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Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw

An institutional inquiry

Parish P. Sedghizadeh, DDS, MS; Kyle Stanley, BS; Matthew Caligiuri, BA; Shawn Hofkes, BS; Brad Lowry, BS; Charles F. Shuler, DMD, PhD

Osteonecrosis generally occurs when damage to bone interrupts nutrient supply or is the end result of a medical condition that undermines bone health.¹ Recently, osteonecrosis affecting only the jaw bones, or osteonecrosis of the jaw (ONJ), has been described as a unique complication secondary to bisphosphonate (BP) therapy and is thought to represent a growing trend.² BPs are a class of pharmaceutical agents used to treat numerous bone disorders, including osteoporosis, cancer metastases to bone and multiple myeloma.³⁻⁵ The most commonly reported initiating factor for ONJ development is tooth extraction, although periodontal disease and denture trauma have been implicated.⁶ ONJ typically occurs in patients who are receiving intravenous BP treatment. However, an increasing frequency of ONJ has been reported recently in people who receive oral BPs.⁶

BPs are thought to function by inhibiting at least one enzyme of the intracellular mevalonate pathway in osteoclasts.⁷ Inhibition of this pathway prevents the modification of important signaling proteins, which disrupts osteoclast function and leads to indirect apoptotic cell death. Antiangiogenic and antineoplastic properties have been attributed to BPs. Once incorporated into mineralized bone, BPs,

ABSTRACT

Background. Initial reports of osteonecrosis of the jaw (ONJ) secondary to bisphosphonate (BP) therapy indicated that patients receiving BPs orally were at a negligible risk of developing ONJ compared with patients receiving BPs intravenously. The authors conducted a study to address a preliminary finding that ONJ secondary to oral BP therapy with alendronate sodium in a patient population at the University of Southern California was more common than previously suggested.

Methods. The authors queried an electronic medical record system to determine the number of patients with a history of alendronate use and all patients receiving alendronate who also were receiving treatment for ONJ.

Results. The authors identified 208 patients with a history of alendronate use. They found that nine had active ONJ and were being treated in the school's clinics. These patients represented one in 23 of the patients receiving alendronate, or approximately 4 percent of the population.

Conclusions. This is the first large institutional study in the United States with respect to the epidemiology of ONJ and oral bisphosphonate use. Further studies along this line will help delineate more clearly the relationship between oral BP use and ONJ.

Clinical Implications. The findings from this study indicated that even short-term oral use of alendronate led to ONJ in a subset of patients after certain dental procedures were performed. These findings have important therapeutic and preventive implications.

Key Words. Osteonecrosis; jaw; oral bisphosphonates; alendronate; extraction.

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BOX

Clinical staging of osteonecrosis of the jaw.*

STAGE 1
Exposed, necrotic bone (sequestra) that is asymptomatic

STAGE 2
Exposed, necrotic bone (sequestra) associated with pain and infection

STAGE 3
Exposed, necrotic bone (sequestra) in patients with pain, infection and pathological fracture; extraoral fistula; or osteolysis extending to the inferior border of the mandible or floor of the sinonasal cavity

* Adapted from Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology volume 102, issue 4, Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management, 433-441, 2006, with permission from Elsevier.²

including oral alendronate sodium (Fosamax, Merck, Whitehouse Station, N.J.), stay in the bone for a long time and have a terminal half-life of many years.⁸ As a result, patients who discontinue BP therapy still may be at risk of developing ONJ several years after they stop taking the drug. Furthermore, most cases of ONJ are associated with long-term use of BPs; thus, a dose-dependent and time-dependent relationship is thought to exist with respect to disease process, meaning that the longer a person is taking alendronate, the greater his or her risk of developing ONJ.⁹ Most cases of ONJ occur in patients who are receiving the newer-generation nitrogen-containing BPs instead of the older-generation nonnitrogen-containing BPs. Many of the newer-generation BPs have been on the market for less than a decade. Therefore, as longer-term use (for example, more than 10 or 15 years) of nitrogen-containing BPs is realized, the prevalence of ONJ could increase to significant proportions, given the large size of the population receiving this medication.

The initial correlation between the use of oral alendronate and ONJ was not statistically significant, with an incidence of 0.7 per 100,000 person-years of exposure, or 170 cases worldwide according to Merck, as cited in an article by the American Dental Association (ADA) Council on Scientific Affairs.¹⁰ This low frequency of ONJ in people who take alendronate prompted an expert panel selected by the ADA Council on Scientific Affairs to suggest in 2006 that routine dental treatment generally should not be modified solely on the basis of oral BP therapy.¹⁰ In December 2008, the ADA expert panel reiterated its 2006 findings

that oral BP use poses a low risk of developing ONJ.¹¹

We conducted a study to address a preliminary finding that in a patient population at the University of Southern California (USC) in Los Angeles, ONJ secondary to alendronate therapy is more common than suggested by the manufacturer and the ADA’s expert panel. Furthermore, most of the patients receiving alendronate at USC who developed ONJ did so after routine tooth extraction, suggesting that perhaps these patients should be identified as an at-risk population and preventive measures should be taken.

MATERIALS AND METHODS

We obtained appropriate institutional review board approval before beginning our study. We queried the electronic medical record system used by the USC School of Dentistry (Axium, Exan Academic, Port Coquitlam, British Columbia, Canada) to determine the number of active patients who had a history of alendronate use. We then identified all patients receiving alendronate at the time of the study or in the past who also were being treated for active ONJ in the Oral Surgery clinic and the Orofacial Pain and Oral Medicine clinic, which are the only clinics at the USC School of Dentistry that treat patients with ONJ. Our inclusion criteria were that patients have clinical features of ONJ, have a BP history consistent with a diagnosis of ONJ and have stage 2 or stage 3 lesions according to Ruggiero and colleagues² staging system (Box). All patients with ONJ who we included in the study had radiographic evidence of an ill-defined lytic lesion of the jawbone in addition to clinical evidence of exposed necrotic bone (sequestra) with mucosal ulceration (Figure). These advanced radiographic and clinical findings likely were due to delays in diagnosis. We also queried the electronic medical record system to identify all patients (those who received and did not receive alendronate) who had undergone tooth extraction—the most common dental procedure associated with ONJ development postoperatively—or had planned to do so.

We identified a list of questions on the USC School of Dentistry patient health history form that related to the question “What drugs or med-

ABBREVIATION KEY. ADA: American Dental Association. BP: Bisphosphonate. ONJ: Osteonecrosis of the jaw. USC: University of Southern California.

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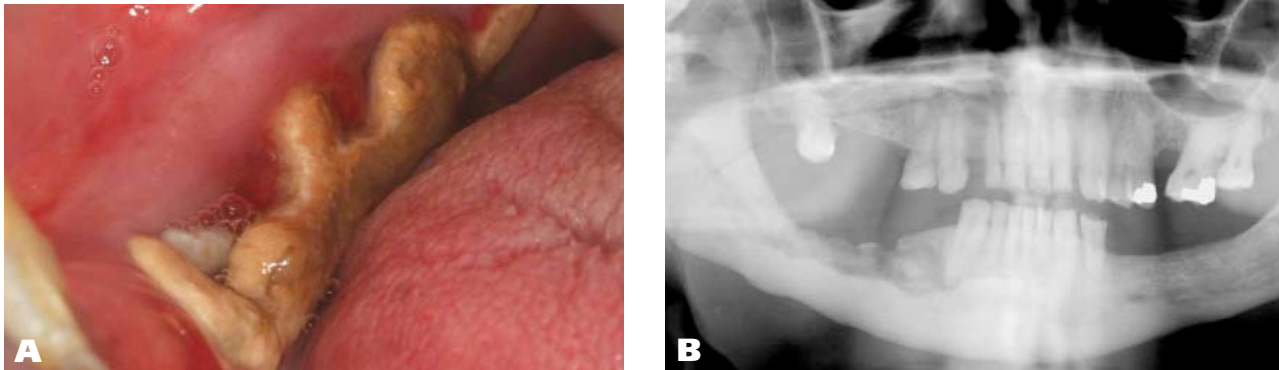


Figure. A. Intraoral photograph of a patient with osteonecrosis of the jaw. **B.** Panoramic radiograph of the same patient.

ications are you taking?” each question’s numerical position on the form (Fitem). We used these numerical values to query the entire electronic medical record system of the dental school. We then identified several ways alendronate can be entered into the answer text by its generic or brand name and misspellings thereof. To correlate the use of alendronate with tooth extraction, we then used the ADA’s Current Dental Terminology dental procedure codes that indicate simple tooth extraction in a structured query language search to identify all of the variations of the drug names and extraction data for a given group or population. This type of query let us assess whether patients receiving alendronate were being treated (for example, tooth extraction) in an identical manner to patients not receiving alendronate and let us identify what we believe to be one of the largest patient populations at risk of developing ONJ at USC. The manner in which we wrote the query allowed for continued flexibility through the list of Fitem values, the list of drug spellings or misspellings, and the list of Current Dental Terminology procedure codes that, for the purposes of this study, indicate simple extractions as opposed to surgical extractions. Theoretically, surgical extractions should be associated with a higher rate of complications than are simple extractions.

RESULTS

Through our query, we identified 208 patients with a history of alendronate use. Of these 208 patients, nine had active ONJ and were being treated in our clinics. These nine patients represent one in 23 of the patients receiving alendronate, or approximately 4 percent of the population. All of the patients were long-standing patients of the dental school, and none were

referred for evaluation or treatment of ONJ, which is important because it excludes the possibility of referral bias. The clinical, pharmacological and pathological details and parameters for these nine patients who had ONJ are presented in Table 1.

All ONJ cases occurred after either simple tooth extraction or denture trauma that resulted in jawbone exposure. The patients affected by ONJ were 63 to 80 years of age, with an average age of 73 years, and all were women who received alendronate for osteoporosis for 12 months or longer. Type 2 diabetes, hypertension, hypercholesterolemia, steroid therapy and chemotherapy were common comorbidities among these patients. Some of these comorbidities have been implicated as compounding risk factors for ONJ.¹² Of our 208 patients who had a history of alendronate use, 66 underwent simple dental extraction (31.7 percent) without treatment modifications or preventive measures; four of these patients developed ONJ at the extraction site postoperatively, and another five developed ONJ after denture-related mucosal ulceration. Of the 13,522 patients without a history of alendronate use, 4,384 (32.4 percent) underwent dental extraction (Table 2, page 66); we observed no cases of ONJ among these patients.

DISCUSSION

Osteoporosis affects more than 10 million Americans.¹³ Alendronate is the most widely prescribed oral BP; it was the 21st most prescribed drug on the market in 2006.¹⁴ Despite the prevalence of patients receiving alendronate therapy, there are no epidemiologic data and research to support there being a significant risk of developing ONJ secondary to oral BP therapy. According to a study published in *The New England Journal of*

TABLE 1

Clinicopathological and pharmacological parameters for participants receiving alendronate who had osteonecrosis of the jaw.						
PARTICIPANT NO.	AGE (YEARS)/SEX	ETHNICITY	MEDICAL REASON FOR BISPSPHONATE USE	OTHER MEDICAL AND COMORBID CONDITIONS	BISPSPHONATE ADMINISTERED	DURATION (MONTHS)
1	73/Female	Asian-American	Osteoporosis	Hypertension, hypercholesterolemia, osteoarthritis, gastroesophageal reflux disease	Alendronate 70 mg orally once per week	36
2	80/Female	Asian-American	Osteoporosis	Type 2 diabetes, osteoarthritis, stroke, heart stent	Alendronate 70 mg orally once per week	120
3	74/Female	Asian-American	Osteoporosis	Peptic ulcer	Alendronate 70 mg orally once per week	60
4	75/Female	Hispanic-American	Osteoporosis	Hypercholesterolemia, hypothyroidism	Alendronate 70 mg orally once per week	36
5	79/Female	Asian-American	Osteoporosis	Type 2 diabetes, hypertension, hypercholesterolemia	Alendronate 70 mg orally once per week	60
6	63/Female	Hispanic-American	Osteoporosis	Hypertension, chemotherapy and steroid therapy for rheumatoid arthritis	Alendronate 70 mg orally once per week	36
7	74/Female	Asian-American	Osteoporosis	Hypertension, hypercholesterolemia	Alendronate 70 mg orally once per week	12
8	76/Female	Asian-American	Osteoporosis	Cancers (ovary, uterus, colon, liver), chemotherapy, hypertension, asthma	Alendronate 70 mg orally once per week	120
9	65/Female	Asian-American	Osteoporosis	Hypertension, hypercholesterolemia	Alendronate 70 mg orally once per week	12

Medicine, the estimate of the incidence of ONJ is based on unsubstantiated claims¹⁵; therefore, well-designed prospective cohort studies with rigorous case ascertainment criteria, as well as documentation of risk factors and risk modifiers, are needed. Investigators in a recent study from Australia that provided appropriate case ascertainment criteria calculated the rate of ONJ in a large population.⁶ This study, which was not supported commercially, reported a minimum and maximum frequency of ONJ in patients receiving oral BPs as one in 2,030 and one in 950, respectively, and a minimum and maximum frequency

of patients receiving oral BPs who have undergone extractions as one in 270 and one in 125, respectively.⁶ Our data similarly showed a significantly higher frequency of ONJ in people taking alendronate. The findings from our study have important therapeutic and preventive implications. ONJ not only is associated with high-dose intravenous administration of BPs,¹⁶ but it also is a possible complication of oral BP therapy.⁶ Longer-term use of oral BPs may have a dose equivalence effect, potentially approximating BP levels in bone thought to be achieved only through high-dose intravenous delivery.

TABLE 1 (CONTINUED)

PREDISPOSING DENTAL CONDITION	LOCATION OF OSTEONECROSIS	TREATMENT
Denture trauma	Left mandible	Daily chlorhexidine mouth rinsing
Denture trauma	Left maxilla	Discontinuation of alendronate, antibiotics, local débridement, daily chlorhexidine mouth rinsing
Denture trauma	Right mandible	Antibiotics, local débridement, daily chlorhexidine mouth rinsing
Denture trauma	Right and left mandible	Antibiotics, daily chlorhexidine mouth rinsing
Tooth extraction	Right mandible	Discontinuation of alendronate, antibiotics, local débridement, daily chlorhexidine mouth rinsing
Denture trauma	Right maxilla	Discontinuation of alendronate, antibiotics, sequestrectomy, local débridement, daily chlorhexidine mouth rinsing
Tooth extraction	Right mandible	Discontinuation of alendronate, antibiotics, sequestrectomy, local débridement, daily chlorhexidine mouth rinsing
Tooth extraction	Left mandible	Discontinuation of alendronate, partial sequestrectomy, local débridement, daily chlorhexidine mouth rinsing
Tooth extraction	Left mandible	Local débridement, daily chlorhexidine mouth rinsing

The findings from our study are significant because, to our knowledge, our study is the first institutional study in the United States to investigate the prevalence of ONJ in patients who have received alendronate. Our data suggest that the risk of developing ONJ is much higher than initially reported in the literature. These findings have important therapeutic and preventive implications. For example, alternate treatment options may be considered for use for nonnecessary extractions, and good oral hygiene should be achieved before necessary extractions to minimize microbial load. In addition to more routine and

vigilant follow-up, using a chlorhexidine rinse preoperatively and postoperatively can be effective in necessary extraction cases to ensure socket and wound healing, as well as mucosal coverage of exposed bone. Furthermore, 33 other dental schools in the United States also use the electronic medical record system we used, which means that similar epidemiologic studies could be conducted at the multi-institutional level. These studies, therefore, could include thousands of patients who are receiving alendronate or other BPs. The ADA Council on Scientific Affairs has suggested a call for institutional studies.

In our study, we evaluated the rate of tooth extractions in a population of patients who received alendronate therapy compared with a control population that did not receive alendronate. Nearly the same percentage of patients taking alendronate and of those who did not underwent dental extractions. Almost one-half of the patients taking alendronate who were affected by ONJ developed it at the extraction site postoperatively, and ONJ did not develop in patients who did not take alendronate. Therefore, it became evident to us that at our school, patients taking alendronate have not been assessed and treated as patients at risk of developing ONJ even after being slated to undergo tooth extraction. Our data suggest that this treatment is inappropriate, especially in patients with comorbidities—in addition to taking BPs that are known to be risk factors for the development of ONJ—and particularly in women with osteoporosis who receive longer term doses of alendronate. Accordingly, as recent evidence is indicating oral microbial biofilms play a role in the pathogenesis of ONJ, an invasive dental procedure such as an extraction could expose the jawbone to oral organisms (for example, through saliva) and be a risk factor in the development of ONJ.¹⁷

ONJ is a risk management and quality assurance concern for dentists and physicians. Because our school is responsible for promoting and providing dental care for the public, current data such as ours that suggest ONJ may develop in people who take BPs orally have prompted us to actively screen every patient and to update consent forms and patient medical history forms to reflect the need for increased awareness and early risk or disease assessment. We have updated our dental surgery consent form for patients who take BPs to include the ADA-recommended statement:

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TABLE 2

CRITERION	ALENDRONATE THERAPY (70 MILLIGRAMS PER WEEK) (NO. OF PARTICIPANTS)	NO ALENDRONATE THERAPY (NO. OF PARTICIPANTS)	TOTAL NO. OF PARTICIPANTS
Tooth Extraction	66	4,384	4,450
No Extraction	142	9,138	9,280
TOTAL	208	13,522	13,730

Tooth extraction patterns in participants receiving alendronate and participants not receiving alendronate.

“Because you are taking a type of drug called a bisphosphonate, you may be at risk for developing osteonecrosis of the jaw and certain dental treatments may increase that risk.”¹⁸ We suggest that institutions and private practitioners add a similar statement to their consent forms for patients who take nitrogen-containing BPs until the results from larger, well-designed and prospective studies are available.

CONCLUSIONS

Our study was the first large institutional study in the United States to investigate the epidemiology of ONJ and oral BP use. The findings from our study indicate that even short-term use of oral alendronate can lead to ONJ in a subset of patients after dental procedures such as extractions, and these findings have important therapeutic and preventive implications. Further studies will help delineate more clearly the relationship between oral BP use and ONJ. ■

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