

Bisphosphonate- Associated Osteonecrosis: Experiences in a Private Practice

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LEARNING OBJECTIVES:

After reading this article, the individual will learn:

- oral clinical presentation of bisphosphonate-associated osteonecrosis (BON)
- a possible treatment of BON using a chlorine dioxide-containing mouthwash.

ABOUT THE AUTHOR



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INTRODUCTION

Bisphosphonate-associated osteonecrosis (BON) is a new and enigmatic disorder that has thus far eluded both pathogenic explanation and consistent, successful treatment. Its occurrence is related to the use of bisphosphonates that are administered both orally and

intravenously. The prevalence of BON is substantially greater with the use of intravenously administered drugs.¹ Oral bisphosphonates such as alendronate (Fosamax [Merck]) and risedronate (Actonel [Procter & Gamble Pharmaceuticals, Sanofi-Aventis Group]) are employed to treat osteoporosis. Intravenously administered bisphosphonates reduce hypercalcemia and bone metastases associated with certain solid tumors as well as lysis of bone in multiple myeloma and Paget's disease of bone.² These medications are essential to preserve patients' lives as well as quality of life.

BON was first described as a pathologic entity of the jaws in 2003³ and has been extensively reported in the literature.² The main initiating factor for BON appears to be dental trauma or oral infection; however, the condition may also arise spontaneously. While several types of therapy for BON have been proposed, regular dental maintenance and preventive dental treatment prior to bisphosphonate administration are now the basis of preventive strategy. The intent is to avoid oral infection and the need for subsequent surgical procedures.

We present our experience with 4 patients in a private dental practice who presented with clinically diagnosed BON. It is emphasized that the therapeutic outcomes presented should be regarded as anecdotal, since the evaluation of treatment was not based on a controlled clinical trial. Presently, treatment is reported only occasionally, and a treatment protocol is not established. This is a case series, and further investigation of different treatment methods is needed.

PATIENT NO. 1

A 60-year-old male presented on July 11, 2002, with extensive caries, periodontitis, and pain associated with tooth No. 18. His medical history revealed that he was being treated for prostate cancer with bone, lymph node, and liver metastases as revealed by CT and bone scans. Therapy included intravenous zoledronate (Zometa [Novartis]) along with 3 other antineoplastic medications that included carboplatin (Paraplatin [Bristol-Myers Squibb]), etoposide (VePesid [Bristol-Myers Squibb]), and docetaxel (Taxotere [Sanofi-Aventis]). It was determined that tooth No. 18 was not amenable to treatment and was

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subsequently extracted on July 16, 2002. Healing progressed uneventfully. On October 17, 2002, the patient returned for treatment and complained of a painful and sharp area that was "cutting his tongue." Clinical examination revealed a 1 x 3-mm exposure of bone along the left mylohyoid ridge in the area of the extraction (Figure 1). Under local anesthesia the bone was smoothed and an antibiotic (Augmentin [Glaxo-SmithKline]) was administered. The lesion did not resolve. From October 17, 2002, to November 6, 2003, his last visit (and also around the time of the first report of BON in the literature²), the osteonecrotic area enlarged to approximately 10 x 35 mm (Figure 2), remained painful, and did not respond to antibiotic therapy. The patient died 9 months later.

PATIENT NO. 2

An 80-year-old female presented on August 17, 2005, for a routine dental visit. Clinical examination revealed a 2-mm-diameter ulceration on the left side of the posterior lobe of a large torus palatinus. The patient was not in pain and was unaware of the lesion. She was told to return in 2 weeks for a re-examination of the lesion, or sooner if symptoms developed. Because the area continued to be asymptomatic, the patient assumed that it had healed and did not return until January 11, 2006, for her next routine dental visit. By this time there was a painless exposure of bone that involved almost the entire distal lobe of the torus (Figure 3).

When questioned, the patient revealed that she had been taking alendronate for the previous 5 years (but had not informed the office as part of the medical history/medication periodic updates). Previous dental surgical experience included extractions of teeth No. 30 in 1998 and No. 4 in 1999 with subsequent implant placement, and endodontic treatment of tooth No. 3 in March 2004. On August 17, 2005, the patient was instructed to rinse with a phosphate buffer-stabilized 0.1% chlorine dioxide-containing mouthwash (CloSYS II [Rowpar Pharmaceuticals]) for 30 seconds 3 to 4 times a day until further notice. On June 30, 2006, the patient reported, "A piece of bone fell off of the roof of my mouth," which was likely exfoliation of a sequestrum. A clinical examination on August 17, 2006, revealed that the area was, and remains as of this writing,



Figure 1. Patient No. 1 approximately 3 months following extraction of tooth No. 18 demonstrating a 1 x 3-mm exposure of bone along the left mylohyoid ridge in that area and several small ulcerations posteriorly.



Figure 2. Same area as Figure 1 approximately 8 months following extraction of tooth No. 18.



Figure 3. Bone exposure and tissue inflammation of the distal one third of the palatal torus (January 11, 2006).



Figure 4. Complete soft-tissue healing (August 17, 2006).

completely healed (Figure 4).

This patient and all subsequently described patients have been instructed to continue using this mouthwash indefinitely.

PATIENT NO. 3

An 83-year-old female presented on February 27, 2006, for routine dental care. Clinical examination revealed

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2 small, painless ulcerations of 2 months' duration along the right mylohyoid ridge in the area of tooth No. 30. Her medical history revealed high blood pressure, atherosclerosis, and the surgical removal of 2 toes on one foot due to gangrene in 1980. She had been taking alendronate from July 2002 to September 2005. Her dental surgical history revealed that in April 2002 tooth No. 31 had been extracted. Previously, in July 1997 tooth No. 27 was removed, as was a failed implant in the area of tooth No. 29. Subsequently, 3 implants were placed in the area of teeth Nos. 28, 29, and 30. On March 23, 2006, clinical examination revealed the presence of a 3.5-mm-diameter area of asymptomatic, ex-posed bone (Figure 5). On July 17, 2006, the patient was instructed to rinse for 30 seconds with a chlorine dioxide mouthwash 3 to 4 times a day. By October 9, 2006, the lesion was mostly healed and the patient reported that the "area felt smoother." On November 11, 2006, this area ap-peared inflamed and was tender; however, the clinical examination did not reveal any exposed bone. On December 18, 2006, a 1.0 x 1.5-mm portion of exposed bone was present. A 4-mm-diameter spicule of bone was removed on January 3, 2007, from the right mylohyoid ridge and was identified histologically as "necrotic bone." On January 31, 2007, another small seques-trum was removed from the same area, and by June 25, 2007, the tissue had (and remains) completely healed (Figure 6).



Figure 5. Bone exposure along the right mylohyoid ridge (March 23, 2006).



Figure 6. Complete soft-tissue healing (June 25, 2007).



Figure 7. Bone exposure and tissue inflammation of the palatal torus of more than 3 weeks' duration (October 12, 2006).



Figure 8. Absence of tissue inflammation and healing of the palatal gingival tissue (November 20, 2006).

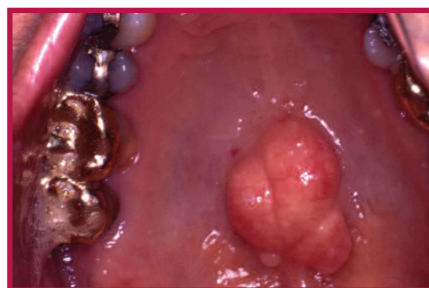


Figure 9. A patient was seen with a 3-mm-diameter inflamed and painful area in the middle of the tissue covering the middle lobe of the torus palatinus (July 17, 2006).

PATIENT NO. 4

A 79-year-old female was referred to our practice on October 12, 2006, for the diagnosis of an ulcerated area on a torus palatinus. Clinical examination revealed a deep ulcer and a 3-mm-diameter bone exposure with surrounding inflammation and mild discomfort of more than 3 weeks' du-ration (Figure 7). She had been prescribed alendronate in 1998 for 6 years, was taken off the drug for 1 year, and had then resumed this medication approximately 18 months before the examination. Her history did not reveal any dental surgical procedures within a 10-year period. The patient was instructed to rinse for 30 seconds with a chlorine dioxide mouthwash 3 to 4 times a day until instructed otherwise. On No-venber 11, 2006, the patient

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reported that she felt “something hard had fallen off” her palate. Clinical examination of her palate on November 13, 2006, revealed epithelialization of the area and no inflammation. An examination one week later revealed a depression in the mucosal tissue without bone exposure (Figure 8). Follow-up on December 18, 2006, revealed additional healing of the affected area.

DISCUSSION

Bisphosphonates are nonmetabolized analogues of pyrophosphate that localize to bone, and are internalized by and ultimately inhibit osteoclast-mediated bone resorption. Bisphosphonate concentrations in bone are maintained for years because they are not metabolized. This fact may help explain why these lesions may occur after these drugs are discontinued, and why the lesions do not resolve after withdrawal of the drug. Bisphosphonates are administered orally to reduce the risk of fractures in women with osteoporosis and osteopenia. They also are used intravenously to treat Paget’s disease of bone, hypercalcemia associated with malignancy, and with antineoplastic agents to treat metastatic bone lesions associated with breast cancer and multiple myeloma.⁴

Bisphosphonates are clinically effective in reducing the morbidity and mortality of various diseases, including some malignancies that affect bone. They therefore improve the quality of life and even extend life for patients so affected. While BON has been reported in more than 1,000 cases worldwide,⁵ the advantages of using these agents far outweigh discouraging their use due to the possibility of BON. By 2006, worldwide more than 190 million prescriptions had been written for oral bisphosphonates,⁶ and by 2005 over 2.8 million cancer patients had received the intra-venous forms of these drugs.⁷ The present strategy is directed toward preventing or minimizing BON.

The reported incidence of bisphosphonate-induced osteonecrosis ranges from 0.8% to 12% in patients receiving the intravenous form⁴ versus about 0.01% for oral bisphosphonate use.⁸ Of the number of reported cases of BON, only 28 were taking oral bisphosphonates (25 alendronate, 3 residronate).⁹ In the case series reported here, patients Nos. 2, 3, and 4 (whose lesions re-

sponded to topical application of a chlorine dioxide-containing mouthwash) had received oral alendronate for osteoporosis. In addition, the diagnosis of BON in patient No. 4 was made even though the area of exposed bone was not observed for 6 to 8 weeks.¹⁰ In this case, treatment could not be postponed to fulfill that requirement.

In addition, a fifth case was seen in our office with clinical symptoms that appeared to be consistent with BON. A 63-year-old female was referred to our practice on July 17, 2006, for diagnosis because of a slightly swollen, painful area of her torus palatinus. Clinical examination revealed a 3-mm-diameter in-flamed area of tissue in the mid-lateral area of the largest lobe of her torus palatinus of one-month duration (Figure 9). The patient was on multiple medications, including zoledronate for approximately one year, bevacizumab (Avastin [Genentech]), and letrozole (Femara [Novartis]) for the treatment of metastatic breast cancer. The patient was advised to use the chlorine dioxide mouthrinse 3 to 4 times per day. On August 2, 2006, clinical examination revealed that neither swelling, inflammation, nor sensitivity of any tissue covering the palatal torus remained. As of this writing the symptoms have not returned.

Maintaining ideal oral health is the simplest approach to prevention of BON. Some treatments for BON beyond the “stage treatment strategies” suggested by the American Association of Oral and Maxillofacial Surgeons¹ include hyperbaric oxygen therapy (HBO),¹¹ long-term antibiotic administration,¹² laser treatment with or without surgery,¹³ bone resection and autologous platelet-derived growth factors,¹⁴ and ozone plus antibiotics plus surgery.¹⁵ Anticipated problems associated with HBO may include stimulation of angiogenesis that may facilitate tumor progression. Long-term antibiotic administration may also create resistant organisms. Antibacterial mouthrinses have been suggested for both preventive and treatment purposes.¹ However, to the best of our knowledge, a phosphate buffer-stabilized 0.1% chlorine dioxide-containing mouthwash formulation has not been proposed as a treatment approach.

Chlorine dioxide has been studied as a decontaminant for water,¹⁶ for the topical treatment of chronic atrophic candidiasis,¹⁷ for the symptomatic treatment of periodontitis,¹⁸ and for the treatment of halitosis.¹⁹⁻²¹ It is reported to be

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bactericidal, fungicidal, and viricidal.²¹ It is also more biocidal and less hazardous to human health than aqueous solutions of chlorine.²¹ In a recent study²² utilizing scanning electron microscopy, the results suggested a role for microbial biofilms in the pathogenesis of BON. **This is very important in attempting to explain the mechanism for the apparent success utilizing a chlorine dioxide-containing mouthwash. In addition, Fosamax has also been implicated in producing an overgrowth of Candida species.**²²

Ingestion of chlorine dioxide by humans has been studied and found to be without observable systemic toxic effects.²³ **When incorporated into an oral rinse formulation, chlorine dioxide demonstrated a substantial reduction in bacterial levels of S. mutans and Lactobacillus,**²¹ **Escherichia coli, Pseudomonas aeruginosa, Yersinia enterocolitica, Klebsiella pneumoniae, Streptococcus pyogenes Group A, Salmonella typhimurium, and Bacillus subtilis.**²⁴ **Stabilized chlorine dioxide mouthwash does not contain alcohol, does not affect taste or cause allergic reactions, does not cause staining of teeth or tissues, and does not cause calculus formation.**²³ **Chlorine dioxide free radical ions do not promote development of resistant species.**²³

Volatile sulfur compounds (VSC) are gases that are a by-product of bacterial putrefaction, and two VSC (hydrogen sulfide and methyl mercaptan [MM]) are considered primarily responsible for halitosis. More importantly, production of MM is associated with periodontal pathogens such as Bacteroides forsythus, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, and Prevotella intermedia.²⁵ Fibroblasts exposed to MM demonstrate aberrations in collagen metabolism.²⁶ MM can also increase the permeability of intact mucosal and gingival tissues, and thereby ultimately play a role in the pathogenesis of periodontal disease. MM is reported to act synergistically with LPS (lipo-polysaccharide) and IL-1 β to increase secretion of prostaglandin E2 and collagenase, both mediators of tissue destruction and inflammation.²⁷ It can

be proposed that production of VSC such as MM may play a role in the pathogenesis of BON; however, additional investigation is required to test this possibility.

None of the patients reported here had removable dental appliances, and BON lesions appeared spontaneously for patient Nos. 2 to 4. There was no history of recent oral surgery, tissue trauma, inflammatory pulpal or periodontal disease, diabetes, or glucocorticoid therapy. This would seem to refute a recent suggestion that BON may result from a direct toxic effect of high concentrations of bisphosphonate accumulation in bone on the healing of overlying oral epithelium subsequent to oral trauma.²⁸ Also, the significance of sequestration of necrotic bone (or surgical removal of a sequestrum) that was reported for patient Nos. 2 to 4 would seem to imply that these most probably were cases of BON versus traumatically induced lesions.²⁹

All patients were instructed to continuously use the phosphate buffer-stabilized 0.1% chlorine dioxide-containing mouthwash, and to date none have had a recurrence or occurrence of new BON. Additionally, it should be noted that the authors' private dental practice attends to about 1,800 patient visits a year. It is primarily a general-restorative dental practice with minor surgical procedures (ie, biopsies, occasional uncomplicated extractions). The significance is the total number of patients with BON (4 to 5), which is a relatively rare disease but perhaps one whose incidence is increasing.

CONCLUSION

We have presented one case of BON in a patient who was administered intravenous bisphosphonates for cancer therapy, and 3 cases of BON in patients who were using, or had previously used, the oral form of bisphosphonates. The latter were successfully treated with the use of a phosphate buffer-stabilized **0.1% chlorine dioxide-containing mouthwash.** Additional clinical research must be conducted to verify these treatment observations.

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POST EXAMINATION QUESTIONS

1. **Bisphosphonate-associated osteonecrosis (BON) can _____.**
 - a. be initiated by dental extractions
 - b. be initiated by dental infection
 - c. arise spontaneously
 - d. all of the above
2. **Intravenously administered bisphosphonates include _____.**
 - a. alendronate
 - b. residronate
 - c. zoledronate
 - d. all of the above
3. **Orally administered bisphosphonates primarily treat _____.**
 - a. Paget's disease of bone
 - b. multiple myeloma
 - c. osteoporosis
 - d. all of the above
4. **Which of the following is NOT true about bisphosphonates?**
 - a. They are rapidly metabolized.
 - b. They inhibit osteoclast-mediated bone resorption.
 - c. They are localized to bone.
 - d. Their concentration in bone is maintained for years.
5. **Until further research validates effective therapy for BON, the most effective approach at this time seems to be _____.**
 - a. long-term antibiotic therapy
 - b. maintaining ideal oral hygiene
 - c. surgical resection
 - d. withdrawing the bisphosphonate therapy
6. **Chlorine dioxide is _____.**
 - a. bacteriocidal
 - b. fungicidal
 - c. viricidal
 - d. all of the above
7. **Volatile sulfur compounds _____.**
 - a. are considered primarily responsible for halitosis
 - b. arise from the stomach and small intestine
 - c. do not cause halitosis
 - d. all of the above
8. **Stabilized chlorine dioxide mouthwash _____.**
 - a. causes calculus formation
 - b. does not promote development of resistant bacterial species
 - c. contains alcohol
 - d. stains teeth

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