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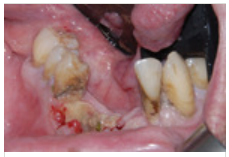
Bisphosphonate-associated jaw osteonecrosis

Osteonecrosis of the jaw is an uncommon, but severe, adverse event associated with oral and intravenous bisphosphonate therapy. A confirmed case of bisphosphonate-associated jaw osteonecrosis is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks of identification by a health care provider, in a patient who currently receives or has been exposed to a bisphosphonate and has not had radiation therapy to the craniofacial region.

Letters, case reports, and small case series of jaw osteonecrosis have been published in the oncology, dental, maxillofacial surgery, and general medical literature during the past 7 years. Patients with jaw osteonecrosis typically present with jaw pain—more often in the mandible than the maxilla—and associated exposed bone.



Osteonecrosis of the jaw

Enlarge

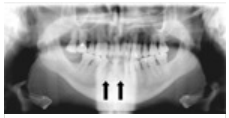
Clinical setting

Of jaw osteonecrosis cases, 60% occur after dental extraction, root canal surgery, dental implantation, or other dentoalveolar surgery, whereas all other cases appear to occur spontaneously. To date, 94% of cases have occurred in patients treated with intravenous bisphosphonates, and 85% of these patients were being treated for cancer with 1 or more of the potent nitrogen-containing intravenous bisphosphonates, usually once a month for several years. The highest risk of jaw osteonecrosis appears to be associated with frequent —typically monthly—infusions of intravenous zoledronic acid, which has been used widely in patients with multiple myeloma or breast or prostate cancer.

Presentation

Sreenivas Koka, D.D.S., Ph.D., of the Department of Dental Specialties-Prosthodontics at Mayo Clinic in Rochester, Minnesota, explains: "Jaw osteonecrosis usually appears as an intraoral lesion with areas of exposed yellowish-white hard bone. It sometimes is associated with extraoral or intraoral sinus tracts and has a delayed healing response—that is, for more than 8 weeks, the bone stays exposed rather than being covered with gingival or mucosal tissue. Painful ulcers may be present in the soft tissues adjacent to the bony margins of the lesion.

"Dental radiographs are typically not helpful in early cases, but advanced cases may present with areas of moth-eaten radiolucencies with or without radiopaque bone sequestra. Dental or surgical trauma sites are commonly associated with development of jaw osteonecrosis. In advanced cases, pathologic jaw fractures may occur or part of the mandible or maxilla may need to be removed."



Nonhealing of extraction sites

Enlarge

Risk factors and prevalence

Bart L. Clarke, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "The main risk factors include cancer, frequent intravenous infusions of nitrogen-containing bisphosphonates, and dentoalveolar trauma.

"Risk factors have not been identified for patients receiving oral bisphosphonates, such as alendronate, risedronate, and ibandronate, for postmenopausal osteoporosis without cancer because only a small number of cases have been published. Most of these cases were associated with alendronate therapy, likely because of its wider use than other oral bisphosphonates."

Dr. Clarke continues: "Unless the number of cases has been greatly underreported, the prevalence of oral bisphosphonate–associated jaw osteonecrosis appears to be low — estimated in 1 European database to be on the order of 0.00038% (3.8 cases per 1 million persons treated). Intravenous bisphosphonate–associated jaw osteonecrosis in cancer patients is much more common, with prevalence estimates ranging between 0.8% and 10% and with most studies reporting estimates from 1% to 4%."

Pathophysiologic factors

No pathophysiologic mechanism has been established by which oral or intravenous bisphosphonate treatments cause jaw osteonecrosis. It is hypothesized that suppressed bone turnover caused by potent bisphosphonate therapy leads to accumulation of fatigue damage in the form of microcracks, which may lead to microfractures.

Also, bisphosphonates are potent inhibitors of angiogenesis, leading to a decreased ability to heal. Dental trauma or infection increases the demand for bone microdamage repair, which may lead to localized osteonecrosis, although it is not yet clear how this occurs.

Prevention

Dr. Koka explains: "No randomized clinical trials have been published describing interventions to prevent or treat jaw osteonecrosis. Patients should have potentially traumatic dental treatment, such as tooth extractions, root canals, or dental implantations, before starting oral or intravenous bisphosphonate therapy.

"The optimal time for withdrawal of bisphosphonates before dental surgery in patients already receiving bisphosphonate therapy is not yet established, but most specialists advocate withdrawal of therapy 3 months before dental surgery. Nevertheless, the risks and benefits from this form of drug holiday are as yet unproven, particularly because bisphosphonates have a long half-life of several years in the skeleton.

"It is suggested, however, that if a dental extraction or other form of dental surgery is necessary, a course of pretreatment and posttreatment antibiotics—from 1 day before to 7 days after surgery—be used because this course may reduce the risk of osteonecrosis of the jaw. Encouragingly, retrospective analyses indicate that dental implants placed in individuals receiving bisphosphonate therapy for osteoporosis or osteopenia are successful."

Treatment

No effective therapy has been established for jaw osteonecrosis in patients receiving oral or intravenous bisphosphonate therapy. Some dental specialists recommend supportive management, starting with withdrawal of oral or intravenous bisphosphonate therapy, avoidance of further dentoalveolar trauma, appropriate use of oral antibiotic rinses, use of hyperbaric oxygen therapy, and adequate time for healing. In some instances, surgery to debride dead bone may exacerbate the condition; however, debridement and local, pedicled soft tissue flaps have been reported to stimulate healing in selected patients.

Recommendations

Dr. Clarke suggests: "Until further relevant clinical data become available, it is reasonable to begin or continue oral or intravenous bisphosphonate therapy in patients with appropriate indications, unless jaw osteonecrosis is present or develops.

"Physicians should review with each patient the decision to continue treatment with frequent infusions of potent intravenous bisphosphonates. Patients contemplating starting therapy with oral or intravenous bisphosphonate for prevention or treatment of osteoporosis should be informed of the rare risk of jaw osteonecrosis with oral bisphosphonates and the relatively infrequent risk of jaw osteonecrosis with intravenous bisphosphonates.

"Patients should undergo dental evaluation and treatment before starting intravenous bisphosphonate therapy and be regularly evaluated to ensure optimal oral health. It is appropriate to encourage patients who express concern about jaw osteonecrosis and who are taking, or about to start taking, oral bisphosphonates to visit their dentist for more information."