ABSTRACT

Bisphosphonates are used to treat osteoporosis, Paget disease of bone and other metabolic bone diseases, multiple myeloma, and skeletal events associated with metastatic neoplasms. In 2003, the first reports describing osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates were published. About 95% of these cases occurred among cancer patients receiving high-dose intravenous bisphosphonates. Approximately 5% of the reported cases have been in osteoporosis patients receiving low dose bisphosphonate therapy. The mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure. Oversuppression of bone turnover is probably the primary mechanism for the development of this condition, although there may be contributing comorbid factors. All sites of potential jaw infection should be eliminated before bisphosphonates therapy is initiated in these patients to reduce the necessity of subsequent dentoalveolar surgery. Conservative debridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are preferable to aggressive surgical measures for treating this condition.

The purpose of the present article is to enlighten the dental fraternity about this frequently prescribed class of drugs with regard to its types and mode of action, and the implication of bisphosphonates-induced ONJ.

Keywords: Bisphosphonates, Jaws, Mandible, Maxilla, Osteonecrosis.


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INTRODUCTION

Osteonecrosis of the jaw (ONJ) is an uncommon condition with many recognized causes. Traditionally, it has been associated with head and neck irradiation. It can also occur in the presence of periodontal disease, local malignancy, chemotherapy, glucocorticoid therapy or trauma.1-6 Recently, however, high-dose intravenous bisphosphonates have been identified as a risk factor for ONJ among oncology patients. Low dose bisphosphonate use in patients with osteoporosis or other metabolic bone disease has not been causally linked to the development of ONJ. Bisphosphonates have been widely used in the management of osteoporosis and metabolic bone disease. They have proven to be effective in reducing the risk of fracture and have recently been shown to improve mortality.7 They are valuable in the management of skeletal complications of malignancy, namely metastatic bone disease and hypercalcemia of malignancy, and are a key treatment option for cancer patients with metastatic disease.8-14

ACTIONS OF BISPHOSPHONATES

Bisphosphonates are powerful inhibitors of osteoclastic activity. They are analogs of inorganic pyrophosphates with low intestinal absorption, are excreted through the kidneys without metabolic alteration, and have a high affinity for hydroxyapatite crystals.15,16 The most recent nitrogen-containing bisphosphonates, or aminobisphosphonates, have greater potency and better selectivity; the most commonly used aminobisphosphonates include alendronate, risedronate, ibandronate, pamidronate and zoledronate. Alendronate, risedronate and ibandronate are used for the prevention and treatment of osteoporosis, while pamidronate and zoledronate have an essential role in the prevention of bone complications and the treatment of severe hypercalcemia associated with multiple myeloma or bone metastases from breast and prostate cancers.9,17

Generally, these drugs are well tolerated, rarely inducing clinically significant side effects: Gastrointestinal symptoms for oral bisphosphonates (alendronate and risedronate); elevated serum creatinine, transient low-grade fever, arthralgias and increased bone pain for the injectable drugs (pamidronate and zoledronate).18

SUSCEPTIBILITY OF THE JAWS TO OSTEONECROSIS

The cause(s) of ONJ are not known. Nor is it clear why some patients develop the condition or suffer it more severely than others. Bone remodeling involves osteoclasts resorbing old damaged bone and osteoblasts replacing this with new bone. Bisphosphonates reduce the rate of bone remodeling and so removal of microdamaged regions of bone may be impaired.19

The jawbones are subjected to constant high stresses from masticatory activity such as chewing, swallowing and talking. The teeth, which are retained in the jaw by the periodontal ligaments, protrude through the mucosa into the mouth and are bathed in saliva. Saliva has a high bacterial load. In healthy individuals there are many physical and immunological mechanisms that cope with these forces and the presence of high bacterial levels.20 Under normal circumstances healing rapidly occurs following tooth extraction. Even though 5% of extractions result in a nonhealing osteitis (dry socket), this spontaneously resolves within 2 to 3 weeks. Normal extraction site healing involves...
osteoclastic activity to remodel the tooth socket and create new bone. It may be that the bisphosphonate affected bone, in combination with the bacterially infested saliva in the socket, results in the inability to respond to this healing and infection challenge.19

INCIDENCE

Among cancer patients receiving high-dose intravenous bisphosphonates, ONJ is dependent on dose and duration of therapy,21-24 and has an estimated incidence of 1 to 12%.21,25-28 Among osteoporosis patients, bisphosphonate-associated ONJ is rare and the incidence might not be greater than the natural background incidence of the condition. Postmarketing data and observational studies indicate an estimated incidence of less than 1 case per 100,000 person-years of exposure to oral aminobisphosphonates.29

CLINICAL FEATURES

The most widespread clinical picture heralding the onset of bisphosphonate-associated ONJ is failure to heal, or slow healing, of bone after extraction of a tooth or other local oral surgery (70-80% of cases).5,23,30,31 In the early stages there is no radiological evidence and the patient often has no symptoms; pain usually indicates a superimposed infection on the exposed bone.32

In 25 to 40% of cases ONJ arises spontaneously, not related to any particular trauma.23,31 In these cases the most frequent initial symptom is an unpleasant sensation in the mouth (numbness, paresthesia and burning sensation), with gradual changes to the mucosa, progressing to ulcers that are sluggish to heal.32

ONJ is a progressive disorder causing extensive exposure of the maxillary or mandibular bone, with sequestration. The mandible and maxilla are normally the only bones involved in bisphosphonate-induced osteonecrosis, the most common site of exposure being the mandible in the area of the molars (about 70% of cases), followed by the posterior maxilla (about 30%); only few cases occur simultaneously in the mandible and maxilla.23 Involvement of the maxilla is a notable difference between bisphosphonate-related ONJ and osteoradionecrosis, a form of osteonecrosis secondary to radiotherapy for head and neck cancer that affects the mandible in 95% of cases.33

Patients may be considered to have bisphosphonates-induced ONJ if all of the following three characteristics are present:34

1. Current or previous treatment with a bisphosphonate;
2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks; and
3. No history of radiation therapy to the jaws.

PREVENTION AND THERAPY

Prior to treatment with monthly intravenous bisphosphonates, the patient should have a thorough oral examination, any unsalvageable teeth should be removed, all invasive dental procedures should be completed and optimal periodontal health should be achieved.35

Three studies reported that preventative dental treatment decreased bisphosphonates-induced ONJ risk among patients with malignancy treated with intravenous bisphosphonates.36-38 These findings suggest that, while bisphosphonates-induced ONJ is not eliminated, dental evaluations and treatment prior to initiating intravenous bisphosphonate therapy among cancer patients reduces bisphosphonates-induced ONJ risk. The risk of developing bisphosphonates-induced ONJ associated with oral bisphosphonates, while exceedingly small, appears to increase when the duration of therapy exceeds 3 years. This time frame may be shortened in the presence of certain comorbidities, such as chronic corticosteroid use. If systemic conditions permit, the clinician may consider discontinuation of oral bisphosphonates for a period of 3 months prior to and 3 months following elective invasive dental surgery in order to lower the risk of bisphosphonates-induced ONJ. The rationale for this approach is based on extrapolated data that demonstrate fluctuations of osteoclast function, which is related to bisphosphonates-induced ONJ treatment with drug cessation.36-39

The goals in a patient with ONJ are, of course, to relieve the pain, but primarily to control secondary infection in the necrotic area; this means abstaining–as far as possible–from dental surgery so as not to enlarge it. Daily topical antimicrobial or anti-inflammatory agents (for example, chlorhexidine gluconate rinses three to four times a day) are recommended. If local infection is suspected, or confirmed by culture, aggressive systemic antibiotics should be started, ideally–unless the antibiotic sensitivity test indicates otherwise–with penicillin-type antibiotics or doxycycline in penicillin-allergic patients.23,40,41 Unlike in radio-osteonecrosis, hyperbaric oxygen has not given encouraging results in ONJ patients.5,23,40

CONCLUSION

ONJ is a newly recognized condition reported in patients treated with bisphosphonates, in particular potent aminobisphosphonates. Most cases have developed in patients with multiple myeloma or metastatic cancer, but the condition has also been identified in patients with osteoporosis. There has been a burgeoning demand for information about bisphosphonates over the past decade due to an increasing awareness of this drug’s rare adverse side effects.
REFERENCES


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