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Bisphosphonates and Osteonecrosis of the Jaw (ONJ)

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The purpose of *Linking Research to Clinical Practice* is to present evidence-based information to clinical dental hygienists so that they can make informed decisions regarding patient treatment and recommendations. Each issue will feature a different topic area of importance to clinical dental hygienists with A BOTTOM LINE to translate the research findings into clinical application.

Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis

Wilkinson, Gregg S. Kuo, Yong-Fang. Freeman, Jean L. Goodwin, James S. Journal of the National Cancer Institute. 99(13):1016-24, 2007 Jul 4.

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Abstract

Background. Recent reports have identified an association between osteonecrosis of the jaw or facial bones and treatment with nitrogen-containing intravenous bisphosphonates. We investigated this association by use of data from the Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims.

Methods. We identified 16,073 cancer patients who were diagnosed between January 1, 1986, and December 31, 2002, and were treated intravenously with the bisphosphonates pamidronate (Aredia®) and/or zoledronic acid (Zometa®) between January 1, 1995, and December 31, 2003. We matched 28,698 bisphosphonate nonusers, at a 2:1 ratio, to 14,349 bisphosphonate users on month and year of the first bisphosphonate administration received by users, cancer type, age, sex, risk factors for osteonecrosis (diabetes, alcoholism, cigarette smoking, obesity, hyperlipemia, pancreatitis, or chemotherapy with L-asparaginase), bone metastasis, and SEER program geographic region. Patients were followed until the study's end on December 31, 2003; loss of coverage from Medicare Parts A and B; or one of the following outcomes: a diagnosis of inflammatory conditions or osteomyelitis of the jaw, surgery on the facial bones, or death, whichever occurred first.

Results. Use of intravenous bisphosphonates was associated with an increased risk of jaw or facial bone surgery (hazard ratio [HR] = 3.15, 95% confidence interval [CI] = 1.86 to 5.32) and an increased risk of being diagnosed with inflammatory conditions or osteomyelitis of the jaw (HR = 11.48, 95% CI = 6.49 to 20.33), compared with nonuse. The absolute risk at 6 years for any jaw toxicity was 5.48 events per 100 patients using intravenous bisphosphonates and 0.30 events per 100 patients not using such drugs. The risk of each outcome increased as cumulative dose increased (e.g., for 4-8 infusions, HR for operations on the jaw and facial bones = 3.63, 95% CI = 0.77 to 17.08; for more than 21 infusions, HR = 9.18, 95% CI = 1.74 to 48.53).

Conclusions. Users of intravenous bisphosphonates had an increased risk of inflammatory conditions, osteomyelitis, and surgical procedures of the jaw and facial bones. The increased risk may reflect an increased risk for osteonecrosis of the jaw.

Commentary

This study comprises one of the most extensive investigations on the increased risk of intravenous ONJ associated with bisphosphonate therapy. For this study, the authors used tumor registry data from the Surveillance, Epidemiology and End Results (SEER) program linked to Medicare claims data to examine the potential toxicity of intravenous administered bisphosphonates. An inherent methodological problem in assessing risk of ONJ in this study was the fact that the International Classification of Diseases, version 9 (also called the ICD-9 codes) did not have a specific classification for ONJ. The ICD classification system, developed by the World Health Organization, is the standard by which disease entities, signs, and symptoms are categorized worldwide. Therefore, these researchers used 2 outcomes that are closely related to ONJ, inflammatory conditions/osteomyelitis of the jaw and jaw or facial surgery, as proxy measures for their analyses to assess the relationship between bisphosphonates and ONJ-related outcomes. Bisphosphonate users were matched to nonusers (at a 1:2 ratio) using very stringent criteria (eg, type of cancer diagnosis, timing of first bisphosphonate treatment, gender, region of the country and other risk factors for osteonecrosis such as smoking, diabetes, and other systemic conditions) and more liberal criteria (type of cancer, age, gender, and number of risk factors). Cumulative dose of bisphosphonate was determined as the number of injections received.

Results from this study showed that the incidence of either ONJ-type outcome for bisphosphonate users versus nonusers at 3, 4, and 6 years were 2.00% versus 0.28%, 2.89% versus 0.30%, and 5.48% versus 0.30%, respectively. In addition, the independent risk for jaw toxicity as a function of intravenous bisphosphonate therapy (after controlling for other risk factors) was 11.48 for inflammatory conditions/osteomyelitis and 3.15 for operations on the facial bones. One of the most interesting findings was the relationship of dose response effect. For each one-dose incremental increase of intravenous bisphosphonate injection, there was an 8% increase in risk for any ONJ-type outcome. These findings also showed that several factors, most notably gender, type of cancer, or other risk factors for oral diseases, were not related to inflammatory conditions/osteomyelitis or operations on facial bones.

The authors were clear to identify that there were specific limitations in their study design. Probably the greatest problem in this study was the potential for misclassification of outcomes since there is no specific ICD-9 code for ONJ. A second limitation is that since Medicare data were used, this would likely result in an underreporting of the conditions. However, the sophisticated statistical analyses allowed the researchers to control for other explanatory factors and thus extract the unique association of ONJ-type events with the independent effects of the drug. More critically, the dose response relationship observed provides very good evidence supporting a causal association. The authors were very pointed in their discussion of needing to balance the risk of ONJ-type outcomes with the overall benefit of bisphosphonate therapy in individuals with advanced cancer with bone metastases. There is clear and substantial evidence that bisphosphonate therapy is very effective in reducing adverse skeletal events (fracture, need for surgery, need for radiation, etc) in patients with multiple myeloma. Therefore, oral health promotion and elimination of significant oral disease prior to implementation of bisphosphonate therapy is crucial.

Safety of Oral Bisphosphonates: Controlled Studies on Alveolar Bone

Jeffcoat, Marjorie K. International Journal of Oral and Maxillofacial Implants 21(3): 349-353; 2006.

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Abtract

Background. Osteoporosis and osteopenia are characterized by reductions in bone mass and may lead to skeletal fragility and fracture. The latest generation of oral bisphosphonate drugs, including alendronate and risendronate, has been approved for the prevention and treatment of osteoporosis. These medications are chemically absorbed into bone, decreasing osteoclast number and activity and thereby decreasing bone resorption. The purpose of this report is to present safety data from 2 controlled studies in patients receiving oral bisphosphonates.

Methods. Study 1 tested the effect of alendronate (Fosamax®), an inhibitor of bone resorption, on alveolar bone. A total of 335 patients (162 men and 173 women, aged 30 to 79 years) with moderate or severe periodontal disease were randomized to either placebo or 70 mg alendronate once weekly. Alveolar bone height and safety were assessed over a 2-year period. Study 2 was a longitudinal single-blind controlled design comparing implant success in 50 consecutive patients (210 implants), 25 patients who received bisphosphonate therapy and 25 age-matched control subjects. Implant success and safety, including incidence of osteonecrosis of the jaws (ONJ), was blindly assessed for at least 3 years.

Results. In study 1, no cases of ONJ were observed in either treatment group. Furthermore, a trend toward lower incidences of infection and tooth loss was observed in the alendronate group. In study 2, no cases of ONJ were observed in either group, and implant success was greater than 99% in both groups.

Conclusions. On the basis of 2 controlled clinical studies, oral bisphosphonate usage was not associated with occurrence of ONJ.

Commentary

This study compiles results from 2 clinical trials on the use of oral bisphosphonates for periodontal patients. The rationale for examining the safety of oral bisphosphonate medications was primarily based on the potential beneficial effect for altering osteoclastic activity in periodontal applications balanced by the potential for ONJ. Recent case studies on ONJ suggest that bisphosphonates as a class of drugs may cause ONJ, although only a very few cases have been associated with oral dosing. In the first study, subjects with moderate to severe periodontal disease were randomly assigned to receive either 70 mg of oral alendronate or placebo. All subjects also received nonsurgical periodontal treatment at the outset of the study period and periodontal maintenance at 3-month intervals across the entire 2-year study. Evaluations consisted of obtaining clinical and radiographic evidence of ONJ, oral infection, and alveolar bone loss at each 3-month observation period by an examiner who was unaware of subjects' treatment group assignment. Results showed that for subjects with low bone mineral density at the beginning of the study, there was significantly less bone loss over the 2 year period in the bisphosphonate-treated subjects compared to placebo. In normal bone mineral density subjects, the difference between bisphosphonate and nonbisphosphonate subjects was not significant. More critically, for these 335 subjects, there were no cases of ONJ observed during the study timeframe. In the second study, implant patients with osteoporosis who had been taking unspecified doses of oral bisphosphonate for 1 to 4 years, were age-matched to a similar group of osteoporotic patients not taking bisphosphonates. Following placement of implants, subjects were followed for a 3 year period. One-hundred percent of bisphosphonate-treated subjects and 99.2% of subjects not taking bisphosphonates were determined to be "treatment successes." In this study, treatment success was defined as having less than 2 mm of bone loss, no mobility, no infection, and no evidence of ONJ during the study period. No cases of ONJ were observed in either group by the end of the 3-year period.

The author concludes that oral bisphosphonate therapy may be beneficial for reducing alveolar bone loss, without greatly predisposing these patients to an increased risk for developing ONJ. However, the author did not adequately address whether cumulative dose of bisphosphonates over an extended period might feasibly increase risk for ONJ. Current evidence suggests that half-life of bisphosphonates in blood is very short (several hours) whereas the half-life in bone may be many years and possibly life long. If indeed these drugs concentrate over time in bone, studies of 2 or 3 years may be insufficient to adequately evaluate the risk of oral bisphosphonates in ONJ. Additionally, there was no mention of whether either of the studies discussed included an assessment of adherence to medication. There is a large body of medical evidence that

suggests that patients often are not adherent to their medication regimes. Without an explicit evaluation of medication adherence, one cannot determine if the lack of ONJ is attributable to taking or failing to take the drug.

The Bottom Line

Currently there is substantial concern in the dental community about the risk of bisphosphonates in the development of osteonecrosis of the jaw. Several abbreviated terms are used when describing this clinical entity and include ONJ, BON, BRON, and BRONJ. Bisphosphonate-related ONJ is associated with decreased bone turnover, which can dramatically reduce healing potential following extraction or trauma. Bisphosphonate-related ONJ signs and symptoms include numbness, pain, tooth mobility, soft tissue swelling, sequestration of bone, and development of nonhealing lesions of exposed bone in the mandible or maxilla. In the past 5 years alone, more than 180 publications (articles, letters, guidelines to clinicians, and commentaries) dealing with bisphosphonates and ONJ have appeared in the medical and dental literature. While the vast majority of published study designs have been either case studies or retrospective, case-control investigations (many with a relatively small number of patients), the consistency of evidence on the risk of **intravenous** bisphosphonate therapy for developing ONJ is compelling. To date, the potential increased risk for ONJ related to **oral** bisphosphonates appears to be less but little evidence has been generated in this regard. However, the extended half-life of bisphosphonates in bone suggests that there is a need for longer follow-up periods to justify the safety of these oral medications as they relate to risk for ONJ.

Whether the link between bisphosphonates and ONJ is causal or not, the strength of evidence for this association cannot be ignored. Dental professionals, however, must comprehensively consider the evidence when providing care and education to patients receiving IV bisphosphonate therapy. Intravenous bisphosphonates are the current standard of care for patients with multiple myeloma and for patients with bone metastases associated with breast or prostate cancer. These medications, delivered intravenously, have significant therapeutic benefits for cancer patients as they reduce bone loss, fractures, need for radiation, and other skeletal events. As such, the focus of dental care should be on reducing oral conditions that may predispose these patients to ONJ. Removing severely diseased teeth prior to bisphosphonate treatment, if at all possible, is prudent. However, as not all cancer patients receive an oral assessment prior to treatment, the dental team must work to reduce the need for future extractions or other dental procedures that rely on bone healing once IV bisphosphonate therapy has been initiated. The role of the dental hygienist in managing the oral health of these patients is critical. Establishing a protocol for care that centers on promoting oral health and preventing future disease should be the primary emphasis for the dental hygienist. The dental hygienist should ensure that the maintenance schedule is appropriately conservative given the patients past level of oral disease activity and that patient education is given very high priority during the dental hygiene appointment.

Therefore the following recommendations can be made based on the findings in these 2 studies:

IV bisphosphonate therapy is a statistically significant independent risk factor for being diagnosed with an inflammatory condition, osteomyelitis of the jaw, or jaw surgery. This may reflect an increased risk for osteonecrosis of the jaw.

Oral bisphosphonate therapy was not associated with an increased risk for ONJ during a 2 to 3 year follow-up.

Summary

Dental hygiene clinicians play a critical role in educating patients. With the recent flurry of information and misinformation about bisphosphonate-related ONJ, clinicians must be proactive in incorporating scientific evidence into their patient education for subjects at potential risk for this condition. Anecdotal evidence suggests that some dental offices are adopting a risk-aversive policy of refusing definitive dental treatment to subjects on either oral or IV bisphosphonate therapy. The current state of evidence suggests that the dental team should be proactive in providing patients on IV bisphosphonate therapy with appropriate care and education aimed at minimizing risk for ONJ. For individuals on oral bisphosphonates, while the risk is very less likely than that observed for IV therapy, education should be a priority. Eliminating frank disease and providing definitive care to reduce gingival and periodontal diseases (thus reducing the need for future dental extractions), as well as providing education and counseling for patients at risk, should be the standard of care for the entire

dental team. Until the dental research community provides definitive evidence of causality between ONJ and bisphosphonates, prevention and health promotion should be the standard for at-risk patients.