ORTHODONTICS & CRANIOFACIAL RESEARCH

REVIEW ARTICLE

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Bisphosphonates treatment and orthodontic considerations

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Dates:
Accepted 22 July 2009

To cite this article:
Ghoneima AA, Allam ES, Zunt SL, Windsor LJ: Bisphosphonates treatment and orthodontic considerations
Orthod Craniofac Res 2010;**13**:1–10

Published 2010

Abstract

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Currently, the use of oral and systemic forms of bisphosphonates is increasing dramatically in a large group of patients either in the form of anti-osteoporosis medications or as a part of a chemotherapeutic regimen for several malignant diseases. As adult orthodontic treatment has become more widely accepted in most orthodontic practices, orthodontists must be aware of the risks, benefits, and effects of bisphosphonates use on the patient's general health status, as well as on their orthodontic treatment outcomes. This review aims to discuss the use of bisphosphonates, the complications associated with their use, and their impact on orthodontic treatment.

Key words: bisphosphonates; orthodontics; osteonecrosis

Introduction

Orthodontists have long observed that teeth move at different rates and that a wide variation exists in individuals' response to orthodontic treatment. Some of these differences are caused by changes in bone remodeling induced by drugs and/or systemic factors. It has been shown that drugs such as bisphosphonates can reduce the rate of orthodontic movement through their effects on a variety of significant cellular processes that results in the inhibition of bone resorption. In addition, several reports have demonstrated an association between patients taking bisphosphonates and serious complications affecting the jaws. Therefore, dental clinicians including orthodontists should pay careful attention to patients using bisphosphonates. The purpose of this review is to address the possible effects of bisphosphonate use on orthodontic treatment and to advise orthodontists to increase their knowledge about the side effects associated with the use of these drugs. The literature was searched based on the mechanism of action of bisphosphonates, their adverse effects, and their relationship to orthodontic treatment and tooth movement. This review is not intended to be a comprehensive review, but rather a focused synopsis of the topic for general dental and orthodontic practitioners.

Bisphosphonate therapy

Bisphosphonates are a class of drugs which are now widely used to treat osteoporosis and the complications associated with malignant bone metastases. They are considered the first-line of therapy in the treatment of osteoporosis and are the most commonly prescribed bone anti-resorptive agents (1). In 2005, the bisphosphonate alendronate was the 15th most commonly prescribed drug with approximately 18 million prescriptions and the bisphosphonate risedronate was 37th with almost 10 million prescriptions. This was a 40% increase in the use of risedronate since 2003 (2, 3). In 2006, the total number of prescriptions filled for oral bisphosphonates in the United States exceeded 30 million (4).

Bisphosphonates work as potent suppressors of osteoclast activity by slowing down the remodeling process. They increase bone mineral density and reduce the risk of fractures in patients with osteopenia or osteoporosis. Osteoporosis is defined as having a bone density of 2.5 standard deviation (SD) below the mean bone density or by the presence of fragility fractures. Osteopenia refers to a bone density between 1 and 2.5 SD below the mean bone density (5). Osteoporosis affects 14 million women and 2 million men in the United States (6). At least 1.5 million bone fractures occur each year in the United States from osteoporosis. These include vertebral, thoracic, pelvic, hip, and humerus fractures. These fractures are associated with long-term morbidity and sometimes mortality. The use of bisphosphonates has reduced the risk of osteoporotic fractures by up to 50% (7).

Bisphosphonate therapy has made a significant impact in the alleviation of cancer morbidity. Its role in decreasing osteoclast-mediated lysis of bone secondary to multiple myeloma, breast cancer, and other solid tumors has been well established in clinical trials (8–10). Based on clinical practice guidelines established by the American Society of Clinical Oncology, the use of bisphosphonates is considered the standard of care for treatment of (1) moderate to severe hypercalcemia associated with malignancy and (2) metastatic osteolytic lesions associated with breast cancer and multiple myeloma in conjunction with antineoplastic chemotherapeutic agents (8).

There are many types of bisphosphonates and these agents can be administered either intravenously or orally (Table 1). Intravenous doses of biphosphonates are up to 12 times larger than that of oral doses (11). These higher drug levels greatly decrease bone turnover to limit bone destruction, fractures, hypercalcemia, and pain from multiple myeloma. In addition, they might decrease bone formation, which subsequently reduces cancer cells from metastasizing into bone. Bisphosphonates have also been given to children for bone conditions such as osteogenesis imperfecta, fibrous dysplasia, juvenile or glucocorticoid osteoporosis, and Gaucher's disease (12, 13).

General properties and mechanisms of action of bisphosphonates

Bisphosphonates are synthetic analogues of inorganic pyrophosphate (PPi), an endogenous regulator of bone mineralization (Fig. 1). The phosphonate-carbon-phosphonate (P-C-P) structure gives the bisphosphonates their ability to bind divalent metal ions such as calcium (14). For this reason, bisphosphonates are rapidly cleared from the circulation and bind to bone mineral surfaces *in vivo* at sites of active bone remodeling, particularly in areas undergoing osteoclastic resorption. In addition, bisphosphonates are highly selective for osteoclasts. This results in the bisphosphonates being targeted to bone and stored there until being locally released upon bone resorption (15). The most likely route through which bisphosphonates

Table 1. **Bisphosphonates currently used in the United States**

Generic Name	Brand name	Delivery	Manufacturer
Pamidronate	Aredia	Intravenous	Novartis (East Hanover, NJ, USA)
Alendronate sodium	Fosamax	Oral	Merck (Whitehouse Station, NJ, USA)
Etidronate	Didronel	Oral	Procter & Gamble (Cincinnati, OH, USA)
Risedronate	Actonel	Oral	Procter & Gamble (Cincinnati, OH, USA)
Zoledronic acid	Zometa	Intravenous	Novartis (East Hanover, NJ, USA)
	Reclast	Intravenous	
Ibandronate	Boniva	Oral	Roche (Basel, Switzerland)

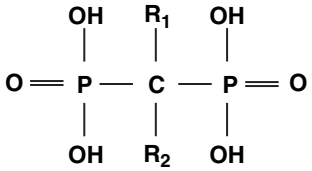

Fig. 1. The structure of simple bisphosphonates. The two phosphonate groups are covalently linked to the central carbon atom. The carbon atom forms two additional covalent bonds and the resulting side chains are referred to as R_1 and R_2. The P-C-P structure is responsible for the strong affinity for calcium ions.

inhibit bone resorption is by their direct effects on osteoclasts. However, this does not exclude the possibility that small amounts of these drugs are internalized by neighboring cells (i.e., osteoblasts, bone marrow cells, or tumor cells), particularly with repeated administrations over extended periods (16).

Some of the molecular mechanisms of action of bisphosphonates have recently been elucidated. Depending on the presence of a nitrogen atom in the alkyl chain of the molecule, bisphosphonates act either by being toxic to osteoclasts or by interfering with specific intracellular pathways within the osteoclasts (14). Non-nitrogen-containing bisphosphonates are converted intracellularly to non-hydrolyzable analogues of adenosine-triphosphate (ATP), which are toxic for cells. Nitrogen-containing bisphosphonates (i.e., pamidronate, alendronate, and risedronate) are taken up by mature osteoclasts and inhibit farnesyl pyrophosphate synthase an enzyme of the mevalonate pathway. This results in inhibition of the synthesis of isoprenoid geranylgeranyl pyrophosphate and thereby of the prenylation of small GTP-binding proteins (i.e., Ras and Rho) that are responsible for cytoskeletal integrity and intracellular signaling (Fig. 2). The consequence of these events initiates a series of results including the suppression of osteoclast activity, loss of osteoclast cytoskeletal integrity and ruffled border, and ultimately apoptosis (Fig. 3) (16).

Bisphosphonates also inhibit osteoclastic activity indirectly by acting on bone marrow stromal cells and osteoblasts. Normally, osteoblasts enhance osteoclast recruitment and activation by interaction of osteoblast cell surface-receptor activator of NFκB ligand (RANKL) with RANK on hematopoietic osteoclast precursor cells. To keep this interaction in check, osteoblasts also secrete osteoprotegerin (OPG), a soluble decoy receptor that competes with RANKL for RANK to inhibit osteoclast recruitment and control the osteoclast to osteoblast balance. Bisphosphonates inhibit RANKL expression and enhance OPG production by bone marrow stromal cells and osteoblasts so that RANK–RANKL interaction is disrupted. These synergistic actions lead to suppression of osteoclast recruitment and reduction in bone resorption (17).

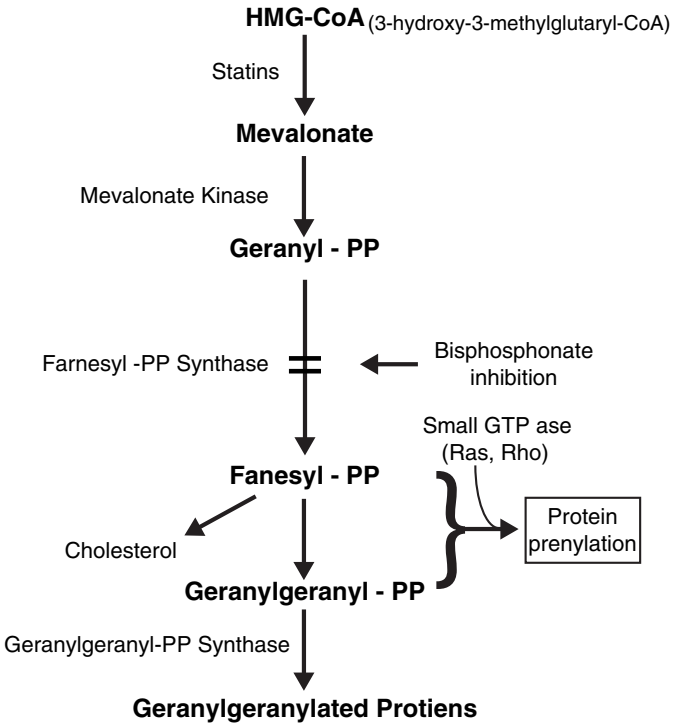

Fig. 2. Effect of bisphosphonates. Nitrogen-containing bisphosphonates mediate their action by inhibiting the mevalonate pathway involved in cholesterol synthesis. Bisphosphonates inhibit farsnesylpyrophosphate (Farnesyl-PP) synthase, an enzyme that catalyzes conversion of geranylpyrophosphate to farnesylpyrophosphate.

Bisphosphonates can induce apoptosis in tumor cells by affecting the mevalonate pathway (18). They also have the ability to inhibit the adhesion of tumor cells to bone matrix *in vitro* (19). In addition, they inhibit numerous matrix metalloproteinases (MMPs) (e.g., MMP-2, -9, and -12) that are involved in cancer growth and metastasis (20). Recently, it has been demonstrated that bisphosphonates have anti-angiogenic properties that inhibit endothelial proliferation and decrease capillary formation. In alveolar bone, over-accumulation of bisphosphonates can cause a lack of capillary formation and a decrease in the blood flow (21).

Bisphosphonates are absorbed, stored, and excreted unchanged from the body. The plasma half-life is short, ranging from 20 min and 2–3 h, while the terminal bone elimination half-life of this drug group is variable and can be extremely long (e.g., ibandronate, 10–60 h;

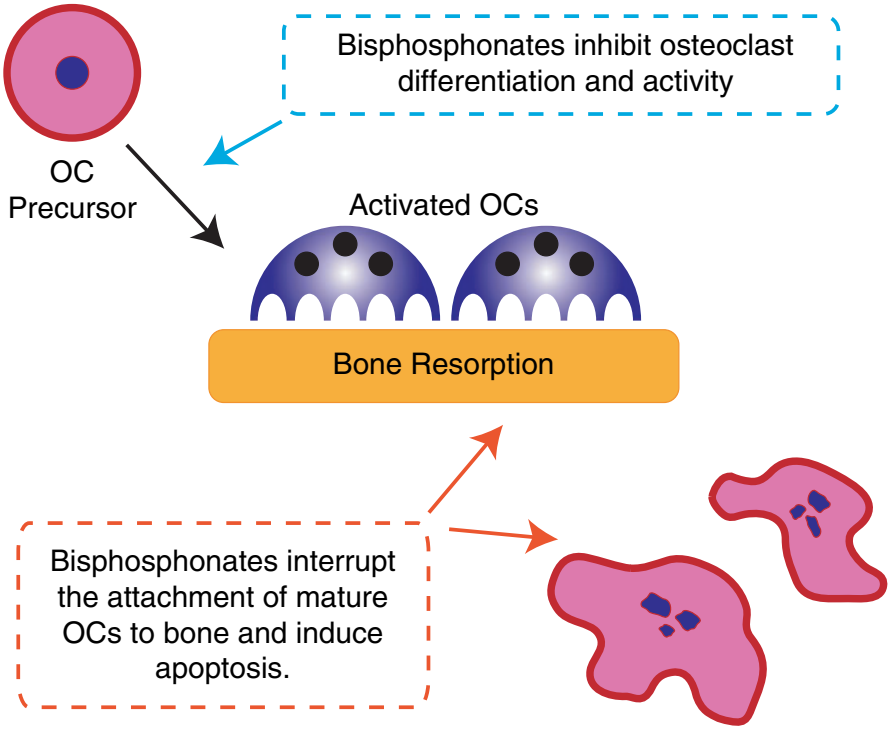

Fig. 3. Routes by which bisphosphonates could affect osteoclast (OC) function.

zoledronic acid, 146 h; risedronate, 480 h; pamidronate, 300 days; and alendronate, more than 10 years) (22). Data surrounding the terminal half-life of bisphosphonates can become confusing when considering clinical relevancy. These figures were derived from animal studies or complex human bone elimination estimates that might not necessarily depend on the specific drugs as much as on the physiological rates of bone turnover during these assays. At a given site on the surface of trabecular bone, a human undergoes remodeling once every 2 years vs. once every month in rats. These differences help explain the variable terminal bone half-life of alendronate, which has been reported to be 200 days in rats, 3 years in dogs, and 12 years in humans (23). In general, this drug group is presumed to be sequestered in bone for an extended time until released by normal bone turnover (24).

Bisphosphonates and jaw osteonecrosis

Despite the benefits related to the use of these medications, bisphosphonate-induced jaw osteonecrosis (BIJON) was reported a few years after their approval for use as a significant complication in a subset of patients receiving these drugs. Reports first appeared in 2003 (25) and alerted the dental and medical communities of this complication. There is an increasing number of BIJON cases being reported and it has occurred in all the countries where bisphosphonates are prescribed. However, a causal relationship has not been definitively proven.

The similarity of BIJON to cases of phosphorous necrosis of the jaw in workers exposed to white phosphorus (phossy jaw) during the late 19th and early 20th century was reported by Hellstein and Marek (26) and Donaghue (27). This historical fact supported the direct link between the phenomenon of jaw osteonecrosis and bisphosphonate medication. Also of a historical note is a 1995 case report by Starck and Epker (28) describing the failure of osseointegrated implants after bisphosphonate therapy for osteoporosis. Since 2003, numerous reports have been published highlighting the adverse effects of bisphosphonates including the development of osteonecrosis of the jaw. In a study by Marx *et al.* (29), one hundred and nineteen well-documented cases of BIJON were reviewed for potential risk factors and etiologies. Aggravating factors such as smoking, alcohol use, and ongoing chemotherapy were identified. Of the 119 cases of osteonecrosis, 45 cases were related to the removal of a tooth or teeth, 34 cases to obvious existing periodontal disease,

five cases to periodontal surgery, four cases to dental implant placement, and one case to an apicoectomy. On the other hand, 30 cases occurred spontaneously without any apparent dental disease, treatment, or trauma. Migliorati *et al.* (30) reported BIJON in 17 cancer patients taking intravenous pamidronate or zoledronate. Two of the cases developed BIJON spontaneously, while the rest of the cases developed BIJON after an oral surgical procedure, primarily dental extractions. As shown in Fig. 4, a 66 years old Caucasian female developed BIJON following tooth extraction after being treated with intravenous zoledronic acid for metastatic breast cancer. The patient complained of pain associated with a large area of exposed bone and non-healing extraction site. Radiographic examination revealed a 2.5 cm osteolytic lesion with sequestration and necrosis (Fig. 5).

The Federal Drug and Food Administration issued Patient Safety News Bulletin #4 in December of 2004 (31) stating that Novartis (NY, USA) has notified healthcare professionals and changed the labeling of their products to include the risks of developing jaw osteonecrosis from the company's two bisphosphonate drugs, zoledronate and pamidronate. Novartis issued a drug precaution for dental health professionals with patients being treated by these drugs. They stated that preventive dentistry should be considered before treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, and poor oral hygiene). They also warned that these patients while in treatment should avoid invasive dental procedures, if possible. For patients who develop BIJON while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no studies available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of BIJON. Clinical judgment of the treating clinician should guide the management plan of each patient based on individual benefit/risk assessment (32).

Although the exact causes of BIJON have not yet been determined, several hypotheses have been proposed. In most cases, the pathogenesis of this process is consistent with a defect in jaw bone physiologic remodeling or wound healing. The inhibition of osteoclast function could also inhibit normal bone turnover to an extent that local microdamage from normal mechanical loading or injury (such as that associated with tooth extraction) cannot be repaired. This could ultimately result in bone necrosis (33). Considerations must also be given to the anti-angiogenic properties of certain bisphosphonates. Zolendronic acid has been demonstrated to exert an inhibitory effect on the circulating levels of vascular endothelial growth factor (a potent stimulator of angiogenesis) (34). This property may affect the local bone blood supply and thus contribute to the apparent ischemic changes noted in the affected patients' jaws or may operate in concert with the metabolic changes mediated by osteoclast suppression to produce local jaw necrosis. Since only a minority of

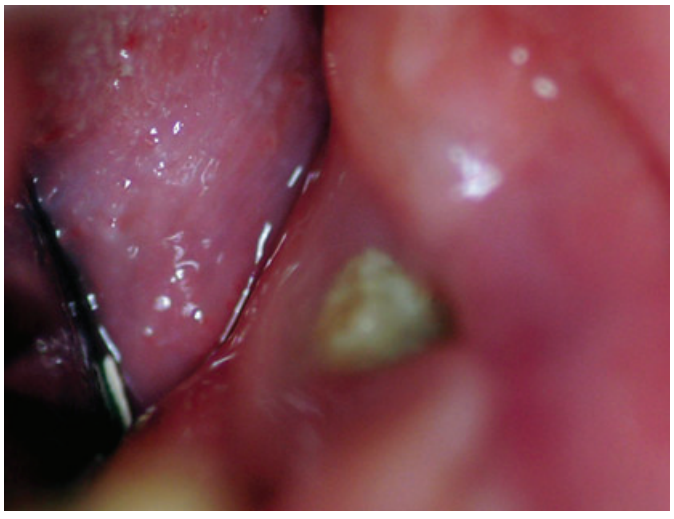

Fig. 4. Bisphosphonate-induced jaw osteonecrosis lesion in a 66 year old Caucasian female who developed osteonecrosis following intravenous treatment with zoledronic acid for metastatic breast cancer presented as a large area of exposed bone along the posterior mandibular alveolar ridge.

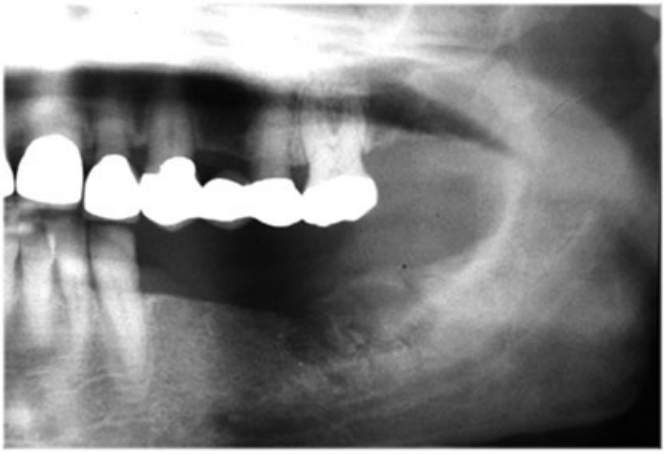

Fig. 5. Close up of panoramic radiograph for the same patient showing non-healing extraction site with a large area of bone sequestration and necrosis.

bisphosphonate users develop bone necrosis, it is also possible that individual genetic variations in drug metabolism or skeletal homeostasis may confer susceptibility or resistance to developing BIJON. These suppositions need to be validated by evidence-based clinical and basic science research.

The apparent selective involvement of the maxilla and mandible may be a reflection of the unique environment of the oral cavity. Typically, healing of an open bone wound (e.g., extraction socket) in the presence of normal oral microflora occurs quickly and without complications. However when the healing potential of the mandible or maxilla is compromised, the minor injuries or diseases in these sites increases the risk for osteonecrosis and possible secondary osteomyelitis. Also, bisphosphonates are preferentially deposited in bones with high turnover rates. Given that the maxilla and mandible are sites of significant bone remodeling, it is possible that the levels of bisphosphonates within the jaws are selectively elevated. It is interesting to note that to date, this complication has not been reported within any bones outside of the craniofacial skeleton (33).

Bisphosphonate-induced jaw osteonecrosis may remain asymptomatic for weeks, months, or years. It is most frequently symptomatic when surrounding tissues become inflamed or when there is clinical evidence of infection. The clinical features of BIJON are a significant delay in wound healing, increased tooth mobility, exposure of the alveolar bone and bony sequestrations. Osteonecrosis lesions are more common in the mandible in areas where the mucosa is thin and a bony prominence, such as a mandibular torus or mylohyoid ridge, exists. Lesions do not appear to be preventable or treatable with extensive bone debridement, hyperbaric oxygen, bone grafting, tissue grafting, or even discontinuation of the drug (29). Except in rare anecdotal situations, osteonecrosis is considered irreversible.

Radiographs can be used for the diagnosis of BIJON and may also be used to rule out metastatic lesions. Bone turnover, the continuous action of bone resorption and replacement, can be evaluated using a test that measures C-terminal cross-linked telopeptide of Type I collagen (CTX) in serum. Type I collagen is the most abundant collagen in bone. CTX as a marker is used to measure bone metabolism. It is a by-product of normal bone metabolism or bone turnover. Having a low value of CTX indicates that bone turnover is low, and thus less likely to recover from trauma (i.e. a tooth extraction or implant placement). With this test, clinicians could assess their patients' risk for developing BIJON. CTX levels less than 100 pg/ml is associated with a high risk for developing BIJON. CTX levels between 100 and 150 pg/ml indicate a moderate risk, while CTX levels greater than 150 pg/ml is associated with minimal to no risk (35). Although this test may be of value in predicting and mitigating the risk, the American Dental Association (ADA) updated recommendations in 2008 stated that such screening test is unreliable in their opinion as it is only based on the clinical observations at one institution that have not been validated and that it remains to be seen if it will be corroborated by well-controlled, randomized clinical trials (36).

Orthodontic considerations

Successful orthodontic treatment depends on osteoclast activity. For a tooth to move, adequately functioning osteoclasts must be formed and present so that they can remove bone from the area adjacent to the compressed part of the PDL. Osteoblasts are also needed to form new bone on the tension side and remodel resorbed areas on the pressure side. The interruption of this cycle by bisphosphonates through osteoclast destruction and reduced bone vasculature may affect orthodontic treatment by impeding tooth movement (37). In rats, tooth movement was decreased by 40% after administration of subcutaneous bisphosphonates for 3 weeks (38). An *in vitro* study also showed that the formation of osteoclast like cells in long-term cultures of human bone marrow is inhibited by various bisphosphonates and that a correlation exists between their inhibitory potency and their antiresorptive potency *in vivo* (39). Several *in vitro* and *in vivo* studies have suggested that bisphosphonates not only affect the function, but also the structure of osteoclasts (40–45). Loss of ruffled border, increased number of nuclei per cell, marked vacuolization, more regular cell margins, and fewer lysosomal structures have been reported in osteoclasts in animals treated with bisphosphonates (45). Furthermore, an inhibition of H+ production and a reduction in protein synthesis in osteoclasts have also been described (46).

It is reasonable to conclude that patients on bisphosphonates treatment poses a significant challenge for orthodontic treatment planning because of the possible pharmacologic inhibition of tooth movement in addition to its potential for the development of jaw osteonecrosis. In 2005, Schwartz (47) reported a case of a female orthodontic patient who was being medicated with bisphosphonates to control bone metastases related to breast cancer. When the patient initiated bisphosphonates therapy, the premolar spaces were about one-third closed, however, no subsequent space closure was observed after the commencement of the bisphosphonates regimen. Rinchuse et al. (37) described the orthodontic treatment and outcome of two patients who had received bisphosphonates. Both patients experienced impeded tooth movement and one patient also had osteonecrosis of the mandible.

One of the keys for successful orthodontic treatment is to avoid undesirable anchored tooth movement. Loss of anchorage may be prevented by using bisphosphonates. Several laboratory studies have demonstrated that orthodontic tooth movement can be controlled by topical injection of bisphosphonates. In 1994, Igarashi et al. (38) reported that 4-amino-1-hydroxybutylidene-1,1-bisphosphonate (AHBuBP) could prevent orthodontic tooth movement or relapse in rats when it was administered systemically or by topical injection. Furthermore, they showed that topical injection of AHBuBP exerted its effect at the local site of injection. They suggested that this bisphosphonate could be used clinically at a specific local site to prevent or control tooth movement (38). This effect was later confirmed by number of investigators (48–50). Adachi et al. (48), using topically injected risedronate, added that the drug anchorage and retentive effects were dose-dependent. A study by Kim et al. (49) demonstrated that this effect was associated with impairment of osteoclast structure including the disappearance of ruffled borders and clear zones, formation of irregular borders, and necrotic degeneration. In 2004, Liu et al. (50) showed that the topical application of the bisposphonate clodronate not only reduced the amount of orthodontic tooth movement and the number of osteoclasts, but also reduced root resorption.

External root resorption is a frequent adverse effect of orthodontic tooth movement and a condition that seems unpredictable and often unavoidable. Along with root resorption associated with orthodontic tooth movement, root resorption of permanent teeth caused by implantation or replantation of teeth is another unsolved problem in dentistry. Bisphosphonates may play an important role in surmounting these problems. If root resorption associated with orthodontic tooth movement and the implantation or replantation of teeth could be prevented by drugs such as bisphosphonates, this complex problem may be overcome. However, only a few studies have been conducted to test such a possibility. Igarashi et al. (51) was the first to report that root resorption incident to orthodontic tooth movement could be prevented by the topical injection of the bisphosphonate risedronate. They suggested that it may be possible to achieve a significant concentration of bisphosphonates on the root surface by devising a special drug delivery system and by determining the optimal timing of drug administration. This could make it possible to inhibit root resorption without significantly affecting orthodontic tooth movement. However, most of these studies that focused on the potential beneficial effects of bisphosphonates either in preventing loss of anchorage or reducing the risk of root resorption were conducted before the emergence of the BIJON reports.

Orthodontists' roles

Millions of peri- and post-menopausal women are currently taking oral bisphosphonates at the recommendation of their physicians for the prevention of skeletal events related to osteoporosis. Tens of thousands of patients are also receiving bisphosphonate therapy as part of their chemotherapeutic regimen for the treatment of malignant diseases. As orthodontists treat adult patients, it is incumbent upon them to be aware of the potential impact of this class of drugs on the patients and to be able to identify the risk factors and means to prevent complications. In fact, orthodontic treatment itself must come into question with these patients (52).

The American Dental Association (ADA) Council on Scientific Affairs have published an expert panel's recommendations for dental management of patients on oral bisphosphonate therapy, which was later updated in 2008 with further recommendations (36, 53). The full report can be accessed at (www.ada.org/prof/resources/topics/topics_osteonecrosis_

bisphosphonate_report.pdf). The nature, complexity, and breadth of this issue underscore the importance for the entire orthodontic community to vigilantly monitor emerging data from this field of study.

Orthodontic tooth movement causes increased alveolar bone turnover and might further increase the uptake of bisphosphonates locally in the jaws. Although no studies have directly attributed orthodontic treatment to increased osteonecrosis risks, evidence from previous studies noting retarded tooth movement in patients receiving bisphosphonates therapy suggests that prolonged orthodontic treatment may increase the potential for osteonecrosis of the jaws.

Zahrowski (54) proposed some recommendations to orthodontists for patients taking bisphosphonates. A summary of his recommendations included obtaining detailed patient information about bisphosphonate administration regarding the duration of treatment, the dose, and the frequency of use. This should be followed by a careful evaluation of the benefits vs. the risks of orthodontic treatment by first assessing whether the patient is at high or low risk for inhibition of orthodontic tooth movement or more serious medical complications such as osteonecrosis. It is unlikely that many high-risk patients would seek orthodontic treatment. But for those who do, it may be prudent to prohibit orthodontic treatment. For low-risk patients, if orthodontic treatment is considered appropriate, plans should be assessed and modified to include compromises such as avoiding or minimizing elective surgery and extractions, favoring interproximation over extractions, minimizing tooth movement, minimizing pressures on tissues during treatment and retention, and limiting treatment to facilitate the possible need for early discontinuation of treatment (54). Rinchuse et al. (37) proposed some additional recommendations for orthodontists dealing with similar cases including adding a specific item on the medical history form asking whether the patient is currently taking or has ever taken bisphosphonate drugs and that they also develop a specific consent form for these patients addressing the potential risks of limited tooth movement and/or development of jaw osteonecrosis.

For patients on bisphosphonates treatment requiring orthodontic treatment, the orthodontist's responsibility is to take into consideration the effects of these drugs on alveolar bone during routine orthodontic treatment. Even if the bisphosphonate drug was discontinued for a period of time before orthodontic treatment, it would probably not significantly reduce the probability of potential complications because of the extremely long duration of storage in bone. In addition, retainers for orthodontic patients on bisphosphonates should be checked regularly to ensure that they are passive and to minimize tissue pressure.

The most important consideration for patients who take bisphosphonates and request orthodontic treatment is to understand the chance that the orthodontic tooth movement could be inhibited even if initial tooth movement appears normal and this may prevent successful orthodontic treatment. In addition, because orthodontic treatment stimulates more alveolar bone turnover which causes more bisphosphonates uptake and release, this may increase the possibility of localized jaw osteonecrosis especially in patients using appliances that exert pressure on the palate or those requiring surgical procedures (e.g., orthognathic surgery, extractions, periodontal surgery, and implants).

This article reviews the potential concerns of bisphosphonates treatment that could affect orthodontic therapy to enhance the understanding of the possible mechanisms by which these drugs could impede tooth movement and adversely affect the jaw bones. With this understanding, orthodontists can better serve those patients on bisphosphonates therapy and make more precise judgments about risk, prognosis, treatment selection, and outcomes.

Clinical relevance

Bisphosphonates are a class of drugs used as the standard of care for osteoporosis and malignant bone metastases. Although their efficacy in reducing skeletal complications is well documented, the reported cases about their adverse effects on the jaw bones have raised concerns about the potential side effects of these drugs. The focus of this article was to review their mechanism of action and complications associated with their use. In addition, the possible effects on orthodontic treatment and tooth movement, as well as precaution strategies and recommendations for orthodontists during treatment of patients receiving bisphosphonates, were reviewed.

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