Bisphosphonates and Osteonecrosis of the Jaw

Bisphosphonate medications are linked to a risk of osteonecrosis of the jaw. The following protocols have been developed by the BC Cancer Agency Department of Oral Oncology.

Bisphosphonate Medications

Bisphosphonates are a class of medications which include pamidronate (AREDIA®), zoledronic acid (ZOMETA®), alendronate (FOSAMAX®), risedronate (ACTONEL®), etidronate (DIDRONEL®), clodronate (BONEFOS®, OSTAC®) and ibandronate (BONAVIA®).

Bisphosphonates are synthetic forms of inorganic pyrophosphates, which prevent formation of calcium phosphate crystals. They have high affinity for hydroxyapetite. Pyrophosphates are rapidly metabolized by the body. Bisphosphonates are not, but they have low intestinal absorption, with only about 2% of the oral dose absorbed. In 24 hours, half of the absorbed dose is excreted unaltered by the kidneys, and the other 1% is absorbed in the bone.

Given intravenously, over 50% of the dose is available for incorporation unchanged into the skeleton.[1] No significant amount accumulates in the soft tissues.

Common Types of Bisphosphonate Medications

Drug Name	Administration	Relative Potency	Terminal Half Life[2]
Pamidronate (AREDIA®)	**IV**	**1**	**27 hours**
Alendronate (FOSAMAX®)	**Oral**	**10**	**10 to 12 years**
Zoledronic Acid (ZOMETRA®)	**IV**	**200**	**146 hours**

How These Drugs Work

In normal bone, osteoclast activity is balanced with osteoblast activity to repair microdamage. Bisphosphonates decrease bone turnover by inhibiting the osteoclast precursors, their attachment to bone, and their transformation into the mature resorbing

[1] Erza, A., Golomb, G., Adv. Drug Deliv. Rev 2000; 42:175-95
[2] Licata, A., Ann. Pharmacother. 2005; 39:668-77

osteoclast. Bisphosphonates disable osteoblast function and induce the osteoblasts to produce an osteoclast-inhibiting factor.[3]

Bone formation continues for six to twelve months after treatment starts so that bone density is seen to increase from pre-treatment levels. After that time, the osteoblasts are completely impaired and normal bone response is suppressed to the point where microdamage persists and accumulates.[4,5,6,7]

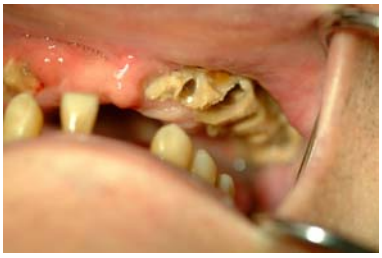
Bisphosphonates Use in Cancer Treatment

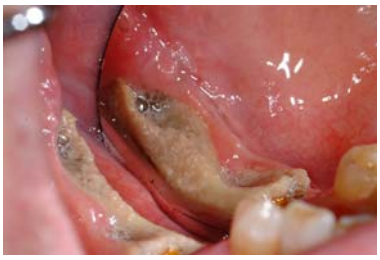
Success of bisphosphonate therapy in cancer treatment has been extensively documented, showing a definite reduction in morbidity in the three million cancer patients who have been prescribed these medications to date.

In multiple myeloma, bisphosphonates have been shown to reduce bone lesions, and to reduce bone pain.[8]

In other cancers, bisphosphonates make bone less favorable for metastases by reducing local release of tumour growth factors and thereby causing an anti-tumour effect.[9]

Bisphosphonate treatment in cancer improves quality of life and extends life. The benefits outweigh the risks, but if bisphosphonate osteonecrosis occurs, it can result in significant pain, dysfunction, and disfigurement.





Bisphosphonate osteonecrosis was first identified in 2001. In early 2005 the FDA in the United States released a statement saying that osteonecrosis is a risk with all forms of bisphosphonate, not just the IV form. The entire class of drug carries the risk of over-suppression of bone turnover. The first published report of osteonecrosis related to oral use was in 2006.

In bisphosphonate osteonecrosis, areas of necrotic bone become exposed and do not heal. It can occur spontaneously, due to dental disease or secondary to dental therapy.

[3] Hughes, D.E., J. Clin. Inv. 1989; 83:1030-35
[4] White, M.P., N. Eng. J. Med. 2003; 349:477-63,
[5] Li, J., Mashiba, T., Burr DB., Calif. Tissue Int. 2001; 69:281-86
[6] Mashiba, T., et al, Bone; 28:524-31
[7] Mashiba, T., et al, Bone Miner. Res. 2000; 15:613-20
[8] Supportive Care in Cancer, 2006; 14:408-18
[9] Vitte, C., Endocrin. 1996; 137:2324-33. Wood, J., J. Pharmac. Exp. Ther. 2001; 302:1055-61

There is no successful treatment. Surgical intervention is likely to produce further exposed bone. When early cases were treated with usual surgical protocols to attempt to remove necrotic bone, total jaw resection was required.

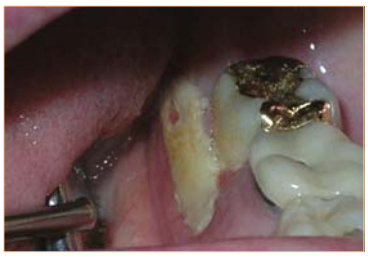
This complication has thus far only been identified in the jaws. More cases occur in the mandible than the maxilla. Approximately 60% of the reported cases have followed dentoalveolar surgery, with the rest occurring spontaneously. The spontaneous incidence rises as time on the drug increases. Some spontaneous cases may actually be initiated by trauma, as from an unstable dental prosthesis.

The inability to manage this untreatable complication compromises the oncological, nutritional and overall health status of cancer patients. There is no evidence that discontinuing the medication is beneficial either before oral surgery or after osteonecrosis has occurred. However, careful pre-treatment screening and preventative care can reduce morbidity.

Clinical Presentation

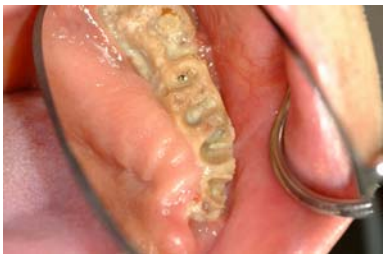
Early bisphosphonate osteonecrosis may present with no indication of necrosis, but with symptoms such as tooth mobilities, soft tissue swelling or infection, parasthesia, feeling of “heavy jaw”, undiagnosed oral pain, or a sudden change in periodontal/mucosal health.

The clinical appearance differs depending on whether the case is post-surgical or spontaneous. The spontaneous form usually presents as a painless oral ulceration with a smooth or ragged border of inflamed mucosa, exposing necrotic bone. The bone becomes hydrated and elevated above the normal tissue contours, through exposure to saliva. The bone sequestra sometimes slough off or can be easily removed.



One third of the lesions are asymptomatic. Soft tissue in the area may become uncomfortable if traumatized by the exposed bone. Symptoms may also develop due to secondary infection. Extraoral or intraoral sinus tracts may be present if infected.

In severe cases, mostly associated with dentoalveolar surgery, there is chronic pain, swelling, irreversible dysfunction and disfigurement of the jaw. In extreme cases, jaw fracture can occur.



Radiographic appearance is normal at the early stage, although there may be widening of the periodontal ligament, such as is seen in chronic periodontitis. With advancement, bone appears moth-eaten, with a poorly defined radiolucency.

Predisposing Factors

Periodontal disease is the most common dental co-morbidity.[10] One case has been published implicating non-surgical periodontal therapy,[11] the condition developed in a smoker with multiple myeloma who had a previous diagnosis of bisphosphonate osteonecrosis following dental surgery.

There have been no randomized clinical trials to date but evidence has implicated poor oral hygiene, smoking, age over 65, diabetes, history of steroid use, history of cyclosporine use, renal insufficiency, intraoral tori, active periodontal disease and previous osteonecrosis as risk factors.

Dental Care Protocol for Patients Prescribed Bisphosphonates

Prevention is the only way to address this complication. It is thought that osteonecrosis risk may be lower early in the drug therapy, and that invasive dental treatment may be safe within this time frame for patients who have no predisposing factors, but further studies are required.

Recognize that those with any significant history of bisphosphonate use are at permanent risk. The extent of this risk has not yet been established. Expert opinion is such that discontinuing the medication does not decrease the risk, even if the patient has not used it for many years. It will persist in bone for months or years after multiple doses are administered.

On initial diagnosis of a condition requiring bisphosphonate therapy, the physician must ensure that the patient see a dentist as soon as possible to follow through with any planned restorative treatment, eliminate any areas of risk, and for hygiene care. Initiation of bisphosphonate therapy should be postponed if possible, until an optimal dental condition is achieved.

[10] Marx, R.E., J. Oral Maxillo. Surg. 2005; 63:1567-75

[11] Braun, E., Iacono, V., Int. Journal Perio. Restorative Dentistry 2006; 26:315-19

Patients taking bisphosphonates must be informed of the potential for osteonecrosis after routine dental treatment, and also that it can occur spontaneously. They should be advised that invasive dental procedures must be avoided in favour of treatments which retain existing teeth and roots.

The pre-bisphosphonate dental appointments should establish a dentition that the patient can maintain for the rest of his or her life. Consideration should be given to the patient's motivation to comply with a lifelong prevention program, and if this is lacking, more aggressive treatment including full mouth clearance could be considered. This treatment option should be weighed against the fact that denture irritation has been known to cause bone exposure in bisphosphonate patients.

Meticulous oral hygiene will be mandatory. Home care instruction and education regarding the importance of symptom reporting should be done. Cariogenic diet should be eliminated. Smoking and excessive alcohol should be avoided.

A three-month dental maintenance schedule is recommended, to monitor for trauma and infection. At these visits, osteonecrosis prevention would be reinforced.

Routine restorative treatment should be encouraged by the physician as well as the dental team, to prevent future dental problems. There is no contraindication to routine procedures, including restorations, crowns and root canal treatment. In the rare cases that oral surgery cannot be avoided, referral to an oral surgeon familiar with bisphosphonate osteonecrosis is recommended.

If Bisphosphonate Osteonecrosis Occurs

Patients taking bisphosphonate medications should be immediately seen by the dentist for evaluation of suspicious changes or symptoms. Early detection of osteonecrosis is important.

Patients with exposures may be able to be maintained pain-free long term using a non-surgical approach consisting of oral hygiene and medications.

Dentures must not be worn in the presence of a bone exposure, or if there are early stage symptoms. In these patients, nutritional intake will decline and morbidity can increase.

If the bisphosphonate was prescribed for cancer treatment, the patient can be referred to Oral Oncology at the BC Cancer Agency. Complete prevention is not possible, but the patient's risk can be decreased by ensuring that invasive dentoalveolar treatment is not required.