The Link between Treatment with Bisphosphonates and Osteonecrosis of the Jaws. A Literature Review

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Abstract

The aim of this presentation is to review the literature concerning the link between drugs called bisphosphonates and the development of a condition called osteonecrosis of the jaws. The bisphosphonates are stable synthetic inorganic pyrophosphate analog drugs that have a high affinity for calcium and are used to treat patients with a variety of pathologies such as cancer and osteoporosis. Some reports linked them as a factor in the development of a condition called bisphosphonate-related osteonecrosis of the jaws, which has presented mostly in patients receiving the drug intravenously. However, oral administration of the drug presents itself as low-risk. This review suggests that any patient who plans to be treated with bisphosphonates should consult a dentist to ensure adequate oral health before treatment is indicated, especially if high doses by an intravenous route are prescribed, to avoid or reduce the need for any dental treatment while the patient is taking the drug and thereby prevent this pathology.

Key words: Bisphosphonate, osteonecrosis, effects, prevention

Introduction

Recently, a new secondary oral pathology called bisphosphonate-related osteonecrosis of the jaws (BRONJ); bisphosphonate-associated osteonecrosis (BON) or osteonecrosis of the jaw (ONJ) has been described in the medical-dental literature. In this paper, we will refer to the condition as BRONJ. Bisphosphonates are stable synthetic inorganic pyrophosphate analog drugs (*Table 1*) commonly prescribed for the treatment and prevention of various diseases such as Paget's disease, bone pain, hypercalcemia associated with malignancy, and osteolysis associated with metastatic bone disease, skeletal complications in patients with multiple myeloma, osteoporosis, and breast, lung and other cancers. This drug may be administered intravenously or orally; depending on the administration time and route used, this drug is presented as a risk factor in certain patient groups to develop BRONJ, especially in patients receiving it intravenously.

Literature Review and Discussion

Since late 2003 the clinical literature has reported a relation between cancer treatment and the appearance of necrosis of the jaws. This kind of necrosis could possibly be the result of an oral side effect of bisphosphonate treatment (Robinson and Yeo, 2004), especially in patients who receive intravenous bisphosphonates such as pamidronate (Aredia, Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) and zolendronic acid (Zometa, Novartis Pharmaceuticals Corp.) for some kinds of cancers (Hohneker and Bess, 2005; Katz, 2005; Ponte *et al.,* 2006). In the meantime, the clinical literature presents few cases of patients who developed BRONJ when treated orally with alendronate (Fosamax, Merck & Co., Inc., Whitehouse Station, NJ, USA) for the treatment of osteoporosis or osteopenia (Migliorati *et al*., 2005).

A clear definition of BRONJ is lacking, but it can be defined as an area of exposed bone that persists for more than six weeks (Sambrook *et al.,* 2006).

The clinical manifestation of this pathology (BRONJ), including signs and symptoms such as pain, soft tissue swelling, infection, drainage, bone necrosis (Robinson and Yeo, 2004; Hohneker and Bess, 2005; Migliorati *et al*., 2005; Katz, 2005; American Dental Association Council on Scientific Affairs, 2006; Ritter and Padilla, 2008), bone fracture, fever and lymphadenopathy (Ritter and Padilla, 2008) was generally reported after some dental treatment such as extraction. In some other cases BRONJ developed spontaneously (Junquera and Granizo, 2008). Trauma induced by prosthodontic

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Table 1. Bisphosphonates on the market (USA)

Brand Name	Generic Name	Administered
Actonel	risedronate	orally
Boniva	ibandronate	orally
Didronel	etidronate	orally
Fosamax	alendronate	orally
Fosamax Plus D	alendronate	orally
Skelid	tiludronate	orally
Aredia	pamidronate	intravenously
Bonefos	clodronate	intravenously
Zometa	zoledronic acid	intravenously

Table 2. Antibiotic treatments that may be used when BRONJ is suspected*

Patient Type	Suggested Drug	Oral Regimen
Patient not allergic to penicillin	amoxicillin, combined with metronidazole if necessary	1500 mg/day for 14 days 750 mg/day for 14 days
Patient allergic to penicillin	clindamycin or azithromycin	900 mg/day for 14 days 250 mg/day for 10 days

*Modified from the American Dental Association Council on Scientific Affairs, 2006.

appliances has also been implicated in the process (Migliorati *et al*., 2005); many of these patients were also receiving chemotherapy and corticosteroids (Hohneker and Bess, 2005).

The mode of action of these drugs is unclear but they are known to inhibit osteoclastic function, to induce apoptosis of osteoclasts, to maintain bone density, to inhibit differentiation of bone marrow precursors into osteoclasts, and to have anti-angiogenic effects. The half-life of bisphosphonates in bone has been estimated to be greater than 10 years because they are administered over months to years (Katz, 2005; Junquera and Granizo, 2008).

Orally administrated bisphosphonates are often used to treat patients with osteoporosis, while intravenous bisphosphonates are used to treat patients with cancer (Migliorati *et al.,* 2005). Patients receiving intravenous bisphosphonates are more susceptible to developing BRONJ than those receiving them orally (Migliorati *et al*., 2005; American Dental Association Council on Scientific Affairs, 2006). This result could be explained because the absorption of the drug is less than 1% via the gastrointestinal tract, and there is a very low risk of developing BRONJ for patients using the oral route (American Dental Association Council on Scientific Affairs, 2006), whereas more than 50% of the dose administrated intravenously is bioavailable for incorporation into the bone matrix (American Dental Association Council on Scientific Affairs, 2006).

The evidence displays that there is some connection between patients treated with intravenous bisphosphonates and the possibility of developing BRONJ. In the meantime, patients with osteoporosis and Paget's disease who take oral bisphosphonates have a significantly reduced risk of fracture and other skeletal complications (Sambrook *et al.,* 2006), and we cannot deny the beneficial effect of this drug on the alveolar bone for those who take it orally (Palomo and Bissada, 2007).

Because in most cases the triggering event for developing BRONJ is a recent history of a dental procedure such as extraction (for most patients who consumed this drug intravenously), prevention emerges as a viable factor to avoid the appearance of BRONJ (Migliorati *et al.,* 2005; Ponte *et al.,* 2006; Sambrook *et al.,* 2006). For this reason, a dental examination should be considered prior to starting treatment with bisphosphonates (Hohneker and Bess, 2005; Migliorati *et al.,* 2005; Fernandez *et al.,* 2006; Sambrook *et al.,* 2006; Palomo and Bissada, 2007; Ritter and Padilla, 2008). It appears to be prudent to recommend assessment of adequate oral health at least one month in advance of starting treatment with bisphosphonates (Ponte *et al.,* 2006), especially in patients whose drugs will be administered intravenously. Once patients are already undergoing treatment with

bisphosphonates, dental visits should be scheduled on a regular basis to ensure adequate oral maintenance; these visits could be every three to six months (Migliorati *et al.,* 2005; Ponte *et al.,* 2006). However, each case should be treated independently and according to individual patient needs. Routine dental treatment should not be modified solely on the basis of oral bisphosphonate therapy (American Dental Association Council on Scientific Affairs, 2006), but caution should be used and the risks versus the benefits of treatment needed by the patient carefully evaluated.

A blood test C-terminal telopeptide that measures bone turnover is being studied as a potential test to determine a patient's risk of developing BRONJ (Ritter and Padilla, 2008). Levels of the C-terminal telopeptide of type I collagen (b-CTx) greater than 150 pg/mL in fasting blood samples indicate that any type of surgery may be performed with minimal risk and without having to discontinue the drug treatment (Junquera and Granizo, 2008); nevertheless, this parameter still requires more scientific evidence to confirm its validity.

Discontinuing bisphosphonate therapy is controversial because of the long-term effect of the drugs on bone (Hohneker and Bess, 2005; Migliorati *et al.,* 2005; Ritter and Padilla, 2008). If a patient needs treatment, we must use conservative techniques, proper sterile techniques, and oral rinses (American Dental Association Council on Scientific Affairs, 2006). A single antibiotic dose of 2 g amoxicillin is recommended (Sambrook *et al.,* 2006).

Before undergoing any invasive procedure that involves manipulation of the bone or periosteum, the patient should be informed about the risk of developing BRONJ (American Dental Association Council on Scientific Affairs, 2006). Scaling, prophylaxis and dental extraction should be performed with as little trauma as possible, using gentle soft tissue management and achieving primary wound closure whenever possible (Robinson and Yeo, 2004; Migliorati *et al.*, 2005). Endodontic treatment instead of extraction (Katz, 2005; American Dental Association Council on Scientific Affairs, 2006; Sambrook *et al.,* 2006) and bridges and partial dentures versus implant treatment should be discussed with the patient (American Dental Association Council on Scientific Affairs, 2006).

Restorative procedures can be performed in these patients, and prosthodontic appliances should be adjusted for fit as needed (American Dental Association Council on Scientific Affairs, 2006). Crowns should be cut off at the gingival margin (Migliorati *et al.,* 2005).

If any patient presents with unexpected pain, purulence or active sequestration after a dental procedure, antibiotics may be used: amoxicillin and clindamycin or other combinations may help to reduce the incidence of local infection (American Dental Association Council on Scientific Affairs, 2006) (*Table 2*).

The treatment of this painful clinical condition is very difficult and prolonged (Robinson and Yeo, 2004). The compromised area should be treated with the objective of eliminating sharp edges of bone that may traumatize soft tissue; superficial debridement may be performed if it is necessary to eliminate areas that may further irritate adjacent tissues (Migliorati *et al.,* 2005). If the area around the exposed bone exhibits tender

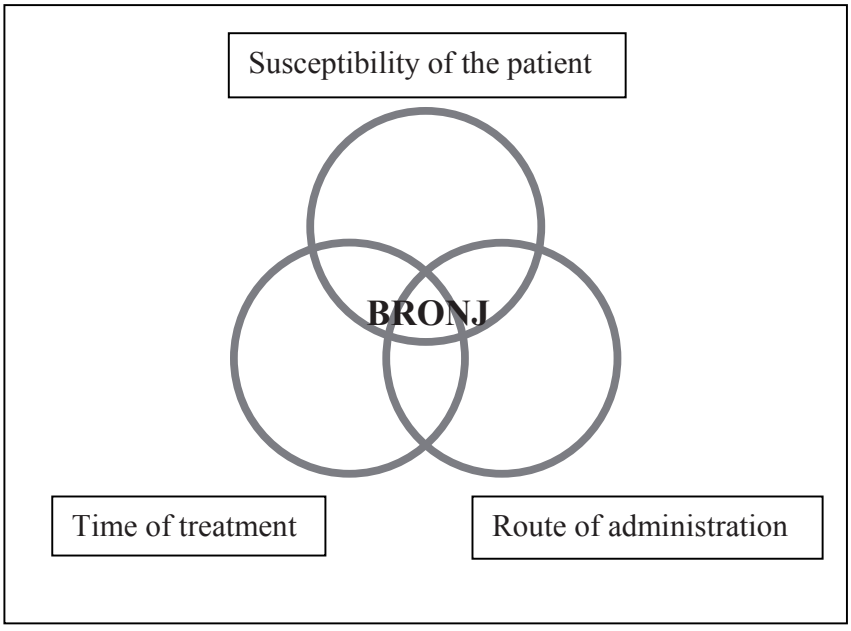

Figure 1. Development of bisphosphonate-related osteonecrosis of the jaw (BRONJ).

erythema, suppuration or sinus tracts, the patient should be treated with antibiotics. Microbiologic culture can help to identify the possible microbial flora present in the affected area (Migliorati *et al*., 2005; Junquera and Granizo, 2008). Removing necrotic bone and closing the site with healthy mucosa may be considered, especially in patients with multiple myeloma (Migliorati *et al*., 2005). Soft vinyl appliances or obturators may help cover the exposed necrotic bone to prevent further trauma to soft tissues; however, these appliances must not rest on the necrotic tissue (Migliorati *et al*., 2005).

An oral rinse of chlorhexidine is also recommended (Migliorati *et al*., 2005; Katz, 2005; Junquera and Granizo, 2008). Administer oral non-steroidal anti-inflammatory drugs (Junquera and Granizo, 2008). Unfortunately, hyperbaric oxygen, used to aid in the treatment of other bone pathologies, does not appear to promote healing in this situation or is controversial (Robinson and Yeo, 2004; Migliorati *et al*., 2005; Katz, 2005; Freiberger *et al*., 2007).

There is no scientific evidence to support the idea that discontinuation of the bisphosphonate treatment would promote healing of necrotic bone tissues in the oral cavity (Migliorati *et al.,* 2005).

Conclusions

This review of the literature concludes that the occurrence of bisphosphonate-related osteonecrosis of the jaws (BRONJ) is affected by factors such as the susceptibility of the patient, the time of the treatment and the administration route of the drugs (*Figure 1*). This is a new disease entity characterized by symptoms and signs that include pain, soft tissue swelling, infection, drainage, bone necrosis, bone fracture, fever and lymphadenopathy. Many of the patients who developed BRONJ were also receiving chemotherapy and corticosteroids, and their recent medical history before the appearance of BRONJ included a treatment such as tooth extraction.

Patients treated intravenously with bisphosphonates such as pamidronate and zolendronic acid have a greater risk factor for developing BRONJ, while patients treated orally have a significantly decreased risk, and dental treatment can be applied. However, special care must be provided for those patients who are taking alendronate orally.

All patients who will receive bisphosphonates should see the dentist at least one month prior to starting any treatment to avoid and/or reduce the risk of developing BRONJ. Medical/dental communication must be constant, the blood test to detect the C-terminal telopeptide of type I collagen must be performed, and the patient must be informed of the possible risk of developing BRONJ. If they are already being treated with bisphosphonate (especially by the intravenous route), the patient should sign a detailed informed consent.

Because bisphosphonates are deposited for long periods of time in the bone, no scientific data support the idea that discontinuing this treatment can prevent the appearance of BRONJ. Nor are there any data to suggest that once BRONJ appears, discontinuing the drug will help the healing process occur more quickly.

There are no explicit recommendations that contraindicate the placement of intraosseous implants, but the insertion of a dental implant before intravenous administration of bisphosphonates cannot be recommended if the osseointegration period is not expected to have concluded before bisphosphonate administration.

The treatment of this condition may include the use of antimicrobial rinses, systemic antibiotics, surgery, pain control, microbiologic culture, and antibiotic susceptibility testing.

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