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Endodontic Implications of Bisphosphonate-Associated Osteonecrosis of the Jaws

AAE Position Statement

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 revised 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 (Edwards 2008; Ruggiero 2009; Junquera 2009; Rustemeyer 2010; Solomon 2009). 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 or

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 (e.g., implant placement) and ill-fitting dentures have also been associated with the occurrence of ONJ.

- Indications in several reports that there is spontaneous development of bisphosphonate-associated ONJ without a prior traumatic dental procedure.

In addition to the usual risk factors, patients receiving high dose I.V. bisphosphonates for greater than two years are most at risk for developing osteonecrosis of the jaw. The estimated risk ranges from 0.8% to 20% in these patients (Ruggerio 2009). The higher the bisphosphonate dose and the longer the exposure time, the more likely that osteonecrosis will develop. The more potent nitrogen-containing bisphosphonates are more likely to be associated with osteonecrosis. Because the oral bisphosphonates are very poorly absorbed (less than 1%), they are less likely overall to cause osteonecrosis (Licata 2005).

Until further information is available, it would appear prudent to consider all patients taking bisphosphonates to be at some risk for ONJ. We should recognize that the magnitude of the risk probably varies depending upon the particular bisphosphonate taken, its duration of use, patient factors (e.g., concurrent drugs, diseases, etc.), and dental treatment history.

Examples of commercially available bisphosphonates include:

Generic Name	Trade Name	Nitrogen Containing	Route of Administration	Relative Potency	Common Use
Alendronate	Fosamax®	Yes	Oral	700	Osteoporosis
Clodronate	Bonefos® Clasteon®	No	Oral	10	Hypercalcemia of malignancy
Etidronate	Didronel®	No	Oral and I.V.	1	Padgett's disease
Ibandronate	Boniva®	Yes	Oral and I.V.	4,000	Osteoporosis
Pamidronate	Aredia®	Yes	Oral and I.V.	325	Cancer
Risedronate	Actonel®	Yes	Oral	2,000	Osteoporosis
Tiludronate	Skelid®	No	Oral	10	Hypercalcemia of malignancy
Zoledronate	Zometa®	Yes	I.V.	700	Cancer
Zoledronate	Reclast®	Yes	I.V. (once per year)	700	Osteoporosis

Recommendations

Consensus guidelines promote careful and complete oral care for all patients receiving bisphosphonates as the cornerstone of osteonecrosis prevention and treatment. The following is recommended when considering the endodontic implications of treating patients taking bisphosphonates:

- Know the risk factors of bisphosphonate-associated ONJ.
- Recognize that patients taking I.V. bisphosphonates are at higher risk for developing bisphosphonate-associated ONJ. 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, management of high risk patients 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. Surgical procedures such as tooth extractions, endodontic surgical procedures or placement of dental implants should be avoided if possible.
- Recognize that patients taking oral bisphosphonates are at low risk for developing bisphosphonate-associated ONJ. 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.
- Obtain, as usual, informed consent for endodontic procedures that 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.
- Report cases of bisphosphonate-associated osteonecrosis of the jaws 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

- Edwards BJ, Gounder M, McKoy JM, et al. Pharmacovigilance and reporting oversight in U.S. FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. *Lancet Oncol* 2008; 9:1166-72.
- Junquera L, Gallefo L, et al. Clinical experiences with bisphosphonate-associated osteonecrosis of the jaws: analysis of 21 cases. *Am J Otolaryngol* 2009; 30:390-5.
- Lee CY, Suzuki JB. CTX biochemical marker of bone metabolism. Is it a reliable predictor of bisphosphonate-associated osteonecrosis of the jaws after surgery? Part II: a prospective clinical study. *Implant Dent* 2010; 19:29-38.
- Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005; 39:668-77.
- Lindsay R, Cosman F. Osteoporosis. In: Brauwald E, Facui A, Kasper D, et al., eds. *Harrison's Principles of Internal Medicine* 15th ed. New York: McGraw-Hill, 2001:2226-37.
- Lipton A. Bisphosphonate therapy in the oncology setting. *Expert Opin Emerg Drugs* 2003; 8:469-88.
- Lipton A. New therapeutic agents for the treatment of bone diseases. *Expert Opin Biol Ther* 2005; 5:817-32.
- 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* 2007; 65:2397-410.
- Ruggiero SL, Mehrota B. Bisphosphonate-related osteonecrosis of the jaw: diagnosis, prevention, and management. *Annu Rev Med* 2009; 60:85-96.
- Ruggiero SL, Dodson TB, Assael LA, et al. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw—2009 Update. Retrieved January 30, 2010 from: http://www.aaoms.org/doc/position_paper/bronj_update.pdf.
- Rustemeyer J, Bremerich A. Bisphosphonate-associated osteonecrosis of the jaw: what do we currently know? A survey of knowledge given in the recent literature. *Clin Oral Investig* 2010; 14:59-64.
- Santini D, Vincenzi B, Dicuonzo G, Avvisati G, Massacesi C, Battistoni F, Gavasci M, Rocci L, Tririndelli MC, Altomare V, Tocchini M, Bonsignori M, Tonini G. Zoledronic acid induces significant and long-lasting modifications of circulating angiogenic factors in cancer patients. *Clin Cancer Res* 2003; 9:2893-7.
- Solomon DH, Rekedal L, Cadarette SM. Osteoporosis treatments and adverse events. *Curr Opin Rheumatol* 2009; 21:363-8.
- Takagi Y, Sumi Y, Harada A. *J Prosthet Dent* 2009; 101:289-92.
- Thumbigere-Math V, Sabino MC, Gopalakrishnan R, et al. Bisphosphonate-related osteonecrosis of the jaw: clinical features, risk factors, management, and treatment outcomes of 26 patients. *J Oral Maxillofac Surg* 2009; 67:1904-13.
- Vincenzi B, Santini D, Dicuonzo G, Battistoni F, Gavasci M, La Cesa A, Grilli C, Virzi V, Gasparro S, Rocci L, Tonini G. Zoledronic acid-related angiogenesis modifications and survival in advanced breast cancer patients. *J Interferon Cytokine Res* 2005; 25:144-51.
- Walters C, Al-Nawas B, duBois A, et al. Incidence of bisphosphonate-associated osteonecrosis of the jaws in breast cancer patients. *Cancer* 2009; 115:1631-7.
- Wood J, Bonjean K, Ruetz S, Bellahcene A, Devy L, Foidart JM, Castronovo V, Green JR. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther* 2002; 302:1055-61.
- Zahrowski JJ. Optimizing orthodontic treatment in patients taking bisphosphonates for osteoporosis. *Am J Orthod Dentofacial Orthop* 2009; 135:361-74.