

The Truth About Osteonecrosis of the Jaw

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What is ONJ?

Osteonecrosis of the jaw (ONJ) refers to the development of avascular necrosis, or dead bone, in the mandible or maxilla. The exposed necrotic bone is not easily treatable with medical or surgical intervention. Necrotic mandibular bone has been previously well documented following radiation therapy—a condition described as osteoradionecrosis. Patients with previous mandibular radiation have often developed this serious avascular necrosis following dental surgery as the precipitating event. The previously radiated bone is hypovascular and hypocellular and is at risk for hypoxia. With surgery such as a tooth extraction, the bone can break down and not heal.

The bone tissue can also become secondarily infected with osteomyelitis complicating the avascular bone necrosis. Steroids can also result in osteonecrosis; however, the maxilla or mandible is rarely involved with steroid-induced bone necrosis. Other conditions in which ONJ has been documented include local invasive tumours, systemic lupus erythematosus and HIV.



What is the relation between bisphosphonate use and ONJ?

Recently, in 2003, bisphosphonate-induced ONJ was first described in medical literature.

Since then, a number of surgical and dental centers have published their experience with this newly described condition. The actual incidence of ONJ related to the use of bisphosphonates is not known, but it is believed to be a rare event, occurring in those individuals at high risk for the condition. According to a recent report, pamidronate and zoledronic acid have been used by more than two million people;¹ however, the incidence of ONJ in association with bisphosphonate use has been rare.

Unfortunately, the lay media has not been able to place the issue in perspective and facts have been inaccurately reported, creating an almost hysterical reaction among the public. As a result, a large number of osteoporotic patients have inappropriately stopped their bisphosphonate therapy.

Bisphosphonate-induced osteonecrosis is an avascular bone necrosis which may occur in patients at risk for this condition. The majority of patients who have been diagnosed with ONJ have had a malignancy—particularly breast cancer or myeloma—and had been receiving intravenous (IV) bisphosphonates (pamidronate or zoledronic acid) repeatedly in large doses for metastatic bone disease. The literature has documented a few cases of ONJ with the use of oral bisphosphonates, namely alendronate and risedronate.

IV administration of potent bisphosphonates provides a number of advantages, including the

ability to effectively control hypercalcemia in patients with metastatic disease, as well as the ability to stabilize metastatic bone lesions, while bypassing the gastrointestinal tract. Thus IV bisphosphonates are of tremendous value in the management of skeletal complications in patients with malignancy and are an important component of therapy in this patient population. The benefits of IV bisphosphonates far outweigh the risks of developing ONJ.

According to the published cases reported to date, the majority of the patients who have developed ONJ have also received radiation therapy and/or chemotherapy, including the use of steroids. A precipitating event—most commonly dental surgery, such as tooth extraction—was present for the majority of patients developing ONJ.

It is not clear from the literature if the bisphosphonate was the sole causative factor for the development of ONJ, or whether it was a contributor to the event in a large number of reported cases.

The M.D. Anderson Cancer Center at the University of Texas, in Houston, recently identified ONJ in 0.825% of 4000 cancer patients treated with IV bisphosphonates.



What is the mechanism for the development of bisphosphonate-induced ONJ?

Bisphosphonates are analogs of naturally occurring pyrophosphate and are used to decrease bone remodeling in osteoporotic patients. In postmenopausal women and elderly men, the rates of bone remodeling are increased, resulting in enhanced bone resorption, decreased bone mineral density and an increase in the risk of fracture. Bisphosphonates are valuable agents in osteoporosis as they reduce the rates of remodeling into the

normal range. This is achieved by inhibition of the osteoclast. As bone resorption and bone formation are coupled processes, there will be an associated decrease in the rate of bone formation as bone resorption decreases. In osteoporotic individuals, bisphosphonates have been shown to significantly decrease the rate of bone resorption and decreases in the rate of fracture have been repeatedly documented with therapy.

As the mandible and maxilla are highly vascular bone tissues, bisphosphonates are heavily deposited at these skeletal sites in the bone and its effects are most pronounced in the bone at these sites. Individuals at risk for ONJ may have excessive reduction in the rates of bone remodeling. This may prevent the repair of areas of local microdamage. With decreases in bone formation, inadequate new bone formation may result in an increased risk of osteonecrosis, particularly after dental procedures, such as a tooth extraction. The normal repair and renewal process necessary for the cavity to heal is suppressed and the bone at the site of the extraction may become avascular and necrotic. Bisphosphonates have also been shown to potentially inhibit the growth of new blood vessels (antiangiogenic effect)² and in individuals at high-risk for this rare complication, may also contribute to the development of local osteonecrosis of the bone. Concomitant use of chemotherapy drugs and steroids also affect wound healing and contribute to the development of bone necrosis.

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Who is at risk for ONJ?

In a recent review of 368 reported cases of bisphosphonate-associated ONJ, 60% of cases occurred after tooth extraction or dental surgery,³ 85% had underlying myeloma or metastatic breast cancer, 4% were using oral bisphosphonates for osteoporosis or Paget's disease; IV bisphosphonates were used in 94% of the cases. The doses of bisphosphonates were much higher when used for oncologic indications than for osteoporosis. The most important risk factor for ONJ was the duration and dose of bisphosphonate used.



How is the condition prevented?

Patients at risk for ONJ should be advised that:

- 1) Any invasive dental work (*i.e.*, root canal, extraction, *etc.*) should be completed prior to initiating bisphosphonate therapy
- 2) Any existing infections should be treated
- 3) If possible, dental procedures should be avoided while on bisphosphonates
- 4) Poorly fitting dentures should be adjusted to ensure that there is no local trauma or friction to the gumline
- 5) Dental hygiene should be maintained at the highest possible level
- 6) Noninvasive dental work does not require that the bisphosphonate be delayed



How is ONJ treated?

Treatment to date has been difficult, with no known effective treatment. Hyperbaric oxygen, antibiotics and careful, limited debridement have been used to treat ONJ. Surgery, if conducted, should be performed cautiously, as the

procedure may actually exacerbate the condition if it leads to further bone exposure. The bisphosphonate can be continued in the presence of metastatic bone disease as it may stabilize the metastatic deposits. Pain is controlled with analgesics and any secondary infections are treated.



What research directions are needed?

There is a great need for further research into this rare, but serious condition. The exact relationship between ONJ and the use of bisphosphonates needs to be clarified. Prospective study data is urgently needed addressing the effects of important comorbidity, such as smoking, steroid use and chemotherapy as well as the effects of diabetes and peripheral vessel disease.



References

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