Implications of Bisphosphonate Usage in Dental Care

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Within the past 10 years, the health sciences literature has suggested important oral/dental implications for patients with a history of bisphosphonate drug use. These drugs have been approved by the U.S. Food and Drug Administration (FDA) for treatment of osteoporosis, metastatic cancer involving the bone, and Paget's disease.[1] Bisphosphonates have been known to chemists since the middle of the 19th century. At first, bisphosphonates were used for industrial purposes, mainly to prevent corrosion; were used in the textile, fertilizer, and oil industries; and were included in washing powders.

The study of bisphosphonates as an important class of drugs for the treatment of bone diseases began only three decades ago. The first report of the biological characteristics of bisphosphonates was published in 1968. At that time, scientists discovered that bisphosphonates could inhibit bone resorption.[1]

There is increasing evidence that patients who have been treated with bisphosphonates may be at risk for osteonecrosis associated with certain dental surgical procedures. This article reviews the rationale for the clinical use of bisphosphonates, and the implications of such use for the dental practitioner.

Bone Structure and Development

Osteoclasts and osteoblasts are the two primary cells responsible for bone homeostasis. Osteoclasts are the cells that resorb or break down bone, and osteoblasts are the cells that produce bone. Beginning during fetal life and continuing during youth and adolescence, bone formation dominates. Once the bones are fully formed, their shape and structure are continually over-turning by two processes known as modeling and remodeling. Both modeling and remodeling result in the replacement of old bone by new bone. Modeling and remodeling begin with bone being removed by osteoclasts, which is then followed by osteoblasts refilling the resorption sites. It is necessary for bone resorption to occur in order to trigger bone formation.[1]

Modeling takes place during an individual's growth, and is the main process through which the skeleton increases in volume and mass. In modeling, new bone is formed at a different location than where the bone was removed. This results in a change in the shape of the skeleton, and can also account for an increase in bone size. As children grow to adulthood, modeling is responsible for the increase in the skeleton and accompanying body mass.

The remodeling process occurs in adults. In remodeling, the process that increases bone shape and size is modified so that the newly formed bone replaces the bone removed at the same site. Therefore, no change occurs in the shape of the bone. Normally, the amount of bone formed during bone remodeling equals the amount of bone that was removed. When more bone is destroyed than what is formed, however, an overall loss of bone occurs, and disorders such as osteoporosis can develop. In some instances (e.g., Paget's disease of bone, osteopetrosis) more bone is produced than is removed, and this bone is architecturally unsound.[1]

How Bisphosphonate Drugs Work

Bisphosphonate drugs suppress or reduce bone resorption by osteoclasts. This is accomplished both directly by hindering the recruitment and function of osteoclasts and indirectly by stimulating osteoblasts to produce an inhibitor of osteoclast formation.[1] Though bisphosphonates suppress the abnormal bone resorption associated with Paget's disease of bone, fibrous dysplasia, and metastatic cancer to bone, they do not cure these disorders.[1] However, bisphosphonates are particularly effective in relieving pain associated with these diseases.

There is increasing evidence that patients who have been treated with bisphosphonates may be susceptible to osteonecrosis following dental surgical procedures or dental infections, such as extractions, implant placement, and infections of periodontal and endodontic origin.[2] It appears that this susceptibility to osteonecrosis is long term and is not reversed by discontinuing usage of the medication.[2] As the half-life of this class of drugs is extremely long (greater then 10 years) and the literature has not concluded that drug-holidays prior to invasive dental treatment (extractions, implant placement etc) discontinuance of the drug does not appear to have any benefit to dental treatment that has been planned. As reported by Cassado, a study showed that discontinuation of alendronate for up to 5 years, after 5 years of treatment, the anti-resorptive effect is slowly lost, mainly in the lumber spine area, which would have little significance for planned dental treatment.[3]

One well conducted study by Lin et al examined the pharmacokinetic properties of bisphosphonates and reported that they persist for up to 12 years once the bisphosphonate has been taken up in human bone. The authors concluded that therapy with bisphosphonate may therefore prove problematic in the management of complications related to bisphosphonate and implied that the potential for bisphosphonate related osteonecrosis to develop may remain for several years even in those who have discontinued the drug.[4] This is supported by the most recent ADA recommendations which stated, "No validated diagnostic technique exists to determine which patients are at increased risk of developing ARONJ (antiresorptive agent-induced osteonecrosis of the jaw). Discontinuing bisphosphonate therapy may not lower the risk but may have a negative effect on low-bone-mass-treatment outcomes."[1]

Uses for Bisphosphonates

Non-malignant bone disorders

Bisphosphonates are being used currently to treat a variety of disorders. In terms of non-malignant bone diseases, the most common are osteoporosis and Paget's disease of bone. Osteoporosis a common disease of bone metabolism is characterized by a decrease in bone mass[5], increased microarchitectural deterioration[6],) and therefore increased susceptibility to fractures. (Nieves J.: Osteoporosis: An evidence based guide to prevention and management. Nutrition. Philadelphia. 85-108, 2002.) Past the age of 60 almost 1/3 of the United States population has this disorder and it occurs in twice as many women as men.[7] The osteoporotic changes in the jaws are similar to other bones in the body. The structure of bone is normal, however, due to uncoupling of the bone resorption/formation process with emphasis on resorption, the cortical plates become thinner, the trabecular bone pattern more discrete and advanced demineralization occurs.[7]

Oral bone loss related to osteoporosis may be expressed in both the dentate and edentulous patient. Osteoporosis affects the trabecular bone mass loss to a greater extent than it does cortical bone.[8]

Paget's disease is a chronic condition that causes abnormal bone growth. Bone is constantly being replaced as bone tissue is broken down and absorbed into the body, then rebuilt with new cells. In the early stages of Paget's disease, bone tissue is broken down and absorbed much faster than normal. To keep up with the rapid breakdown of bone tissue, the body speeds up the bone rebuilding process. But this new bone is often weak and brittle causing an increased susceptibility to bone fractures.

Paget's disease usually affects the bones in the pelvis, spine, thigh (femur), skull, tibia and humerus.[9] Most often, Paget's disease is discovered when the patient is seen medically for a different reason such as hip or back pain. A bone x-ray or a blood test with above normal levels of the enzyme alkaline phosphatase often leads to the discovery of the disease. Doctors usually diagnose Paget's disease based on your medical history, a physical exam, bone x-rays, lab tests and possibly a bone scan.[10]

Bisphosphonates are also being studied for use in patients with osteogenesis imperfecta, fibrous dysplasia, and primary hyperparathyroidism.[11]

Malignant Disorders

Since abnormal bone resorption is present in certain cancer-related conditions, bisphosphonates are also being used or studied as a means to prevent or treat this complication of cancer. Hypercalcemia of malignancy (HCM; elevated levels of calcium in the blood) is the most common life-threatening metabolic complication of cancer. Bisphosphonates may have an important role in treating this condition. Two

bisphosphonates, Aredia (Pamidronate disodium) and Zometa (zoledronic acid for injection), are currently approved for this use in the United States.

FDA-Approved Bisphosphonates

Nine bisphosphonates are currently FDA-approved in the United States. Seven are in oral form and four are administered intravenously. (Table 1)

Table 1: Biphosphates approved by FDA

Trade Name	Generic Name	Administration Usage	
Actonel®	Risedronate	Oral	Osteoporosis
Aredia®	Pamidronate	IV	Cancer, Paget's
Boniva®	Ibandronate	Oral, IV	Cancer
Bonivia®	Ibandronate	Oral, IV	Osteoporosis
Didronel®	Etidronate	Oral	Paget's
Fosamax®	Alendronate	Oral	Osteoporosis, Paget's
Didronel®	Clodronate	Oral	Cancer
Skelid®	Tiludronate	Oral	Paget's
Zometa®	Zoledronic Acid	IV	Osteoporosis, Cancer

Biphosphates approved by FDA

Osteoporosis treatment and its dental implications

Osteoporosis (porous bone) is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist.[4] Although both men and women are affected, women represent 90% of hospitalized patients being treated for osteoporosis.[5] The number of patients with osteoporosis has increased since 2000 (Figures 1-3). The disease affects 20 to 30% of postmenopausal women, 50% of the women over 60 years old, and 13% of the men over 50 years old, with fracture risk increasing sharply with age.

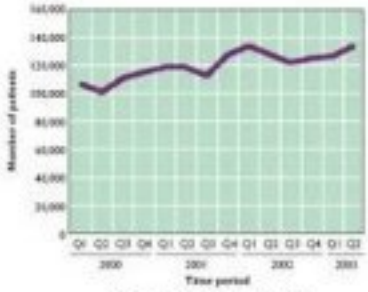

Fig. 1 : Incidence of osteoporosis

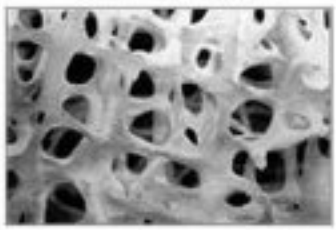

Fig. 2: 3D image of normal bone trabecular structure.

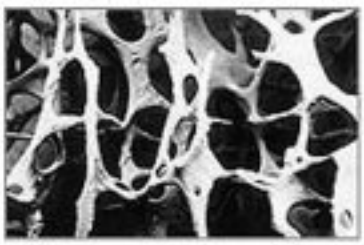

Fig. 3: 3D image of osteoporotic bone showing thin weak trabecular bone.

Dentists must ask patients about bisphosphonate use for bone disease, and take appropriate action to avoid the development of osteonecrosis in susceptible patients.[6]

Bisphosphonates inhibit bone resorption and thus bone remodeling by suppressing the recruitment and activity of osteoclasts, hence only bone deposition occurs which eventually obliterates blood vessel channels, which then leads to bone necrosis and apoptosis.[7] Marx reviewed 119 cases of bisphosphonate-related bone exposure. These cases demonstrated dental comorbidities including the presence of periodontitis (84%), dental caries (28.6%), abscessed teeth (13.4%), endodontic therapy (10.9%), and the presence of mandibular tori (9.2%). The precipitating event that produced the bone exposures were not identified (25.2%), tooth extraction (37.8%), advanced periodontitis (28.6%), periodontal surgery (11.2%), dental implants (3.4%), and endodontic surgery (0.8%).[14] Complete prevention of this complication is not currently possible. However, dental care prior to initiation of bisphosphonate therapy reduces this complication, and non-surgical dental procedures can prevent new cases. According to Australian Adverse Drug Reaction Advisory Committee, patients and their dentists should be advised of the risk of osteonecrosis of the jaw so that any "toothache" developing before treatment should be fully assessed for cause before taking bisphosphonates, especially intravenously.[15]

Osteonecrosis[16]

Osteonecrosis of the jaws is a rare complication in patients receiving radiation, chemotherapy, other cancer treatment regimens, with tumors of the jaws, and who experience an infectious embolism. Recently, there have been an unusually significant number of reports of osteonecrosis of the jaws in cancer patients receiving intravenous (IV) bisphosphonate therapy.[17, 18] In the cases reported to date, the majority of patients were receiving long-term chemotherapy, and many were receiving short-term intermittent steroid therapy with concomitant bisphosphonate therapy for cancer and symptom management. In the majority of cases, patients were managed in a pain-free state with exposed bone using a non-surgical approach consisting of oral systemic antibiotics and oral rinses containing 0.12% chlorhexidine gluconate. Surgical intervention was counterproductive and often produced additional exposed bone. Bisphosphonates and other cancer therapies were continued in the majority of patients.

Drug induced osteonecrosis of the mandible or maxilla has recently been recognized as a sequela of treatment with the new generation of bisphosphonates.[19] This lesion is seen mainly with drugs such as Zometa or Aredia, which are bisphosphonates administered to reduce hypercalcemia associated with certain cancers. A recent report from the UCLA/VA (VAMC Dayton, Ohio and VAMC Cleveland, Ohio) indicated that patients receiving IV Fosamax have a higher incidence of failed implant integration than patients who are not taking bisphosphonates, or are taking them orally.[20] The bisphosphonates persist in bone for very long periods of time, so discontinuing use may not eliminate the risk.[21]

Clinical presentation and diagnosis of osteonecrosis of the jaws

Osteonecrosis of the jaws may remain asymptomatic for many weeks or months, and may only be recognized by the presence of exposed bone in the oral cavity. These lesions are most frequently symptomatic when sites become secondarily infected or there is trauma to the soft tissues via the sharp edges of the exposed bone. (Figures 4 and 5) These sharp edges may occur spontaneously, or more commonly are at the site of a previous tooth extraction. Some patients may present with atypical complaints, such as "numbness," the feeling of a "heavy jaw," and various dysesthesias.[22] Ruggiero et al. described a large group of patients (63) with jaw bone necrosis that appeared to be related to the use of biphosphonates. It should be noted that all the patients in the group described either underwent head and neck radiotherapy or had a dental extraction while taking bisphosphonates. Fifty-six patients had received intravenous bisphosphonates for at least 1 year and 7 patients were on chronic oral bisphosphonate therapy.[23]

Fig. 4 - A large osteonecrotic lesion evident in the posterior mandible.

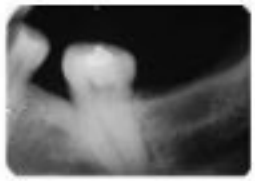

Fig. 5 - Loss of trabecular pattern is evident in the area of the missing second molar.

The mechanism leading to osteonecrosis may be related to the inhibition of bone remodeling and decreased intraosseous blood flow caused by bisphosphonates.[24] These drugs can initiate vascular endothelial cell damage and accelerate disturbances in the microcirculation of the jaws, possibly resulting in thrombosis of nutrient end arteries.[25]

Typical signs and symptoms of osteonecrosis include pain, soft-tissue swelling and infection, loosening of teeth, and drainage. Signs and symptoms that may occur before the development of clinical osteonecrosis include a sudden change in the health of periodontal or mucosal tissues, failure of the oral mucosa to heal, undiagnosed oral pain, loose teeth, or soft-tissue infection. (figure 6) If osteonecrosis is suspected, panoramic and tomographic imaging may be performed to rule out other etiologies (e.g., cysts or impacted teeth). (figure 7 and 8) Intraoral periapical radiographs can be useful to demonstrate subtle bone changes. Microbial cultures may provide a differential diagnosis for co-morbid oral infections. Tissue biopsy should be performed only if metastatic disease is suspected. If a biopsy is performed to rule out metastatic tumor, microbial cultures (for aerobic and anaerobic organisms) may provide identification of the pathogens causing the secondary infection (Note: *Actinomyces* organisms are often seen microscopically or identified upon culture).[26]

Figure 6: Clinical appearance of a patient with early soft tissue changes associated with underlying osteonecrosis.

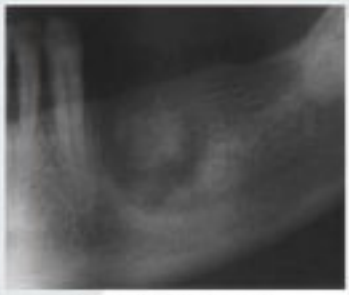

Figure 7: Trabecular change associated with osteonecrosis.

Figure 8: Panoramic radiograph of the patient showing trabecular changes in the lower left quadrant.

Potential risk factors for the development of osteonecrosis of the jaws

In addition to the relationship of osteonecrosis of the jaws to the use of bisphosphonates and a history of trauma to the jaws, other risk factors that have previously been identified for osteonecrosis occurring anywhere in the body include:

- Radiotherapy, chemotherapy, immunotherapy, or other cancer treatment regimens
- Female gender, coagulopathies, infections, bony exostosis, arthritis, blood dyscrasias, vascular disorders, alcohol abuse, smoking, and malnutrition. Specific to the jaws, local anesthetics with vasoconstrictors have been reported to contribute to some cases of osteonecrosis.

If bisphosphonate therapy can be briefly delayed without the risk of a skeletal-related complication, teeth with a poor prognosis or in need of extraction should be extracted and other dental surgeries should be completed prior to the initiation of bisphosphonate therapy. Elective procedures involving trauma to and healing of the jaws should be avoided. In one study it was found that tooth extraction preceded the onset of osteonecrosis of the mandible.[11] The benefit or risk of withholding bisphosphonate therapy has not been evaluated to date. Therefore, the decision to withhold bisphosphonate treatment must be made by the treating oncologist in consultation with the oral and maxillofacial surgeon or treating dentist.

A suggested preventive regimen before initiation of chemotherapy, immunotherapy, and/or bisphosphonate therapy can include:

- A thorough clinical examination that includes a panoramic radiograph of the jaws to identify any dental/oral pathology
- Removal of abscessed and non-restorable teeth and treatment of periodontal disease
- Treatment of salvageable teeth, including endodontic therapy
- Dental prophylaxis, caries control, and emphasis on the importance of proper oral hygiene
- Examination of dentures to ensure proper fit (with instruction to the patient to remove dentures at night)
- Emphasis on early reporting of symptoms
- Regularly scheduled recall appointments, with examination of the hard and soft tissues (every 3-4 months)
- Prophylactic antibiotics are not indicated before routine dentistry unless otherwise required for an existing medical condition.

Dental treatment recommendations for patients currently receiving bisphosphonate therapy include:

- Maintain oral hygiene to reduce the risk of dental and periodontal infections.
- Check and adjust removable dentures for potential soft-tissue injury, especially in edentulous areas.
- Perform routine dental cleanings, being sure to avoid soft-tissue injury.
- Aggressively manage dental infections nonsurgically with endodontic treatment if possible, or with minimal surgical intervention.
- When possible, endodontic therapy is preferable to extractions. It may be prudent to perform a coronal amputation with subsequent endodontic therapy for the retained roots as a means to avoid the need for tooth extraction and, therefore, the potential development of osteonecrosis.

Management of patients with osteonecrosis of the jaws

Consultation with an oral surgeon or dentist who is familiar with the care of patients being treated for malignancy (i.e., hospital dental service) is suggested if osteonecrosis is suspected. A conservative approach to management is recommended.[10] Minimal bony debridement is used only to reduce sharp edges, to reduce trauma to surrounding or opposing tissues (e.g., lateral tongue where lingual mandibular bone is exposed). A removable appliance may be used to cover and protect the exposed bone.[10] A protective stent may be of benefit for patients with exposed bone when there is trauma to adjacent tissues, or when the osteonecrotic site is repeatedly traumatized during normal oral function. A thin vacuformed mouth guard may be used, provided that the device does not traumatize the osteonecrotic site, and if it can be kept free of bacterial plaque and debris.[6] It would seem to be prudent to place the patient on a broad spectrum antibiotic starting prior to patient procedures and continued for a week. Dentures can be worn, but should be adjusted to minimize soft-tissue trauma or irritation, especially in light of ongoing antibiotic therapy, and should be removed at night. Further, 0.12% chlorhexidine gluconate rinses can be prescribed to reduce the intraoral bacterial load. All patients should be monitored every 3 months if symptoms continue or worsen.

One study found that the most common clinical presentation of osteonecrosis included infection and necrotic bone in the mandible. Associated events included dental extractions, infection, and trauma. Two patients appeared to develop disease spontaneously, without any clinical or radiographic evidence of local pathology. Despite surgical intervention, antibiotic therapy, hyperbaric oxygen therapy, and topical use of chemotherapeutic mouth rinses, most of the lesions did not respond to therapy. Discontinuance of bisphosphonate therapy did not result in healing.[11]

Cessation or interruption of bisphosphonate therapy may be considered in severe cases. However, consultation between the dentist and the medical oncologist is recommended, taking into consideration the risk of skeletal complications of the malignancy (including hypercalcemia of malignancy). It is important to emphasize that at this time cessation of bisphosphonate therapy appears to have no effect on established osteonecrosis.[12] However, further study is needed. In addition, hyperbaric oxygen has not been shown to be effective and, therefore, is not recommended.

Aggressive surgical treatment may occasionally results in even larger areas of exposed and painful infected bone. Surgical debridement or resection in combination with antibiotic therapy may offer long-term palliation with resolution of acute infection and pain. Mobile segments of bony sequestrum should be removed without exposing unaffected bone. If pathological fractures or complete mandibular involvement are observed, if the medical condition of the patients allows it the affected bone portion may be resected and primary bone reconstruction or revascularization graft may be carried out.

Laser therapy of the osteonecrotic lesions has shown promise in treatment. Biostimulation effects of the laser improve the reparative process, increasing the inorganic matrix of bone and osteoblast mitotic index and stimulate lymphatic and blood capillarys growth into the site. Laser can be used for a conservative surgerical approach, whereby the necrotic bone is vaporized and is less traumatic than prior surgical methods of grinding or cutting the exposed bone until healthy bone is reached. As the Er:YAG laser wavelength has a high degree of affinity for water and hydroxyapatite, both soft and bone tissues can be easily treated. An additional advantage of the Er:YAG laser is its bactericidal action sterilizing the exposed bone in the lesion allowing better tissue healing.[13,14] Ozone therapy in the management of bone necrosis or in extractive sites during and after oral surgery in patients treated with BPs may stimulate cell proliferation and soft tissue healing.[15]

Placement of Dental Implants in patients taking Bisphosphonate Drugs

Rehabilitation of patients with dental implants for edentulous areas or for whom tooth prognosis was considered hopeless has been successful. There are limited data at this time regarding the effects of implant placement in patients taking bisphosphonates. Thus, treatment plans for patients taking bisphosphonates should be considered carefully, since implant placement requires the preparation of the bone of the maxilla or mandible. These patients may be at increased risk of developing osteonecrosis when extensive implant placement or guided bone regeneration to augment the deficient alveolar ridge before implant placement is necessary.[16]

In patients taking oral bisphosphonates, a failure to integrate or subsequent loss of integration may occur when oral bisphosphonates are started after successful implant placement. But as Goss reports that rate of failure is low, at less than 1%.[17] Both the patient and practitioner needs to acknowledge there is an increased risk of failure in those patients who have been on oral bisphosphonate drugs to treat osteoporosis than in those patients who have not taken these drugs prior to implant surgical placement.[18] Once integration has occurred there does not appear to be risk around the implants in those patient who then initiate bisphosphonate drug therapy.

Prior to implant placement, the dentist and patient should discuss the risks, benefits and treatment alternatives, which may include but are not limited to periodontal, endodontic or non-implant prosthetic treatments. This discussion should be documented and the patient's written acknowledgment of that discussion and consent for the chosen course of treatment should be obtained.

Maintenance of implants should follow accepted mechanical and pharmaceutical methods to prevent peri-implantitis, with regular monitoring of the patient.

Conclusion

Increasing evidence indicates that patients with a history of bisphosphate therapy either taken by IV for cancer or orally for treatment and prevention of osteoporosis have a higher risk of spontaneous osteonecrosis. These patients are also at a higher risk of osteonecrosis following dental procedures that involve the bone. If possible, procedures such as extractions and implant placement should be avoided in patients with a history of bisphosphate therapy.[11] Prevention of osteonecrosis should include identifying those at risk. A thorough medical history is essential. There should be open communication between physicians and dentists before patients begin bisphosphonate therapy.[6] Early identification of this lesion may prevent or reduce the morbidity resulting from advanced destructive lesions of the jaw bone.

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FDA approved Bisphosphates

Generic Name	Trade Name	Administration	Usage
Alendronate	Fosamax®	Oral	Osteoporosis, Paget's
Risedronate	Actonel®	Oral	Osteoporosis
Etidronate	Didronel®	Oral	Paget's
Tiludronate	Skelid®	Oral	Paget's
Ostac®	Clondronate	Oral	Cancer
Bonefos®	Clondronate	Oral, IV	Cancer
Pamidronate	Aredia®	IV	Cancer, Paget's
Zoledronic Acid	Zometa®	IV	Osteoporosis, Cancer

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