

Bisphosphonates and Jaw Bone Damage

What is osteonecrosis of the jaw?

Osteonecrosis of the jaw (jaw bone damage) is a rare condition that occurs when the bone is injured and dies. It happens when bones don't heal properly after certain dental procedures, such as having a tooth pulled. Patients who have osteonecrosis of the jaw may have severe pain and swelling in the jaw and loose teeth. Recently in the news there have been reports of jaw bone damage in patients taking medications called bisphosphonates. Bisphosphonates are a widely used class of medications that help make bones strong and less likely to break. Bisphosphonate pills or capsules are commonly used for the prevention or treatment of osteoporosis. There are also some bisphosphonates given intravenously (through the vein) to prevent bone complications related to certain types of cancers. There are six oral bisphosphonates and four intravenous bisphosphonates available:

Oral (by mouth)

- *Actonel* (risedronate)
- *Bonefos, Ostac, Clasteon* (clodronate) (Canada only)
- *Boniva* (ibandronate) (U.S. only)
- *Didronel* (etidronate)
- *Fosamax* (alendronate)
- *Skelid* (tiludronate) (U.S. only)

Intravenous

- *Aredia* (pamidronate)
- *Bonefos, Ostac, Clasteon* (clodronate) (Canada only)
- *Boniva* (ibandronate) (U.S. only)
- *Zometa* (zoledronic acid)

Should I be worried if I'm taking a bisphosphonate?

In general, osteonecrosis of the jaw is a RARE condition. The chances of developing jaw bone damage from using any bisphosphonate is very small. Of the millions of people who have used bisphosphonates over the years, only 368 cases of jaw damage have been reported as of May 2006. Of those cases, the majority are in cancer patients using the intravenous form of a bisphosphonate (e.g., *Zometa* or *Aredia*). Your risk could increase, however, if you have certain dental procedures such as having a tooth pulled. Even though your chances of developing osteonecrosis of the jaw are rare, it is a good idea to tell your dentist if you are taking a bisphosphonate.

What is the best way to prevent osteonecrosis of the jaw?

The best way to prevent jaw osteonecrosis is to take good care of your teeth. It is important to brush and floss your teeth at least once a day to keep your teeth and gums healthy. Also, be sure to visit your dentist regularly for routine dental exams and cleaning. If you are not currently taking a bisphosphonate, but will be starting one soon, be sure to tell your dentist NOW. They may want to take care of necessary dental work before you start taking your bisphosphonate.

Should I continue taking my bisphosphonate?

Yes. Bisphosphonates are very safe drugs that have been used by millions of people. Bisphosphonates can help make your bones stronger and prevent them from breaking. Your chances of developing jaw bone damage are very small, while the overall benefits of using a bisphosphonate are large. Be sure to take good care of your teeth and have routine dental exams and cleaning to prevent the need for dental procedures. If you're concerned about taking a bisphosphonate, talk with your physician about what would be best for you. Don't stop taking your bisphosphonate on your own.

Bisphosphonate-associated Jaw Osteonecrosis

Background

Jaw osteonecrosis associated with bisphosphonates is getting a lot of press recently as lawyers are advertising to recruit potential plaintiffs to file class action law suits against Merck, the maker of *Fosamax*. Due to the heightened awareness, the American Dental Association (ADA) Council of Scientific Affairs recently developed a set of recommendations on how to manage patients who are on oral bisphosphonate therapy. The recommendations are available online at http://www.ada.org/prof/resources/topics/topics_osteonecrosis_recommendations.pdf and will be published in the August issue of *The Journal of the American Dental Association*. The recommendations will be updated as new information becomes available. Dentists are encouraged to check <http://www.ada.org/prof/resources/topics/osteonecrosis.asp> before treating patients on oral bisphosphonates. Information on jaw osteonecrosis associated with intravenous bisphosphonates is also available at the above web link.

Bisphosphonates and Jaw Osteonecrosis

Bisphosphonates are frequently used for prevention and treatment of osteoporosis. They are also helpful in treating Paget's disease of bone, hypercalcemia associated with malignancy, and osteolytic lesions associated with metastatic bone disease and multiple myeloma. These bone resorption inhibitors increase bone density by binding to the bone matrix and slowing down osteoclastic (bone breakdown) activity, thereby facilitating osteoblastic (bone building) effectiveness.¹⁻⁷ The bisphosphonate group of drugs includes: alendronate (*Fosamax*), etidronate (*Didronel*), ibandronate (*Boniva*), pamidronate (*Aredia*), risedronate (*Actonel*), tiludronate (*Skelid*), and zoledronic acid (*Zometa*) in the U.S. In Canada, alendronate (*Fosamax*), clodronate (*Bonefos*, *Clasteon*, *Ostac*), etidronate (*Didronel*), pamidronate (*Aredia*), risedronate

(*Actonel*), and zoledronic acid (*Zometa*) are available.⁴

Boniva, *Bonefos* (or *Clasteon*, *Ostac*), *Aredia*, and *Zometa* are currently available in intravenous dosage forms.⁴

In 2003 and 2004, there were several reports of osteonecrosis of the jaw (ONJ) in cancer patients receiving chronic intravenous bisphosphonates.⁸⁻¹⁰ The reports associated pamidronate (*Aredia*) and zoledronic acid (*Zometa*) with ONJ. Both products are produced by Novartis Pharmaceuticals Corporation and used for treating hypercalcemia of malignancy, multiple myeloma, and metastatic bone disease. As a result, product labeling was updated in the U.S. in August 2004 and in Canada in December 2004 to include precautions about ONJ.¹¹⁻¹³ In addition, a Dear Healthcare Professional Letter warning of the risk of ONJ associated with *Aredia* or *Zometa* use was issued by the FDA and Novartis in May 2005.¹⁴

More recently, cases of ONJ have also been reported in patients taking oral bisphosphonates.¹⁵ As of early 2006, the approximate number of ONJ cases associated with individual oral bisphosphonates world wide are as follows: 170 cases with alendronate, 20 cases with risedronate, and one case with ibandronate.¹⁵ All three of these oral bisphosphonates carry warnings of ONJ in their package inserts. The risk for ONJ associated with alendronate (the most used bisphosphonate) is estimated at 0.7 cases per 100,000 person-years exposure.¹⁵ Oral bisphosphonates have not been reported to have the same degree of association with ONJ as the intravenous products. To date, the true cause-and-effect relationship between bisphosphates and ONJ has not been established.¹⁵

Osteonecrosis of the Jaw

Osteonecrosis, also called avascular necrosis of the bone or osteochondritis dissecans, is the death of bone resulting in the collapse of the bone's structural architecture. It leads to bone pain, loss of bone function, and bone destruction.

More . . .

It is the result of a number of conditions leading to an impairment of the blood supply to the bone.¹⁶

Possible risk factors for ONJ include concomitant use of estrogen or glucocorticoids, being >65 years of age, and prolonged use of bisphosphonates.¹⁵ In cancer patients receiving IV bisphosphonate therapy, the median time from starting therapy to developing ONJ was 25 months.¹⁵ The most common dental comorbidity in these patients is clinically and radiographically apparent periodontitis.¹⁵ Osteonecrosis is a well documented complication of anticancer treatment. Jaw bone is particularly vulnerable to osteonecrosis because of tooth and gum susceptibility to infection. Special added risk factors for ONJ are trauma, as from dental procedures, and local anesthetics.¹⁷

In normal bone homeostasis, osteoclastic (bone breakdown) and osteoblastic (bone building) activities work together to facilitate bone metabolism and repair damages in bones. Prolonged use of bisphosphonates may suppress bone turnover to the point where the normal bone healing activity is impaired.⁶ In addition, bisphosphonates may present a unique role in the initiation of ONJ because of their novel antiangiogenic effects.⁶ Wood et al identified that zoledronic acid has marked antiangiogenic properties, which could enhance its efficacy in treatment of malignant bone disease.¹⁸ At the same time this property may increase the risk of ONJ. In addition, because bisphosphonates are not metabolized, they remain in bone tissue for long periods of time.^{8,15} Based on the information available, the risk of ONJ is much higher for cancer patients on IV bisphosphonate therapy than the risk for patients on oral bisphosphonate therapy.¹⁵ The bone antiresorptive potency of the bisphosphonate may play an important role in the risk for ONJ. Less than 1% of the dose of a bisphosphonate taken orally is absorbed by the gastrointestinal tract, whereas over 50% of the dose of a bisphosphonate administered intravenously is bioavailable for incorporation into the bone matrix.¹⁵ This may account for the higher number of cases of ONJ in patients taking the IV formulation.¹⁵

Commentary

The majority of cases with osteonecrotic jaw lesions occurred after a dental extraction; yet some occurred spontaneously.^{7-9,14} A recent

systematic review cited that about 60% of ONJ cases occur after dentoalveolar surgery (e.g., tooth extraction) to treat infections and the remaining 40% are probably related to infection, denture trauma, or other physical trauma.²⁰ Because of this association with dental procedures, potential preventative measures are suggested prior to or as soon as possible (within 3 months) after bisphosphonate initiation.^{6,15,20}

Preventative measures include:^{15,19,20}

- Avoiding any elective jaw procedure
- Baseline and routine dental exams including panoramic jaw radiography
- Delaying bisphosphonate therapy, if risk factors allow, to complete dental procedures for teeth or dental structures with poor prognosis (e.g. treat active oral infections, eliminate sites at high risk for infection)
- Educating patients about the importance of good oral hygiene, symptom reporting, and regularly scheduled dental assessments

Patients already receiving bisphosphonates should:^{15,19,20}

- Maintain excellent oral hygiene and have routine dental examinations
- Obtain routine dental cleanings where careful attention is given to avoiding soft-tissue injury
- Seek conservative alternatives to surgical procedures
- Have root canal treatment if needed rather than dental extraction when possible
- In cases where the medullary bone and/or periosteum is going to be involved, treat one sextant or tooth first if possible and allow for a two month disease-free follow-up covering with antimicrobials, before other sextants are treated with similar therapy
- If no adverse events emerge from the first sextant after two months (or longer if the area remains inflamed, irritated, or erythematous), treatment may accelerate to a more normal multi-sextant treatment and follow-up schedule

In most cases, the benefits of bisphosphonate therapy outweigh the risks. Holding bisphosphonates prior to dental procedures is not likely beneficial due to their long half-lives.^{6,20} The estimated half-life for alendronate is up to 12 years in the bone.²⁰ Patients should be instructed

More . . .

to inform their dentist if they are being treated with a bisphosphonate. Reassure patients that the risk of ONJ associated with oral bisphosphonates is low.¹⁵ Patients with osteonecrosis or suspected osteonecrosis should receive immediate attention from an oral surgeon or dental oncologist.¹⁹

Healthcare professionals are encouraged to report suspected problems associated with bisphosphonates. To report adverse events in the U.S., call the FDA MEDWATCH program at 1-800-FDA-1088. The MEDWATCH program is also available on-line at www.fda.gov/medwatch. In Canada, call the Canadian Adverse Drug Reaction Monitoring Program at 1-866-234-2345. The Canadian adverse reaction reporting form can be found at: http://www.hc-sc.gc.ca/dhp-mpps/medeff/report-declaration/form/index_e.html. It should be completed and faxed to 1-866-678-6789.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Project Leader in preparation of this Detail-Document: Joseph A. Woelfel, Ph.D., FASCP, R.Ph., Wan-Chih Tom, Pharm.D.

References

- Robinson NA, Yeo JF. Bisphosphonates – a word of caution. *Ann Acad Med Singapore* 2004;33:48-9.
- Bisphosphonates and ocular side effects. *Pharmacist's Letter/Prescriber's Letter* 2003;19(5):190515.
- Alendronate (Fosamax) vs. risedronate (Actonel): comparison of upper gastrointestinal side effects. *Pharmacist's Letter/Prescriber's Letter* 2003;19(8):190809.
- Hochadel MA (ed). *Clinical Pharmacology* 2005. Gold Standard Multimedia Inc., Tampa, FL. <http://www.clinicalpharmacology.com>. (Accessed April 14, 2005).
- Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005;165:346-7.
- Migliorati CA, Casiglia J, Epstein J, et al. Managing the care of patients with bisphosphonate-associated osteonecrosis: a American Academy of Oral Medicine position paper. *J Am Dent Assoc* 2005;136:1658-68.
- Bone, muscle, and joint problems with bisphosphonates. *Pharmacist's Letter/Prescriber's Letter* 2005;21(4):210403.
- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-7.
- Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003;21:4253-4.
- 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;62:527-34.
- Product information for Aredia (pamidronate disodium) injection. Novartis Pharmaceuticals Corporation. East Hanover, NJ 07936. August 2004.
- Product information for Zometa (zoledronic acid) injection. Novartis Pharmaceuticals Corporation. East Hanover, NJ 07936. August 2004.
- Health Canada. Public Advisory. Updated safety information on Aredia (pamidronate disodium) and/or Zometa (zoledronic acid). November 5, 2004. http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/aredia_zometa_pa_e.html. (Accessed April 17, 2005).
- Hohneker JA, Bess AL. Important drug precaution for dental health professionals with patients being treated for cancer. May 5, 2005. http://www.fda.gov/medwatch/safety/2005/zometa_deardentite_5-5-05.pdf. (Accessed June 7, 2006).
- Edwards BJ, Hellstein JW, Jacobsen PL, et al. Expert panel recommendations: dental management of patients on oral bisphosphonate therapy. Report of the council on scientific affairs. American Dental Association. June 2006.
- Assouline-Dayana Y, Chang C, Greenspan A, et al. Pathogenesis and natural history of osteonecrosis. *Semin Arthritis Rheum* 2002;32:94-124.
- Anon. Osteonecrosis in cancer patients. Appendix 2. Oncologic Drug Advisory Committee Meeting. Novartis Pharmaceuticals Corporation. East Hanover, NJ 07936. March 4, 2005.
- Wood J, Bonjean K, Ruetz S, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther* 2002;302:1055-61.
- Anon. Expert panel recommendation for the prevention, diagnosis and treatment of osteonecrosis of the jaw. Appendix 11. Oncologic Drug Advisory Committee Meeting. Novartis Pharmaceuticals Corporation. East Hanover, NJ 07936. March 4, 2005.
- Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-61.

More . . .

Cite this Detail-Document as follows: Bisphosphonate-associated jaw osteonecrosis. Pharmacist's Letter/Prescriber's Letter 2006;22(8):220801.



Evidence and Advice You Can Trust...



3120 West March Lane, P.O. Box 8190, Stockton, CA 95208 ~ TEL (209) 472-2240 ~ FAX (209) 472-2249
Copyright © 2006 by Therapeutic Research Center

Subscribers to *Pharmacist's Letter* and *Prescriber's Letter* can get *Detail-Documents*, like this one, on any topic covered in any issue by going to www.pharmacistsletter.com or www.prescribersletter.com