

Oral Bisphosphonates and the Risk for Osteonecrosis of the Jaw

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Abstract

Several recent reports have described osteonecrosis of the jaws (ONJ) associated with the use of bisphosphonates. Osteonecrosis of the jaws is recognized as a serious complication of bisphosphonate therapy, more commonly with the intravenous form of the drugs. However, there is limited scientific understanding about the association between osteonecrosis of the jaws and bisphosphonates. Primary care physicians treating bone diseases with bisphosphonate need, therefore, to be aware of this potential risk and plan the prophylaxis, early diagnosis and prevention of potential consequences. In this article, I review the literature on this newly described complication, with particular focus on systemic and local predisposing pathologies, preventive measures suggested before and during therapy with oral bisphosphonates, and the frequent clinical presentation of the oral lesions. The expert panel recommendations for the management of care of patients who develop ONJ are summarized also.

ONJ has been linked with high-dose intravenous bisphosphonate use in patients with bony cancers and the observation has been extended at a much lower incidence to patients on oral bisphosphonates taken for osteoporosis. The benefit-risk ratio is still heavily weighted towards therapy but primary care physicians need to be aware of this link. The risk is greatest in those with poor oral health who are undergoing dental surgery. If there is doubt, then a review by an experienced oral surgeon is appropriate.

Key words: Oral Bisphosphonates, Osteoporosis, Osteonecrosis

Osteoporotic fracture is common, expensive, and associated with increased morbidity and mortality. The incidence of osteoporosis fracture annually is greater than the risk of stroke, breast cancer, and heart attack combined. Bisphosphonates (BPs) have recently been the subject of clinical controversies because of the reported incidence of osteonecrosis of jaw (ONJ). Bisphosphonates as a group of drugs were introduced for the management of various conditions such as osteoporosis, Paget's disease, multiple myeloma, and hypercalcemia of malignancy. This group of drugs has improved the quality of life in many patients with proven efficacy in limiting pain and skeletal-related events. The efficacy of BPs as one method to prevent and treat osteoporosis and avert future fractures, particularly vertebral fractures, is well documented in large clinical trials. However, despite this evidence, many patients at risk for osteoporosis are not screened or treated. The controversy of osteonecrosis of the jaws and bisphosphonates is a recent and growing problem.

Bisphosphonates:

Bisphosphonates are fairly safe drugs to be used in the long term. There is a significant amount of safety data for up to 10 years with alendronate or Fosamax and up to 7 years with risedronate or Actonel. Every year, an estimated 30 million BP prescriptions are written in the U.S. alone.¹ The bisphosphonates alendronate, risedronate, ibandronate, and zoledronic acid are nitrogen containing compounds that increase bone mineral density (BMD) by inhibiting osteoclast-mediated bone resorption.² They have been shown to increase BMD approximately 2–8%, depending upon the dose and site

measured, and have demonstrated efficacy in primary and secondary prevention of osteoporotic fractures.^{3–10}

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).¹¹ Bisphosphonates reduce the survival and function of osteoclasts, the bone-resorbing cells. The clinical pharmacology of intravenous (IV) BPs is characterized by low intestinal absorption but highly selective localization and deposition in bone. Oral BPs have a bioavailability of less than 5%.¹² Once in the blood, BPs disappear very rapidly into the bone.¹³ After BPs are buried in the skeleton, they are released only when the bone is destroyed in the course of turnover. In humans, the skeletal half-lives of various BPs range from 3 months to as long as 10 years.¹⁴

Osteoporosis:

Osteoporosis is a devastating disease that may lead to significant morbidity and mortality from resultant fractures. Approximately one in two women and one in four men over age 50 will have an osteoporosis related fracture in their remaining lifetime.¹⁵ According to estimated figures, osteoporosis was responsible for more than 2 million fractures in US in 2005¹⁵ (including approximately 297,000 hip fractures, 547,000 vertebral fractures, 397,000 wrist fractures ,

135,000 pelvic fractures, 675,000 fractures at other sites). The number of fractures due to osteoporosis is expected to rise to more than 3 million by 2025.¹⁵

Osteoporotic fractures are associated with significant morbidity and mortality. Patients who sustain a fracture are more likely to have lower health-related quality of life, depression, pain, disability, physical deconditioning due to inactivity, vertebral deformities with a resultant decrease in pulmonary function and increase in gastrointestinal complications (e.g., refractory reflux esophagitis), pressure ulcers, increased likelihood of nursing home placement, and changes in self-image.¹⁶⁻²³ Hip fractures, which are the most serious complication of osteoporosis, are associated with significant mortality.²⁴⁻²⁷ Up to 38% of patients may die within one year after a hip fracture, and the risk of death is approximately double that of patients who do not sustain a hip fracture.^{24, 25, 27}

The economic consequences of osteoporosis are enormous. In 1995 in USA, osteoporotic fractures were responsible for approximately 432,000 hospital admissions, 2.5 million physician's office visits, and 180,000 nursing home admissions.¹⁵ Health care costs associated with osteoporotic fractures in 2005 were an estimated \$19 billion. By 2025, experts predict that these costs will rise to approximately \$25.3 billion.¹⁵ As the population of the United States continues to age, these costs will likely increase, with the number of hip fractures and associated costs possibly tripling by 2040.¹⁵

Oral bisphosphonate associated osteonecrosis of the jaw:

Osteonecrosis of the jaws (ONJ) is characterized by the death of bone as a natural consequence of a wide variety of systemic and local factors compromising the blood flow of the bone. Clinically it is diagnosed 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. Approximately two thirds of cases involve the mandible and the rest involve the maxilla. The lesion is painful in many, but not all, patients, and infection is often present. In one unusual case, osteonecrosis of the external auditory canal developed in a patient with myeloma who had received intravenous zoledronic acid and amidronate.²⁸ 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. The risk factors for developing ONJ include trauma, female gender, advanced age, edentulous regions, radiotherapy, chemotherapy, steroid therapy, blood dyscrasias/metastatic disease, anemia, coagulopathy, surgical dental procedures, alcohol or tobacco use, prior infection, and bisphosphonate therapy.²⁹⁻³² Although there have been some reports in the literature about osteonecrosis caused by steroids, this form is different from ONJ in the sense that steroid-induced osteonecrosis does not cause bone exposure.^{1, 33}

ONJ in connection with bisphosphonate use was first reported in 2003³⁴, 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.^{35, 36, 11} Myeloma and breast cancer are by far the most common cancers associated with intravenous bisphosphonate use and osteonecrosis of the jaw.³⁵

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.³⁵ 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.¹¹ The exact incidence of ONJ is unknown. However, some reports have estimated it to be about 1 in 10,000 for Intravenous use of BPs.³⁷ 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.¹¹ The risk of developing ONJ for patients taking alendronate, the most commonly prescribed oral bisphosphonate, has been estimated to occur in approximately 0.7 per 100,000 persons per years' exposure³⁸; on the other hand, the incidence of ONJ for risedronate and ibandronate cannot yet be quantified because too few cases have been reported (12 cases for risedronate and one for ibandronate).³⁸

The Cartosol medical claims database study also surveyed 260,000 subjects with osteoporosis, and found an odds ratio for inflammatory necrosis of the jaw to be 0.65 in oral bisphosphonate users, and that for surgery for a necrotic process to be 0.86.³⁹ Both these values are consistent with the other data suggesting that oral bisphosphonate use does not increase ONJ risk in osteoporosis patients. These findings are very similar to those from a case-control study using a claims database, which found that receiving

at least one oral bisphosphonate prescription was associated with an odds

ratio for jaw surgery of 0.91.⁴⁰ As per one consensus panel, there have been 33 cases [reported] in the literature as of January 2007 -- out of the 33 million patients who have been treated worldwide with an oral bisphosphonate -- which translates into approximately 200 million prescriptions written.

⁴¹ In addition, there has been spontaneous reporting in 1 of 100,000 patient-years for all of the approved bisphosphonates.

⁴¹ 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.¹¹

Prevention and management of bisphosphonate-associated osteonecrosis of the jaw:

Published recommendations are based upon expert experience from a variety of sources.^{35,36,1, 42-45} As yet, there have been no randomized, controlled trials that have evaluated strategies to prevent or manage ONJ in individuals receiving long-term high-dose bisphosphonate therapy. Before initiating BP therapy, all medical and dental practitioners are encouraged to follow these guidelines:

1. All patients should undergo a routine dental exam to rule out any dental source of infection.
2. All medical practitioners also should perform a baseline oral exam.
3. Invasive dental or/and oral surgical procedures should be completed before initiating therapy.
4. Practice preventive dentistry, involving procedures such as oral prophylaxis, dental restorations, and endodontic therapy, and check dentures for irritational foci.
5. Schedule routine follow-up every 3 months to check for any signs of developing ONJ.
6. The risks associated with oral surgical procedures such as dental implants, extractions, and extensive periodontal surgeries must be discussed with the patient and weighted against the benefits.

The following recommendations are made by the American Association of Oral and Maxillofacial Surgeons for management of patients on BP therapy and patients with proven ONJ.⁴⁶

Management of patients with proven ONJ based on staging of the condition:

- a. Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.
- b. Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection.
- c. Stage 3: Exposed/necrotic bone in patients with pain, infection, and 1 or more of the following: Pathologic fracture, extra oral fistula, or osteolysis extending to the inferior border.

Treatment of patients with established ONJ:

- i. Patients with stage 1 ONJ: Conservative management with oral rinse such as 0.12% chlorhexidine.
 - ii. Patients with stage 2 ONJ: Manage with antibiotics and antimicrobial oral rinses.
 - iii. Patients with stage 3 ONJ: Surgical debridement/ resection in combination with antibiotic therapy.
- Extraction of symptomatic teeth can be performed without any additional risks of worsening the condition.

General recommendations:

As with all dental patients, routine dental examinations are recommended. A comprehensive oral evaluation should be carried out of all patients about to begin therapy with oral bisphosphonates (or as soon as possible after beginning therapy). The dentist should inform the patient taking oral bisphosphonates that there is a very low risk (estimated at 0.7 cases per 100,000 person-years' exposure) of developing ONJ; there are ways to minimize the risk, but not to eliminate the already low risk; the consensus is that good oral hygiene along with regular dental care is the best way to lower risk; there are no diagnostic techniques to identify those at increased risk of developing ONJ.

Before undergoing any invasive procedure that involves manipulation of the bone the patient should understand that at this time, the risk of developing osteonecrosis of the jaw is considered very small, and that the vast majority of patients taking an oral bisphosphonate do not develop any oral complications. (Dental management of patients receiving oral bisphosphonate therapy: Expert panel recommendations)

Based on the currently available information, National Osteoporosis Foundation believes that in the vast majority of patient who are receiving them, the benefits of oral bisphosphonate medications outweigh the potential risk of ONJ. Patients for whom bisphosphonates are appropriate would be at higher risk of fractures without treatment, and fractures are the source of significant pain and disability that impact on function and quality of life. If a patient receiving bisphosphonates has planned dental surgery that involves the bone, a drug holiday beginning shortly before the procedure and lasting until there is local healing could be considered, although there is as yet no clinical evidence that this will affect the incidence or severity of ONJ. (Osteonecrosis of the Jaw (ONJ) June 14, 2006 / Reviewed and approved by the Science and Research Committee of the NOF Board of Trustees March 3, 2007).

Conclusion:

There is a need to clearly delineate the incidence of ONJ in osteoporosis patients treated with oral bisphosphonates, and in appropriate control populations. Based on current evidence, the risk of ONJ in osteoporosis patients taking oral BPs appears to be comparable to that in the general population. With the likely prevalence sitting at approximately 1 per 100,000 patient-years, it is quite clear that this is no different from that in the general population, since these problems can certainly occur in the absence of bisphosphonate use. The documented benefits of using bisphosphonates for established indications clearly outweigh whatever small risk of osteonecrosis of the jaw might be incurred.^{11, 47} Even if the number of cases of ONJ in patients taking oral bisphosphonates are still rare compared to the total exposure, primary care physicians treating bone

diseases with bisphosphonates need to be aware there is a small risk their patients may develop this new complication, allowing for prophylaxis, early diagnosis and prevention of potential consequences. The benefits and risks of bisphosphonate therapy should be individually discussed and, when necessary and possible, alternative therapy for postmenopausal osteoporosis should be considered.

It is important to understand that, based on the information currently available; the risk for developing BON is much higher for cancer patients on intra venous bisphosphonate therapy than the risk for patients on oral bisphosphonate therapy. Therefore, there are different recommendations for dental management of these patients.

In conclusion, the risk of ONJ is extraordinarily low. The risk of being in a fatal car accident is 10-15 times as high as the risk of ONJ from taking an oral bisphosphonate.⁴¹

COMPETEING INTERESTS:

Serves as a speaker for Eisai Inc. and Pfizer Inc. for the 2008 ARICEPT LTC DELTA 2 (Dementia Education Leadership Training in Alzheimer's) Promotional Education Program

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