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Hotline

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Bisphosphonate-Associated Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has recently been recognized as an uncommon but severe adverse event associated with oral or intravenous bisphosphonate therapy in humans. Letters, case reports, and small case series published in the oncology, dental, and maxillofacial surgery literature since September 2003 describe ONJ as typically causing jaw pain, more often in the mandible than the maxilla, with associated exposed bone (1-3).

How common is ONJ?
In a systematic review of 368 cases of bisphosphonate-associated ONJ published between 1966 and January 31, 2006, Woo et al. (4) reported that 65% of cases affected the mandible, 26% the maxilla, and 9% both mandible and maxilla. About two-thirds of the lesions were painful at diagnosis, with the remaining one-third painless, and 60% of cases occurred in women. Multifocal or bilateral involvement was more common in the maxilla than the mandible, with most lesions occurring on the posterior lingual mandible near the mylohyoid ridge. Sixty percent of cases occurred after oral surgery for dental extraction or other dentoalveolar surgery, whereas the remainder occurred spontaneously, some in patients wearing dentures. Most cases (94%) occurred in patients treated with intravenous bisphosphonates, and most (85%) had multiple myeloma or breast cancer metastatic to the skeleton. Patients receiving intravenous bisphosphonates for cancer were most often treated with one or more of the potent nitrogen-containing intravenous bisphosphonates, i.e., zoledronic acid or pamidronate, typically once a month for several years. Some patients developed ONJ within 4 months of starting therapy, but the median duration of therapy before diagnosis ranged from 22 to 39 months, with the mean duration ranging from 9 to 14 months. The highest risk of ONJ appears to be associated with frequent, typically monthly, infusions of intravenous zoledronic acid, which has been widely used in patients with myeloma, breast cancer, and prostate cancer in recent years.

What is the clinical presentation of ONJ?
ONJ typically appears as an intraoral lesion with areas of exposed yellow-white hard bone with smooth or ragged borders, sometimes with associated extraoral or intraoral sinus tracts (4,5). Painful ulcers may be present in the soft tissues adjacent to the ragged bony margins of the lesion. Dental x-rays may be unremarkable in early cases, but advanced cases demonstrate poorly defined areas of moth-eaten radiolucencies, with or without radioopaque bone sequestra. Pathological jaw fractures have occurred in some cases. In its most severe form, ONJ may cause loss of a significant part of the mandible or maxilla.

What are the risk factors for ONJ?
The main risk factors identified to date include cancer, frequent infusions of intravenous nitrogen-containing bisphosphonates, and dentoalveolar trauma (4-6). Risk factors have not been identified in patients receiving oral bisphosphonates for postmenopausal osteoporosis without cancer due to the very small number of published cases.

What about ONJ in patients without cancer, including rheumatic diseases?
Although under-reporting is always a potential consideration in pharmacovigilance data, the total number of cases of non-cancer patients with ONJ associated with oral bisphosphonate therapy reported among several million estimated patients who have been exposed to these drugs over the last 20 years appears small. To date, fewer than 20 cases of ONJ have been reported in the medical literature among patients without cancer treated with oral bisphosphonates. The risk of development of ONJ in patients with Paget's disease of bone treated with oral or intravenous bisphosphonates is not known, with only 3 cases reported in this review. None of the reported cases describe bisphosphonate related ONJ in women or men treated with glucocorticoid therapy for rheumatologic disease. The overall risk of ONJ in these patients appears low, but not yet well quantified.

Which type of bisphosphonate causes ONJ?
Most cases of ONJ reported have occurred with intravenous zoledronic acid and pamidronate. The risk of development of ONJ in postmenopausal osteoporotic patients treated with oral bisphosphonates such as alendronate, risedronate, and ibandronate is not known, as only a small number of cases have been reported. Most of these cases are associated with alendronate therapy, likely due to its wider use than other oral bisphosphonates. The review by Woo et al. (4) reported only 15 patients treated for osteoporosis without cancer with any bisphosphonate. Of the 368 total cases of ONJ reported, 18 were associated with oral alendronate, and of these, 15 occurred without exposure to intravenous or other oral bisphosphonates. Thirteen of the alendronate-treated cases occurred in patients treated for osteoporosis without cancer. One case of ONJ was associated with oral risedronate, and one case with oral ibandronate, both in patients treated for osteoporosis without cancer.

How do bisphosphonates cause ONJ?
There is no established pathophysiological mechanism by which oral or intravenous bisphosphonates may cause ONJ, although it is hypothesized that suppressed bone turnover caused by potent bisphosphonate therapy leads to accumulation of microdamage, which may eventually lead to microfractures (7,8). Trauma or infection increase demand for bone microdamage repair, which might lead to localized osteonecrosis, although it is not yet clear how exactly this might occur. The antiangiogenic properties of some bisphosphonates (9) and other medications and comorbidities may increase the risk of persistence and progression of ONJ.

How can ONJ be prevented?
No randomized clinical trials have been published describing either prevention or treatment of ONJ. The American Academy of Oral Medicine (AAOM) guidelines (10) call for prevention of ONJ in patients requiring therapy with bisphosphonates by conducting a dental examination and completing any traumatic treatment, such as dental extractions, before starting oral or intravenous bisphosphonate therapy, and avoiding dental trauma in patients who have begun such therapy. Woo et al. (4) advised treating active oral infections and obtaining routine dental care before starting nitrogen-containing bisphosphonate therapy, using the least traumatic surgical approach when tooth extraction or other dental surgery is required, and avoiding wide excision of dead bone in patients with ONJ.

How can ONJ be treated?
Once ONJ develops, there is no current recognized effective therapy (11). Dental specialists typically recommend supportive management, with withdrawal of bisphosphonate therapy, avoidance of further dentoalveolar trauma, appropriate use of oral antibiotic rinses, and allowing time for healing. Further aggressive surgery to debride dead bone may exacerbate the condition, but dental gingival flap placement may help stimulate healing.

For established ONJ, Marx et al. (6) recommended systemic and topical antibiotic therapy with oral penicillin VK or amoxicillin, concurrent with use of chlorhexidine gluconate 0.12% oral rinses. The authors reported that this palliative regimen is over 90% effective in controlling pain in patients with ONJ, but resolution of lesions did not occur with this regimen. A surgical approach to treat ONJ lesions by means of pedicled flaps may be helpful (12).

Current Clinical Practice
Until more clinical data become available, it is reasonable to continue oral or intravenous bisphosphonate therapy in patients with appropriate indications, unless ONJ develops. The decision to continue to treat cancer patients with frequent infusions of potent intravenous bisphosphonates should be discussed with each patient's oncologist. Patients contemplating starting therapy with oral or intravenous bisphosphonate therapy for prevention or treatment of postmenopausal or glucocorticoid-induced osteoporosis should be informed of the rare risk of ONJ with oral or infrequent intravenous doses of bisphosphonates. Patients should be informed that caries and periodontal disease may increase the risk of ONJ in patients taking bisphosphonates. Dental examination and treatment should be completed either prior to or as early as possible after beginning bisphosphonate therapy.

The Bottom Line
- ONJ is most common in patients with cancer who receive frequent intravenous infusions of potent nitrogen-containing bisphosphonates, but rare in postmenopausal women or men with osteoporosis. The

actual prevalence or incidence of ONJ in women or men treated with glucocorticoid therapy for rheumatologic disease is not known but appears to be very low.

- ONJ may occur during treatment with zoledronic acid, pamidronate, alendronate, risedronate, and ibandronate, but 94% of cases have occurred with intravenous zoledronic acid or pamidronate.
- Risk factors for ONJ include cancer, frequent infusions of intravenous nitrogen-containing bisphosphonates, and dentoalveolar trauma or infection.
- Before beginning therapy with oral or intravenous bisphosphonates, patients should be referred for dental care to address dental issues. Bisphosphonate therapy should not be started until dental issues have resolved.
- In patients with established ONJ, treatment with systemic antibiotics and oral antibiotic rinses may help with pain and infrequently may lead to healing. Stopping bisphosphonate therapy may be prudent, as anecdotal evidence suggests that this may help in some cases. Aggressive dental surgery should generally be avoided.

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