

Effect of Bisphosphonates on Orthodontic Tooth Movement—An Update

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ABSTRACT

Bisphosphonates are a synthetic class of pyrophosphate analogues that are powerful inhibitors of bone resorption which are commonly used as a medication for the prevention and therapy of osteoporosis and osteopenia, also used to treat tumor diseases. As it affects bone metabolism, it is said to have an influence on orthodontic treatment and tooth movement. Also, this review gives an insight into the reported effects of Bisphosphonate medication in literature highlighting the status quo of scientific research regarding effects of Bisphosphonates on orthodontic tooth movement. A systematic literature search was done in Medline database (Pubmed) for the appropriate keywords. Manual handsearch was also done. From the available evidence it can be concluded that the duration of orthodontic treatment is increased for patients under Bisphosphonate therapy as they interfere with the osteoclastic resorption. However, they may be beneficial for anchorage procedures. Further long term prospective randomized controlled trials are required to assess possible benefits and adverse effects of bisphosphonate treatment, before Bisphosphonates can be therapeutically used in orthodontics.

Keywords: Bisphosphonates, Orthodontic tooth movement, Orthodontic anchorage, Root resorption

INTRODUCTION

Bisphosphonates are drugs used to treat bone metabolism disorders such as osteoporosis, bone diseases, and bone pain from some types of cancer. They have an inhibiting effect on osteoclastic activity and therefore decrease the bone resorption. Bisphosphonates have unique pharmacological characteristics unlike those of any other drug group. Their half-life can be more than 10 y [1]. Zahrowski explains that the levels of Bisphosphonates taken systemically are 12 times greater when compared to oral intake [2,3]. The effects of Bisphosphonates due to this higher drug level contribute to the decreased bone turnover and thus limit the bone destruction in fractures and hypercalcemia. It has been used to relieve pain from multiple myeloma. Also, metastasis of cancers could be slowed down as the rate of bone formation is deteriorated due to Bisphosphonate medication [4,5].

The fundamentals of orthodontics is that teeth move through the alveolar bone when adequate forces are delivered. Various local and systemic factors like age, nutrition, consumption of drugs, etc seem to affect orthodontic tooth movement. As bisphosphonates have a mode of action that interferes with the bone resorption by osteoclasts, they can have side effects in dental treatment, including inhibited tooth movement, impaired bone healing, and induced osteonecrosis in the maxilla and the mandible.

Zahrowski insisted that potential orthodontic patients on Bisphosphonate therapy should be given additional patient counseling and modifying treatment according to specific needs would be required. The patients should be well informed about the possible side effects and that treatment should begun only after obtaining the patient's informed consent [1]. Thus in the field of orthodontics, the pharmacology of these drugs that can change bone physiology and could possibly hinder treatment should be known. One important side effect is the Bisphosphonate associated osteonecrosis of the jaws [6-12]. The risk of Bisphosphonate associated osteonecrosis of the jaws seems to depend on the type of Bisphosphonate dose, duration and application form (intravenous or oral). Patients with intravenous bisphosphonate and malignant disease are at a higher risk compared to patients with oral BP and benign diseases [6-12].

Alendronate, risedronate, and ibandronate are commonly administered orally to treat osteoporosis and osteopenia in postmenopausal women [13]. Osteoporosis is defined as bone density of 2.5 SD below the mean or the presence of a fragility fracture [14-15]. Osteopenia is bone density between 1 and 2.5 SD below the mean [14] Vertebral, thoracic, pelvic, hip, and humerus fractures are associated with long-term morbidity and sometimes mortality. Oral bisphosphonates have been shown to decrease fractures up to 50%. Nitrogen-containing bisphosphonates can cause esophagitis and limit their oral use if not taken properly [15].

Alendronate (Fosamax and Fosamax Plus D, Merck, Whitehouse Station, NJ) tablets; etidronate (Didronel, Procter & Gamble, Cincinnati, Ohio) tablets and intravenous; pamidronate (Aredia, Novartis, Basel, Switzerland) IV; risedronate (Actonel, Procter & Gamble, Cincinnati, Ohio) tablets; and zoledronic acid (Zometa, Novartis, Basel, Switzerland) IV are few commonly used Bisphosphonates [2].

In orthodontics, the use of Bisphosphonates has been suggested as possible means to control relapse and even to generate "pharmacological anchorage" [16]. The clinical utility of Bisphosphonates resides in their ability to inhibit bone resorption. The two major concerns in orthodontic treatment is the anchorage loss (mesial movement of anchor teeth) and post treatment relapse which could occur. There are numerous references in the literature describing the use of bisphosphonates with dental patients in general [17], and orthodontic patients in particular [18]. Therefore, the aim of this review article was to analyse the literature reporting on the combination of orthodontic treatment and BP medication in humans and animals and to evaluate the reported effects and the current state of scientific research regarding orthodontic treatment and bisphosphonate medication.

MATERIALS AND METHODS

A systematic research in PubMed was performed covering publications from Jan 1990-2014. In conjunction with this, a hand search was also done on google and google scholar. In addition, the citations in identified articles were analysed as well. Inclusion criteria were reports on animal or human study, clinical or in vitro investigation.

Pharmacological aspects of Bisphosphonates

The structure of Bisphosphonates relates to its pharmacological activity. Basically they are analogues of inorganic pyrophosphates. BP has a chemical structure change in which carbon, substituted for oxygen in pyrophosphate, is between 2 phosphates [19]. Pyrophosphate, rapidly inactivated into 2 phosphates by tissue alkaline phosphatase, is secreted by the smooth muscle and can prevent vascular or soft-tissue calcification. Bisphosphonates affects bone regulation because of the structural carbon change [20-21].

Bisphosphonates are of two types: nitrogenous and non nitrogenous. Bone resorption is inhibited by induction of osteoclast apoptosis [16]. The nitrogenous type prevent protein lipidation by inhibiting the production of isoprenoid compounds in the mevalonate pathway. They are more potent than non nitrogenous type [22]. Non nitrogenous bisphosphonates act by inhibiting protein synthesis and inducing osteoclast apoptosis [16,19-23]. Both the types inhibit bone resorption but, act by different pathways.

The incorporation of bisphosphonates by the osteoclast, triggers apoptosis (programmed cell death) [24]. It competes with ATP or interferes with the 3-hydroxy-3- methyl-glutaryl pathway. The bone metabolism of patients using bisphosphonates may be affected for many years after pharmacological therapy has ceased as it has a half life of >10 y [25].

Accumulation of high concentrations of Bisphosphonates in bone tissues inhibits endothelial proliferation and reduce capillary formation which contributes to the antiangiogenic properties of bisphosphonates [26,27]. Caution should be taken as excessive accumulation of bisphosphonates in alveolar bone may predispose for avascular necrosis due to decrease in capillary neof ormation and endothelial cells [28].

Bisphosphonates might also prevent osteoclast activating factors, such as receptor activator of nuclear factor KB ligand (RANKL), the primary mediator of osteoclastic differentiation, activation, and survival [28].

Pharmacokinetics of bisphosphonates

Pharmacokinetics is the study of a drug's action in the human body, including absorption, distribution into tissues, metabolism, and elimination [29]. Bioavailability is the fraction of the drug that reaches systemic circulation after oral intake, and it depends on the amount absorbed and the amount that escapes the first-pass liver metabolism. The bioavailability of oral bisphosphonates is very low, usually less than 2%; that of a standard IV dose is 100% [30].

After bisphosphonate is in the bloodstream, it quickly binds to the exposed hydroxyapatite in the osseous matrix, and the excess drug leaves the body through the kidneys. Generally, 50% to 60% of the drug is bound to bone, with the remainder excreted through the kidneys rapidly over several hours [29].

Once the drug is bound to bone, it is considered inactive until it is released during bone remodeling. The released drug might be transported into the osteoclast, rebound to another site of exposed hydroxyapatite, or be eliminated by the kidneys. When transported into the + osteoclast cell, it inhibits cell function and shortens cell life span [30-32]. The amount of drug released from bone depends on the rate of bone turnover [32].

Orthodontic tooth movement and bisphosphonates— All the studies reveal that orthodontic tooth movement is reduced after bisphosphonate administration, thereby supporting its clinical usage of augmenting anchorage. Studies by Liu, et al., used similar models and protocols. Subperiosteal injections adjacent to the molar under study (topical administration) [10,33,34] or after subcutaneous injections (systemic administration) [33] revealed a

significant decrease in orthodontic tooth movement when expansion forces of between 120 and 165 mN were applied. Comparison of the studies reveal that risedronate appears to be the most effective in reducing orthodontic tooth movement, followed by 4-amino-1-hydroxybutylidene-1,1-bisphosphonate (AHBuBP), then clodronate. However, in a study by Keles et al., conflicting results were obtained wherein there was no significant reduction in orthodontic tooth movement after systemic pamidronate administration and the application of contraction forces. However there was a significant decrease in osteoclasts of around 70% [35].

Generally, Bisphosphonates are prescribed for osteoporosis in postmenopausal women. Sirisoontorn et al., compared three groups , an untreated control group of rats, a group of ovariectomized rats and a group of ovariectomized rats with zolendronate treatment. The results showed that ovariectomized rats with zolendronate treatment had similar results when compared with the controls. Further, increased root resorption and tooth movement was evident in the ovariectomized rats [36].

Literature revealed only one retrospective cohort study which was done on orthodontic patients who underwent bisphosphonate medication [37]. 113 women patients <50 y of age were divided into two groups n = 20; (19 with oral bisphosphonate, 1 with IV bisphosphonate) and one group without (n = 93) bisphosphonate treatment. The conclusions of the study were that in the Bisphosphonate medicated group, treatment duration was longer and that they has a higher chance of incomplete extraction space closure at the end of treatment. However, the alignment of lower incisors was found to be similar in both the groups.

Reason for the reduction in tooth movement

Several authors [10,33,38,39] reported a reduction in the orthodontic post treatment relapse. This can be explained by the decrease in osteoclasts [10] and structural changes in the cell which include undulating margins, cytoplasmic polarity. This significantly reduces the subcellular localization and expression of H(+)-ATPase and cathepsin K during orthodontic movement [40].

In an in vitro study [41] by Liu et al., the author attributed the reduction in the tooth movement to the decreased stress on the periodontal ligament. Lower prostaglandin E2 levels , cyclooxygenase 2 and the messenger ribonucleic acid levels of receptor activator of nuclear factor kappa B ligand indicated that resorption pathway was decelerated.

Root resorption and Bisphosphonates

Root resorption after local administration of clodronate showed to reduce root resorption [34]. In a study by Igarashi et al., [33,38] they found a reduction in root resorption after systemic (AHBuBP) or topical (risedronate) administration of bisphosphonate. In a later study by the same author [38], a significant dose-dependent reduction in root resorption with local subperiosteal injections every 3 days for 21 days was seen during orthodontic force application from day 7. Histologically, morphological change of osteoblasts on treated side was seen, including loss of polarity and an increase in the number of nuclei. No evidence of root resorption repair after bisphosphonate administration was seen after the device was removed.

In a study by Alatli et al., in the year 1996, the author reported that formation of atypical hyperplastic cementum instead of acellular cementum occurred when single injection of systemic bisphosphonate was given prior to application of orthodontic forces. He also noticed that there was root resorption on both the pressure and tension sides in the 1-hydroxyethylidene- 1,1-bisphosphonate-treated rats. However, in the untreated group resorption occurred only on the pressure side. Hyperplastic cementum is said to protect

the teeth from resorption. But due to the small sample size, these results should be interpreted with caution [42].

Rapid palatal expansion and Bisphosphonates

Rapid maxillary expansion is a procedure indicated in orthodontics for constricted maxillary arches. An orthopaedic appliance is used to produce sutural expansion wherein new bone fill in occurs due to normal physiological activity of the tissues. The suture undergoes remodeling including deposition, resorption and change in the orientation of the fibres. Routinely in clinical orthodontics, to ensure stability of the obtained results various retainers are used to hold the positions of the teeth and allow for periodontal reorganization soon after the maxillary expansion procedures. The association of mechanical expansion with suture remodeling has been discussed by many authors [43-45]. Thus, owing to its mode of action Bisphosphonates might prevent skeletal relapse after therapeutic maxillary expansion procedures.

In a study that was conducted addressing this issue in 2004, the authors suggested combining the administration of a local bisphosphonate injection with mechanical retention for a much safer retention of rapid palatine expansion. In this study, rapid palatal expansion was done to 44 Wistar rats. A group of these received mechanical. The results of this study was that a lower relapse rate was seen in animals (6.86%) which were subcutaneously injected with etidronate after 3 days of treatment and a much lower rate after 7 days of treatment (relapse in 9.60% of treated vs. 25.13% of untreated animals). Less favourable effects were obtained in the group without mechanical retention with relapses in 32.53% of treated animals (versus 54.11% of untreated animals) after 7 days of etidronate treatment.

High affinity of BP to hydroxyapatite crystals may also be pertinent to reduce the bone resorption essential for the relapse. Histological examination in this study revealed that the number of multinuclear giant cells decreased in the BP injection group compared with the saline injection group. Warita et al., [46] have recently reported that topical application of 1-hydroxyethylidene-1,1-bisphosphonate (HEBP) inhibited experimental tooth movement in rats and decreased the number of multinuclear giant cells on the pressure side. Evans et al., [47] indicated that the number of osteoclasts decreased after the injection of BP, ethane-1-hydroxy 1,1-diphosphonate of 2 mg/kg/d given to male rats for 140 days. They also revealed that metaphyseal bone areas increased with a decrease in the number of osteoclasts, although diaphyseal bone area did not vary.

Therefore, it is considered that biologic responses of osteoclasts to Bisphosphonates may exhibit site-specific difference. Consequently, number of osteoclasts were much lower in the bisphosphonate-treated groups [48].

Mandibular osteogenic distraction and Bisphosphonates

In osteogenic distraction procedures, the bone adjacent to the pins used in distraction may become osteoporotic. This is one of the major disadvantages as the stability of the distraction is affected due to the decreased mineral bone density. On literature review, only two studies which addressed the effects of zoledronic acid on mandibular osteogenic distraction were obtained. A single intra operative systemic administration of bisphosphonate shortened the consolidation period and favoured bone formation around mandibular gaps. An 23% increase in bone density was found in the anterior pin region, 20% in the regeneration region and 31% in the region posterior to the pin, with significant mineral bone content increases of 22, 24 and 32%, respectively in the same regions. The authors concluded that use of zoledronic acid had the following effects [49].

- 1) Accelerated bone remodeling process in osteogenic distractions of the craniofacial region.
- 2) Decreased osteoporosis around pins.
- 3) Reduced risk of infection around the external pins.
- 4) Time taken for consolidation period lessened.

In another study in 2008 [50] alendronate was used postoperatively after activation of the distractor. However the results found a greater acceleration of bone formation in the distraction gap when bisphosphonate was administered. But, it was not specified whether systemic or topical administration was given.

A recent study by Pampu et al., evaluated histomorphometrically the effects of zoledronic acid on mandibular distraction osteogenesis in rabbits. The study showed a significant increase in the number of osteoblasts and a significant decrease in the number of osteoclasts in both the pin and the regeneration regions. This causes an increase in callus length at an early stage and permits the functional improvement of the jaw by shortening the fixation period. Results showed significant improvements in bone remodelling during osteogenic distraction [51].

As suggested by Zahrowski [1] and Rinchuse et al., [52] there is a need to consider BPs with regard to patient health histories, treatment planning, and informed consent as the possibility of reduced OTM due to bisphosphonate administration has been confirmed. Furthermore, staying informed regarding current drugs used to treat bone disorders as recommended by Zahrowski is important because of changes and advances in the treatment of these disorders. For example, administration of recombinant osteoprotegerin was evaluated recently as a possible pharmacologic means of decreasing osteoclastic activity and has also been shown to be a potent inhibitor of OTM in animal studies [35,53]. Development of a human monoclonal antibody that targets a molecule critical for osteoclastic activity (RANKL) is well underway and could see widespread use soon [53].

Importantly, the studies on bisphosphonates were mostly animal or in vitro studies and cannot be directly extrapolated to the clinical setting because there was no clinical trial research or studies involving patients. The quality of evidence is still not sufficient to derive any conclusive results on the therapeutic use. The former studies demonstrated a significant and dose-dependent decrease in the range of orthodontic tooth movement after both topical and systemic bisphosphonate administration, suggesting that it might possibly be used clinically to improve anchorage. The mean administration period for bisphosphonate is around 21 days, and most authors report that animals remain in good health during this time. However, no data are available on the effect of longer treatment, which is an important issue given the well-known side effects of this type of drug, which include maxillary osteonecrosis.

CONCLUSION

- 1) From the experimental studies it can be extrapolated that the duration of orthodontic treatment is increased for patients under Bisphosphonate therapy as the bone turnover is delayed.
- 2) Root resorption in orthodontics is a major concern. Bisphosphonates have proven to reduce the amount of root resorption in experimental animals. This could prove to be a valuable adjunct in orthodontics to reduce the orthodontically induced root resorption.
- 3) Enhanced retention has been obtained experimentally when bisphosphonates have been combined with mechanical retention after mechanical expansion procedures. However more clinical evidence would be required before using pharmaceutically assisted retention in orthodontics.

- 4) To address the problem of anchorage loss, topical or systemic administration of Bisphosphonates could be considered as they decelerate the tooth movement. Thus, if we could use pharmacological agents to prevent undesirable tooth movement it would reduce the retention duration and also provide better orthodontic force system. However, the results from the various animal studies need to be verified on patients in trials before they could be advocated for routine therapeutic usage.
- 5) The post treatment stability of orthodontic procedures like maxillary expansion or mandibular distraction which require new bone formation can be augmented and supplemented by either systemic or topical administration of Bisphosphonates. Again these proven animal studies needs to be confirmed on humans aforesaid.

To conclude, it is imperative that more prospective randomized clinical trials are undertaken in order to procure a better quality of scientific evidence regarding the effects of Bisphosphonates on orthodontic tooth movement. In orthodontics, the therapeutic usage of Bisphosphonates should be handled with caution considering the pros and cons.

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