J Oral Maxillofac Surg
67:53-60, 2009, Suppl 1

Bisphosphonates—What the Dentist Needs to Know: Practical Considerations

*John E. Fantasia, DDS**

Osteonecrosis of the jaws has been identified as a potential adverse side effect of nitrogen-containing bisphosphonate (nBP) medications.[1-3] These medications are also known as amino bisphosphonates. Earlier bisphosphonates usually did not have nitrogen-containing side chains or the opposed hydroxyl group and thus were less effective.[4] The overall risk of osteonecrosis in individuals taking the nBPs has not been clearly defined; however, epidemiologic studies and clinical experience have indicated that an increased risk exists of bisphosphonate-related osteonecrosis of the jaws (BRONJ) developing in patients receiving intravenous nBPs and a lesser risk with oral nBP medications.[3] The jaws are preferentially involved, likely related to the dynamics of bone-forming osteoblasts and bone-resorbing osteoclasts of the alveolar bone compartment, because cellular activity in bone is controlled by hormones, cytokines, and mechanical loading.[4]

A recent study has identified a potential genetic predisposition for the development of BRONJ in a group of myeloma patients treated with the intravenous nBP pamidronate or zoledronic acid.[5] In addition, Scheper et al[6] suggested that zoledronic acid, at low concentrations, directly affected oral mucosal tissues by induction of gene-regulated apoptotic processes; thus, these soft tissue effects of the medication might induce or potentiate osteonecrosis. Landesberg et al[7] have also identified inhibitory effects of bisphosphonates on oral keratinocyte cell proliferation and wound healing. However, the specific mechanism by which osteonecrosis of the jaws develops is not clearly understood. Yet, the dental professional is placed in a position of recommending certain procedures and the avoidance of others.[8] These treatment decisions are determined by the understanding of the pharmacokinetics of nBPs on bone metabolism and emerging clinical data. The following represents information that the dentist should be aware of regarding patients currently receiving or who have previously received nBP medications. These include patients at risk of BRONJ and those diagnosed with the condition.

Bisphosphonates, particularly the nBPs, have a strong affinity for circulating calcium and bind to calcium at the bone surfaces.[4] Therefore, they are potent inhibitors of bone resorption and bone remodeling.[9] These medications chelate circulating calcium, and the nBPs inhibit enzyme activity in osteoclasts, thus inhibiting bone dissolution and collagen degradation; inhibit osteoclast differentiation; and at greater concentrations, can induce osteoclast apoptosis.[4] These drugs remain in the bone for many years.[4]

The primary indications for the use of nBPs are the treatment of osteoporosis[3,4,10] and bone resorption related to metastatic tumors to the bone[11,12] or the osteolytic lesions of multiple myeloma.[13,14] The nBPs are also effective in treating hypercalcemia of malignancy. Some of these drugs, and at specific concentrations, can also inhibit angiogenesis[15] and might have direct antitumoral effects; hence, the increased use of these drugs in the treatment of a select group of cancer patients. The rationales for the use of these drugs are discussed in other sections of this supplement.

The common uses of these drugs are listed in Table 1. Patients should be queried about diseases such as osteoporosis, long-term use of glucocorticoids, a history of metastatic cancer to bone, multiple myeloma, and bone diseases such as Paget's, because these are the conditions for which nBPs are most frequently prescribed. Patients should be specifically questioned about the use of any of the medications listed in Table 2, and the treating clinician should have knowledge of both the proprietary and generic nomenclature for the nBP medications currently in use. The relative potency of the nBP drugs is listed in Table 3.

*Chief, Division of Oral and Maxillofacial Pathology, Department of Dental Medicine, North Shore-Long Island Jewish Health System, Long Island Jewish Medical Center, New Hyde Park, NY.

The author states no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this article.

Address correspondence and reprint requests to Dr Fantasia: Division of Oral and Maxillofacial Pathology, Department of Dental Medicine, North Shore-Long Island Jewish Health System, Long Island Jewish Medical Center, 270-05 76th Avenue, New Hyde Park, NY 11040; e-mail: fantasia@lij.edu

© 2009 American Association of Oral and Maxillofacial Surgeons

0278-2391/09/6705-0108$36.00/0
doi:10.1016/j.joms.2009.01.011

Table 1. BISPHOSPHONATES: COMMON INDICATIONS FOR USE

Prevention and treatment of osteoporosis in postmenopausal women
Increase bone mass in men with osteoporosis
Treatment of glucocorticoid-induced osteoporosis
Treatment of Paget's disease of bone
Hypercalcemia of malignancy
Bone metastases of solid tumors (eg, breast and prostate carcinoma; other solid tumors)
Osteolytic lesions of multiple myeloma

John E. Fantasia. Bisphosphonates: Practical Considerations. J Oral Maxillofac Surg 2009.

Table 3. RELATIVE POTENCY OF NITROGEN-CONTAINING BISPHOSPHONATES

Drug Name	Generic Name	Relative Potency*
Foasmax	Alendronate	1,000
Actonel	Risedronate	5,000
Boniva	Ibandronate	10,000
Aredia	Pamidronate	100
Zometa	Zoledronic acid	100,000
Reclast	Zoledronic acid	100,000

Adapted from Hillner et al.[11]

*Relative to etidronate (a non-nitrogen-containing bisphosphonate with relative potency of 1).

John E. Fantasia. Bisphosphonates: Practical Considerations. J Oral Maxillofac Surg 2009.

Overall Considerations

Dentists and physicians know quite well that patients frequently do not remember the medications they are taking; therefore, a request for an accurate medication listing is advisable. Also, a patient might have received 1 of these medications in the past, and perhaps because of side effects or other reasons are not currently taking them. The period that the patient has taken a particular bisphosphonate medication, as well as previous use of one of the other bisphosphonates is of clinical importance. It has been our clinical experience that patients often have taken a medication much longer than they remember. This is critical information, because it appears that not only what nBP, but also the dosage, frequency, and duration of taking that drug or combination of nBPs, can also influence the potential for developing osteonecrosis. A history of the use of nBP medication would also be of value in discussing any potential risks of bisphosphonate-related osteonecrosis. Some uncommon, off-label uses of bisphosphonates have been described in published reports, such as the treatment of patients with chronic recurrent multifocal osteomyelitis,[16] bone compromise related to beta-thalassemia, central giant cell lesions of bone, Langerhans cell histiocytosis, fibrous dysplasia, and osteogenesis imperfecta.[17] Thus, diligence in questioning a patient with any bone pathologic findings, including metastatic bone disease, metabolic bone disease, an endocrinopathy, or a condition associated with the risk of secondary osteoporosis related to possible bisphosphonate exposure would be prudent.

Physicians are the health care professionals prescribing and dosing the bisphosphonates, given the approved clinical indications and use of these medications. These principally include family practitioners, internists, gynecologists, endocrinologists, rheumatologists, and medical oncologists. These practitioners are not necessarily cognizant of the oral manifestations of bisphosphonate osteonecrosis of the jaws. Physicians are prescribing these drugs according to currently available data that indicate the use of the medication outweighs the potential adverse side effects.[18-20] It is important that the dentist and physician communicate regarding the best available treatment options for their mutual patient. Therefore, the professions require careful attention to the emerging basic science

Table 2. NITROGEN-CONTAINING BISPHOSPHONATE MEDICATIONS (AMINO BISPHOSPHONATES)

Drug Name	Active Ingredients	Dosage Form; Route	FDA Approval
Fosamax*	Alendronate sodium	Tablet; oral	1995
Actonel†	Risedronate sodium	Tablet; oral	1998
Boniva‡	Ibandronate sodium	Tablet/injectable; oral/IV injection	2003, 2006
Aredia§	Pamidronate disodium	Injectable; IV infusion	1991
Zometa§	Zoledronic acid	Injectable; IV infusion	2001
Reclast§	Zoledronic acid	Injectable; IV infusion	2007

Abbreviations: FDA, US Food and Drug Administration; IV, intravenous.

*Merck & Company.

†Procter & Gamble.

‡Roche Laboratories.

§Norvartis Pharmaceuticals.

John E. Fantasia. Bisphosphonates: Practical Considerations. J Oral Maxillofac Surg 2009.

and clinical data related to bisphosphonate osteonecrosis. The professions should also be aware of the novel therapies[21] aimed at preventing bone resorption with similar or improved efficacy and less of a deleterious effect on the jaws than the nBP medications currently available.

Clinical Features

Exposed devitalized bone is the hallmark of osteonecrosis of the jaws.[22-24] This clinical finding can be preceded by vague pain or discomfort in the region of involvement.[24] Bisphosphonate-related osteonecrosis is something that should be included in the clinical differential diagnosis of any patient with a history of bisphosphonate exposure presenting with pain in a tooth-bearing area or edentulous region of the jaw with no obvious clinical or radiographic evidence of a defined inflammatory, reactive, metabolic, cystic, or neoplastic pathologic entity. Most cases of bisphosphonate osteonecrosis of the jaws occurs after wounding of the bone, such as tooth removal; however, spontaneous cases of bisphosphonate-related osteonecrosis have been recognized and documented.[3] The process is more common in the mandible, but the maxilla can be affected.[2] Some patients have multifocal osteonecrosis of the jaws.[3] Spontaneous osteonecrosis of palatal and mandibular tori have been described in bisphosphonate users.[22] Inflammation and infection are noted in advanced cases and are the more significant reasons for the symptomatic features of BRONJ. Pathologic fracture, oral cutaneous fistula, oral antral fistula, or oral nasal fistula formation can occur in advanced cases of BRONJ. Table 4 lists the clinical staging scheme proposed by Ruggiero et al[23]; adopted by the American Association of Oral and Maxillofacial Surgeons in 2007[24]; and further modified and revised by the AAOMS in 2009. (See Ruggiero et al, this supplement, pp 2-12.)

Table 4. CLINICAL STRATIFICATION AND STAGING GUIDELINES OF PATIENTS TAKING BISPHOSPHONATES AND THOSE WITH OSTEONECROSIS OF JAW

Stage	Description
At risk	No apparent exposed/necrotic bone in asymptomatic patients treated with either intravenous, injectable, or oral bisphosphonates
Stage 0	No clinical evidence of exposed/necrotic bone but nonspecific symptoms or clinical and radiographic findings suspicious for possible BRONJ
Stage 1	Exposed, necrotic bone that is asymptomatic and no evidence of inflammation or infection
Stage 2	Exposed, necrotic bone that is associated with pain, erythema, and inflammation or infection with or without purulent drainage
Stage 3	Exposed, necrotic bone in patients with pain, inflammation or infection, and 1 or more of the following: exposed and necrotic bone extending beyond the region of the alveolar bone resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor

Adapted from American Association of Oral and Maxillofacial Surgeons revised stratification and staging guidelines, with permission.

John E. Fantasia. Bisphosphonates: Practical Considerations. J Oral Maxillofac Surg 2009.

Radiographic Features

The early stages of BRONJ can exhibit little to no change in the bony architecture noted on periapical or panoramic radiographs or with computed tomography (CT) or magnetic resonance imaging. The effect on bone of the nBP is the inhibition of osteoclasts; thus, the anticipated effect of increased bone mineral density can yield a more radiodense appearance to the involved bone. Because this effect is systemic and affects the jaws uniformly, no comparative change will be present in the bone architecture that is typical of the more common focally occurring pathologic entities. As the osteonecrosis progresses and the bone becomes exposed, with breakdown of overlying soft tissues, secondary bacterial colonization and attendant focal demineralization of the bone can occur. At that point, a mottled appearance can be recognized that should raise the suspicion of an osteolytic process such as that noted in osteomyelitis, metastatic disease, primary lymphoma of the bone, and some other focal or diffuse mixed radiolucent and radiodense pathologic processes. Osteonecrosis of the bones other than the jaw have rarely been reported.[25] Osteonecrosis of the jaws in patients with known metastatic disease, with few exceptions, have not had histologic documentation of tumor metastases in the jaw bone affected with osteonecrosis. One could speculate that this might be because the jaws are an uncommon site of metastatic bone disease; or because of the aforementioned antitumoral effects of the bisphosphonates; or the likely preferential localization of the medications in the jaws that might prevent viable metastatic deposits from forming. The progression of the osteonecrosis can result in a distinct sequestrum, typically characterized by a sclerotic or mottled bone fragment surrounded by a peripheral radiolucency. This finding might give the clinician reason to attempt sequestrectomy.

Additional radiographic findings associated with bisphosphonate use include extraction sockets that do not fill with bone in the anticipated time frame; and prominent residual osteosclerotic lamina dura. These latter 2 radiographic findings should heighten the clinician's awareness of the potential for osteonecrosis, if not already clinically evident. Prominent lamina dura in dentate areas of the jaws should be viewed with concern related to BRONJ risk. As soft tissue inflammation and secondary infection manifest, soft tissue changes might be noted on routine dental radiographs and the more detailed cone-beam CT, CT, and magnetic resonance imaging studies. Positron emission tomography, frequently used to monitor disease activity in the cancer patient, can demonstrate an increased standardized uptake value in areas of BRONJ, and the standardized uptake value might also be influenced by an associated inflammatory component. Sodium fluoride positron emission tomography/CT and fluorodeoxyglucose-positron emission tomography/CT have both demonstrated uptake in BRONJ.[13]

Pathologic Features

Grossly, BRONJ specimens are composed of gray-tan hard tissue with or without fragmented friable soft tissue. Large specimens can require significant decalcification in acidic solutions, a testament to the sclerotic nature of the involved bone. Some smaller bone specimens might have a soft consistency, possibly the result of bacterial acids, resulting in demineralization in vivo. Microbial cultures have not consistently identified specific pathogens related to this disease process.[13,26,27] I believe that a diagnosis of microbial infection requires confirmation with microbial cultures and should not be made solely on histologic identification of bacterial debris adherent to exposed necrotic bone.

Debridement specimens, sequestra, and resection specimens of BRONJ are all similar histologically. Necrotic bone characterized by the absence of osteocytes is the hallmark. The bone is invariably sclerotic and if exposed to the oral cavity will have bacterial debris adherent to the necrotic bone surface. Osteoclasts are typically absent, a finding that might be reflective of osteoclastic apoptosis caused by the bisphosphonate. Adjacent soft tissues typically consist of granulation tissue with or without abscess formation. We have not identified evidence of metastatic deposits in BRONJ bone or surrounding soft tissues, and this would be an unusual finding according to the data from cases of BRONJ reported to date. Multiple myeloma affecting the mandible or maxilla might be identified. It should be recognized that myeloma is a primary malignancy of the bone, and deposits of myeloma are not considered "metastatic."

Biochemical Markers of Bone Turnover

Clinical trials and the assessment of morbidity from skeletal-related events have documented the effectiveness of the bisphosphonate medications.[18-20] Surrogate markers of bone turnover represent a noninvasive means of assessing bone disease activity and the response to therapy. This area of clinical pathologic research is a focus of interest in BRONJ.[13,26,28-32]

Bone-forming markers, such as serum osteocalcin, serum bone specific alkaline phosphatase, and serum bone sialoprotein, provide an indication of osteoblastic activity. Bone resorption markers are many and include, but are not limited to, serum and urine collagen type I C-telopeptide fragment assays, serum and urine *N*-telopeptide assays, and urine deoxypyridinoline assay. Other bone resorption markers such as urine pyridinoline, urinary hydroxyproline, and serum tartrate-resistant acid phosphatase are not bone specific, being identified in tissue sources other than bone, and therefore less-specific surrogate markers of bone metabolism. Additional surrogate markers of bone turnover include, but are not limited to, serum calcium, serum parathyroid hormone, serum 1,25-dihydroxy vitamin D, serum osteoprotegrin, serum osteopontin, serum procollagen type I *N* propeptide, and receptor activator of nuclear factor κ β ligand.

Bone resorption markers are of interest in patients being considered for nBP therapy, assessing the effectiveness of those receiving nBP, assessing those at risk of BRONJ, and in patients with BRONJ. The application of bone turnover markers includes the assessment of bone disease activity, the response to therapy, and whether markers normalize or exceed normal values with discontinuance of nBP. This latter indication for assessing the utility of bone turnover markers could influence the treatment decisions faced by both physicians and dentists. The selective use of these bone markers might be of value in studying specific diseases and the evaluation of treatment regimens related to specific bisphosphonates.[26,29]

The collagen breakdown product assays, specifically C-telopeptide immunoassay, measures collagen type-I fragments generated by bone resorbing osteoclasts. Marx et al[26] have suggested this assay be used to assess renewed osteoclast activity in patients who have discontinued the use of an oral nBP for osteoporosis. These values might allow for specific treatment decisions related to the capacity for bone remodeling to occur once oral bisphosphonates have been discontinued. However, it must be recognized that intraindividual variability, gender, age, physical activity, and seasonal and circadian variation exist that

can result in difficulty interpreting these assays. Procedures such as fasting, morning draw of serum samples, and appropriate handling of specimens have minimized these problems. However, concern still exists regarding the potential utility of these assays to accurately reflect bone turnover that is specific to the alveolar bone compartment of the jaws, the site of bisphosphonate-specific osteonecrosis. More investigation into the utility of bone resorption markers, either single markers or likely combinations of markers, is needed before being used to make clinical treatment decisions. It is also important to recognize that there are potency-related issues with the various nBP medications (Table 3)[11] and differences in the disease states being treated with the various doses and formulations; therefore, extrapolation of data from one subset of clinical circumstances might not apply to another. Bone turnover marker assays and significant change data will be of interest as additional well-designed studies are conducted assessing patients' response to therapy or discontinuation of nBP therapy.

Case Studies

CASE 1

A 63-year-old man sustained a fracture of his right humerus on applying slight pressure to his arm while holding onto a stairway banister in his home. The examination revealed this was a pathologic fracture related to an as yet unidentified lytic lesion of the humerus. The skeletal survey revealed several other lytic lesions of bone involving the hip, spine, rib, and femur. The lytic bone lesions represented metastatic renal cell carcinoma. The patient was treated with nephrectomy of the involved kidney and began a regimen of chemotherapy that included monthly intravenous administration of zoledronic acid for the described bony metastases. After the third monthly infusion of zoledronic acid, the patient experienced mobility of the left maxillary second molar tooth and a progressive feeling of roughness to the surrounding tissues. The molar spontaneously exfoliated, the tooth socket did not heal, and the surrounding maxillary alveolar bone was exposed. The medical oncologist discontinued the zoledronic acid. Several weeks later, the patient experienced pain in the right mandibular premolar area. He presented to his dentist and because of the pain and clinical and radiographic evidence of bone loss, the premolars were extracted. Two months later, he had continued pain in the right mandibular premolar area, incomplete soft tissue coverage of the extraction sockets, and "dry sockets." The patient developed progression of the area of exposed bone in the left maxillary alveolus, with minimal radiographic changes noted on panoramic imaging and minimal symptoms at this site. However, he has since experienced pain and swelling of the right mandible and swelling of the right floor of the mouth. With pressure to the floor of mouth swelling, pus emanated from the nonhealed premolar extraction sockets.

This case represents one of the more common clinical scenarios concerning BRONJ. The patient was receiving a potent intravenous nBP, zoledronic acid. Although after only 3 infusions, he developed BRONJ of the maxilla and contralateral mandible. The maxillary BRONJ developed spontaneously, and the mandibular BRONJ secondary to tooth extraction. The patient's symptom of pain raises the possibility that the BRONJ might have started at the premolar site before the classic signs of BRONJ developed. Whether the mandibular BRONJ would have been avoided if no extraction had been performed is speculative. Treatment has been supportive, with the use of chlorhexidine 0.12% rinses twice daily, and antibiotic coverage with penicillin when pain, swelling, or signs of infection are identified. Several months later, sequestra had not developed and despite extensive exposed bone in the maxilla, the alveolus is solid. Microbial cultures have not been helpful in directing therapy, because specific pathogens have not been identified. The discontinuation of the intravenous nBP might or might not affect the progression of BRONJ; thus, often, patients will continue their use of nBPs on re-evaluation of the potential risks and benefits of this therapy.

CASE 2

A 61-year-old woman was evaluated for possible tooth extraction and implant placement because she had fractured the crown portion of an endodontically treated left mandibular first molar. She had a full complement of maxillary and mandibular teeth. Her medical history was significant for Still's disease (juvenile systemic rheumatoid arthritis). For this condition, she had been taken varying doses of systemic steroids (prednisone) since her diagnosis. She had been taking 5 mg of prednisone daily for the previous 10 years. Earlier, she had been taking relatively high doses to control the symptoms of her rheumatologic condition. Because of her significant exposure to glucocorticoids, she was prescribed alendronate in 1995 and had continued the use of this medication to date. Because of her many years of systemic steroid use and long-term use of the oral nBP alendronate, we had considerable concern about the potential for BRONJ. After discussions with the patient, periodontist, oral surgeon, and general dentist, it was decided not to extract the fractured endodontically treated tooth and to leave these roots in place, with no attempt at prosthetic replacement.

The combination of long-term steroid use, for longer than 45 years, coupled with the long-term use of oral bisphosphonates, heightened concern about the possible development of BRONJ. It was determined that the prudent approach was no treatment at all. Conventional endodontics of the molar roots would have been advised, if the patient had not undergone previous endodontic treatment. Because, currently no marker has been established for those at greatest risk of BRONJ, a conservative approach was taken in this case.

CASE 3

A 68-year-old woman had had a left mandibular molar extracted because of periodontal bone loss and recurrent decay under a large amalgam restoration. The tooth was deemed nonrestorable because of the amount of decay and localized periodontal bone loss. The patient had a history of osteoporosis that had been treated with oral bisphosphonates since 1995. She had taken alendronate initially daily, then weekly for 10 years, and then had switched to monthly use of ibandronate. The extraction site healed, but the patient had continuing discomfort in the left posterior mandible area. It was this continued discomfort that delayed the planned implant at this site. On evaluation of this patient some 12 months after extraction, the anticipated bone fill of the extraction sockets was not identified and thickening of the lamina dura was present that outlined the extraction sockets. It was advised that the tooth replacement should not be attempted because we believed there was potential risk of BRONJ with additional wounding of the bone (implant placement) at this site.

This case illustrates the difficulties related to vague pain and possible causes. This clinical scenario is the reason the American Association of Oral and Maxillofacial Surgeons recently added a stage 0 to the stratification and staging guidelines. Although the possible etiologies are many, the early manifestations of BRONJ need to be considered in such a patient with nBP exposure; especially, the patient with a many-year history of oral bisphosphonate use. More reports have been published of intravenous nBPs causing BRONJ, but concern is growing that patients taking oral nBPs for an increasing number of years could be at increased risk of BRONJ than currently realized. It has been our clinical experience related to specimen submission for histopathologic analysis that this is a concern and should receive consideration in clinical decision making.

CASE 4

A 70-year-old woman had had a long history of xerostomia and xerophthalmia. A recent evaluation by her internist, and specialty consultation with rheumatology, ophthalmology, and her dentist all raised concerns about Sjögren syndrome. During her recent evaluation, she was noted to have osteoporosis according to bone mineral density studies. Risedronate was prescribed for osteoporosis. The patient had clinical evidence of xerostomia, because little to no salivary flow from the major salivary gland ducts could be appreciated. Extensive cervical, interproximal, and incisal edge caries were present. She had clinical and radiographic evidence of focally advanced periodontal disease. Rheumatologic evaluation with positive serology studies and minor salivary gland biopsy confirmed the diagnosis of Sjögren syndrome. Extensive dental procedures were planned, including extraction of the periodontally involved teeth with crown coverage of multiple teeth and construction of maxillary and mandibular removable partial dentures. Implants were considered, but for economic and other reasons, removable prostheses were selected. The patient had been taking bisphosphonates for 4 months. Because she needed extraction of multiple teeth that were nonrestorable and periodontally involved, the internist was consulted and the oral nBP was stopped. The preliminary periodontal procedures of root planning and curettage and caries control of the restorable dentition took several months. At 5 months after discontinuing her oral nBP, extractions were completed, and her restorative and prosthetic dentistry was started. She had developed no complications at her last follow-up visit.

This case illustrates the generally held opinion that the duration of treatment with nBP is an important consideration in making treatment decisions for patients exposed to these drugs. The oral bisphosphonates are generally considered less potent than the intravenous/injectable formulations. It appears from clinical experience that the less-potent oral formulations of the nBPs might have a dose and duration risk profile (ie, the longer the duration of nBPs, the greater the risk of BRONJ). This is also likely for the intravenous bisphosphonates as well, but the circumstances illustrated in case 1 indicate that even after a few infusions of zoledronic acid, BRONJ can occur. However, long-term data related to oral nBPs are lacking and the ability to predict which patients are at risk of developing BRONJ is lacking. However, concerns exist that the oral bisphosphonate problem might be quite significant, because more cases are being reported.[33-35] This particular case, however, would have been considered low risk, given the short duration of exposure and discontinuation of the medication for several months before the tooth extraction.

Phossy Jaw

The similarity of BRONJ to cases of jaw necrosis in workers exposed to white phosphorous (phossy jaw) during the late 19th and early 20th century was reviewed by Hellstein and Marek,[36] Donaghue,[37] and Marx.[38] This historical perspective is of interest now that current nBP medications also have the potential to result in jaw osteonecrosis.

Summary

nBPs are associated with osteonecrosis of the jaws. This includes the intravenous, injectable, and oral formulations of nBPs.[2,33,34,38] The increased potency of the nBPs, frequent dosing, and prolonged duration of use, independently or in combination, appear to be associated with an increased risk of BRONJ. The frequency with which this complication develops is difficult to determine. The overall incidence of BRONJ is low, given the frequency with which the medications are prescribed, but of sufficient concern because of the associated morbidity.

The difficulty in obtaining accurate incidence data appears to be related to physicians prescribing the medications and, often, dentists and dental specialists diagnosing and managing the condition, often without full knowledge of the patient's medication history, specifically the dosing, duration, and awareness of significant patient comorbidities.

BRONJ is a difficult condition to treat. Some patients have resolution with discontinuation of their nBP medications, with sequestration of necrotic bone and healing of the involved site. However, some patients have prolonged painful symptoms that are progressive, despite a variety of medical or surgical interventions.

The earliest manifestation of BRONJ can be difficult to recognize clinically and radiographically. Clinical data, in the form of standardized trials, related to the efficacy of using bone marker turnover assays to assess potential risk for BRONJ are currently lacking. At present, therapies or procedures requiring bone remodeling or repair should be avoided and selected treatment alternatives substituted, if clinically in the best interest of the nBP-exposed patient.

Routine dental care, including dental prophylaxis, nonoperative periodontal care, restorative procedures, and conventional fixed and removable prosthodontics, is not contraindicated in the nBP patient. Elective oral surgery, apical surgery, periodontal bone recontouring, implants, and, possibly, orthodontic tooth movement should be subjected to an assessment of the risks and potential benefits of the treatment procedure in the context of the patient's unique circumstances.

Updates on the bisphosphonate problem issued by the dental and medical societies, specialty groups, and bone biologists should be followed carefully because new data will likely result in improved identification of patients at risk and more efficacious treatment protocols.

References

1. Mehrotra B, Fantasia J, Nissel-Horowitz S, et al: Osteonecrosis of the maxilla: An unusual complication of prolonged bisphosphonate therapy: A case report. Proc Am Soc Clin Oncol 22: 795, 2003
2. Ruggiero SL, Mehrotra B, Rosenberg TJ, et al: Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. J Oral Maxillofac Surg 62:527, 2004
3. Ruggiero SL, Drew SJ: Osteonecrosis of the jaws and bisphosphonate therapy. J Dent Res 86:1013, 2007
4. Kimmel DB: Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. J Dent Res 86:1022, 2007
5. Sarasquete ME, Garcia-Sanz R, Marin L, et al: Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 *CYP2C8* in multiple myeloma: A genome-wide single nucleotide polymorphism analysis. Blood 112:2709, 2008
6. Scheper MA, Baros A, Chaisuparat R, et al: Effect of zoledronic acid on oral fibroblasts and epithelial cells: A potential mechanism of bisphosphonate-associated osteonecrosis. Br J Haematol Epub 2008 Nov 27
7. Landesberg R, Cozin M, Cremers S, et al: Inhibition of oral mucosal cell wound healing by bisphosphonates. J Oral Maxillofac Surg 66:839, 2008
8. Hellstein JW: Bisphosphonate induced osteochemonecrosis of the jaws: An ounce of prevention may be worth a pound of cure. Spec Care Dentistry 26:8, 2006
9. Lerner UH: Bone remodeling in post-menopausal osteoporosis. J Dent Res 85:584, 2006
10. Saag K, Lindsay R, Kreigman A, et al: A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone 40:1238, 2007
11. Hillner BE, Ingle JN, Berenson JR, et al: American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. J Clin Oncol 18:1378, 2000
12. Chen T, Berenson J, Vescio R, et al: Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. J Clin Pharmacol 42:1228, 2002
13. Raje N, Woo SB, Hande K, et al: Clinical, radiographic, and biochemical characterization of multiple myeloma patients with osteonecrosis of the jaw. Clin Cancer Res 14:2387, 2008
14. Berenson JR, Yellin O, Boccia RV, et al: Zoledronic acid markedly improves bone mineral density for patients with monoclonal gammopathy of undetermined significance and bone loss. Clin Cancer Res 14:6289, 2008
15. Santini D, Vincenzi B, Hannon RA, et al: Changes in bone resorption and vascular endothelial growth factor after a single zoledronic acid infusion in cancer patients with bone metastases from solid tumours. Oncol Reports 15:1351, 2006
16. Gleeson H, Wiltshire E, Briody J, et al: Childhood chronic recurrent multifocal osteomyelitis: Pamidronate therapy decreases pain and improves vertebral shape. J Rheumatol 35: 707, 2008
17. Gibbons CLMH, Petra M, Smith R, et al: Bisphosphonate treatment of benign multifocal and unifocal osteolytic tumours of bone. Sarcoma 7:35, 2003
18. Cartos VM, Zhu S, Zavras A: Bisphosphonate use and the risk of adverse jaw outcomes: A medical claims study of 714,217 people. J Am Dent Assoc 139:23, 2008
19. Grbic JT, Landesberg R, Lin SQ, et al: Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in

the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial. J Am Dent Assoc 139:32, 2008
20. Carey JJ, Palomo L: Bisphosphonates and osteonecrosis of the jaw: Innocent association or significant risk? Cleveland Clinic J Med 75:871, 2008
21. Miller PD, Bolognese MA, Lewiecki EM, et al: Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long term continued, discontinued, and restarting of therapy: A randomized blinded phase 2 clinical trial. Bone 43:222, 2008
22. Woo SB, Hellstein JW, Kalmar JR: Systematic review: Bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 144: 753, 2006
23. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: Background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:433, 2006
24. American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 65:369, 2007
25. Polizzotto MN, Cousins V, Schwarer AP: Bisphosphonate-associated osteonecrosis of the auditory canal. Br J Haematol 132:114, 2006
26. Marx RE, Cillo JE, Ulloa JJ: Oral bisphosphonate-induced osteonecrosis: Risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 65:2397, 2007
27. Sedghizadeh PP, Kumar SKS, Gorur A, et al: Identification of microbial biofilms in osteonecrosis of the jaws secondary to bisphosphonate therapy. J Oral Maxillofac Surg 66:767, 2008
28. Christgau S, Cloos PAC: Current and future applications of bone turnover markers. Clin Lab 49:439, 2003
29. Bolland MJ, Grey AB, Horne AM, et al: Effects of intravenous zoledronate on bone turnover and BMD persists for at least 24 months. J Bone Miner Res 23:1304, 2008
30. Generali D, Dovio A, Tampellini M: Changes of bone turnover markers and serum PTH after night or morning administration of zoledronic acid in breast cancer patients with bone metastases. Br J Cancer 98:1753, 2008
31. Lehrer S, Montazem A, Ramanathan L, et al: Normal serum bone markers in bisphosphonate-induced osteonecrosis of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 106: 389, 2008
32. Alexandersen P, Peris P, Guañabens N, et al: Non-isomerized C-telopeptide fragments are highly sensitive markers for monitoring disease activity and treatment efficacy in Paget's disease of bone. J Bone Miner Res 20:588, 2005
33. Chan KC, Fantasia J: Oral bisphosphonates and jaw osteonecrosis: Preliminary results of a single institution, retrospective analysis. Joint Meeting of the International Association of Oral Pathologists and American Academy of Oral and Maxillofacial Pathology, San Francisco, June 2008. AAOMP abstract 174
34. Edwards BJ, Hellstein JW, Jacobsen PL, et al: Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: An advisor statement from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 139:1674, 2008
35. Sedghizadeh PP, Stanley BS, Caligiuri M, et al: Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw. J Am Dent Assoc 140:61, 2009
36. Hellstein JW, Marek CL: Bisphosphonate osteochemonecrosis (bis-phossy jaw): Is this phossy jaw of the 21st century? J Oral Maxillofac Surg 63:682, 2005
37. Donaghue AM: Bisphosphonates and osteonecrosis: Analogy to phossy jaw. Med J Aust 183:163, 2005
38. Marx RE: Uncovering the cause of "phossy jaw" circa 1858 to 1906: Oral and maxillofacial surgery closed case file—Case closed. J Oral Maxillofac Surg 66:2356, 2008