontitis in addiction to mechanical procedure. The treatment has induced a significant decrease in the probing depth and an increase of the clinical attachment level [39].

A large review of Chen 2016 has included 8 randomized controlled trials (RCT) comparing scaling and root planing (SRP) plus alendronate to SRP plus placebo in the treatment of periodontitis. After 6 months changes in bone defect fill, probing depth (PD), and clinical attachment level (CAL) were examined and compared with baseline data. Compared with SRP alone, the adjunctive mean benefits of locally delivered alendronate were 38.25% for bone defect fill increase, 2.29 mm for PD reduction and 1.92 mm for CAL gain. The systemically administered alendronate with SRP was less effective with a PD reduction of 0.36 mm and increased CAL by 0.39 mm. However, although alendronate has a good safety record, recent reports indicate that systemic alendronate may have some side effects, such as osteonecrosis of the jaws [40], although after long term use.

In a clinical study by Jeffcoat., *et al*. (2007) 335 patients with periodontal disease were randomized to receive Alendronate (70 mg/w) or placebo during 2 years with a final examination of the change of the alveolar bone loss [41]. The Alendronate treatment did not significantly change the rate of bone loss as well the density. There was a reduced bone loss only in a subgroup of patients with lower bone mass at baseline.

Another study has explored the efficacy of Alendronate as 1% gel formulation locally delivered in periodontal pockets in adjunction to scaling and root planing in diabetic patients affected by chronic periodontitis. At 2 and 6 months there was a greater gain in the clinical attachment gain and a greater reduction in the mean probing depth in the AL group of patients in comparison to the placebo group. Furthermore, significantly more bone fill was found in AL group [42].

However, it should be noted that not all clinical studies have provided equivalent results, in effect a retrospective cohort study on 26 subjects receiving oral BP in comparison to 26 subjects who did not receive BPs any time along the study, was unable to demonstrate any improvement in maintaining alveolar bone level [43].

The lack of significativity of the results can be justified by the low number of subjects and the different BPs drugs used during the study but it is also possible that oral BPs may not be effective in reducing annual alveolar bone loss while adjunctive local delivery medication with BPs may offer sensible advantages.

Same conclusion were stated by Akram., *et al*. in a large review that Delivery of bisphosphonates as an adjunct to scaling and root planing in the management of periodontal disease appears to be effective in the short-term; however, due to the potential risk of osteonecrosis of the jaws, their long-term clinical application remains debatable [44].

Surgical wounding

BPs have been additionally tested on the potential effects in relation to the regional accelerated phenomenon (RAP) associated with surgical wounding of cortical bone as it happens after a mucoperiostal flap surgery [45].

Following elevation of a full thickness flap of rat mandible, the intravenous administration of 0.5 mg/kg Alendronate was able to significantly reduce the bone resorption while the local injection of 0.15-0.75-1.5 mg/kg had no inhibiting effect [46].

With a similar experimental model different concentration of Alendronate solution were included into gelatin sponge pellets applied to the alveolar bone on buccal and lingual side in the region of premolars and molars of the mandible. While the surgery produced 40% of

bone loss relative to normal mandible, the topical application of the pellets soaked with 0.5 mg induced marked reduction of bone resorption maintaining the height of the alveolar crest [47].

The same investigators have demonstrated that also a concentration of 0.2 mg in a gelatin sponge placed at the surgical mucoperiostal side, reduced the amount of total alveolar bone resorption as well as when the drug was delivered in a distant submucosal area [48]. The result obtained leads us to believe that the local administration of BP allows a longer stay in the operated site than the more fleeting presence due to systemic administration.

Orthodontics

Several studies have demonstrated that cytokines (IL-1, IL-6, TNFalfa), as well as prostaglandin E (PGE) are released by fibroblast of periodontal ligament by mechanical stress [49-51]; on this base it was investigated if BPs are able to modulate the orthodontic tooth movement and root resorption.

In a study done in rats [52], the right and left upper first molars were moved buccally with a standardized expansion spring and treated systemically every other day or locally with an amino-bisphosphonate (Alendronate) either during the presence of the spring or after its removal. In both the cases there was a reduction of the teeth movement respectively of 40% and 50% at the dose of 0.5 mg P/kg.

In a similar experimental model [53] a solution of Clodronate, a not-amino-BP derivative, was locally applied by subperiosteal injections. The local administration at 2.5, 10 and 40 mM was well tolerated and induced a dose dependent significant reduction in teeth movement on the treated side in comparison to the control side. The root resorption area was also inhibited by the drug. Similar results have been obtained after the local application of Risedronate in rats [54], suggesting again that the topical or systemic application of BPs may be helpful in anchoring and retaining teeth under orthodontic treatment.

Implantology

The increase in bone mass and density induced by the systemic and local application of BPs has stimulated investigations on the effects on bone regeneration around dental implant. In a study done in dogs [55] two types of dental implants were analyzed. Six adult hound dogs were evenly divided into 2 groups, with one group receiving alendronate-coated dental implants and the other group serving as controls. Dental implants were placed immediately after extraction of mandibular premolars. After 28 days the histological examination indicated a significant increase amounts of bone ($P < 0.0002$, ANOVA) in the peripheral area.

Several studies have demonstrated the efficacy of BPs in increasing periprosthetic bone stock in rats and rabbits due to their antiresorptive and osteoanabolic effects [56,57].

A study in rats of Abtahi., *et al*. 2013 showed that locally applied BPs through coated implants are able to improve the fixation of metal implants in bone with higher removal torque. Differently the systemic treatment of the same BP plus dexamethasone developed ONJ-like change [58].

Similar data are reported in a clinical randomized investigation on 16 patients receiving two dental titanium implant in the maxilla with or without a coating of fibrinogen containing a BP. The implant stability quotient (ISQ) after 6 months, showed less bone resorption around the implant margin due to the BP released from the fibrinogen coating. The authors suggest the possibility of using a similar method not only in the bone implantology but also in the orthopedic surgery [59].

Similar data have been also reported in other studies where BP-treated implants showed a larger amount of bone around the implants [60-62].

Although numerous clinical studies have reported different data on the outcomes of implants performed on subjects treated with BPs for osteoporosis, the more widespread opinion is that BP-releasing dental implants may have a positive effect on osteointegration [63].

Despite various studies showing how BP-releasing dental implants as well as the topical application of BPs included in different vehicles, may have positive effects on osteointegration or improving periodontal parameters also improving the efficacy of scaling and root planning, still different results can be obtained as a consequence of the numerous variables due to the quality of the materials used for the implants, the type of coating, the greater or lesser release of the BPs from the vehicles, the different types of BP and the concentration applied both on the implants or locally. These are all variables, with others, that can determine the differences found in the various studies carried out.

Conclusions

It is our opinion that the results obtained with the use of BPs in the field of dentistry, either in animals as well as in preliminary clinical studies, are a strong and justified motivation to a more extensive use of these compounds in the medical practice for the advantage and the safety that they may offer to the patients. It must be mandatory condition a correct selection of the doses supplied to the patient or the concentration of the BP locally delivered, both elements depending on the type of BP, its bone affinity and degree of activity, keeping on mind the difference between aminate or not-aminate BP. A too low dose or concentration could be ineffective and an excessive one could be cytotoxic and dangerous; the knowledge of BPs pharmacology and kinetic is a prerequisite for the correct use of these compounds.

The experiences acquired in the clinical field with the treatment of systemic and chronic diseases, like osteoporosis, indicate the existence of a large margin of safety when BPs are used on the dental practice and also the condition known as "osteonecrosis of the jaw" (ONJ), which has created a lot of concern in the dental communities, it may not represent a problem on the basis of the low BP concentrations applied and the limited exposure times to these drugs. The ONJ etiology and pathology, has been described elsewhere and is related to a chronic treatment and to special conditions of the patients, prerequisites not involved in the dental practice which, on the contrary, could receive several benefits from the use of bisphosphonates.

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