

Osteonecrosis of the jaw and oral bisphosphonate treatment

John B. Nase, DDS, FAGD, FICD; Jon B. Suzuki, DDS, PhD, MBA

Bisphosphonates are important pharmacological agents in the clinical management of such diseases as osteoporosis, Paget's disease of bone, multiple myeloma bone disease, metastatic cancers and breast carcinoma. Recent reports of dental complications in patients receiving bisphosphonate therapy have appeared in the literature.¹⁻⁵ These reports have linked dental complications primarily with the extraction of teeth. The intravenous drugs zoledronic acid and pamidronate disodium specifically have been associated with dental complications, as recognized in a recent pharmaceutical statement.⁶ However, other drugs in the family of nitrogen-containing bisphosphonates (including oral forms) also may result in dental complications. These drugs include alendronate, risedronate and ibandronate.

MECHANISMS OF ACTION

The mechanisms of action for bisphosphonates and bone metabolism are complex and involve interference of multiple sites in the bio-

ABSTRACT



Background. Bisphosphonates are becoming recognized increasingly as having a significant impact on dental therapies. This case report describes adverse clinical sequelae and successful treatment following periodontal surgery in a dental patient receiving bisphosphonate treatment.

Case Description. A 78-year-old woman experienced a nonhealing interproximal wound subsequent to a minor periodontal procedure performed to facilitate restoration of an adjacent tooth. Her medical history revealed that she had been taking an oral bisphosphonate every day for the previous five years for treatment of osteoporosis. After three months of periodic débridement and meticulous oral home care, one of the authors recovered a large piece of necrotic bone. The wound healed after the author performed surgery at the site.

Clinical Implications. Dentists should exercise caution when considering surgical procedures for patients with a history of oral bisphosphonate use. Thorough treatment of nonhealing wounds in these patients can lead to favorable outcomes.

Key Words. Osteonecrosis of the jaw; bisphosphonate; systemic drug side effects; osteoporosis.

JADA 2006;137(8):1115-9.

Dr. Nase is an associate professor of restorative dentistry (adjunct), Temple University School of Dentistry, Philadelphia. He also has a private practice in Harleysville, Pa. Address reprint requests to Dr. Nase, 404 Main St., Harleysville, Pa. 19438, e-mail "DrJohn@adamember.net".

Dr. Suzuki is a professor and associate dean for graduate education, research, and international relations, Temple University, Philadelphia.

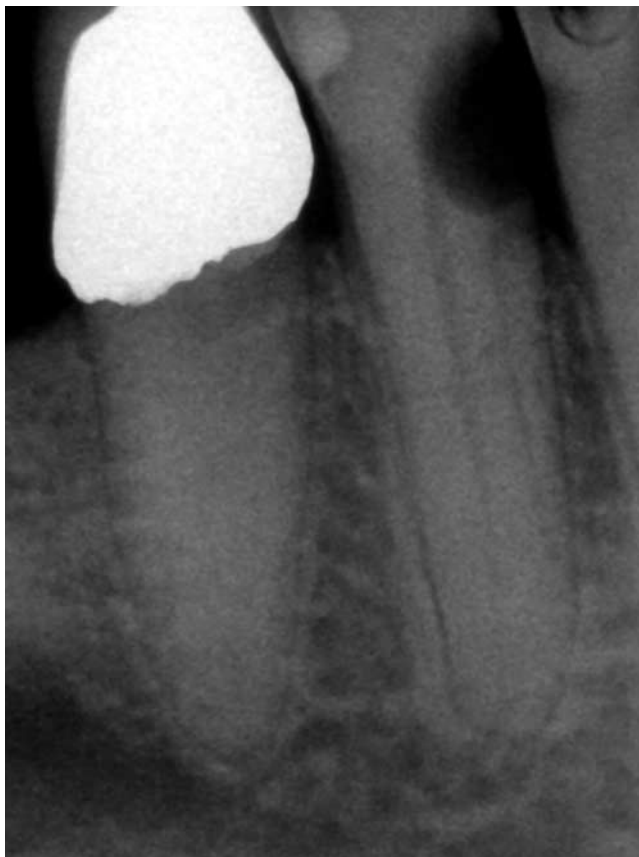


Figure 1. Preoperative radiograph showing tooth no. 27 with a deep carious lesion. The osseous architecture is unremarkable.

chemical and cellular pathways of bone apposition and resorption.⁷ Essentially, bisphosphonates act to decrease resorption by osteoclasts. Osteoblasts continue to function by enhancing bone growth, resulting in increased bone mass or density, which is the desired clinical result. However, osteoclast suppression, which also is intended to enhance overall bone quality, may have an adverse clinical effect on the mandible and maxilla and, ultimately, on periodontal surgical procedures.

Histopathologic analysis of biopsy specimens from osteonecrotic bone demonstrates tissue with lacunae devoid of bone cells such as osteoblasts, osteocytes and osteoclasts.⁸ In addition, Migliorati and colleagues² reported the presence of bacteria and inflammatory cells consistent with osteomyelitis in the specimen.

Periodontal surgical procedures performed in a dental patient receiving bisphosphonate treatment may result in significant postoperative complications as a result of the pharmacological disruption of the delicate biological balance of

osteoblasts, osteocytes and osteoclasts.

In this case report, we describe complications and treatment of a patient receiving bisphosphonate therapy who had undergone a minor periodontal procedure involving radiosurgery. The necrotic tooth no. 27, which was treated subsequently with endodontic therapy, also may have been a risk factor for osteonecrosis of the jaw in this case. Postoperative care for this patient included use of 0.12 percent chlorhexidine gluconate rinse and extraordinary reinforcement of oral hygiene practices. One of the authors (J.N.) performed subsequent periodontal surgical procedures that included placement of full-thickness flaps, removal of bone spicules and fenestration of the remaining dense cortical bone to encourage the migration of wound healing cells and osteogenic factors into the wound healing site.

CASE REPORT

In March 2005, a 78-year-old woman was referred for comprehensive dental care by her local community college's dental hygiene program. She had received a routine prophylaxis and cursory examination. The patient's medical history revealed that she was being treated for moderate-to-severe osteoporosis, subsequent to a right hip fracture in 2000 and a right femur fracture in 2004. She also had renal insufficiency, diverticulosis and clinical depression. The patient's physician had confirmed the diagnosis of osteoporosis using dual-energy X-ray absorptiometry (or DEXA scanning). The patient had no known drug allergies.

Her medications included alendronate (10 milligrams once per day) (since July 2000), tolterodine, sertraline, atorvastatin, aspirin (325 mg once per day), calcium salt and cholecalciferol supplement, and ginkgo biloba.

One of the authors (J.N.) performed a clinical examination that revealed partial edentulism with no prosthodontic replacement, signs of generally poor oral home care, gingivitis and multiple carious teeth. The patient reported having chronic moderate xerostomia. A full series of radiographs revealed no osseous abnormalities, periodontal bone loss or periapical lesions. Tooth no. 27 had caries extending into the pulp. Despite this finding, the clinician noted no periapical lesion (Figure 1). The cavitation on this tooth was located cervically, on the mesiolingual aspect. Exophytic gingival tissue extended into the cavity.

Periodontal procedure. The clinician infil-

trated one carpule of 4 percent articaine hydrochloride and epinephrine bitartrate (1:100,000). He excised the invading gingival tissue using a radiofrequency device, a small loop electrode and a fully rectified filtered current for the purpose of clinical crown lengthening. Although the dentist did not remove bone and used a low resistance setting, the interproximal bone may have been affected thermally by its close proximity to the operating current.

The dentist used coagulation sparingly for hemostasis, using a conical brass tip and a partially rectified current on the marginal gingiva, away from the bone. Extensive excavation of the cavitated Class III lesion confirmed the presence of endodontic involvement. The clinician removed the remaining caries and placed a resin-based composite restoration using a total etch/wet bond technique. He placed a rubber dam and prepared the tooth for lingual endodontic access. The clinician completed endodontic treatment at the same appointment, using conventional lateral condensation with gutta percha.

Open wound. Six days later, the patient visited the dentist with a chief complaint of an open wound and soreness at the surgical site. Clinical inspection revealed loss of the interproximal col between teeth nos. 26 and 27. Denuded and sloughing osseous tissue was apparent clinically (Figure 2). The dentist instructed the patient to rinse with warm saline several times per day, débride the area with floss and an interproximal brush, and return for follow-up in two weeks.

The patient returned on the 27th postoperative day. An examination revealed that no progress in wound healing had been made at the site. The clinician noted that her oral home care regimen was poor and that the site (and rest of the mouth) was covered with plaque, despite her reports of adequate care, including flossing. The clinician performed ultrasonic and hand débridement on the entire mandibular arch, and curetted the wound heavily to produce bleeding at its margins. The patient did not require anesthesia. The dentist prescribed chlorhexidine gluconate (0.12 percent) rinse to be used twice daily.

The dentist recommended that the patient undergo the débridement procedure every day until signs of healing were apparent. He also reinforced the need for her to perform good oral hygiene. She returned three times during the following week for débridement. By the third appointment, the dentist observed that the



Figure 2. Osteonecrosis between teeth nos. 26 and 27 is evident six days after surgery.



Figure 3. Necrotic interproximal bone removed during débridement.

patient had improved her home care regimen dramatically, and he allowed her to monitor the site and return for intermittent follow-up appointments. He saw her three times during the following seven-week period and performed similar débridement procedures at each visit.

Bone sequestrum. On the 80th postoperative day, the dentist recovered a $0.5 \times 0.2 \times 0.2$ -centimeter piece of bone sequestrum from the interproximal site while débriding the area with a

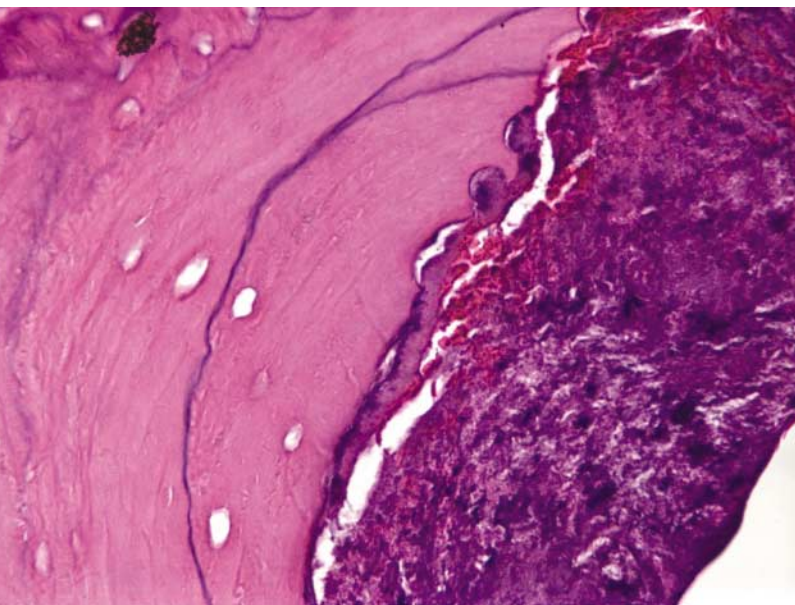


Figure 4. Histologic specimen of the removed bone showing empty lacunae and an irregular border populated by filamentous bacteria, plaque and inflammatory infiltrate.



Figure 5. The healed surgical and osteonecrotic site.

periodontal curette (Figure 3). He observed minimal bleeding after this sequestrectomy. He infiltrated anesthetic without vasoconstrictor and perforated the remaining cortical bone multiple times with a high-speed bur and irrigation to create bleeding fenestrations. The dentist approximated the soft-tissue flaps and sutured them in place using 4-0 polygalactac acid suture in a “figure-8” pattern. He submitted the excised necrotic tissue for histopathologic analysis. He

instructed the patient to continue her oral hygiene procedures and return in two weeks for follow-up.

Microscopy revealed a decalcified section of nonviable bone with lacunae devoid of osteocytes. Also present were inflammatory cells and bacteria (Figure 4). These findings were consistent with the microscopic diagnosis of osteonecrosis.

One hundred days after the initial procedure, the lesion had healed completely with apparent loss of attachment around the adjacent teeth (Figure 5). The postoperative healing proceeded uneventfully after sequestrectomy and secondary management, and, eight months later, there had been no recurrence of the lesion. The dentist consulted with the patient’s physician, which resulted in the decision for her to continue the bisphosphonate treatment without modification.

DISCUSSION

This case illustrates osteonecrosis of the alveolar bone after periodontal radiosurgery and endodontic therapy in a patient who had been receiving bisphosphonate therapy for osteoporosis for nearly five years. The potential for jaw bone changes resulting from use of this family of medications remains a plausible complicating factor in her adverse postoperative course, including the bone necrosis and sequestration. Secondary infection as a result of the necrotic tooth and the possible implication of radiosurgical thermal trauma cannot be ruled out as contributory factors to the adverse sequelae observed in this case.

It is important for dentists to obtain and update all medical and medication histories regularly. If patients are receiving bisphosphonate treatment, the clinician should exercise caution in planning any dental procedures that may involve surgery. These procedures include, but are not necessarily limited to, periodontal surgical crown lengthening, periodontal osseous surgery, extractions, placement of dental implants and hard-tissue biopsies of the jawbones.

The dentist performed a second, corrective, periodontal surgical procedure in this patient, taking into consideration the probability of bisphosphonate-induced osteonecrosis at the primary surgical site. Full-thickness mucoperiosteal flaps incorporating fenestrations of the bone permitted greater migration of osteogenerating cells (that is, osteoblasts) and molecules (for example, bone morphogenetic proteins, platelet-derived growth factors) into the wound healing area. The

dentist used local anesthetic without epinephrine to promote a reparative clot through maximization of vascularity. He monitored the patient's postoperative course more closely than typically is done, with an emphasis on plaque removal, reduction of microbial load (with use of an antimicrobial mouthrinse) and serial débridement of the surgical site.

The periodontal surgical approach to treating bone sequestrum and impaired wound healing used in this case may not be indicated for every complication of osteonecrosis of the jaws. Further delineation of the adverse clinical impact of intravenous versus oral bisphosphonates also requires additional study.

CONCLUSION

We have presented a case of a patient with a history of osteoporosis who had been treated with an oral bisphosphonate for nearly five years. A periodontal radiosurgical procedure and endodontic therapy on a nonvital tooth resulted in significant postoperative complications, including sloughing of bone spicules from the surgical site. A corrective periodontal surgical procedure consisting of a full-thickness flap, sequestrectomy and fenestra-

tion of remaining cortical bone improved the dental health of this patient. ■

The authors thank Gordon A. Pringle, DDS, PhD, professor of pathology, Temple University School of Medicine, Philadelphia, for preparation and diagnosis of the histologic specimen described in this article.

1. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;62(5):527-34.

2. Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. *JADA* 2005;136(12):1658-68.

3. Melo MD, Obeid G. Osteonecrosis of the jaws in patients with a history of receiving bisphosphonate therapy: strategies for prevention and early recognition. *JADA* 2005;136(12):1675-81.

4. Hellstein JW, Marek CL. Bisphosphonate osteonecrosis (bis-phossy jaw): is this phossy jaw of the 21st century? *J Oral Maxillofac Surg* 2005;63(5):682-9.

5. Melo MD, Obeid G. Osteonecrosis of the maxilla in a patient with a history of bisphosphonate therapy. *J Can Dent Assoc* 2005;71(2):111-3.

6. Novartis Pharmaceuticals Corp. Appendix 11: Expert panel recommendation for the prevention, diagnosis and treatment of osteonecrosis of the jaw: Zometa (zoledronic acid) injection and Aredia (pamidronate disodium) injection. Submitted as an appendix at the FDA Oncologic Drugs Advisory Committee Meeting, March 4, 2005. Available at: "www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2_02_12-Novartis-Zometa-App-11.htm". Accessed June 13, 2006.

7. Dunford JE, Thompson K, Coxon FP, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 2001;296(2):235-42.

8. Markiewicz MR, Margarone JE 3rd, Campbell JH, Aguirre A. Bisphosphonate-associated osteonecrosis of the jaws: a review of current knowledge. *JADA* 2005;136(12):1669-74.