



AAE POSITION STATEMENT

The following statement was prepared by the AAE Special Committee on Bisphosphonates. AAE members may photocopy this position statement for distribution to patients or referring dentists.

ENDODONTIC IMPLICATIONS OF BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAWS

Introduction

Bisphosphonates are an important class of drugs that have widespread use in managing osteoporosis and treating certain cancers. A recently recognized adverse effect, bisphosphonate-associated osteonecrosis of the jaws (ONJ), has important medical and dental implications. The American Association of Endodontists offers this Position Statement to help make our members aware of these implications. It is, of course, up to the individual endodontist to determine what course of treatment to undertake with respect to any given patient.

Bisphosphonates

Bisphosphonates are commonly used to treat certain resorptive bone diseases such as osteoporosis, Paget's disease and hypercalcemia associated with certain malignancies such as multiple myeloma and bone metastasis from the breast or prostate (Lipton 2003; Licata 2005; Lipton 2005). Bisphosphonates inhibit bone resorption by inhibiting osteoclast activity (Lindsay and Cosman 2001), although other actions such as inhibition of angiogenesis have also been reported (Wood et al. 2002; Santini et al. 2003; Vincenzi et al. 2005).

Bisphosphonate-Associated Osteonecrosis of the Jaws

There is growing recognition that bisphosphonates may be associated with a rare adverse event called osteonecrosis of the jaws (ONJ). Several case reports, letters to the editor, reviews and position statements from the U.S. FDA and interested pharmaceutical companies have been published on bisphosphonate-associated ONJ (Carter and Goss 2003; Marx 2003; Migliorati 2003; Hellstein and Marek 2004; Ruggiero and Mehrotra 2004; Carter et al. 2005; Cheng et al. 2005; Durie et al. 2005; Katz 2005; Markiewicz et al. 2005; Marx et al. 2005; Melo and Obeid 2005; Melo and Obeid 2005; Migliorati 2005; Migliorati et al. 2005; Migliorati et al. 2005; Novartis Pharmaceuticals Corporation 2005; Purcell and Boyd 2005; Sarathy et al. 2005; Woollorton 2005; Zarychanski et al. 2006). Because there currently are no available randomized controlled trials or higher levels of clinical evidence, the following information is presented based on retrospective analysis of case reports and expert opinions.

Patients presenting with bisphosphonate-associated ONJ typically present with at least some of the following signs and symptoms:

- An irregular mucosal ulceration with exposed bone in the mandible or maxilla
- Pain or swelling in the affected jaw
- Infection, possibly with purulence
- Altered sensation (e.g., numbness or heavy sensation).

Additional important issues related to bisphosphonate-associated ONJ include:

- The site of occurrence of the osteonecrosis is the jaws, and presentation occurs more frequently in the mandible than in the maxilla. The reasons for the presentation of osteonecrosis in the jaws versus other parts of the skeleton are unknown at this time.

- The mechanism for bisphosphonate-associated ONJ is unknown.
- The treatment for bisphosphonate-associated ONJ is problematic. Case reports document no response or a limited response to local surgical wound debridement, marginal or segmental resection, antibiotics and hyperbaric oxygen. Therefore, recognition of risk factors and application of preventive dental treatment procedures are important for patients taking I.V. or oral bisphosphonates.

Common risk factors associated with the development of bisphosphonate-associated ONJ include:

- History of taking bisphosphonates, especially I.V. formulations. The concurrent use of steroids appears to contribute to this risk.
- Previous history of cancer (e.g., multiple myeloma or metastatic disease to bone), osteoporosis, Paget's disease or other indications for bisphosphonate treatment.
- A history of a traumatic dental procedure. Most case reports occur after a tooth extraction, although other traumatic dental procedures may also be associated with the occurrence of ONJ. One case report describes bisphosphonate-associated ONJ occurring 6 months after placement of five dental implants with the subsequent loss of all implants (Starck and Epker 1995).
- Several reports indicate the spontaneous development of bisphosphonate-associated ONJ without a prior traumatic dental procedure.

A question exists as to whether bisphosphonate-associated ONJ is a drug effect (i.e., observed with only a few bisphosphonates) or a class effect (i.e., may occur with all bisphosphonates with the incidence varying according to potency or other factors). To date, the majority of reports have described ONJ occurring in patients taking I.V. bisphosphonates (e.g., zoledronate [Zometa®], or pamidronate [Aredia®]). However, in several publications, oral bisphosphonates have been associated with the development of ONJ (Starck and Epker 1995; Carter and Goss 2003; Marx 2003; Chang 2004; Ruggiero and Mehrotra 2004; Migliorati et al. 2005; Purcell and Boyd 2005). In addition, a recent FDA ODS Postmarketing Safety Review stated that bisphosphonate-associated ONJ "may be a class effect" (Chang 2004). Recently revised product packages for oral bisphosphonate medications (e.g., alendronate [Fosamax®] and risedronate [Actonel®]) now describe a risk for bisphosphonate-associated ONJ (Merck 2005; P&G 2005).

Therefore, until further information is available, it would appear prudent to consider all patients taking bisphosphonates to be at some risk for ONJ, with the recognition that the magnitude of the risk probably varies depending upon the particular bisphosphonate taken, patient factors (e.g., concurrent drugs, diseases, etc.), and dental treatment history. The information at this time suggest that patients taking I.V. bisphosphonates have a higher risk for developing ONJ, while patients taking oral bisphosphonates have a lower risk.

Examples of commercially available bisphosphonates include:

Subclass of Bisphosphonate	Generic Name	Trade Name	Route of Administration
Aminobisphosphonate	Zoledronate	Zometa®	I.V.
Aminobisphosphonate	Pamidronate	Aredia®	Oral and I.V.
Aminobisphosphonate	Alendronate	Fosamax®	Oral
Aminobisphosphonate	Ibandronate	Boniva®	Oral and I.V.
Aminobisphosphonate	Risedronate	Actonel®	Oral
Nonaminobisphosphonate	Tiludronate	Skelid®	Oral
Nonaminobisphosphonate	Clodronate	Bonefos®, Ostac®	Oral
Nonaminobisphosphonate	Etidronate	DidroneI®	Oral

Recommendations

The following is recommended when considering the endodontic implications of treating patients taking bisphosphonates:

- Recognize the risk factors of bisphosphonate-associated ONJ.
- Patients at higher risk for bisphosphonate-associated ONJ include those patients taking I.V. bisphosphonates. Preventive procedures for high risk patients are important to reduce the risk of developing ONJ because treatment of ONJ is not predictable at this time. Preventive care might include caries control, conservative periodontal and restorative treatments, and, if necessary, appropriate endodontic treatment. Similar to the management of the patient with osteoradionecrosis, this might include nonsurgical endodontic treatment of teeth that otherwise would be extracted. Teeth with extensive carious lesions might be treated by nonsurgical endodontic therapy possibly followed by crown resection and restoration similar to preparing an overdenture abutment. For patients at higher risk of developing bisphosphonate-associated ONJ, surgical procedures such as tooth extractions, endodontic surgical procedures or placement of dental implants should be avoided if possible.
- Patients at low risk for bisphosphonate-associated ONJ include those patients taking oral bisphosphonates. Appropriate clinical procedures might include intraoral examination, indicated dental procedures (e.g., regular checkups, caries control, appropriate periodontal and restorative treatments), and patient education about the symptoms of bisphosphonate-associated osteonecrosis of the jaws and their low risk for developing ONJ from surgical or soft tissue procedures.
- As usual, informed consent for endodontic procedures should involve a discussion of risks, benefits and alternative treatments with the patient.
- Consider bisphosphonate-associated ONJ when developing a differential diagnosis of nonodontogenic pain.
- Utilize the entire health care team, including the patient's general dentist, oncologist and oral surgeon, when developing treatment plans for these patients.
- Cases of bisphosphonate-associated osteonecrosis of the jaws should be reported to the U.S. FDA MedWatch Online at: <https://www.accessdata.fda.gov/scripts/medwatch/>. Additional background information on how to report adverse effects of drugs can be found at: www.fda.gov/opacom/backgrounders/problem.html.
- Be aware that the knowledge base for bisphosphonate-associated ONJ is rapidly increasing, and it is likely that these recommendations may change over time. Thus, the practitioner is encouraged to monitor developments in this area.

References

- Carter, G., A. N. Goss and C. Doecke (2005). "Bisphosphonates and avascular necrosis of the jaw: a possible association." *Med J Aust* **182**(8): 413-5.
- Carter, G. D. and A. N. Goss (2003). "Bisphosphonates and avascular necrosis of the jaws." *Aust Dent J* **48**(4): 268.
- Chang, J. S. (2004). "ODS Postmarketing Safety Review." *Department of Health and Human Services, Public Health Service, Food and Drug Administration* Retrieved Jan 4, 2006, from: www.fda.gov/ohrtms/dockets/ac/05/briefing/2005-4095B2_03_04-FDA-TAB3.pdf.
- Cheng, A., A. Mavrokokki, G. Carter, B. Stein, N. Fazzalari, D. Wislon and A. N. Goss (2005). "The dental implications of bisphosphonates and bone disease." *2005 50 Suppl*: S4-13.
- Durie, B. G., M. Katz and J. Crowley (2005). "Osteonecrosis of the jaw and bisphosphonates." *N Engl J Med* **353**(1): 99-102; discussion 99-102.
- Hellstein, J. W. and C. L. Marek (2004). "Bis-phossy jaw, phossy jaw, and the 21st century: bisphosphonate-associated complications of the jaws." *J Oral Maxillofac Surg* **62**(12): 1563-5.
- Katz, H. (2005). "Endodontic implications of bisphosphonate-associated osteonecrosis of the jaws: a report of three cases." *J Endod* **31**(11): 831-4.
- Licata, A. A. (2005). "Discovery, clinical development, and therapeutic uses of bisphosphonates." *Ann Pharmacother* **39**(4): 668-77.
- Lindsay, R. and F. Cosman (2001). Osteoporosis. *Harrison's Principles of Internal Medicine*. E. Braunwald, A. Facui, D. Kasperet al. New York, McGraw-Hill: 2226-37.

- Lipton, A. (2003). "Bisphosphonate therapy in the oncology setting." *Expert Opin Emerg Drugs* **8**(2): 469-88.
- Lipton, A. (2005). "New therapeutic agents for the treatment of bone diseases." *Expert Opin Biol Ther* **5**(6): 817-32.
- Markiewicz, M. R., J. E. Margarone, 3rd, J. H. Campbell and A. Aguirre (2005). "Bisphosphonate-associated osteonecrosis of the jaws: a review of current knowledge." *J Am Dent Assoc* **136**(12): 1669-74.
- Marx, R. E. (2003). "Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic." *J Oral Maxillofac Surg* **61**(9): 1115-7.
- Marx, R. E., Y. Sawatari, M. Fortin and V. Broumand (2005). "Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment." *J Oral Maxillofac Surg* **63**(11): 1567-75.
- Melo, M. D. and G. Obeid (2005). "Osteonecrosis of the jaws in patients with a history of receiving bisphosphonate therapy: strategies for prevention and early recognition." *J Am Dent Assoc* **136**(12): 1675-81.
- Melo, M. D. and G. Obeid (2005). "Osteonecrosis of the maxilla in a patient with a history of bisphosphonate therapy." *J Can Dent Assoc* **71**(2): 111-3.
- Merck (2005) "Merck Product Description of Fosamax." Retrieved Jan 4, 2006, from: www.fosamax.com/fosamax/shared/documents/english/pi.pdf.
- Migliorati, C.A. (2003). "Bisphosphonates and oral cavity avascular bone necrosis." *J Clin Oncol* **21**(22): 4253-4.
- Migliorati, C.A. (2005). "Bisphosphonate-associated oral osteonecrosis." *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **99**(2): 135.
- Migliorati, C.A., J. Casiglia, J. Epstein, P.L. Jacobsen, M.A. Siegel and S. B. Woo (2005). "Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper." *J Am Dent Assoc* **136**(12): 1658-68.
- Migliorati, C.A., M. M. Schubert, D. E. Peterson and L. M. Seneda (2005). "Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy." *Cancer* **104**(1): 83-93.
- Novartis Pharmaceuticals Corporation. Appendix 11: Expert Panel Recommendations for the Prevention, Diagnosis and Treatment of Osteonecrosis of the Jaw. March 4, 2005, Retrieved Jan 25, 2006, from: www.fda.gov/obrms/dockets/ac/05/briefing/2005-4095B2_02_12-Novartis-Zometa-App-11.pdf.
- P&G (2005) "Procter and Gamble. Actonel Product Information Sheet." Retrieved Jan 6, 2006, from: www.actonel.com/global/prescribingInfo.jsp
- Purcell, P. M. and I. W. Boyd (2005). "Bisphosphonates and osteonecrosis of the jaw." *Med J Aust* **182**(8): 417-8.
- Ruggiero, S. L. and B. Mehrotra (2004). "Ten years of alendronate treatment for osteoporosis in postmenopausal women." *N Engl J Med* **351**(2): 190-2; author reply 190-2.
- Santini, D., B. Vincenzi, G. Dicuonzo, G. Avvisati, C. Masscesi, F. Battistoni, M. Gavasci, L. Rocci, M. C. Tirindelli, V. Altomare, M. Tocchini, M. Bonsignori and G. Tonini (2003). "Zoledronic acid induces significant and long-lasting modifications of circulating angiogenic factors in cancer patients." *Clin Cancer Res* **9**(8): 2893-7.
- Sarathy, A. P., S. L. Bourgeois, Jr. and G. G. Goodell (2005). "Bisphosphonate-associated osteonecrosis of the jaws and endodontic treatment: two case reports." *J Endod* **31**(10): 759-63.
- Starck, W. J. and B. N. Epker (1995). "Failure of osseointegrated dental implants after diphosphonate therapy for osteoporosis: a case report." *Int J Oral Maxillofac Implants* **10**(1): 74-8.
- Vincenzi, B., D. Santini, G. Dicuonzo, F. Battistoni, M. Gavasci, A. La Cesa, C. Grilli, V. Virzi, S. Gasparro, L. Rocci and G. Tonini (2005). "Zoledronic acid-related angiogenesis modifications and survival in advanced breast cancer patients." *J Interferon Cytokine Res* **25**(3): 144-51.
- Wood, J., K. Bonjean, S. Ruetz, A. Bellahcene, L. Devy, J. M. Foidart, V. Castronovo and J. R. Green (2002). "Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid." *J Pharmacol Exp Ther* **302**(3): 1055-61.
- Wooltorton, E. (2005). "Patients receiving intravenous bisphosphonates should avoid invasive dental procedures." *Cmaj* **172**(13): 1684.
- Zarychanski, R., E. Elphee, P. Walton and J. Johnston (2006). "Osteonecrosis of the jaw associated with pamidronate therapy." *Am J Hematol* **81**(1): 73-5.