Implications of bisphosphonate use for the dentist

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Abstract

The authors look into the research studies into bisphosphonates, the important classification of drugs for the treatment of bone diseases. Are bisphosphonates safe when used during or around implant treatment? The authors have some good news for us.

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ecently, literature from the health sciences field has suggested important oral/dental implications for patients with a history of bisphosphonate drug use. The US Food and Drug Administration (FDA) have approved these drugs for the treatment of osteoporosis, metastatic cancer involving the bone, and Paget’s disease1. Chemists have known bisphosphonates since the middle of the 19th century. At first, they were used for industrial purposes, mainly to prevent corrosion. They were used in the textile, fertiliser, 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 resorption2. There is increasing evidence that patients who have been treated with bisphosphonates may be at risk of 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 the 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 build up bone.

During the start of fetal life and continuing during youth and adolescence, bone formation is dominant. Once the bones are fully formed, their shape and structure are continually replaced by two processes known as modelling and remodelling. Both modelling and remodelling result in the replacement of old bone by new bone. Modelling and remodelling 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 formation3. Modelling takes place during an individual's growth and is the main process by which the skeleton increases in volume and mass. In modelling, 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.

The remodelling process occurs in adults. In remodelling, 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, osteoporosis) more bone is produced than is removed, and this bone is architecturally unsound4.

How bisphosphonates work

Bisphosphonates 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 formation5. 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 disorders6.

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 infections or dental surgical procedures such as extractions, implant placement, and infections of periodontal and endodontic origin7. It appears that this susceptibility to osteonecrosis is long term and is not reversed by discontinuing usage of the medication8. A study by Lin et al (1993) examined the pharmacokinetic properties of bisphosphonates (BP) and reported that they persist for up to 12 years once the BP has been taken up in human bone. The authors concluded that therapy

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with BP may therefore prove problematic in the management of complications related to BP and implied that the potential for BP-related osteonecrosis to develop may remain for several years even in those who have discontinued the drug.

**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 characterised by a decrease in bone mass, increased microarchitectural deterioration, and therefore increased susceptibility to fractures. Past the age of 60, almost one third of the United States’ population has this disorder, and it occurs in twice as many women as men. 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 an emphasis on resorption, the cortical plates become thinner, the trabecular bone pattern is more discrete, and advanced demineralisation occurs. Oral bone loss related to osteoporosis may be expressed in both the dentate and edentulous patient. Osteoporosis affects the trabecular bone to a greater extent than it does on the cortical bone. 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, then rebuilt. 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 fractures.

Paget’s disease usually affects the bones in the pelvis, spine, thigh (femur), skull, tibia, and humerus. 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 diagnosis of the disease. Paget’s disease is usually diagnosed based on medical history, a physical
Bisphosphonates are also being studied for use in patients with osteogenesis imperfecta, fibrous dysplasia, and primary hyperparathyroidism.

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. Hypercalcaemia 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, pamidronate disodium (Aredia [Novartis]) and zoledronic acid for injection (Zometa [Novartis]), are currently approved for this use in the United States.

USA FDA-approved bisphosphonates
Nine bisphosphonates are currently FDA-approved in the United States. These are administered either orally or via intravenous administration (see Table - right).

Osteoporosis treatment and its dental implications
Osteoporosis (porous bone) is a disease characterised 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.

Although both men and women are affected, women represent 90% of hospitalized patients being treated for osteoporosis. The number of patients with osteoporosis has increased since 2000 (Figures 1-3). The disease affects 20 to 30% of postmenopausal women, 50% of women over 60 years old, and 13% of men over 50 years old, with fracture risk increasing sharply with age.

Dentists must ask patients about bisphosphonate use and take appropriate action to avoid the development of osteonecrosis in susceptible patients. Bisphosphonates inhibit bone resorption and thus bone remodelling by suppressing the recruitment and activity of osteoclasts. Therefore bone deposition predominates, which eventually obliterates blood vessels channels, that can predispose to bone necrosis and apoptosis. Marx reviewed 119 cases of bisphosphonate-related bone exposure. These cases demonstrated dental co-morbidities 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 exposure was tooth extraction (37.8%), advanced periodontitis (28.6%), not identified (25.2%), periodontal surgery (11.2%), dental implants (3.4%), and endodontic surgery (0.8%). Complete prevention of this complication in not currently possible.

However, dental care prior to initiation of bisphosphonate therapy reduces this complication, and nonsurgical dental procedures can prevent new cases. According to the 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 can be fully assessed for cause before taking bisphosphonates. This is especially true when the drugs are administered intravenously.

Osteonecrosis
Osteonecrosis of the jaws is a rare complication in patients receiving radiation, chemotherapy, or other cancer treatment regimens, those with tumours of the jaws, and those who experience an infectious embolism. Recently, there have been an unusual number of reports of osteonecrosis of the jaws in cancer patients receiving intravenous (IV) bisphosphonate therapy. 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 nonsurgical 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 recognised as a sequel of treatment with the new generation of bisphosphonates. This lesion is seen mainly with drugs such as Zometa or Aredia, which are bisphosphonates administered to reduce hypercalcaemia 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 who are taking them orally. The bisphosphonates persist in bone for very long periods of time, so discontinuing use may not eliminate the risk.

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 recognised 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 typical complaints such as numbness, the feeling of a ‘heavy jaw’, and various dysesthesias.

**Bisphosphates approved by the USA FDA**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Administration</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actonel®</td>
<td>Risedronate</td>
<td>Oral</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Aredia®</td>
<td>Pamidronate</td>
<td>IV</td>
<td>Cancer, Paget’s</td>
</tr>
<tr>
<td>Bonefos®</td>
<td>Clodronate</td>
<td>Oral, IV</td>
<td>Cancer</td>
</tr>
<tr>
<td>Boniva®</td>
<td>Ibandronate</td>
<td>Oral, IV</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Didronel®</td>
<td>Etidronate</td>
<td>Oral</td>
<td>Paget’s</td>
</tr>
<tr>
<td>Fosamax®</td>
<td>Alendronate</td>
<td>Oral</td>
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<td>Zometa®</td>
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</tr>
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Ruggiero et al (2004) described a large group of patients (63) with jawbone necrosis that appeared to be related to the use of bisphosphonates. 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.

Intravenous bisphosphonates were received by fifty-six patients for at least a year, and seven patients were on chronic oral bisphosphonate therapy. The mechanism leading to osteonecrosis may be related to the inhibition of bone remodelling and decreased intraosseous blood flow caused by bisphosphonates. 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.

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. If osteonecrosis is suspected, panoramic and tomographic imaging may be performed to rule out other etiologies (e.g. cysts or impacted teeth).

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 tumour, microbial cultures (for aerobic and anaerobic organisms) may provide identification of the pathogens causing the secondary infection (note that Actinomyces organisms are often seen microscopically or identified upon culture).

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 the following:

- 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 skeletal related complications, teeth with a poor prognosis or in need of extraction should be extracted and other dental surgery 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. 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 the following:

• 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 three to four 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 the following:
  • 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 non-surgically with endodontic treatment if possible or with minimal surgical intervention.
  • When possible, endodontic therapy is preferable to extraction. 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.

It is important for dentists to maintain communication with appropriate medical specialists when treating patients who are at risk for osteonecrosis. These specialists include endocrinologists, oncologists, hematologists, and internists.

**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. Minimal bony debridement is used only to reduce sharp edges and 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. 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 traumatised during normal oral function. A thin, vacuformed mouthguard may be used, provided that the device does not traumatise the osteonecrotic site and that it can be kept free of bacterial plaque and debris.

It would seem to be prudent to place the patient on a broad-spectrum antibiotic prior to beginning a dental procedure and continue the antibiotic for a week. Dentures can be worn, but should be adjusted to minimise soft-tissue trauma or irritation, and should be removed at night. Furthermore, 0.12% chlorhexidine gluconate rinses can be prescribed to reduce the intraoral bacterial load. All patients should be monitored every three months if symptoms continue or worsen. One study found that the most common clinical presentation of osteonecrosis included infection and necrotic one 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. 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 emphasise that at this time cessation of bisphosphonate therapy appears to have no effect on established osteonecrosis. However, further study is needed. In addition, hyperbaric oxygen has not been shown to be effective and, therefore, is not recommended.

**Conclusion**

Increasing evidence indicates that patients with a history of bisphosphonate therapy either taken intravenously as part of cancer treatment 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 bisphosphonate therapy. 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. Early identification of this lesion may prevent or reduce the morbidity resulting from advanced destructive lesions of the jaws.

**References**

patients: clinical features and risk factors. J Clin Oncol; 24: 945-952