NEWS LETTER

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Osteonecrosis of the Jaw Associated with the Use of Bisphosphonates: Part I

by Kathryn B. Nguyen, Pharm.D.

Introduction: Osteonecrosis of the jaw (ONJ) typically occurs secondary to avascularity caused by radiotherapy for head and neck cancer.[1] However, a number of case reports have recently been published regarding bisphosphonate-induced ONJ. This is the first long-term adverse event described for bisphosphonates and is depicted as a sudden growth of necrotic bone in the oral cavity of patients receiving bisphosphonate therapy.[2] The most common bisphosphonates reported to be associated with ONJ are pamidronate (Aredia®) and zoledronic acid (Zometa®).

This article will consist of two parts. Part I focuses on pharmacokinetics, mechanism of bisphosphonate-induced ONJ, clinical presentation, incidence and risk factors for ONJ, select case series, and radiographic and histopathologic findings. Part II will review the management of ONJ.

Bisphosphonates are medications used for the treatment of metastatic bone disease, multiple myeloma, osteoporosis, hypercalcemia caused by malignant disease, and Paget's disease. Once absorbed, the effect of bisphosphonates on the bone is complex. Terminology involving bone resorption is provided in Table 1. Bisphosphonates inhibit bone resorption through two mechanisms. First, they adsorb to the surface of hydroxyapatite crystals in the mineralized bone matrix, decreasing the solubility of the matrix and making it more resistant to osteoclastic resorption.[3-6] Second, bisphosphonates block attachment of osteoclast precursors to the mineralized matrix preventing them from transforming into mature, functioning osteoclasts.[3-5] Once integrated into the bone tissue, bisphosphonates, even after discontinuation, can remain for up to 10 years, depending on the rate of bone turnover.[1,7]

Table 1. Terms and Definitions of Bone Resorption[7a]

Term	Definition
Bone resorption	A process of dissolving and assimilating bone tissue
Bone remodeling	A process that involves resorption, reversal, formation, and quiescence; a process of bone destruction and formation
Osteoblast	A basic multicellular unit that is responsible for formation of new bone
Osteoclast	A basic multicellular unit that is responsible for bone resorption

Currently, there are two types of bisphosphonates: non-nitrogen containing and nitrogen-containing.[1] Non-nitrogen containing compounds include etidronate (Didronel®) and tiludronate (Skelid®).[1] The newer generation and more potent class of bisphosphonates are nitrogen-containing compounds. These agents include alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), pamidronate (Aredia®), and zoledronic acid (Zometa®) (see Figure 1).[1,5,8,11] The more potent bisphosphonates have an additional mechanism of action involving inhibition of farnesyl diphosphate synthase in the mevalonate pathway. This causes failure of intracellular proteins prenylation (i.e., transfer of fatty acid chains) resulting in earlier apoptosis of osteoclasts.[2,4,6,8-10] At the cellular level, the loss of osteoclastic activity leads to a reduction in bone resorption.[8,9]

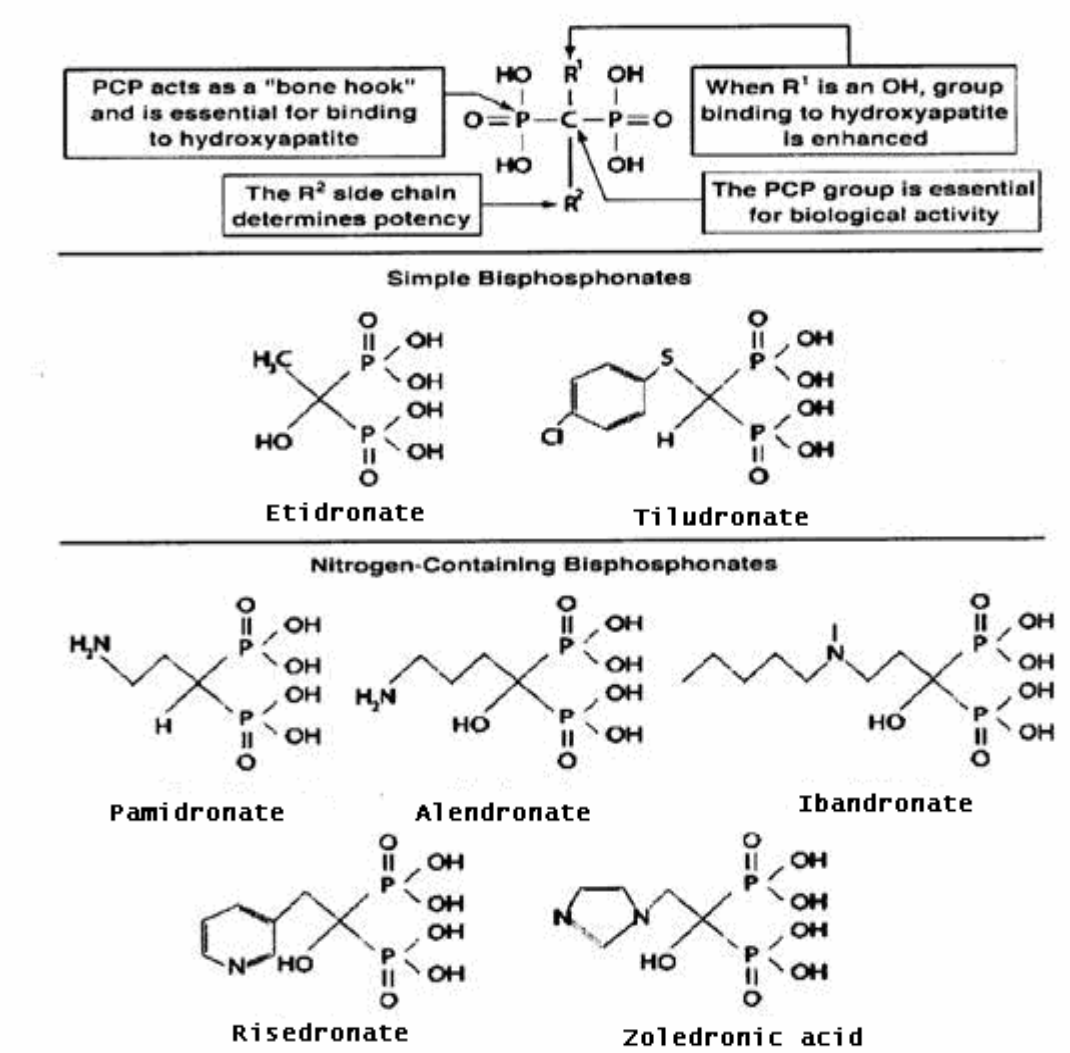
The pharmacokinetics, pharmacodynamics, and long-term adverse effect profile of bisphosphonates have not been fully elucidated. Even though they are effective agents, it is unknown how long the treatment for bone metastasis should be maintained, whether the amounts of bisphosphonates penetrating the skeleton differ between patients, and whether different dosing regimens change efficacy.[2]

Single case reports of ONJ associated with intravenous (IV) and oral bisphosphonates have also been published with similar clinical presentation, radiographic findings, and treatment.[12-26] Additionally, case series have been published on bisphosphonate-induced ONJ (see Table 2).

Mechanism of Bisphosphonate-Induced ONJ: Various mechanisms by which bisphosphonates cause ONJ of the jaw have been postulated. First, the jaw normally has a greater blood supply and faster bone turnover rate; therefore, bisphosphonates concentrate in this area.[6,27,28] It has been suggested that bisphosphonates produce changes in the vasculature (i.e., compromising the blood supply) of the mandible and maxilla.[1,10,27] As a result, dental extraction or manipulation in an ischemic area can cause delays in healing.[1,14,27] Also, oral microflora can flourish and cause infection leading to osteomyelitis.[1,27]

The second theory involves the potent inhibitory effect of bisphosphonates on osteoclasts.[2,5,8,29] Inhibition of osteoclast function decreases bone resorption and inhibits normal bone remodeling resulting in jaw microfractures. After the microfractures form, the functioning osteoblasts identify the

Figure 1. Bisphosphonate compounds[11]



need to deposit new bone and still initiate the bone-remodeling process in small bone multicellular units.[2,5,10,29] These units are surrounded with cells and blood vessels and their function is to resorb damaged bone and form new bone.[10] However, in bisphosphonate-treated patients, these units are no longer functional and newly formed bone is more brittle and at risk for new microfractures.[2,5,10,29] The bone then becomes avascular and necrotic, and any form of injury or invasive procedure causes bone exposure and failure to heal.[5,10,28]

A third mechanism involves the effects of bisphosphonates on angiogenesis. Santini and colleagues recently conducted a study evaluating the angiogenic modifications by pamidronate.[30] The authors found a statistically significant decrease, compared with basal values, in vascular endothelial growth factor (VEGF) levels after 1, 2, and 7 days of pamidronate administration. Vascular endothelial growth factor is a potent and specific angiogenic factor of cancer-induced angiogenesis. Wood and co-workers also demonstrated that zoledronic acid has significant antiangiogenic activity in several different *in vitro* and *in vivo* models.[31] Inhibition of angiogenesis causes compromise of the vascularity of the bone matrix, resulting in loss of blood vessels and avascular necrosis.[6,8,28,29]

The final proposed mechanism is the cytotoxic effects of bisphosphonates on stromal cells (i.e., connective tissue cells).[6,29] During an infection, the release of bisphosphonates from the bone is increased due to the acidic environment.[6] The bisphosphonates then cause cytotoxic effects on stromal cells, causing an inflammatory response. This response stimulates the release of IL-1 and IL-6 resulting in a constant cycle of inflammation and release of bisphosphonates from the bones.[6]

Clinical Presentation: Patients suffering from bisphosphonate-associated ONJ often present with similar initial symptoms. In the majority of patients, the exposed necrotic bone areas occur in sites of non-healing dental extraction sockets or sites of other routine dental procedures; some patients may have accidental trauma to the involved areas.[2,4,5,8,10,27,34] The exposed bones are mainly localized to the mandible and maxilla.[2,5,8,10,33-35] Spontaneous ONJ (i.e., without previous trauma or invasive procedure performed) can also develop, often on the lingual surface of the mandible.[2,4,12,34]

Patients can initially present with burning sensation, swelling at the affected site, loosening of teeth, draining fistula, and gingival hemorrhage; few patients have no symptoms in the presence of exposed bone.[4,8,10,15,29,34,35] Once the exposed bone becomes necrotic, the lesions are often painless; however, the patient suffers from pain due to the inflammation of surrounding soft tissue.[2,29,35] Furthermore, patients may complain of difficulty in eating and speaking and lower-lip numbness.[4,12,29] Signs and symptoms usually begin 1 to 10 months after initiating bisphosphonate therapy.[12]

Upon physical exam, there is yellow-white discoloration to the exposed bone, with inflamed adjacent areas secondary to mucosal infection.[2,27] Probing of the exposed bone is asymptomatic and bleeding does not occur.[27] Debridement of this necrotic tissue can lead to an increase in size of the necrosis and no healing of the wound.[2] Often times, if nearby teeth are affected by periodontal disease, necrosis can expand to those areas, resulting in further dental extraction and manipulation.[2] Other clinical signs present include trismus (i.e., jaw muscles tighten or spasm), halitosis, and recurrent abscesses.[4] Chronic sinusitis with purulent discharge is also common.[4,34]

Incidence and Risk Factors: There have been various published studies evaluating incidence and risk factors for the development of ONJ. Bamias and colleagues prospectively evaluated these characteristics in patients treated with bisphosphonates for bone metastases.[36] The authors noted that approximately 7% (17/252) of these patients developed ONJ. Of the 17 patients, there were 11 patients with multiple myeloma, two patients with breast cancer, three patients with prostate cancer, and one patient with an unspecified neoplasm. The median number of bisphosphonate infusions was 35 for those with ONJ and 15 for those without ONJ ($p < 0.001$). In addition, the type of bisphosphonate was also a factor in the development of ONJ. Results indicated that zoledronic acid may be responsible for earlier occurrence of ONJ. The authors concluded ONJ is a complication associated with long-term use of bisphosphonates and may have future implications in the current standards for use of these agents in cancer patients. In view of the data reported, the authors cautioned physicians about using pamidronate and zoledronic acid beyond 2 years.

Dimopoulous and colleagues retrospectively evaluated the incidence and risk factors in multiple myeloma for developing ONJ.[37] The incidence of ONJ was 7% (15/202) with the majority of cases involving the mandible and presence of dental extraction 1 year prior to diagnosis of disease. In this study, zoledronic acid was associated with a higher risk of developing ONJ. Time of exposure to the drug was also a significant risk factor for development of ONJ. The median time from the start of bisphosphonate therapy to the time of development of ONJ was decreased by half with zoledronic acid monotherapy. The authors suggested that the risk of developing ONJ is increased after 4 years of exposure to bisphosphonates. Dental extraction, artificial dentures, and periodontitis were risk factors predisposing patients to develop ONJ. These authors concluded health care professionals must be vigilant when using pamidronate and zoledronic acid for more than 2 years. Also, avoidance of invasive dental procedures and better oral hygiene may decrease the incidence of ONJ. Finally, risk factors should also be identified in patients starting and currently receiving bisphosphonate therapy.

Badros and co-workers performed a retrospective review of 90 multiple myeloma patients.[34] The incidence of ONJ in this group was 24% (22/90; six patients did not receive a bisphosphonate). Zoledronic acid was used alone in 34 patients, pamidronate monotherapy in 17 patients, and pamidronate fol-

lowed by zoledronic acid therapy in 33 patients. Twenty-seven patients had recent dental extractions including 12 patients in the bisphosphonate-induced ONJ group. Their results demonstrated that the risk of ONJ increased with presence of dental extraction ($p = 0.009$), treatment with both bisphosphonates consecutively ($p = 0.009$), with each additional year of follow-up ($p = 0.03$), and with increasing age at diagnosis of multiple myeloma ($p = 0.006$). The authors concluded ONJ is an increasing dilemma among multiple myeloma patients; although the consequences of ONJ are considerable, the incidence is low and justifies the continued use of monthly bisphosphonates for bone metastasis. Beyond 2 years, the risk-to-benefit ratio should be re-evaluated in multiple myeloma patients.

Another study assessing incidence, risk factors, and management of ONJ in multiple myeloma patients treated with pamidronate and zoledronic acid was completed by Zervas and colleagues.[38] The incidence of ONJ was 11% (28/254). The median number of bisphosphonate infusions was 15 and the median time of exposure was 24 months. The majority of patients diagnosed were treated with zoledronic acid alone or following pamidronate. The authors noted zoledronic acid produced a 9.5-fold higher risk for developing ONJ than pamidronate alone ($p = 0.042$), and a 4.5-fold higher risk than subsequent use of pamidronate plus zoledronic acid ($p = 0.018$). Other significant risk factors included the use of thalidomide and the number of bisphosphonate infusions. The authors concluded bisphosphonates are critical agents in the management of multiple myeloma; therefore, oncologists and dentists must be diligent in reducing the risk of ONJ in these patient populations by improving the patient's oral hygiene and educating patients about this complication.

Other risk factors for developing bisphosphonate-associated ONJ include advanced age, trauma, smoking, alcohol abuse, infection, chemotherapy, radiation, coagulopathy, corticosteroids, and vascular insufficiency.[6,7] Comorbid conditions may also play a role, but the degree of influence has not been determined; these conditions include diabetes mellitus, overall tumor burden and stage of disease, extent of skeletal involvement in cancer, overall systemic health, immunosuppression, history of stem cell transplantation, and current and past use of antiangiogenic medications such as thalidomide, glucocorticoids, and bortezomib.[29]

Radiographic Findings: Radiographic evaluation shows progressive periodontal involvement resulting in bone loss around the involved areas in ONJ.[27,32,33] Most patients have co-existing malignancies and have radiographs demonstrating bone metastasis in solid tumors and generalized bone lesions in hematological tumors. However, no other specific radiographic changes observed during the ONJ diagnosis relating to metastatic disease were documented in the majority of cases.[12,27,32,33]

Histopathologic Findings: Histopathology studies often reveal areas of chronic inflammation characterized by a mixed cellular infiltration and bacterial colonies (see Table 3).[1,12,27,35] In addition, the pattern of necrotic lesions consist of multiple, partially merging areas of necrotic bone mixed with remaining areas of vital bone.[35] Hansen and colleagues performed a histomorphologic analysis of patients with bisphosphonate-induced ONJ in comparison to patients with infected osteoradionecrosis (IORN).[35] In all cases, the authors found *Actinomyces* colonies at the site of necrotic bone. Numerous osteoclasts were also found in close contact to bone which demonstrates a sign of bone resorption. Epithelial proliferation mainly of neutrophilic granulocytes occurs in the medullary spaces covering the bone trabeculae. As far as cultures are concerned, *Candida albicans* has also been observed in some cases.[12]

Part II will appear in the September/October 2006 issue of Pharmacotherapy Update along with the references for both Part I and Part II.

Table 2. Overview of Select Case Series Involving Bisphosphonate-Induced Osteonecrosis of the Jaw

Author	# of Patients	Primary Diagnosis (# of patients)	Bisphosphonate (# of patients)	Site of Necrosis (# of patients)	Stimulated Cause (# of patients)
Ficarra et al.[4]	9	Breast cancer (3) Multiple myeloma (3) Lung cancer (1) Non-Hodgkin's Lymphoma (1) Prostate cancer (1)	Zoledronic acid (6) Pamidronate/ Zoledronic acid (3)	Mandible (9) Maxilla (2) Both* (2)	Dental extraction (9)
Bagan et al.[32]	10	Breast cancer (6) Multiple myeloma (4)	Pamidronate (4) Zoledronic acid (2) Both† (4)	Mandible (10) Maxilla (5) Both* (5)	Dental extraction (7)
Dimitrakopoulos et al.[8]	11	Multiple myeloma (5) Breast cancer (1) Lung cancer (1) Prostate cancer (2) Neuroendocrine cancer (1) Fibrous dysplasia (1)	Zoledronic acid (6) Pamidronate/ Zoledronic acid (4) Pamidronate/ Ibandronate/ Zoledronic acid (1)	Mandible (7) Maxilla (3) Both* (1)	Dental extraction (7) Dental trauma (1) Spontaneous (3)
Purcell et al.[7]	13	Breast cancer (5) Prostate cancer (4) Multiple myeloma (3) Osteoporosis (1)	Pamidronate (2) Zoledronic acid (10) Alendronate (1)	Mandible (4) Maxilla (2) Not specified (7)	Dental extraction (4) Spontaneous (1)
Pires et al.[33]	14	Breast cancer (6) Multiple myeloma (6) Lung adenocarcinoma (2)	Pamidronate and/or Zoledronic acid (not specified)	Mandible (9) Maxilla (3) Both* (1) Hard palate (1)	Dental procedure (9)
Cheng et al.[1]	15	Multiple myeloma (5) Paget’s disease (5) Bone cancer (2) Osteoporosis (3)	Pamidronate (8) Zoledronic acid (1) Alendronate (5) Pamidronate/ Alendronate (1)	Mandible (6) Maxilla (8) Both* (1)	Dental extraction (14)
Thakkar et al.[6]	17	Multiple myeloma (17)	Pamidronate (4) Zoledronic acid (7) Both† (6)	N/A	Invasive dental procedure (3)

Table 2. Overview of Select Case Series Involving Bisphosphonate-Induced Osteonecrosis of the Jaw (continued)

Author	# of Patients	Primary Diagnosis (# of patients)	Bisphosphonate (# of patients)	Site of Necrosis (# of patients)	Stimulated Cause (# of patients)
Migliorati et al.[27]	18	Breast cancer (10) Ovarian cancer (1) Breast/Ovarian cancer (1) Prostate cancer/lymphoma (1) Prostate cancer (1) Multiple myeloma (3) Osteopenia (1)	Pamidronate (3) Zoledronic acid (8) Both† (6) Alendronate (1)	Mandible (8) Maxilla (3)	Dental extraction (5) Post-trauma (2) Spontaneous (2)
Farrugia et al.[5]	23	Breast cancer (6) Prostate cancer (2) Multiple myeloma (9) Renal cell carcinoma (1) Osteoporosis (4) Paget's disease (1)	Pamidronate (4) Zoledronic acid (11) Both† (3) Alendronate (5)	Mandible (12) Maxilla (10) Both* (1)	Dental extraction (9)
Ruggiero et al. [10]	63	Breast cancer (21) Multiple myeloma (28) Lung cancer (1) Prostate cancer (3) Osteoporosis (7) Uterine sarcoma (1) Chronic Myelogenous Leukemia (1) Plasmacytoma((1)	Pamidronate (34) Zoledronic acid (9) Both† (13) Alendronate (5) Alendronate/ Zoledronic acid (1) Risedronate (1)	Mandible (39) Maxilla (23) Both* (1)	Not specified
Marx et al.[28]	119	Breast cancer (50) Multiple myeloma (62) Prostate cancer (4) Osteoporosis (3)	Pamidronate (32) Zoledronic acid (48) Both† (36) Alendronate (3)	Mandible (81) Maxilla (33) Both* (5)	Dental extraction (45) Existing periodontal disease (34) Periodontal surgery (5) Implant placement (4) Apicoectomy (1) Spontaneous (30)

*Mandible and Maxilla
†Pamidronate and Zoledronic acid
Duration of therapy: 6 - 96 months
Typical dose used: Pamidronate 90 mg IV every 3 weeks or monthly, Zoledronic acid 4 mg IV every 3 weeks or monthly, Alendronate 10 mg orally daily

Table 3. Histopathology and Treatment

Author	Radiography/Histopathology Performed (# of patients)	Treatment (# of patients)
Ficarra et al.[4]	Yes (7)	Cessation of bisphosphonates, Antibiotics (9), Debridement (9)
Bagan et al.[32]	Yes (10)	Antibiotics (10), Periodic debridement
Dimitrakopoulos et al.[8]	Not specified	Cessation of bisphosphonates, Antibiotics, Hyperbaric oxygen, debridement, sequestrectomy
Purcell et al.[7]	Not specified	Not specified
Pires et al.[33]	Yes (12)	Antibiotics (3), Antibiotics and debridement (11)
Cheng et al.[1]	Yes (2)	Hyperbaric oxygen/re-section (1), Re-section (1), Hyperbaric oxygen/curettage (1), Curettage (6) , Non-surgical (6), Antibiotics (not specified)
Thakkar et al.[6]	Not specified	Antibiotics (17)
Migliorati et al.[27]	Yes (12)	Antibiotics (17), Sequestrectomy (14), Hyperbaric oxygen (1)
Farrugia et al.[5]	Not specified	Antibiotics (22), Local debridement (13), Both (13), Partial maxillectomy (1), Hyperbaric oxygen (1)
Ruggiero et al.[10]	Not specified	Sequestrectomy (44), Mandibulectomy (10), Maxillectomy (7), Conservative management (2)
Marx et al.[28]	Yes (87)	Antibiotics (97)

Time to onset: 1 week – > 2 years
Radiography/Histopathology: signs of bone necrosis & chronic osteomyelitis
Culture: *Actinomyces isareli, Escherichia coli, Bacteroides melaninogenicous*, normal flora
Medications used: clindamycin, amoxicillin/clavulanate, penicillin G, 0.12% chlorhexidine

Missing Dose and Refill Line

The Department of Pharmacy has established a missing dose line to help manage the volume of calls to the inpatient pharmacy. **The phone number is 444-6599.**

This automated phone line is available for nurses to report **non-urgent** missing doses as well as to request PRN refills and refills on items such as topical creams or bulk liquids. Messages will be checked frequently (approximately every 30 minutes) by pharmacy technicians and the medication will be processed for the next scheduled delivery to the nursing area.

Requests for **urgently needed** medications should use the following phone numbers: 444-6590 for the main pharmacy and 444-4301 for the areas served by the 6th floor Pharmacy satellite. The pharmacy technician should be informed that this is a request for an urgently needed medication.

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