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Bisphosphonate-associated Jaw Osteonecrosis

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Background

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 slow down osteoclastic activity, thereby facilitating osteoblastic effectiveness.¹⁻⁵ The bisphosphonate group of drugs include: 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*, *Ostac*), etidronate (*Didronel*), pamidronate (*Aredia*), risedronate (*Actonel*), and zoledronic acid (*Zometa*) are available.⁴

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

The most common side effect of the oral bisphosphonates is gastrointestinal upset.³ Post-marketing adverse event reports for both oral and intravenous bisphosphonates have caused product information changes in their labeling. Ocular side effects such as nonspecific conjunctivitis, scleritis, and uveitis have been reported.² Recent reports from several countries have revealed severe bone, joint, and muscle pain associated with bisphosphonate use.^{5,6}

In 2003 and 2004, there were several reports of osteonecrosis of the jaw (ONJ) in cancer patients receiving chronic intravenous bisphosphonates.⁷⁻⁹ 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. As a result, the products' labeling was updated in the U.S. in

August 2004 and in Canada in December 2004 to include precautions about ONJ.¹⁰⁻¹²

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 bones' structural architecture. It leads to bone pain, loss of bone function, and bone destruction. It is the result of a number of conditions leading to an impairment of the blood supply to the bone.¹³

Systemic corticosteroid therapy is a risk factor for osteonecrosis. Osteonecrosis is a well documented complication of anti-cancer 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.¹⁴

Bisphosphonates may present a unique role in the initiation of ONJ because of their novel antiangiogenic effects. Wood et al identified that zoledronic acid has marked antiangiogenic properties which could enhance its efficacy in treatment of malignant bone disease.¹⁵ 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.⁹

Oral bisphosphonates have not been reported to have the same degree of association with ONJ as the intravenous products. In a 2004 report from the FDA Adverse Event Reports database a total of 139 cases of osteonecrosis were identified from the marketing approval date of *Aredia*, *Zometa*, *Fosamax*, and *Actonel* until May 24, 2004. Thirty-four percent were associated with *Aredia* use, 24% per associated with *Zometa*, 42% per associated with patients who received both *Aredia* and *Zometa*, 8.6% were associated with *Fosamax* use, and one case was associated with *Actonel*. The majority of these patients were diagnosed

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with osteonecrosis of the jaw. Some had a diagnosis of mixed osteonecrosis and osteomyelitis. Because of these findings, the report stated that osteonecrosis may be a class effect of the bisphosphonates. The oral bisphosphonates are not as potent as the intravenous agents but they all have the same mechanism of action.¹⁶ Labeling for both *Fosamax* and *Actonel* is in the process of being updated to include this class osteonecrosis risk. *Boniva* labeling already has been updated.¹⁷

Commentary

The majority of cases with osteonecrotic jaw lesions occurred after a dental extraction yet some occurred spontaneously.⁷⁻⁹ Because of this association with dental procedures, potential preventative measures are suggested prior to bisphosphonate initiation.

Preventative measures include:

- 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
- Educating patients about the importance of good oral hygiene, symptom reporting, and regularly scheduled dental assessments¹⁸

Patients already receiving bisphosphonates should:

- Maintain excellent oral hygiene and have routine dental examinations
- Obtain routine dental cleanings where careful attention is given to avoiding soft-tissue injury
- Have aggressive nonsurgical management of any dental infection
- Have root canal treatment if needed rather than dental extraction when possible¹⁸

Patients with osteonecrosis or suspected osteonecrosis should receive immediate attention from an oral surgeon or dental oncologist.¹⁸

Suspected problems associated with bisphosphonates should be reported. To report adverse events in the US, 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/hpfb-dgpsa/tpd-dpt/adverse_e.pdf. 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.

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