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REVIEW ARTICLE

Bisphosphonates and the field of dentistry

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ABSTRACT

Bisphosphonates are the drugs used to prevent loss of bone and to treat bone diseases and conditions that feature bone fragility. Bisphosphonates, according to the potency levels, are divided into three generations and potency levels have increased with successive generations and, according to mechanism of action, they are divided into Non-nitrogenous and Nitrogenous bisphosphonates. Clinically, nitrogen containing bisphosphonates are more potent. Oral bisphosphonates are safer than intravenous infusion. Oral bisphosphonates may cause recurrent ulcers with burning sensation and blisters in the oral cavity, while intravenous bisphosphonates may cause renal failure. The most serious complication of intravenous bisphosphonates is osteonecrosis of jaw bones especially after tooth extraction. Endodontic therapy is not a significant risk factor for promoting bisphosphonates-related osteonecrosis, so endodontic therapy can be an alternative to tooth extraction when possible. Regarding treatment, parathyroid hormone can be helpful because it stimulates bone formation by promoting bone turnover.

Key words
Bisphosphonates, dentistry, osteonecrosis, pamidronate, zoledronic acid

INTRODUCTION

Bisphosphonates are the drugs that prevent bone loss and are used for the treatment of diseases and conditions that feature bone fragility.[1-4] They reduce the fracture rates in children with the disease osteogenesis imperfecta. High potency bisphosphonates have also been used to modify the progression of skeletal metastases in several forms of cancer.[1-4] Bisphosphonates basically inhibit osteoclastic resorption by encouraging osteoclasts to undergo apoptosis, thus slowing down the bone loss.[1-4]

Bisphosphonates are divided into three generations. Their potency levels, mode of administration and main indications of drugs are described in Table 1 and types and mode of action of bisphosphonates are described in Table 2.

ADVERSE EFFECTS OF BISPHOSPHONATES

GIT complications

Patients taking oral bisphosphonates are at low risk. Oral bisphosphonates may induce recurrent ulcers with burning sensation and blisters in the oral cavity. Alendronate may cause upper gastrointestinal upset. Erosive esophagitis, esophageal stenosis, stomach upset with ulceration, and abdominal pain are also the adverse effects of oral bisphosphonates. They may result from gastro-esophageal reflux and acidification of the esophagus causing the release of alendronic acid. To avoid this patient should take alendronate with a glass of water at least half an hour before the meal and remain upright for an hour.[3,4]

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Acute systemic inflammatory reactions

Occasional inflammatory reactions may occur with intravenous infusion of bisphosphonates that are characterized by fever, myalgia, arthralgia, nausea, vomiting, and edema. Fever is low grade with rigors. Accompanying bone pain has also been seen in some patients.[5,6] Acute dyspnea and pneumonitis have also been reported with Pamidronate infusion in children with osteogenesis imperfecta, who have underlying pulmonary disease.[5,6] These reactions usually are self-limiting and resolve completely in 24-48 hrs. Supportive and symptomatic management with Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen is sufficient.[5,7]

Ocular complications

Among ocular effects, orbital inflammation is potentially most serious, but this complication is uncommon

Table 1: Bisphosphonates: Potency, administration, and main indications[1]

Generation	Potency	Administration	Main indication
First			
Etidronate	1	Oral	Osteoporosis, Paget's disease of bone
Clodronate	10	Oral/ Intravenous	Osteoporosis, Paget's disease of bone
Tiludronate	10	Oral	Paget's disease of bone
Second			
Pamidronate	100	Intravenous	Osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myloma, Paget's disease of bone
Alendronate	500	Oral	Osteoporosis, Paget's disease of bone
Ibandronate	1,000	Oral/ Intravenous	Osteoporosis
Third			
Risedronate	2,000	Oral/ Intravenous	Osteoporosis, Paget's disease of bone, Osteolytic lesions of multiple myeloma, hypocalcemia of malignancy
Zoledronate	10,000	Intravenous	Osteolytic lesions of multiple myeloma and metastases from solid tumors, hypocalcemia of malignancy

Table 2: Bisphosphonates; types and mode of action[1]

Type	Example	Mode of action
NNBPs	Etidronate Clodronate Tiludronate	Formation of an ATP der ivative that impairs osteoclast function and induces osteoclastic apoptosis
Aklyl-amino NBPs	Pamidronate Alendronate Ibandronate Olpadronate	Inhibits sterol synthesis via the mevalonate pathway, specifically inhibiting its Farnesyl diphosphate synthase enzyme
Heterocyclic NBPs	Risedronate Zoledronate	Inhibits Farnesyldiphosphate enzyme and stabilize conformational changes

with an estimated incidence of around 0.05%.[5,8,9] In order of frequency conjunctivitis, uveitis, scleritis, episcleritis, eyelid edema have been reported.[5,8,9] Red eyes, photophobia, blurred vision, orbital pain, epiphora, and diplopia usually occur in both eyes. In some cases, hypopyon, chemosis or proptosis indicating uveitis may also occur.[5,8,9] There may be periorbital edema and erythma causing orbital cellulitis. Oculomotor and trochlear nerve palsy due to swollen rectus muscle may occur and vision can rapidly deteriorate.[5,8,9]

Renal complications

Pamidronate and zoledronic acid can cause acute and chronic renal failure. It has been reported that patients who are taking zoledronic acid are more prone to renal failure than those who are on pamidronate treatment that is why zoledronic acid is contraindicated in patients with severe renal impairment[10]. Pamidronate is basically associated with nehprotic syndrome, tubulointerstitial nephritis, and Fanconi's syndrome.[5] Patients with baseline renal impairment, who often have functional hypertrophy of the remaining nephrons, are at greater risk. In a report of zoldronic acid-associated renal failure containing 72 patients, the complication was diagnosed 2 months after infusion. Eighteen patients developed renal failure after a single infusion.[5]

Long-term follow up indicated that 38% of patients required dialysis, the rest often sustained a permanent renal damage with serum creatinine, not returning to baseline level. A return of serum creatinine to baseline has been described as early as few days to up to four months after discontinuation of drug.[5]

Treatments available are discontinuation of bisphosphonates. Other preventive measures are adequate hydration, avoiding concurrent nephrotoxic agents, reducing the dose for patients with mild renal insufficiency and withholding treatment in the presence of renal deterioration. Pamidronate can be safely used for short term treatment of hypocalcemia among patients already undergoing dialysis and zoledronic acid can be safely resumed when serum creatinine level returns within 10% of baseline but it should be stopped permanently if no improvement is seen after 4-8 weeks.[5]

Electrolyte abnormalities

Pamidronate increases the incidence of hypocalcemia and hypophosphatemia in patients with multiple myeloma or those with bone metastases from breast cancer. Hypophosphatemia is common during the treatment of hypercalcemia of malignancy. Both hypocalcemia and hypophosphatemia may lead to seizure among patients with brain metastases. Coma has also been described in elderly patients with moderate hypophosphatemia.[5]

Signs and symptoms may include peri-oral paresthesia, tetany, carpopedal spasm, and QT prolongation but non-specific lethargy, shakiness, tingling or weakness can only be the presenting symptoms.[5] Daily calcium and vitamin D supplementation is recommended during treatment with zoledronic acid, but hypocalcemia can still occur.[5]

Anti-angiogenesis

Intravenous infusion of zoledronic acid promotes reduction in messenger ribonucleic acid (mRNA) and protein expression of vascular endothelial growth factor (VEGF).[1] Serum VEGF levels and cytokines involved in angiogenesis have also been found to decrease after administration of zoledronate and pamidronate.[1] Some authors have reported that nitrogen containing

bisphosphonates have significant anti-angiogenic effect inhibiting human umbilical vein endothelial cells (HUVEC) proliferation, adhesion, survival, migration, and actin stress fiber formation by interfering with protein prenylation.[1]

OSTEONECROSIS OF MAXILLA AND MANDIBLE

Osteonecrosis of jaw is a condition, once endemic among the workers of phosphorus-containing match factories in 1800s, has now been reported in patients who are taking bisphosphonate treatment.

Important predisposing factors for the development of bisphosphonate-associated osteonecrosis of the jaw are the type and total dose of bisphosphonates and history of trauma, dental surgery or any dental infection, smoking, alcohol abuse, menopause, advanced age, low body weight.[11-13] Patients who are on oral bisphosphonate are considered safer than patients who are taking bisphosphonates intravenously.[14] Those who are taking zoledronic acid, are at greater risk, probably because of the long half-life of these drugs.[3,13] Bisphosphonates affect the jaw bones mostly because of the greater remodeling and turnover rate of this area of skeleton. They cause marked suppression of bone metabolism, which results in accumulation of physiologic micro damage in jaw bones, compromising their biomechanical properties. Trauma and infection increase the damage for osseous repair that exceeds the capacity of the hypo dynamic bone, resulting in localized bone necrosis.[3,13]

Clinical presentation

Osteonecrosis of the jaw bones presents as an area of exposed bone in the maxillofacial region in absence of radiotherapy that has not healed within 7-8 weeks after identification.[12] The earlier condition was initially compared with osteoradionecrosis, in much the same fashion as is now occurring with bisphosphonate-associated osteonecrosis.

Early lesion may appear as subtle periodontal widening equal to the findings in periodontal disease. Advanced cases show a moth-eaten, poorly defined radiolucency with or without radio-opaque sequestra.[14]

Classification for the diagnosis of bisphosphonate-related osteonecrosis of jaw according to the stage of disease, as proposed by the American Association of Maxillofacial Surgeons is described in Table 3.[15]

Table 3: Classification for the diagnosis of the bisphosphonate-related osteonecrosis of the jaw as proposed by the American association of maxillofacial surgeons[11]

Stages	Description
At risk category	The patient has been treated with bisphosphonates (either oral or intravenous) and there is no apparent necrotic bone
Stage 0	Presence of nonspecific clinical findings and symptoms and no clinical evidence of bone necrosis
Stage 1	Presence of exposed and necrotic bone in asymptomatic patients and no evidence of infection
Stage 2	Presence of exposed necrotic bone associated with infection (pain and erythema, with or without purulent drainage)
Stage 3	Presence of exposed necrotic bone, pain, infection and one of the following clinical manifestations: Exposed and necrotic bone extending beyond the region of alveolar bone, resulting in pathologic fracture, extra oral fistulas, oral antral/oral nasal communication or osteolysis extending to the inferior border of the mandible or the sinus floor

Role of oral bacteria in development of bisphosphonate-related osteonecrosis of jaw

Aseptic or radiation necrosis occurs in most bones but it is mainly limited to the oral cavity and mostly reported cases showed the relation of bisphosphonate to osteonecrosis of the jaw.[16]

The presence of oral microflora distinct to oral cavity, have been implicated as a factor that may initiate or encourage the progress of bisphosphonate related osteonecrosis. Biopsies and cultured sample from the lesion noted the presence of species like *Fusobacterium, Eikenella, Bacillus, Actinomyces, Staphylococcus,* and *Streptococcus*. Although some of these bacteria were considered biofilm colonizers rather than invasive pathogens, none studies has yet elucidated the relevance of oral micro flora in the context of bisphosphonate associated osteonecrosis.[16]

BISPHOSPHONATES AND DIFFERENT DENTAL PROCEDURES

As discussed above, bisphosphonates use cause osteonecrosis of jaw bones but they affect the other dental procedures as well. Association of these treatments with bisphosphonates is discussed below.

Tooth extraction in patients taking bisphosphonates

Two studies were done on bisphosphonates and their association with intraoral surgeries. In one study, all patients were taking alendronate orally.[17] Extractions were done by three surgeons in the Oral Surgery Department of the Dental School of the University of Torino.[17] Oral hygiene instructions regarding maintenance of extraction sites were given to all patients.[17] The study group had total follow-up periods of 12-72 months. The patients were examined via an evaluation of clinical signs of osteonecrosis of jaw: Pain, swelling, non-healing, exposed necrotic bone, and/or fistulas with connection to the bone. The absence of these signs was determined to indicate successful

treatment.[17] Another review was done on 481 patients who were taking intravenous bisphosphonates. Out of 481, 453 developed osteonecrosis of the jaw indicating that bisphosphonate associated osteonecrosis of the jaw bone occurs mostly in patients who receive intravenous bisphosphonate than in patients who are on oral bisphosphonates. Out of 453 patients who developed osteonecrosis of jaw, 451 had cancer with multiple myeloma being most common. Nearly one-third of the patients had history of glucocorticoid use. The inciting event reported in 449 patients preceding the diagnosis of osteonecrosis of jaw was tooth extraction or other oral surgery or invasive dental procedure, whereas 93 patients developed osteonecrosis spontaneously. These two reported studies clearly indicate that bisphosphonate-related osteonecrosis of the jaw followed by tooth extractions or any other intraoral surgery is common among patients, who are on intravenous treatment of bisphosphonates rather than oral bisphosphonates.[17]

Bisphosphonates and their clinical implication in endodontic therapy

Non-surgical endodontic treatment has been recommended as an alternative to extraction to minimize the risk of bisphosphonate-related osteonecrosis of the jaw. Indeed, non-surgical endodontic treatment aims to control and prevent the spread of infection to periapical tissues. Two steps during non-surgical endodontic treatment may be able to trigger the pathophysiological process of bisphosphonate-associated osteonecrosis of jaw. First, soft tissue damage may cause osteonecrosis of jaw. Several studies insisted on the fact that one should try to be cautious and atraumatic when placing rubber dam clamp. This was emphasized by Gallego *et al.*, who questioned the role played by the rubber dam clamp as a trigger of bisphosphonate associated osteonecrosis of jaw. It is, therefore, prudent to avoid damage to gingival tissues during tooth isolation and caries excavation.[15] Secondly, primary or secondary infection may trigger osteonecrosis. *Actinomyces* species seem to be ubiquitous once infection has been identified. It has also been demonstrated that microbial of peripheral lesions refractory to endodontic treatment is often composed of *Actinomyces* species. Endodontic therapy has not been identified as a significant risk factor for promoting osteonecrosis of jaw related to bisphosphonates, and is, therefore, considered as the favored alternative to extraction when possible. However, as soft tissue damage during tooth isolation might occur as well as extrusion of micro-organisms during root canal instrumentation, care is recommended.[15]

Implant failure in patients associated with oral bisphosphonates

Adult post-menopausal women are routinely prescribed oral bisphosphonates for treatment of osteoporosis. Bisphosphonates reduces the life span of osteoclasts and may create an imbalance between normal creation and normal destruction of the bone. Some authors cited this reason as an increased incidence of bone necrosis of the jaws. However, there may be certain local factors which may act in a synergistic manner in increasing the risk of osteonecrosis. A 54-year-old woman with missing left central and lateral incisors, aiming at the replacement of teeth with endosseous implants. Left central incisor was extracted because of the failed endodontic treatment. Patient was wearing removable appliance since the extraction of lateral incisor 3 years back. The soft tissue dimensions were adequate for the functional and esthetic acceptability. Patient gave the history of postmenopausal osteoporosis and was on oral bisphosphonates, 3 mg Residronate twice/week for past 2 years. The patient was informed about the treatment options and possible failure of implants, but patient insisted in implant-supported restorations. A pre-fabricated surgical template was used to locate the desired implant position. Two dental implants were placed. Antibiotic therapy was initiated and maintained for 7 days along with the chlorhexidine rinses. The surgical dressing and sutures were removed on the 10th day, and non-loaded removable partial denture was placed.[18,19]

After 6 weeks, patient reported metallic hue on the palatal aspect of central incisor. After 2 more weeks, an implant and a piece of necrotic bone were exposed from the palatal aspects. The implant was removed. Other implant was stable in position with no evidence of necrosis.[18]

In above presented case, an implant placed in central incisor location was failed. The area was associated with previous-failed endodontic treatment and perhaps periapical infection. This might have augmented the effect of bisphosphonates on risk of osteonecrosis. During the management of failed implant, conservative and selective removal of the necrotic bone was advised. Some authors have shown that, bone contouring procedures may produce counterproductive results and could lead to further exposure of bone and worsening of the symptoms.[18]

Influence of bisphosphonates in orthodontic therapy

There is a general consensus in paper that orthodontic tooth movement is decreased after bisphosphonate administration, which supports its clinical use in improving anchorage Risedronate is most effective in decreasing orthodontic tooth movement, followed Clodronate. The reduction in orthodontic tooth movement can be explained by the decrease osteoclasts, structural changes, and resorptive functions, significantly reducing the subcellular localization and expression of (H+)-ATPase and cathepsin K during orthodontic movement.[20] Decrease in tooth movement on the other hand increases the treatment time period

in patient who are taking bisphosphonates for the treatment of bone diseases. To counter this effect the drug can be used that has less effect on orthodontic tooth movement for example Clodronate is effective in improving the anchorage but it will not increase the treatment time period that much if we compare it with Risedronate which decreases tooth movement more than Clodronate.

Bisphosphonates also affect the root resorption. Some authors found a reduction in root resorption after systemic or topical administration of bisphosphonates. There is a wider study with local subperiosteal injections every 3 days for 21 days. From day 7, there was a significant dose-dependent reduction in root resorption with the orthodontic device still in the mouth. There were no significant differences between the treated and untreated sides in odontoclast numbers. However, the osteoblasts on the treated side showed evidence of morphological change, including loss of polarity, and an increase in the number of nuclei. When the device was removed, there was no evidence of root resorption repair after bisphosphonate administration.[20] Rapid maxillary expansion is widely used technique in clinical orthodontics that produces the separation of two halves of the maxilla and sutural remodeling with an orthopedic appliance. When the active expansion period ends, the suture undergoes remodeling, including resorption, bone formation, and changes in fibers. It was postulated that bisphosphonates might prevent relapse after palatine expansion.[20] Moreover, two studies reported that a single intraoperative application of zoledronate shortened the consolidation period and favored bone formation around mandibular gaps. This result demonstrates that the use of zoledronic acid accelerates the bone remodeling process in osteogenic distraction of the craniofacial region.[20]

Estimated Incidence

Oral bisphonates and incidence of osteonecrosis

Alendronate is an orally taking bisphosphonate. Based on the data from the manufacturers of Alendronate, the incidence of bisphosphonate associated osteonecrosis was calculated to be 0.7/1,00,000 person/year exposure. Estimated events of bisphosphonate associated osteonecrosis for patients treated weekly with Alendronate is 0.001-0.04%. dental extraction increases the incidence of osteonecrosis with bisphosphonates.[21]

IV bisphosphonates and incidence of osteonecrosis

About 90% of cases bisphosphonate associated osteonecrosis have been reported in patients who are treated with IV bisphosphonates. Based on the studies, estimates of the cumulative incidence on bisphosphonate associated osteonerosis of jaw ranges from 0.8 to 12%, however some authors have reported its incidence ranging from 0.8 to 18.6%.[21]

PARATHYROID HORMONE: A PROMISING THERAPY FOR BISPHOSPHONATES-RELATED OSTEONECROSIS OF JAW

Bisphosphonate-related osteonecrosis of jaw is rare but severe adverse effect of bisphosphonate treatment due to excessive inhibition of bone resorption. Normal bone formation and resorption is the fundamental concept in bone remodeling, where a certain amount of bone removed will be replaced by a similar amount of new bone. If new bone formation cannot keep pace with bone resorption, osteoporosis may occur. If bone resorption is severely blocked, bisphosphonate associated osteonecrosis of jaw may occur. Both osteoporosis and bisphosphonate associated osteonecrosis of jaw are due to abnormal bone turnover.[22] Most of the patients can be treated with conservative surgical debridement and cessation of bisphosphonates.[23,24] Since excessive inhibition of bone turnover is the main reason for bisphosphonate associated osteonecrosis of jaw, it may be treated by the restoration of normal bone turnover. In other words, promotion of bone turnover may be beneficial for patients with osteonecrosis of jaw. Parathyroid hormone is the representative anabolic drug which can stimulate bone formation by promoting bone turnover. In fact, several previous reports have suggested that parathyroid hormone could be helpful for treatment of bisphosphonate-associated osteoncrosis of jaw. In one report in 2008, the clinical features of bisphosphonate-related osteonecrosis of jaw occurred after tooth extraction in the mandible of 74-year-old woman who had received alendronate treatment for 5 years. There was no improvement in lesions despite repeated surgical procedures. The alendronate therapy was stopped and teriparatide (20 μg/day) begun. Two months later, the exposed oral mucosa healed, four months later, the pain subsided completely, six months later, the patient's eating and drinking habits returned, and the serum osteocalcin increased 174% compared to baseline.[3,22] In the USA, there is a black box warning on the teriparatide label against using it on patients with metastatic cancer due to concerns that increased bone remodeling by parathyroid hormone may also promote the development or exacerbation of skeletal metastases. Considering this FDA warning, as well as compliance and the potential adverse effects of the daily parathyroid hormone injection, it may be used in short term on patients with bisphosphonate-related osteonecrosis of jaw without malignant bone diseases.[22]

CONCLUSION

Our review concludes that oral bisphosphonates are safer than intravenous bisphosphonates. Intravenous bisphosphonates can cause osteonecrosis of jaw but it may be treated with teriparatide. Moreover, even though bisphosphonates cause osteonecrosis of jaw and some other minor adverse effects, they are still prescribed for

the treatment and prevention of bone diseases. But it is better to avoid any dental surgery before or during bisphosphonate treatment or if treatment is mandatory, find an alternative, like endodontic treatment is safer alternative to extraction of tooth unless tooth extraction is the only possible option available.

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