

## Osteonecrosis of the Jaw — Do Bisphosphonates Pose a Risk?

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Nitrogen-containing bisphosphonates are used widely for the management of metastatic cancer in bone (intravenous zoledronic acid or pamidronate), for the prevention and treatment of osteoporosis (oral alendronate, risedronate, and ibandronate and intravenous ibandronate), for the treatment of Paget's disease of bone (intravenous pamidronate and oral alendronate and risedronate), and for the short-term management of acute hypercalcemia (intravenous zoledronic acid and pamidronate). The nitrogen moiety attached to the side chain of the middle carbon of the phosphorus-carbon-phosphorus bisphosphonate backbone renders these drugs much more potent as inhibitors of bone resorption than the bisphosphonates that do not contain nitrogen (etidronate and clodronate). Bisphosphonates reduce the survival and function of osteoclasts, the bone-resorbing cells. These antiresorptive actions largely account for the drugs' ef-

ficacy in conditions in which the rate of bone resorption exceeds the rate of bone formation.

Until recently, the only adverse events of substantial consequence

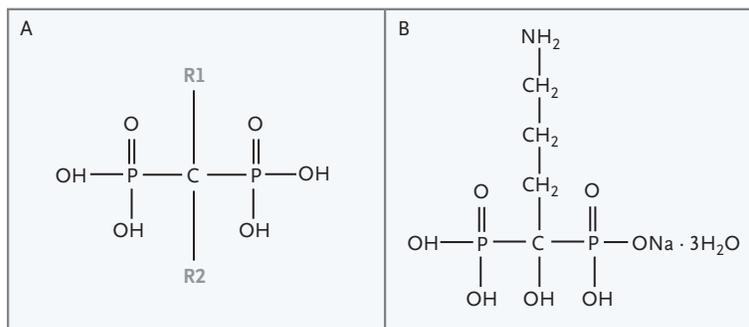
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associated with the nitrogen-containing bisphosphonates were upper gastrointestinal intolerance (with oral administration) and a short-lived acute-phase reaction characterized by fever, myalgias, and an influenza-like syndrome (with intravenous administration).

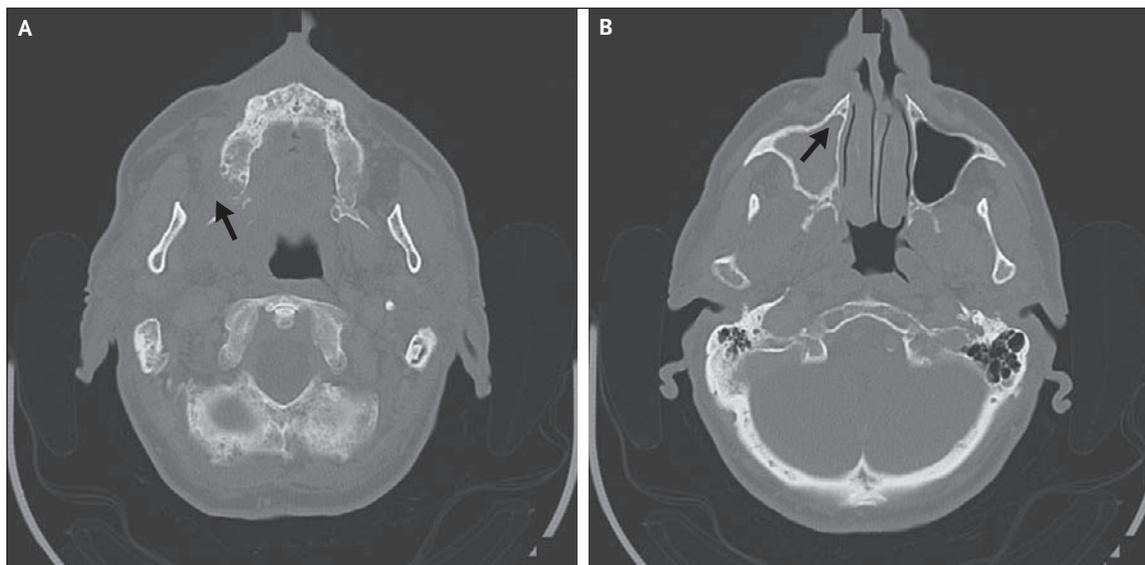
Now another potential complication of these agents — osteonecrosis of the jaw — has surfaced.

Osteonecrosis of the jaw is characterized clinically by an area of exposed bone in the mandible, maxilla, or palate that typically heals poorly or does not heal over a period of 6 to 8 weeks. The diagnosis is primarily a clinical one, but imaging studies such as computed tomography can be helpful (see images). This condition in connection with bisphosphonate use was first reported in 2003, or 5 to 10 years after these drugs were approved in the United States for their current indications; it was rarely seen before then. Most of the reported cases (95%) have been associated with zoledronic acid or pamidronate given intravenously to control metastatic bone disease.<sup>1,2</sup> When these drugs have been administered intravenously in patients with cancer, the reported incidence of osteonecrosis of the jaw has ranged from 1.3% in a preliminary retrospective survey<sup>3</sup> to 4 to 7% in another report.<sup>1</sup> Myeloma and breast cancer are by far the most common cancers associated with intravenous bisphosphonate use and osteonecrosis of the jaw.<sup>1</sup>

Predisposing factors for the development of osteonecrosis of the jaw appear to be dental disease, dental surgery (e.g., tooth extraction), oral trauma, periodontitis, and poor dental hygiene. Treatment with chemotherapy or



Structures of a Generic Bisphosphonate (Panel A) and a Nitrogen-Containing Bisphosphonate (Panel B).



Computed Tomographic Scans Showing Osteonecrosis of the Right Maxilla (Panel A, arrow) and Resultant Opacification of the Sinus (Panel B, arrow).

corticosteroids is also common among affected patients. The lesion is painful in many, but not all, patients, and infection is often present. Approximately two thirds of cases involve the mandible and the rest involve the maxilla. In one unusual case, osteonecrosis of the external auditory canal developed in a patient with myeloma who had received intravenous zoledronic acid and pamidronate.<sup>4</sup>

Typically, patients in whom osteonecrosis of the jaw develops have been receiving intravenous bisphosphonate therapy for 1.5 to 3 years. With conservative management (minimal surgical débridement, rinses with cyclohexidine or hydrogen peroxide, antibiotics, and analgesics), the lesions usually heal, although some cases of osteonecrosis of the jaw have become chronic and some patients have had complications.

For metastatic cancer, the doses of nitrogen-containing bisphosphonates are typically 4 to 12

times as high as those used to treat osteoporosis. Whether lower doses can be used effectively to control metastatic bone disease is a matter for further study. Osteonecrosis of the jaw has developed far less often among patients who have received oral bisphosphonates at the lower doses used for osteoporosis than among patients who received the higher doses used for metastatic cancer. Among several million patients who have received oral treatment for osteoporosis, fewer than 50 cases of osteonecrosis of the jaw have been reported to date.<sup>1</sup> Moreover, with more than 60,000 patient-years of exposure to nitrogen-containing bisphosphonates in clinical trials of treatment for osteoporosis (involving follow-up for as long as 10 years in some patients), osteonecrosis of the jaw was not reported among the adverse events. Unpublished post-marketing surveillance data are also consistent with the infre-

quent occurrence of osteonecrosis of the jaw among persons being treated for osteoporosis.

On the one hand, given that not all reported cases have been confirmed to be osteonecrosis of the jaw, and on the other hand, that there may be underreporting, 1 in 100,000 patient-years is a reasonable estimate of the incidence of osteonecrosis of the jaw in patients receiving oral nitrogen-containing bisphosphonates for osteoporosis. Fewer than five cases of osteonecrosis of the jaw have been reported among patients with Paget's disease of bone that was being treated with nitrogen-containing bisphosphonates.

Because the estimate of the incidence of osteonecrosis of the jaw is based on incomplete data, well-designed prospective cohort studies with rigorous case-ascertainment criteria as well as documentation of risk factors and risk modifiers are needed.<sup>5</sup> The Food and Drug Administration now re-

quires a precaution regarding osteonecrosis of the jaw in package inserts for all nitrogen-containing bisphosphonates.

If there is a relationship between bisphosphonates and osteonecrosis of the jaw, what might explain it? The jaw is often subject to spontaneous, local trauma as well as trauma caused by dental procedures. The mucosa of the mouth is very thin and may therefore permit unroofing of the alveolar bone immediately beneath it when trauma or infection occurs. As potent inhibitors of osteoclast activity, the nitrogen-containing bisphosphonates might retard skeletal repair processes associated with trauma to or infection of the oral mucosa that involves the underlying bone. Since the jawbones are in constant use and are characterized by active remodeling, bisphosphonates might accumulate there preferentially, resulting in concentrations that exceed those found elsewhere in the skeleton. Other potential mechanisms include the possible antiangiogenic effects of nitrogen-containing bisphosphonates and the effects of these agents on T-cell function.

The fact that the majority of reported cases of osteonecrosis of the jaw are associated with the use of high-dose intravenous bisphosphonates for metastatic bone disease suggests that the dose, duration of treatment, and route of administration, as well as coexisting conditions, concomitant treatments (glucocorticoids or immunosuppressive agents), and dental health, could all be related to the incidence of this complication. The use of bisphosphonates for osteoporosis in doses that are

much smaller than those used for metastatic bone disease is consistent with the current view that osteonecrosis of the jaw is much less common in this setting. In Paget's disease of bone, bisphos-

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phonate therapy is even more limited and osteonecrosis of the jaw is truly rare.

The possibility that the risk of osteonecrosis of the jaw may be increased with the duration of therapy has led some to emphasize the need for a "drug holiday" for patients who are being treated with bisphosphonates for osteoporosis — perhaps a 1-year period without bisphosphonate therapy after 5 or more years of treatment. Clearly, more research is needed to clarify the magnitude and basis of the risk of osteonecrosis of the jaw associated with the dose of bisphosphonates and the duration of their use.

In the meantime, how should clinicians respond? The documented benefits of using bisphosphonates for established indications clearly outweigh whatever small risk of osteonecrosis of the jaw might be incurred. To withhold bisphosphonate therapy from patients who are at high risk for

progressive metastatic bone disease, osteoporotic fractures, or complications of Paget's disease seems to me to be the wrong call.

At the same time, we must inform our patients about the risk of osteonecrosis of the jaw. Patients should be advised to see their dentists before beginning intravenous bisphosphonate therapy so that their dental hygiene can be optimized and any necessary procedures can be performed in advance. Patients who are to receive oral bisphosphonates should also follow a regular program of oral health maintenance. Routine dental hygiene is important; this point should be emphasized, given that some dentists are reluctant to provide even routine oral health care for patients who are taking bisphosphonates. Such reluctance, however, seems unwarranted.

Although there is no reason to stop bisphosphonate treatment for patients who are about to receive routine dental care, there is a debate about whether treatment should be withheld temporarily when more invasive dental care, such as a surgical procedure, is needed. Given the long half-life (measured in years) of bisphosphonates in bone, whether temporary cessation of treatment with these agents would reduce associated risks is not known; this question warrants study. For patients who are receiving bisphosphonate therapy for cancer and who are to undergo a major dental procedure, it seems reasonable to continue therapy in order to maximize control of the underlying malignant disease. For patients who are being treated for osteoporosis, however, it is unclear

whether bisphosphonate therapy should continue or should be stopped until healing after the dental procedure is complete. Opinions, but little data, can be advanced for both approaches. It is generally agreed that one should use caution in recommending elective, invasive dental work such as dental-implant surgery in patients who are receiving nitrogen-containing bisphosphonates. Patients should contact their dentists if tooth or jaw pain develops while they are receiving such therapy.

As always, physicians and patients must carefully weigh the

benefits and risks when considering drug treatment. For patients with recognized indications for nitrogen-containing bisphosphonates, using these agents is likely to do far more good than withholding them.

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