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Bisphosphonate-Associated Osteonecrosis of the Jaw: A Literature Review and Clinical Practice Guidelines

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Background. Osteonecrosis of the jaw has recently been reported as a possible adverse drug effect from bisphosphonate therapy. Reports are coming from all over the world. Norvartis, a pharmaceutical manufacturer of two implicated drug products, has notified dentists in the United States and made recommendations for dental management of cases.

Mechanism of Action. The exact mechanism of bisphosphonate effects leading to osteonecrosis of the jaw is unknown. The condition can affect both the maxilla and the mandible. Most cases developed following oral infection or dental treatment.

Prevention and Management. Clinical guidelines for prevention and management have recently been published. Dental hygienists have a major role in patient education related to awareness of the potential drug effect and to preventive oral health education.

Keywords: Bisphosphonate, osteonecrosis of the jaw, pamidronate disodium, zoledronic acid

Abbreviations:

ADR - adverse drug reaction, also called adverse drug effect

ONJ - osteonecrosis of the jaw, also called avascular bone necrosis

BIS - bisphosphonate

BON - bisphosphonate-associated osteonecrosis of jaw

IV - intravenous route of administration

FDA - Food and Drug Administration

Introduction

In May 2005 the drug company Novartis Pharmaceuticals Corporation sent a letter to dentists across the United States to warn them of reports of an adverse drug reaction (ADR), osteonecrosis of the jaw (ONJ), observed in cancer patients receiving treatment with intravenous (IV) bisphosphonates (BIS), Aredia (pamidronate disodium) and Zometa (zoledronic

acid). Both drugs are manufactured by Novartis. The warning letter recommended that in dental patients who were being treated with these drugs "invasive dental procedures should be avoided if possible."[1] An additional recommendation was that cancer patients receive a dental examination prior to initiating therapy with IV administered bisphosphonates (Aredia, Zometa).

The letter cautioned that dental surgery may exacerbate alveolar destruction in patients who developed ONJ while being treated with the drugs. When ONJ was observed in patients using BIS, healthcare professionals were asked to submit a report of the serious ADR to the drug company via telephone (800-882-6577) or to the Food and Drug Administration's (FDA) MedWatch Adverse Drug Event Reporting program via telephone (800-FDA-1088) or online at www.fda.gov/MedWatch/report.htm. The FDA form to report an ADR can be downloaded from the FDA Web site, http://www.fda.gov/MedWatch/getforms.htm.

Aredia is used to treat conditions such as hypercalcemia of malignancy, Paget's disease, osteolytic bone metastases of breast cancer, and osteolytic lesions of multiple myeloma. Zometa is indicated for hypercalcemia of malignancy, boney destruction from multiple myeloma, and bone metastases from solid tumors. Patients treated for malignancy can have accelerated reduction in bone density leaving them at an increased risk for fractures, especially of the hip and vertebrae. The use of a BIS is considered the standard of care for treatment of moderate to severe hypercalcemia associated with malignancy and for metastatic osteolytic lesions associated with breast cancer and multiple myeloma. The company has added the following statement to the US package insert for both drugs, in the *Precautions* section:

"Osteonecrosis of the jaw has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (eg, cancer chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures, if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis. Clinical judgment of the treating physician should guide the management plan of each patient based on individual risk assessment."[2]

Novartis published a patient brochure entitled "Taking Care of Yourself While Living With Cancer" in April 2005, which includes information on dental health during cancer treatment and ONJ as a potential ADR. A Dental Consultation Form is included in the brochure to assist the client in coordinating medical and dental care. This brochure is free from the company and can be obtained by calling 800-521-9445 (publication #ONC-8155(03)). As the discussions of the association between BIS drug therapy and ONJ have emerged, another anachronism has been proposed, namely bisphosphonate-associated osteonecrosis of the jaw (BON). The overall prevalence of BON is unknown. The prevalence of BON in patients treated for cancer and who received IV BIS therapy at Sloan-Kettering Cancer Center was reported by the Dental Service of Memorial Sloan-Kettering Cancer Center to be 10.5%.[3] Currently, BON can only be considered to be *associated* with BIS, as causality has not been determined.

ONJ in patients who have taken a BIS closely resembles the occupational disorder formerly referred to as "fossy jaw," which occurred in workers in match factories using white phosphorus in manufacturing. In the process of making matches, the worker would often put the match in the mouth to shape the end, thereby introducing phosphorus into the system. The condition was distressingly painful, refractory to treatment, and disfiguring to the extent that some sufferers committed suicide. One author has noted similarities between osteonecrotic lesions in phosphorus-related cases with lesions of BON and has coined the term "bis-phossy jaw" to describe the recent reports.[4] Both the mandible and the maxilla are affected, with most cases found in the mandible, especially lingual to the prominent mylohyoid ridge. The signs and symptoms that can occur before the appearance of clinically evident ONJ include changes in the health of periodontal tissues, nonhealing mucosal ulcers, loose teeth, and unexplained soft tissue infection.[5]

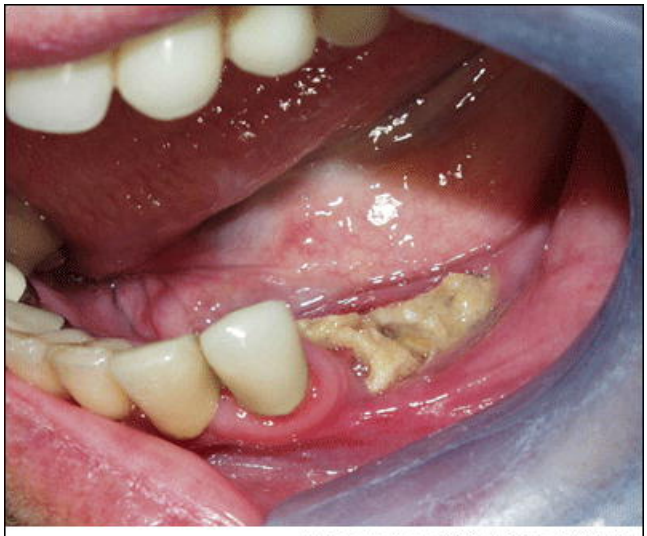
Other drugs in the BIS class are taken by mouth (tablets) and include alendronate (Fosamax), risedronate (Actonel), etidronate (Didronel), tiludronate (Skelid) and a new BIS approved for once per month dosing, ibandronate (Boniva).

Fosamax, Actonel, and Boniva are approved to treat or prevent osteoporosis and are widely prescribed. In January 2006, the FDA approved an IV dose form of Boniva for the client who cannot swallow or sit upright for 30 minutes. In the early published reports, it was thought the ADR only occurred in the IV dose form, but as more reports emerged, it was discovered that BON developed in some patients taking the oral dose form of the medication. Product labeling for oral dose forms was recently revised to include the possibility of BON. The oral dose forms are manufactured by a variety of pharmaceutical companies. So far, only the Novartis group has issued a warning letter to dentists. It is important for the oral health professional to be aware of this potential ADR in a client reporting a history of taking a BIS because most of the affected patients had jaw disease that was not detected by their physicians or oncologists. Diagnosis was made after the oral problems developed (pain, loose teeth, loss of mucosa, and/or exposed bone) and the patient sought out dental consultation or was referred for dental evaluation by the medical practitioner.

This article will give the timeline of the reports of BON (also referred to by some authors as avascular necrosis of the jaw) and the proposed mechanisms of action leading to ONJ. Prevention and treatment guidelines recently published by the American Academy of Oral Medicine will be provided.

History of ONJ Associated with Bisphosphonates

The first report of dentally-related problems in a patient with osteoporosis being treated with alendronate (Fosamax) was published in 1995. In this case report, 5 fully integrated dental implants failed 6 months after initiation of BIS therapy.[6] The authors attributed the failure to the bisphosphonates (BIS) and suggested that prolonged use of the medication may represent a contraindication to implant placement.



Images courtesy of Sal Rugierro, DMD, MD

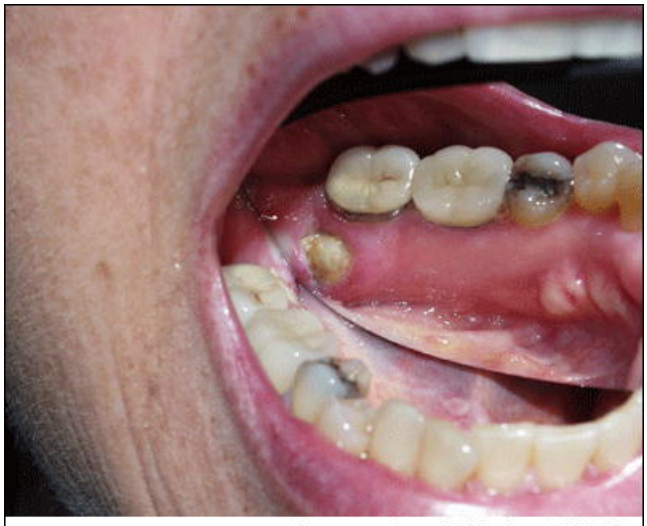
The first published reports of osteonecrosis of the jaw (ONJ) secondary to BIS drug therapy appeared in September 2003. One report was contained in a lengthy letter by an oral surgeon associated with a medical college in Florida.[7] The other was a paper written by a group of oral surgeons from the University of California-San Francisco.8 Robert Marx, DDS, Division of Oral & Maxillofacial Surgery at the University of Miami School of Medicine, called the condition *avascular necrosis of the jaw* and described it as "a growing epidemic" associated with the intravenous route of administration (IV) of BIS. In his report of 36 cases, 24 had received pamidronate, 6 were treated with zoledronate, and 6 received both drugs.[7] Although all of the patients were taking other medications, some of which could reduce wound healing, the one single drug class taken by *all* patients was a BIS. The report described painful exposure of bone in the mandible (80.5%), maxilla (14%), or both locations (5.5%), resulting in dental abscess, "toothaches," denture sore spots, osteomyelitis, and/or exposed bone. The typical presentation upon referral was an extraction site that failed to heal and exposed alveolar bone that progressed to formation of sequestrum, with associated localized swelling and purulent exudate. The author explained that

all cases were unresponsive to surgical or medical treatments (antibiotics). The dental procedure that most commonly seemed to exacerbate the appearance of the above signs was tooth extraction; however, 8 (22.3%) patients had a spontaneous manifestation of bone exposure unassociated with prior dental disease. Twenty-two (61%) patients were taking a systemic corticosteroid and 24 (67%) patients were on maintenance chemotherapy for cancer. Only 4 patients had a history of radiation therapy.

A report by Wang et al described 3 patients who were receiving cancer chemotherapy and BIS therapy and who subsequently developed ONJ in the maxillofacial region of the jaw.[8] In their discussion, they dismissed the relationship of ONJ to BIS therapy due to a lack of reports of the adverse drug reaction and the meta bolic action of BIS to reduce bone loss. They attributed the ONJ event as being secondary to taxoid classification chemotherapy drugs (Taxol, Taxotere) used in cancer treatment. Later, however, in a letter to the editor the following year they attributed their cases to BIS therapy.[9]

Later that year (November 2003) Migliorati reported on 5 patients who developed intraoral bone necrosis while taking pamidronate (Aredia) or zoledronic acid (Zometa).[10] Three of these patients experienced spontaneous necrosis of the mylohyoid boney plate in the mandible and 2 patients developed ONJ following extraction of molars (arch unidentified).

A large case series was published in 2004 when Ruggiero reported that over a 3-year-period (February 2001 to November 2003) his clinic had treated 63 cases of bisphosphonate-associated osteonecrosis of jaw (BON).[11] Both males and females were affected. The age range was from 43 years to 89 years. Most patients had a history of various malignancies and received IV administered BIS, but 7 cases had no history of malignancy and were being treated with an oral dose form for osteoporosis. This was the first report of the oral dose form leading to BON. The small number of cases in the report may indicate that the risk of the complication is very low with the oral dose form, or it may represent underreporting of BON in patients taking oral dose forms. The disease was described as resembling osteoradionecrosis seen following radiation to the head and neck. The most common presenting symptoms were either a nonhealing extraction socket or an alveolar bone exposure. Oroantral fistula formation secondary to necrosis in the posterior maxillary area occurred in several patients. Radiographs revealed a mottled radiographic appearance with evidence of sequestrum. Six patients had abnormal bone in pre-extraction radiographs, suggesting alveolar changes prior to tooth extraction. Since some patients had received BIS as part of cancer chemotherapy, it was thought that the necrosis may represent metastatic cancer. However, a biopsy of lesions showed no evidence of malignancy. Most patients presented with pain and exposed bone following previous tooth extraction, but 9 patients (14%) had no history of recent dental surgery and had spontaneous breakdown and exposure of necrotic alveolar bone with no known cause. Conservative debridement of the bone and administration of antibiotics were not effective in resolving the disease and most patients required surgery to remove affected bone. Five patients had persistent necrosis of alveolar bone or new regions of bone necrosis, although they were no longer taking BIS, so discontinuing the drug didn't seem to help resolve the condition. All patients on oral BIS were managed with sequestrectomy (removal of exfoliated bone); none had to have resection of the affected area. This infers, perhaps, less serious damage to alveolar bone with the oral dose form. The authors concluded that dentists should be aware of this formerly unrecognized potential complication of BIS therapy and should monitor patients for untreated dental disease as a strategy to prevent the future need for tooth extraction or osseous surgery. A follow-up of Ruggiero's cases includes information that he now has 130 cases, with 16 cases of ONJ in patients taking oral dose forms of BIS (S. Ruggiero, DDS, email communication, September 25, 2005). This is still a very small group since over 21 million prescriptions for alendronate were prescribed in the United States in 2004 (http://www.pharmacytimes.com/article.cfm?ID=2534) and over 6 million prescriptions of risedronate. Risk factors leading to development of BON are unclear at this time and the appearance of the ADR developing spontaneously in clients with no dental disease is troubling.



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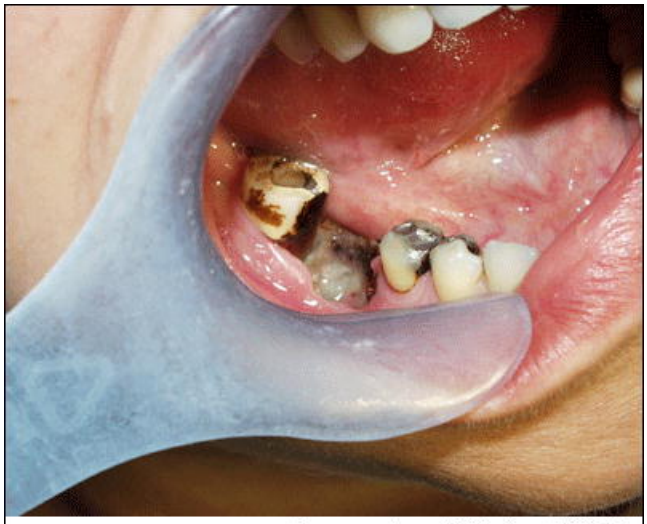
In February 2005, Bagan et al published a report of 10 cases of BON that developed following cancer chemotherapy. [12] All 10 cases had mandibular involvement and 5 had maxillary involvement as well, with an average of 2 painful areas of exposed bone. In 7 patients, tooth extraction preceded the onset of ONJ. Two patients developed oroantral communications and another developed a cutaneous fistula to the neck with suppuration. Histopathological diagnosis was chronic osteomyelitis with no evidence of metastatic disease in the jaws. All patients had received a BIS as part of the cancer chemotherapy and a BIS was the only drug used by all patients. They concluded that there appears to be a relationship with the use of BIS and subsequent development of ONJ.

Another case report in February 2005 from Canada described the development of ONJ following tooth extraction in a client with a history of BIS therapy. [13] They recommended that medical professionals should request that a dental examination be completed before prescribing BIS therapy.

In April 2005, a report from Australia, Adverse Drug Reactions Advisory Committee, Department of Health and Ageing, identified 13 cases of BON reported to the Agency.[14] Twelve patients received IV administered BIS therapy as part of cancer chemotherapy and one took oral alendronate (Fosamax) for osteoporosis. Time from administration of drug therapy to onset of ONJ ranged from one month to more than 4 years. Four cases involved the mandible, 2 in the maxilla, and the others did not specify the location, other than the "jaw." Four reports documented that dental extraction occurred in the months before the onset of BON. One patient had teeth extracted because they became loose during BIS therapy. A further report to the Agency stated that onset of ONJ occurred, in some cases, before dental extraction. They reported that the condition caused chronic pain, dysfunction and disfigurement, and that no treatment has been consistently effective. Withdrawing the BIS did not seem to hasten recovery. Six cases had not recovered following dental management, one case was slowly improving, and 6 case reports did not comment on the outcome of therapy. The medical officer in charge of the governmental committee recommended that necessary dental treatment be completed before BIS therapy begins, as a measure to prevent BON.



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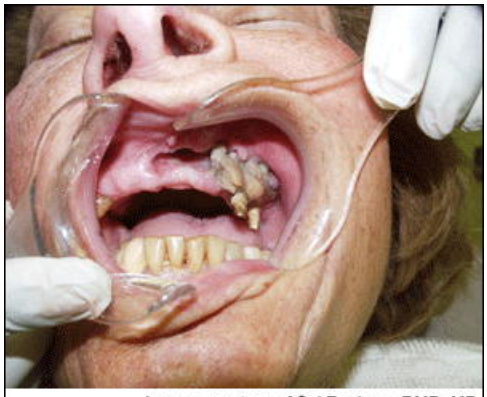
In the same issue of the medical journal, a group of oral surgeons reported on 5 ONJ cases from 2003 who were treated in the Oral and Maxillofacial Surgery Unit at Royal Adelaide Hospital, South Australia, with painful exposed bone in the maxilla or both the maxilla and mandible.[15] Bisphosphonates involved included IV pamidronate (Aredia) or an oral daily dose of 40 mg alendronate (Fosamax), which is the recommended dose for Paget's disease. Duration of therapy was 6 months to 6 years. Histology revealed no evidence of metastatic malignancy or Paget's disease from the affected sites in the jaws. Only 2 of the 5 cases resolved with treatment and those were treated with local debridement and removal of sequestrum. Of the cases that did not resolve with treatment, 2 received hyperbaric oxygen treatment. Hyperbaric oxygen therapy has been reported to be helpful in treating radiation-induced osteonecrosis of the jaw. The outcome following hyperbaric oxygen therapy was not identified in the report.

A recent report involving periodontally involved clients describes BON in 9 clients with a history of various malignancies who took IV administered BIS treatment.[5] The mandible was affected in all cases and 2 cases had maxillary involvement, as well. All clients developed ONJ following tooth extraction of hopeless periodontally-involved teeth. In 2 clients, the lesions appeared spontaneously in edentulous areas. The duration of BIS therapy ranged from 10 months to 70 months. The time of extraction to diagnosis of BON ranged from 3 months to 12 months. All cases, but one (who died due to progression of metastatic bone disease), were treated with debridement and cyclic oral antibiotics. The majority of patients experienced regression of pain and local infection, although despite treatment, areas of exposed bone persisted in all cases.

The most recent case report by Marx and associates includes 119 cases.[16] The vast majority of patients had received IV administered BIS as part of cancer chemotherapy and 3 cases took alendronate (Fosamax) for osteoporosis. The mean time from initial BIS administration to symptomatic bone exposure ranged from 9.4 months (IV dose forms) to 3 years (oral dose form). The posterior molar area of the mandible was involved most often, although some patients had BON in both arches or exclusively in the maxilla. Most patients presented for dental examination due to pain, although BON was discovered during routine oral examination or through self-examination in about 30% of patients. Precipitating events leading to development of BON, from those most common to least common, included tooth extraction, periodontitis, periodontal surgery, dental implants, and endodontic surgery. Spontaneous bone exposure with no recent history of dental treatment occurred in about 25% of cases. Pain was controlled using a regimen of antibiotics and chlorhexidine mouthrinse, although exposed bone remained in all cases.



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Reports of BON are being published in a variety of countries outside the United States There are reports in Australia (www.mja.com.au/public/issues/182_08_180405/pur10144_fm.html), (www.mja.com.au/public/issues/182_08_180405/car10429_fm.html); Canada (www.cda-adc.ca/jcda/vol-71/issue-2/111.pdf); Singapore (www.annals.edu.sg/pdf200409/V33N4p48S.pdf); Europe (http://annonc.oxfordjournals.org/cgi/content/extract/16/7/1207); Israel[17], Germany,[18] and Italy.[5]

Most likely, an accurate report of the worldwide prevalence of BON is unknown since only 1% to 10% of ADRs are reported to the FDA and other drug safety reporting agencies (FDA Medwatch, personal e-mail communication, November 7, 2005).

Mechanism of Action of Bisphosphonates and ONJ Complication

Bisphosphonates (BIS) are prescribed for prevention of bone resorption in metastatic malignant disease and other osteolytic diseases, and to increase bone density and reduce fractures in osteoporosis. The precise mechanism attributed to inhibition of bone resorption of BIS is unclear. BIS bind to bone and are very slowly metabolized. They are internalized by osteoclasts in the process of bone resorption and the life span of these cells and their activity are diminished. Additionally, osteoclastic breakdown of necrotic bone is inhibited. These combined effects reduce bone resorption which is the reason for Food and Drug Administration (FDA) approval of BIS to treat osteoporosis and other disease conditions where osteolysis occurs. BIS are reported to be helpful in preventing loss of bone density and fractures in the hip, spine, and other skeletal regions, but in the jaw, where osteoclastic remodeling of bone is natural in the dynamic cycle of alveolar bone maintenance, this depression of osteoclastic activity may impair the structure of jaw bone in a manner as yet unidentified. As diseased bone is not removed (by depression of osteocytes) and new bone is formed (by unaffected osteoblasts), the result is that diseased bone is "walled off" and healthy bone is laid over diseased bone.[4] It was believed up until recently that oral BIS protected long bones and spinal bone and that only the jaw was affected adversely by BIS drugs. However, a group from the Center for Mineral Metabolism and Clinical Research recently reported 9 cases of spontaneous nonspinal fractures in patients after 1 year to 8 years of alendronate (Fosamax) treatment.[19] Six of these cases displayed either delayed or absent fracture healing for 3 months to 2 years during therapy. Histological examination revealed diminished matrix synthesis, suppressed bone formation, with absent or reduced osteoblastic surface in most patients. They concluded there is a possibility of severe suppression of bone turnover during long-term alendronate therapy, resulting in increased susceptibility to and delayed healing of nonspinal fractures.

Physiology of Alveolar Bone Turnover.

It is well known that remodeling of bone in the jaws via osteoclastic and osteoblastic activity is a normal physiologic process. The osteoblast secretes both the collagen and mineral, which form the mineralized bone. When osteoblasts are

entrapped within the developing bone and become surrounded by this mineralized bone, they are termed osteocytes. The cellular change results in the osteoclast surrounded by this mineralized bone within cavities called lacunae. The life span of the osteoclast is about 150 days. The osteoclast resorbs the nonvital bone and releases growth factors, which induce differentiation of osteoblasts capable of new bone formation. The interruption of this cycle by the bisphosphonates' (BIS) action, which inhibits bone resorption, may result in an accumulation of nonvital osteoclasts and microfractures of old mineral matrix.[8]

The mechanism involved in bisphosphonate-associated osteonecrosis of jaw (BON) is unknown. The leading theory to explain the mechanism suggests that it is caused by cessation of bone remodeling and bone turnover by the inhibition of osteoclasts by BIS.[16] One postulation is that it may be due to an antiangiogenic effect leading to inhibition of blood vessel formation within bone.[20] During the process where a BIS reduces the vascular supply to bone (by inhibiting the formation of blood vessels, endothelial cells, fibroblast growth factor, and endothelial growth factor), this may promote an avascular bone necrosis effect. Because daily bone remodeling related to the periodontal ligament results in a greater blood supply and a faster bone turnover rate in the jaw than in other bones in the body, BIS are highly concentrated in the jaws. Thus, exposed necrotic bone in the jaws may represent a direct result of BIS action on the daily remodeling and replenishment of bone.[16] The rich blood supply in the oral cavity generally promotes rapid healing of oral wounds. Reduction of this blood supply, leading to delayed wound healing, may be a major factor in BON. Observations of "bone that does not bleed normally" have been reported.[11]

Prevention and Management

The American Academy of Oral Medicine has proposed clinical guidelines for prevention and management of bisphosphonate-associated osteonecrosis of jaw (BON).[21] The recommendations are based on expert opinion as there are no available randomized controlled trials to support prevention and management strategies. Prevention of BON is not possible at this time, but the incidence possibly can be reduced by treating all dental disease prior to initiating bisphosphonate (BIS) therapy. It has been noted that the most common clinical history associated with this process is absent or delayed hard- and soft-tissue healing after dental extractions.[7,11,22] In patients who develop BON spontaneously, the most common initial complaint is the sudden presence of intraoral discomfort and the presence of roughness irritating the tongue in the area of necrotic bone. Nonsurgical dental procedures should be used to manage osteonecrosis of the jaw in patients reporting a history of BIS therapy.[16] The majority of patients (90.1%) gained a pain-free state (although exposed bone remained) using a regimen of antibiotics (when secondary infection developed) and a daily 0.12% chlorhexidine mouthrinse. The recommendations of the AAOM include implementation of measures to *prevent* the condition in patients at risk for developing BON with the dentist and physician working collaboratively.[21] When the collaborative relationship is established, a preventive/management protocol should include:

Prevention:

- A dental examination should be recommended by the MD/oncologist before intravenous route of administration (IV) BIS therapy is initiated.
- " Patients who have been given oral forms of a BIS within the last 3 months should have a complete dental evaluation.
- Dental therapy to remove disease or inflammation should be provided before the risk of developing BON increases.
- Dentists should follow existing guidelines for a dental consultation for the prevention of oral complications of cancer therapy (chemotherapy, radiation therapy, pre-hematopoietic stem cell transplantation). Elimination of all potential sites of infection must be the primary objective of the consultation. The goal of therapy should be to attain oral and dental health so that during the active phase of BIS therapy, only 3 to 6 months of maintenance hygiene appointments will be necessary.

- A comprehensive extraoral and intraoral examination should be performed by a dental professional, including a full radiographic series and panoramic radiograph, to assist in the diagnosis of dental disease, the evaluation of third molars, and the identification of metastatic cancer and other bone pathology.
- The periodontal health status should be determined and appropriate therapy provided. Pocket elimination is of importance to reduce plaque accumulation, minimize chronic periodontal inflammation, and minimize acute periodontal infections.
- Extraction of teeth should be completed as soon as possible.
- Restorative treatment to eliminate caries and defective restorations should be completed. Crowns and extensive fixed prosthodontic appliances may not be appropriate for some patients. Prosthodontic appliances should be evaluated for fit, stability, and occlusion, and adjustments made when necessary.
- Prophylaxis should be performed and oral health instructions given, including the possible, but uncommon adverse effect of BON in patients who have taken BIS medications. Instructions should include early signs of BON so the patient may be able to recognize the condition should it develop. This is an essential component of the regimen and one in which the dental hygienist can play a major role.
- " Periodic maintenance visits should be included in the treatment plan to reinforce the importance of oral hygiene maintenance and to conduct a new oral examination. It has been estimated that BIS can remain within the bone for at least seven, possibly more, years.

Management:

When lesions suggestive of BON are reported the following is recommended:

- Routine restorative care may be provided and local anesthetics used as necessary.
- Scaling and prophylaxis should be done as atraumatically as possible, with gentle soft-tissue management.
- Avoid dental extractions if possible unless the teeth have a mobility score of 3 or greater. Extractions should be performed as atraumatically as possible. Patients should be followed up weekly for the first 4 weeks afterward, then monthly until the sockets are completely closed and healed. If there is an indication for antibiotic use (due to secondary infection), amoxicillin (alone or in combination with clindamycin) may help to reduce the incidence of local infection.
- Teeth with extensive decay should be considered for endodontic therapy. They should be prepared as overdenture abutments. The crown should be excised at the gingival margin. This is especially important in patients with a history of previous extractions that resulted in BON. In these patients, extraction should be avoided.
- The area of BON should be treated only with the objective of eliminating sharp edges of bone that may traumatize soft tissues, especially when the lingual aspect of the posterior mandibular arch is involved. Superficial debridement may be performed, as needed, to eliminate areas that may further traumatize adjacent tissues.
- Clinicians should follow up with the patient every 2 weeks to 3 weeks to reevaluate the areas and to ensure that suppuration has not developed.
- If the area around the exposed bone exhibits tender erythema and suppuration and/or sinus tracts, the patient should be treated with antibiotics until the areas resolve. Microbiologic culture and sensitivity tests may be helpful; however, the clinician must realize that culture results do not always guarantee microbiological etiology since host oral flora can colonize the necrotic bone surface.
- The use of a chlorhexidine mouthrinse 3 or 4 times a day is recommended to reduce bacterial load and colonization. Irrigation of areas of BON with chlorhexidine may be performed in the evaluation visit.
- A surgical approach with the goal of removing necrotic bone and closing the site with a healthy mucosa may be considered for patients with multiple myeloma who require hematopoietic stem cell transplantation. In a patient with exposed necrotic bone, the risk of undergoing high-dose conditioning chemotherapy in preparation for transplantation is unclear. The necrotic area may act as a portal of entry for bacteria; it may traumatize the adjacent soft tissues and cause ulceration, forming another portal for bacterial contamination. Furthermore, surgical manipulation may not

lead to the closure of the necrotic site but to further increase of the osseous breakdown and dehiscence. If a surgical procedure is needed, patients should be informed of the potential risks and benefits.

- The role of hyperbaric oxygen therapy in BON is unknown at this time.
- Soft vinyl appliances or obturators may help cover exposed necrotic bone to prevent further trauma to soft tissues. These appliances should not rest on the necrotic bone. The interior portion of the flanges must be relieved so as not to deliver pressure to the diseased tissues, but rather to serve as a barrier to protect them. Appliances should not be designed for use during mastication.
- Existing prosthetic appliances should be reevaluated to ensure they are properly fitted. Relining a denture with a soft liner to promote a better fit and to minimize soft-tissue trauma and pressure points is recommended.
- Odontogenic infections should be treated aggressively with systemic antibiotics. When possible, identification of the responsible microorganisms and respective antibiogram (chart produced by laboratories, which documents the percentage of microbes that are sensitive to particular antibiotics) is indicated. If empiric therapy is to be used, although penicillin is the first-choice antibiotic in dentistry, amoxicillin and/or clindamycin provide better bone penetration and a wider spectrum of coverage.

At this time, management of BON is empirical and based on individual experience. As new information becomes available and the results of well-designed clinical trials are known, better guidelines and management protocols based on results of scientific evidence will be developed. At the present time, dentists, physicians, and oncologists should establish communication to ensure patients are referred for oral examination prior to initiation of BIS therapy. The dental hygienist should be involved in the consultations to facilitate the communication of appropriate information in the oral health education care plan. Evidence indicates that the risk of BON may persist for years after discontinuation of the drug, so long-term follow-up is needed. The dental hygienist must be able to recognize signs of BON and assist the dentist in the maintenance and periodic evaluations of patients at risk for the condition. Patients who are receiving BIS drug therapy should be informed of the possibility of developing BON following routine dental treatment. A consensus must be reached among the patient, the dentist, and the physician before dental therapy is initiated.

Future Research

Research should be initiated to determine if there are radiographic features to identify the client at risk for BON. Since not all patients develop BON, determination of cofactors that increase the risk for development of the condition need to be made. Histologic studies to determine the extent of damage to alveolar bone should be completed in order to answer the following questions:

- Is alveolar bone adversely affected in all people who have taken a bisphosphonate (BIS)?
- Is healthy bone ever available in the jaw when BIS drugs have been received?
- How long after taking a BIS is bone likely to be affected?
- What factors place a person at risk for developing BON?

Reports continue to be published on bisphosphonate-associated ONJ.23,24,25,26 The International Myeloma Foundation conducted a Web-based survey in July 2004 to determine prevalence of ONJ with IV administered BIS (http://www.myeloma.org/main.jsp?type=article&tab_id=1&menu_id=0&id=1259). They report a 10% incidence among patients receiving zoledronic acid and a 4% incidence among patients receiving pamidronate.27 Dental authors are informing the medical community.22 Dentists are being cautioned regarding the need for accurate pulpal and periradicular testing procedures to establish a clear diagnosis before proceeding with endodontic treatment when clinical signs of ONJ are present in patients with a history of taking BIS drug therapy.28 In this report of 2 cases referred for endodontic therapy, medical evaluation determined that both clients with periapical disease who developed ONJ had received BIS therapy. Endodontic therapy and long- term antibiotic therapy did not resolve BON in these patients.28

Conclusion

Many questions remain concerning the degree of risk for future manifestation of bisphosphonate-associated osteonecrosis of jaw among the huge population who are taking bisphosphonate (BIS) drugs or who have done so in the past. The association between osteonecrosis of the jaw and BIS is not considered by some authors to be causal at this point. Further research needs to be completed to determine causality. Fortunately, there are other non-bisphosphonate drugs for prevention and treatment of osteoporosis that have not yet been reported to cause ONJ. These agents include raloxifene (Evista), calcitonin (Micalcin Nasal spray) and teriparatide (Forteo). Both Evista and Miacalcin affect the osteoclast to reduce bone resorption, but since there are no reports of ONJ with either drug, hopefully the action of these drugs is insufficient to cause the effect.

Note: Since this article was accepted for publication, a systematic review on BON has been published (Woo et al. Ann Intern Med. 2006;144:753-761), which represents a position paper of the American Academy of Oral and Maxillofacial Pathology. Recommendations for dental management concur with AAOM guidelines discussed in this article.

Other drugs in the bisphosphonate class are taken by mouth and include alendronate (Fosamax), risedronate (Actonel)... and a newly approved bisphosphonate for once/month dosing, ibandronate (Boniva). In January 2006 an IV administered dose form of Boniva was approved for patient who cannot swallow or sit upright for 30 minutes.

It is important for the oral health professional to be aware of this potential ADR in a client taking bisphosphonates because most of the affected patients had bone disease that was not detected by their physicians nor their oncologists.

Instructions should include early signs of BON so the patient may be able to recognize the condition should it develop. This is an essential component of the regimen and one in which the dental hygienist can play a major role.

Web Resources

Maxillofacial Center for Diagnostics & Research, Morgantown WVA [http://maxillofacialcenter.com/NICOhistory.html] Accessed 10/2005 International Myeloma Foundation (http://www.myeloma.org) Food and Drug Administration www.fda.gov/medwatch/safety/2005/zometa_deardentite_5-5-05.pdf Accessed 10/2005

Acknowledgements

Notes

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