

Effects of Bisphosphonates on the Jaw Bones

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Abstract

Bisphosphonates (BPs) are potent inhibitors of bone resorption and are widely used in the treatment of osteoporosis and other diseases that cause loss of bone mass such as Paget's disease, hypercalcaemia of malignancy, cancer-bone metastases and multiple myeloma to prevent pathological fracture. Review of literature has suggested that bisphosphonate (BP) use, especially intravenous preparations, may be associated with osteonecrosis of the jaw bones. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a severe complication that has recently emerged in patients treated with intravenous bisphosphonates for malignant disease. Several risk factors such as dentoalveolar surgery, duration of therapy, concomitant steroid usage has been linked to (BRONJ). Preventive measures are of great importance for the patients at high risk. This review paper elucidates the mechanism of action and clinical indications of bisphosphonates, etiopathogenesis and risk factors for BRONJ, clinical presentation of BRONJ and the available treatment modalities.

Conclusion : Dentists must be aware of this condition and all dental preventive measures must be taken to avoid complications of BRONJ before and during Bisphosphonate (BP) therapy. During therapy, strict review and maintenance of oral hygiene practices should occur in order to prevent pathology necessitating surgical management. Conservative approach is sufficient in treating most of the cases of BRONJ.

Keywords-Bisphosphonate, Osteonecrosis, Jaw bone, Osteoporosis

INTRODUCTION

Bisphosphonates (BPs) have been first synthesized in Germany dating back to 1865 [1]. They are stable analogs of pyrophosphate which are naturally occurring modulators of bone metabolism and have been synthesized and used since the 19th century, but their in-vitro ability to inhibit the precipitation of calcium phosphate was applied clinically in 1960s. In 2002, Food and Drug Association (FDA) received reports of several patients with cancer, treated with the intravenous (IV) BPs (Zoledronic acid) developed osteonecrosis of the jaw (ONJ) [1,2]. While in 2003, Marx was the first person who reported BPs induced ONJ in the medical literature [2]. The mechanism by which BPs may cause ONJ and actual incidence of ONJ related to the use of BPs is not very clearly known until today [2-4]. The majority of patients who have been diagnosed with BPs induced ONJ have had certain resorptive bone diseases, hypercalcaemia, bone metastasis, and under BPs therapy. Principal action of BPs is to inhibit resorption of bone by inhibiting osteoclast activity and its life span leads to modulation of the osteoclast-osteoblast interrelation, which results in an increase in the mineral density of bone and a reduction in serum calcium, although other actions such as inhibition of angiogenesis, anti-human endothelial cell proliferation and to modulate endothelial cell adhesion and migration have also been reported [3,4]. However, according to previous literature, all the three above mentioned pharmacological actions produced by BPs becomes more aggressive in the presence of other risk factors (drug related, local, demographic/systemic, genetic and preventive) that finally leads to a rare but serious clinical condition called BPs induced ONJ [4].

PHARMACOLOGY

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate [4,5]. Because of their affinity for the major constituent of bone (hydroxyapatite), they are incorporated into sites of active osteoclast-mediated bone resorption on the bone surface, allowing them to achieve a high concentration at local sites, where they can affect osteoclast activity [5]. Bisphosphonates not bound to the skeleton are rapidly cleared from the circulation via renal elimination. They are extremely hydrophilic and are only poorly absorbed from the gastrointestinal (GI) tract (<1% for an oral dose). Once absorbed, skeletal retention is thought to reflect host factors (including the prevalent rate of bone turnover that determines binding site availability and renal function that determines clearance of unbound bisphosphonate) and bisphosphonate potency for bone matrix [5,6].

Early-generation bisphosphonates (etidronate, clodronate, and tiludronate) are distinguished from later-generation bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronate) by the lack of a nitrogen-containing side chain [6]. This difference accounts for the ability of nitrogen-containing bisphosphonates to inhibit bone resorption by 100- to 10,000-fold more than the non-nitrogen-containing etidronate [6,7]. The remainder of this review focuses on bisphosphonates that contain nitrogen because they are currently the most widely used in clinical practice. Maximal reduction in biochemical markers of bone resorption typically occurs within 3 months of initiating oral bisphosphonate therapy and remains approximately constant thereafter with bisphosphonate continuance [7]. Suppression of resorption occurs even

more rapidly after intravenous (IV) bisphosphonate therapy [7,8]. The duration of suppression parallels bisphosphonate potency for osteoclast inhibition, such that administration of a single 5-mg dose of the potent IV bisphosphonate zoledronic acid to postmenopausal women leads to continued suppression of biochemical markers of bone resorption upto two years after drug administration [9]. Although the precise biological half-lives of nitrogen-containing bisphosphonates in bone remain poorly characterized, it is estimated to be at least 10 years.

MECHANISM OF ACTION

Bisphosphonates' mechanisms of action, all stem from their structures' similarity to pyrophosphate [10]. A bisphosphonate group mimics pyrophosphate's structure, thereby inhibiting activation of enzymes that utilize pyrophosphate. Bisphosphonate-based drugs' specificity comes from the two phosphonate groups and possibly a hydroxyl at R that work together to coordinate calcium ions [11]. Bisphosphonate molecules preferentially "stick" to calcium and bind to it. The largest store of calcium in the human body is in bones, so bisphosphonates accumulate to a high concentration only in bones. Bisphosphonates, when attached to bone tissue, are "ingested" by osteoclasts, the bone cells that break down bone tissue [12,13].

There are two classes of bisphosphonates: the N-containing and non-N-containing bisphosphonates. The two types of bisphosphonates work differently in killing osteoclast cells [13].

Non-nitrogenous (Non-N containing) bisphosphonates:

- Etidronate — 1 (potency relative to that of etidronate)
- Clodronate — 10
- Tiludronate — 10

The non-nitrogenous bisphosphonates (disphosphonates) are metabolised in the cell to compounds that replace the terminal pyrophosphate moiety of ATP, forming a non-functional molecule that competes with adenosine triphosphate (ATP) in the cellular energy metabolism [13,14]. The osteoclast initiates apoptosis and dies, leading to an overall decrease in the breakdown of bone. This type of bisphosphonate has overall more negative effects than the nitrogen containing group, and is prescribed far less often.

Nitrogenous (N-containing) bisphosphonates:

- Pamidronate - 100 (potency relative to that of etidronate)
- Alendronate - 500
- Ibandronate - 1000
- Risedronate - 2000
- Zoledronate - 10000

Nitrogenous bisphosphonates act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway) [14,15].

Bisphosphonates that contain isoprene chains at the R1 or R2 position can impart specificity for inhibition of GGPS1. Disruption of the HMG CoA-reductase pathway at the level of FPPS prevents the formation of two metabolites (farnesol and geranylgeraniol) that are essential for connecting some small proteins to the cell membrane.

This phenomenon is known as prenylation, and is important for proper sub-cellular protein trafficking [15]. While inhibition of protein prenylation may affect many proteins found in an osteoclast, disruption to the lipid modification of Ras, Rho, Rac proteins has been speculated to underlie the effects of bisphosphonates. These proteins can affect both osteoclastogenesis, cell survival, and cytoskeletal dynamics. In particular, the cytoskeleton is vital for maintaining the "ruffled border" that is required for contact between a resorbing osteoclast and a bone surface [16].

Indications for Bisphosphonates therapy

Bisphosphonates are in widespread use to stabilize bone loss in post-menopausal women [17]. The aim of therapy is to preserve bone density by inhibiting osteoclastic resorption of trabecular bone. Oral bisphosphonates such as etidronate, risedronate, tiludronate and alendronate are examples of bisphosphonates commonly used in the management of osteoporosis. In the case of metastatic osteolytic disease of bone and primary resorptive malignancies of bone (multiple myeloma, Paget's disease), more potent intravenous bisphosphonates (pamidronate and zoledronate) are used. The dual outcome of reduced resorptive effects of the disease process, along with correction of severe hypercalcaemia of malignancy, has served to considerably enhance both the quantity and quality of life in these individuals [18]. Worldwide, over 3 million patients have been treated with zoledronate and it is currently the mainstay of treatment for hypercalcaemia of malignancy. According to the American Society of Clinical Oncology, bisphosphonate therapy is considered a standard in cases of moderate to severe hypercalcaemia associated with malignancy, metastatic osteolytic lesions associated with breast cancer and multiple myeloma [19].

Etiopathogenesis of BRONJ

So far, the etiopathogenesis of BRONJ remains uncertain. It is worth noting that BPs act at the following levels: physical, chemical, tissue, cellular, and molecular. Studies have reported that BRONJ is secondary to the mechanism of action of BPs involving anti-osteoclastic and anti-angiogenic activities, which alter bone metabolism, inhibiting bone resorption and reducing bone turnover [20,21]. In addition, it is worth noting the anatomical peculiarities of the maxillary and mandibular bones, separated from the oral cavity by a thin mucosa, a barrier that can be easily broken by physiological activities, such as mastication. These peculiarities are more marked in the mandible than in the maxilla, which could explain the higher prevalence of BRONJ in the former. The mouth is colonized by a large number of bacteria, and the maxillary bones are frequently involved in septic processes of periodontal or pulpal origin [21]. In the presence of BP accumulation capable of decreasing bone metabolism, tissue repair following an induced or a physiological trauma does not occur properly, leading to the exposure of a necrotic bone area to the oral environment. Thus, the hypothesis that best explains the development of BRONJ would be an alteration in bone turnover associated with the

particular characteristics of the maxillary bones, such as their mucosal coating, frequent risk of infection, and constant potential for trauma [22]. Some authors have discussed the appearance of BRONJ and infection by Actinomyces, and have reported several cases associating bone necrosis and osteomyelitis caused by that microorganism. The following predisposing factors for the development of BRONJ have been reported: BP type, BP administration route, BP use duration, concomitant administration of other drugs (mainly corticosteroids, chemotherapeutic drugs, and estrogen) and invasive dental procedures [23]. Anti-angiogenic and chemotherapeutic drugs, such as thalidomide or bevacizumab, have been suggested as factors that can predispose to BRONJ or increase the risk of developing BRONJ. Some studies have reported that, when using zoledronic acid for controlling bone metastases, approximately six doses of intravenous BP per month are associated with the risk of developing BRONJ [24]. For BPs orally administered, such as alendronate, three years or 156 week doses would be required for the development of BRONJ. According to the authors, such difference is due to the low lipid solubility of BPs orally administered, which results in an intestinal absorption of only 0.63% of the drug. Orally administered BPs are accumulated slowly in the bones, and the clinical exposure of the necrotic bone does not occur before three years of BP administration, its incidence and severity increasing with each additional year of BP use.[8,12,20] The BP administration route can be associated with the occurrence of BRONJ. In patients using the intravenous route, the prevalence is of 1%–10%, while in those using the oral route the prevalence is of 0.00007%–0.04% [25]. There is no doubt that the risk of BP users developing BRONJ is greater when the drug is intravenously administered as compared with the oral route. Both the American Dental Association (ADA) and AAOMS have confirmed that such risk is dose/time dependent [26]. The concomitant use of other drugs, such as corticosteroids and chemotherapeutic drugs can potentiate the risk for developing BRONJ [27]. Duration of BP use, concomitant use of estrogen and age over 65 years can also potentiate the risk of BRONJ. Some theories try to explain that the lack of epithelial repair of intraoral exposed bone secondary to the use of BPs can be attributed to the toxicity of BPs on the epithelial tissue caused by the high concentrations of those drugs in the bone tissue [28,15].

RISK FACTORS FOR BRONJ

BRONJ risks were categorized as drug-related, local, and demographic and systemic factors. Other medications, such as steroids, thalidomide, and other chemotherapeutic agents were thought to be risk factors, but no measurable associations were identified [29]. Subsequently, two new sets of factors, genetic and preventative, are available to report.

Drug-related risk factors

Bisphosphonate potency:

Zoledronate is more potent than pamidronate and pamidronate is more potent than the oral

bisphosphonates; the IV route of administration results in a greater drug exposure than the oral route. Using a number of different risk measures, the BRONJ risk among cancer patients given IV bisphosphonate exposure ranged from 2.7 to 4.2, suggesting that cancer patients receiving IV bisphosphonates have a 2.7 to 4.2-fold increased risk for BRONJ than cancer patients not exposed to IV bisphosphonates [30].

Duration of therapy:

Longer duration appears to be associated with increased risk.

Local risk factors

Dentoalveolar surgery, including, but not limited to :

Extractions , Dental implant placement, Periapical surgery, Periodontal surgery involving osseous injury.

Local anatomy:

Mandible, Lingual tori, Mylohyoid ridge, Maxilla, Palatal tori and the mylohyoid ridge [30].

It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses and the mylohyoid ridge.

Concomitant oral disease :

Cancer patient exposed to IV bisphosphonates with a history of inflammatory dental disease, e.g., periodontal and dental abscesses, are at a seven-fold increased risk for developing BRONJ [31].

Demographic and systemic factors

Age, race, and cancer diagnosis with or without osteoporosis were reported as risk factors for BRONJ. Seven studies report increasing age as consistently associated with BRONJ. Sex was not statistically associated with BRONJ. Race was reported in one study to be a risk factor, with Caucasians having an increased risk for BRONJ compared with blacks.

Other systemic factors or conditions, i.e., renal dialysis, low hemoglobin, obesity, and diabetes, were variably reported to increase the risk for BRONJ. Malignancy type was not statistically associated with an increased risk for BRONJ, although the presence of metastatic disease reached near statistical significance, i.e., $p = 0.051$, in Wessel's report. In contrast to the original Position Paper, a few current studies noted an increased risk for BRONJ among patients exposed to chemotherapeutic agents, i.e., cyclophosphamide, erythropoietin, and steroids. Others, however failed to confirm the association between chemotherapeutic agents and BRONJ risk. Another study reported an increased risk for BRONJ among tobacco users, but no increased risk associated with alcohol exposure [32].

Genetic factors

Sawatari et al, demonstrated that genetic perturbations, i.e. single nucleotide polymorphisms (SNPs), in the cytochrome P450-2C gene (CYP2C8) gene were associated with an increased risk for BRONJ among multiple myeloma patients treated with IV bisphosphonates [32].

CLINICAL PRESENTATION OF BRONJ

The diagnosis of BRONJ is primarily based on the patient's history and clinical examination. Most of the time, patients have necrotic bone exposure ranging from a few millimeters to larger areas, which can be asymptomatic for weeks, months, or years. Usually, the lesion becomes symptomatic when inflammation or infection of adjacent tissues occurs, and in 60% of the cases pain in the exposed bone is reported [33]. The first signs and symptoms reported are deep pain in the bone and dental mobility with no relation to periodontal diseases, heavy jaw, non-healing extraction site, numbness and loss of sensation, dental trauma, or other lesions, such as increased volume, erythema, ulceration, and sinus fistula [34]. The incidence of BRONJ is higher in the mandible than in the maxilla, in areas of thin mucosa overlying bony prominences, such as tori and mylohyoid ridge. The amount of exposed bone varies. Initially it is a single point that can remain or progress to a larger exposure. Radiographically, thickening of lamina dura and periodontal ligament in the alveolar bone can be observed at the starting point of BRONJ [35]. Patients receiving the drug orally require a longer period of drug use to develop exposed bone, which is usually smaller than that of patients receiving the drug systemically. The symptoms are less intense, and might improve with BP discontinuation.

The clinical presentation is tabulated according to its BRONJ staging as below: [15]

STAGE 1 : Asymptomatic exposed bone with little soft tissue inflammation.

STAGE 2 : Exposed bone with pain, and usually with associated surrounding soft tissue inflammation or infection.

STAGE 3 : Exposed bone with pain and usually with associated soft tissue inflammation or infection; may see osteolysis extending to the inferior border of mandible or pathologic fracture; may see extraoral fistula.

Treatment

The strategies for the treatment of BRONJ have been proposed depending on the stages. [15]

STAGE 1 : Conservative management with oral rinse such as 0.12 % chlorhexidine.

STAGE 2: Symptomatic treatment with oral antibiotics, antimicrobial oral rinses, pain control and superficial debridement to relieve soft tissue irritation.

STAGE 3 : Antibacterial mouth rinse, Antibiotic therapy and pain control and surgical debridement/resection for longer term palliation of infection and pain.

Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease [36]. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. If systemic conditions permit,

modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Drug holiday

In the patients treated with oral BP therapy, a drug holiday, discontinuation of BP therapy, seems to be effective to restore bone turnover of the jaw and support the treatment of BRONJ. In the position papers, the discontinuation of BP is recommended for more than 3 months before tooth extraction if the patients have received oral BP therapy for more than 3 years. It is expected that bone turnover of the jaw once disturbed with BP will be recovered during a 3-month drug holiday. [37] This concept is supported by the report of Marx et al [32], where the serum concentrations of C-terminal telopeptide [CTX], which is a cross-linking peptide of type I collagen, released from the bones during bone resorption and utilized as a marker of bone turnover, were measured in the patients with BRONJ. They found that the serum concentrations of CTX increased from 72.4 pg/ml to 150 pg/ml, which is in the level for low risk of BRONJ, with the discontinuation of BP for 3-4 months. Hence, a 3-month holiday from BP may restore bone turnover of the jaw. In fact, Woo [29] reported that the mucosa completely covered the exposed bone in stage 2 of BRONJ, 4 months after the discontinuation of BP and local rinse. Discontinuation of oral BP therapy is thought to be the first step to care for patients with BRONJ. It remains controversial whether serum CTX concentration can be used as a predictive marker for BRONJ, because the values of CTX concentration seem to vary from case to case. Rosen et al [38] considered serum CTX concentration values to be more predictable in assessing bisphosphonate therapy outcome and bone resorption rates.

Hyperbaric oxygen Therapy

Since hyperbaric oxygen (HBO) is known to be effective adjunctive therapy for the treatment of chronic osteomyelitis and osteoradionecrosis of the jaw, then, it has also been applied to the treatment of BRONJ. The efficacy of HBO in the treatment of BRONJ has not yet been elucidated, but may be promising because it is expected to improve the hypoxia condition in the jaw and generate reactive oxygen species (ROS) to stimulate the differentiation and activity of osteoclasts [31].

Teriparatide (recombinant human parathyroid hormone [PTH] 1-34)

Recently, it has been reported that BRONJ was dramatically improved with teriparatide therapy. Teriparatide consists of 1-34 amino acids of recombinant human parathyroid hormone (PTH) (a full PTH includes 84 amino acids), and has been used for the treatment of GC-induced osteoporosis. PTH plays an essential role in the regulation of calcium metabolism. When PTH levels are continuously elevated, bones are severely degraded to increase the serum calcium concentration because of osteoclast activation. In contrast, intermittent pulsatile administration of PTH stimulates the differentiation and

function of osteoblasts, rather than osteoclasts, to lead to anabolic effects on bone. Hence, intermittent subcutaneous injection of teriparatide once a day is expected to promote bone formation. In the treatment of BRONJ, teriparatide may cause activation of osteoblasts to restore the bone turnover once inhibited with N -BP, and promote the production of receptor activation of nuclear factor-kB ligand (RANKL) from osteoblasts to reactivate osteoclasts [39].

SUMMARY

Oral bisphosphonates are used widely in the treatment of osteoporosis, whereas intravenous regimens are designed to treat complications of metastatic and primary osteolytic pathology of the bone and have been integral in moderating the effects of hypercalcaemia of malignancy and pain associated with bony pathology. Presentation of BRONJ is currently more commonly seen in patients taking the intravenous forms of the drug; however, prescriptions for oral bisphosphonates continue to rise, and there is fear that the long term cumulative effects of these drugs may see BRONJ occurring in this patient group at a rate equal to that seen in patients undertaking intravenous therapy. Bisphosphonate-related ON of the jaws can appear spontaneously, but more commonly it is associated with local trauma, predominantly dental extraction. Currently, there is no way of predicting which individuals taking bisphosphonates are at greatest risk of developing BRONJ. Equally, there are no prognostic indicators predictive of outcomes. The only persistent finding is a correlation between duration of therapy and occurrence of BRONJ. Antibiotics have been used in the treatment of BRONJ, but with little sustained effect. Surgical debridement and wound closure worsens symptoms, and excessive osseous surgery has resulted in enlargement of areas of necrotic bone. Simple measures such as the use of topical antimicrobials like 0.12% chlorhexidine may protect denuded areas from surface bacteria. Unfortunately, the symptomatic and radiographic improvement is often not forthcoming, and intermittent, conservative debridement is required.

CONCLUSION

Dentists must be aware of this condition and all dental preventive measures must be taken to avoid complications of BRONJ before and during BP therapy. Prevention is superior to treatment, and as such the establishment of meticulous oral hygiene and pre-emptive surgical treatment prior to commencement of bisphosphonate therapy is recommended. During therapy, strict review and maintenance of oral hygiene practices should occur in order to prevent pathology necessitating surgical management. Patients treated with these drugs need to be aware of complications that can arise in the jaws, especially related to trauma. It should be stressed upon those taking bisphosphonates, especially the intravenous forms, the need to avoid invasive dental management. Conservative approach is sufficient in treating most of the cases of BRONJ.

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