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Bisphosphonate Induced Osteonecrosis of the Jaw

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ABSTRACT

Osteonecrosis of the jaw is an important but uncommon side effect of bisphosphonate therapy. It may result in disabling and sometimes disfiguring complications that may affect the quality of life of patients. It occurs more frequently in patients on intravenous nitrogen-containing forms of bisphosphonates and is thought to be time and dose dependent. Currently, there is no recognized effective treatment apart from controlling pain and accompanied infection. Prevention of this complication is therefore important. In this article, some of the key issues of bisphosphonate-associated osteonecrosis of jaw are being reviewed.

Keywords: Osteonecrosis, Bisphosphonate, Jaw, Osteogenesis Imperfecta.

INTRODUCTION

Osteonecrosis means areas of dead bone. It may occur in one or more bones, particularly the hip or knee, as a result of treatment with cortisone-like drugs such as prednisone, or after injury.

Osteonecrosis of the Jaw (ONJ) has recently been reported in people receiving intravenous or oral bisphosphonate drugs. Osteonecrotic or dead bone in the jaw becomes exposed after a routine tooth extraction or, in about 40% of the cases, from a denture rubbing against the mucosa in the mouth. The area of necrotic bone is very painful to touch. It heals very slowly. There are a number of bisphosphonates currently used for people with Osteogenesis imperfect (OI) on an "off-label" basis, or as part of a clinical trial. These include: pamidronate and zoledronic acid given by intravenous infusion, and alendronate, risedronate, and ibandronate sodium given in tablet (oral) form. At this time, ONJ appears to be a rare complication of bisphosphonate treatment. Millions of people with osteoporosis are being treated with bisphosphonates, and ONJ appears to be a complication in an extremely small percentage of these people.

Most people with ONJ have received frequent doses of intravenous pamidronate or zoledronic acid for cancer in bone. Some people have developed ONJ from oral bisphosphonates, which in some cases were used to treat osteoporosis. People who have cancer, and receive frequent high-doses of intravenous bisphosphonates over an extended period of time, to counteract the bone loss from chemotherapy and radiation, and to reduce bone invasion by cancer cells. The dose for these people generally is much higher, and the dosing schedule more frequent, (typically once a month for several years) than those typically given for treatment of low bone density disorders such as osteoporosis or OI.

People who receive frequent, high doses of intravenous bisphosphonates over a long period of time and have periodontal (gum) disease, poor oral hygiene, damage to dentures, or invasive oral surgery, such as dental extractions.

People who are taking intravenous bisphosphonates for cancer treatment, people who have received chemotherapy or corticosteroids, and those with poor oral hygiene, may have an increased risk of ONJ if they undergo invasive dental procedures.

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Actions of Bisphosphonates

Bisphosphonates are powerful inhibitors of osteoclastic activity. They are analogues of inorganic pyrophosphates with low intestinal absorption, are excreted through the kidneys without metabolic alteration, and have a high affinity for hydroxyapatite crystals. Because they are incorporated into the skeleton without being degraded, they are remarkably persistent drugs; the estimated half-life for alendronate is up to 12 years. Alendronate, risedronate, pamidronate, zoledronic

acid, and ibandronate, which are called aminobisphosphonates, have much higher potency because they contain nitrogen in a side chain.[1]
Chemically, BPs represents pyrophosphate analogs possessing two variable regions, R1 and R2 on the carbon atom of BPs molecule attached to basic P-C-P structure. This allows variations in molecular structure and a range of potency corresponding to the changes in the structure. The group occupying R1 position, usually hydroxyl, enhances the molecule's affinity to bone (calcium crystals) and the variable group at R2 position decides its antiresorptive action, specifically its potency and efficacy. [Figure 1] Classically, BPs have been classified into: non-nitrogen containing BPs (NNBP) and nitrogen containing BPs (NBP) depending on the presence or absence of nitrogen in their R2 group.[2]

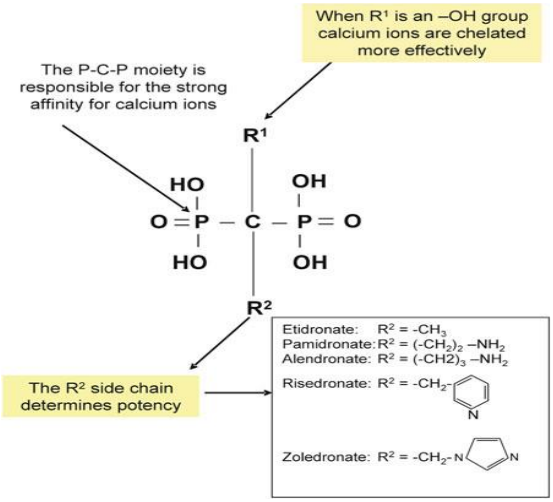

Figure 1: Illustration of the chemical structure of the involved bisphosphonates. The ligands R1 and R2 vary between the different compounds and determine the class and potency of the compound. Altering the R2 side chain changes the antiresorptive potency, particularly when it contains at least one nitrogen atom.

The bisphosphonates are divided into two subclasses based on whether or not one of the side chains contains a nitrogen atom. The less potent non-nitrogen containing bisphosphonates (e.g. etidronate, clodronate, tiludronate) are believed to induce osteoclast cell-death by the formation of cytotoxic metabolites of adenosine triphosphate (ATP) that accumulate and interfere with intracellular metabolic enzymes.The potent nitrogen-containing bisphosphonates (e.g. pamidronate, alendronate, risedronate, ibandronate, zoledronic acid) on the other hand inhibit the mevalonate pathway. By blocking the enzyme farnesyl diphosphate synthase an intracellular shortage is created of amongst others geranyl diphosphate and farnesyl diphosphate, both required for the post-translational lipid modification (prenylation) of small signaling proteins with GTPase activity. The resulting dysfunction hampers the regulation of osteoclast morphology and activity, leading to poor cell functioning and apoptosis.[3]

Clinical staging of ONJ

Stage 0 Subclinical condition, microscopically characterized by initial hypocellularity and apoptosis of osteoclasts, reduction of endosteal osteoblasts, and reduction of osteoid tissue synthesis

Stage 1a Painless bone exposure<1 cm
Stage 1b Painless bone exposure>1 cm
Stage 2a Single exposed area<2 cm associated with pain and/or clinical signs of infection
Stage 2b Single exposed area>2 cm associated with pain and/or clinical signs of infection
Stage 3a Multiple areas of bone exposure without clinical signs of osteolysis, oral cutaneous fistulas, or pathological fractures
Stage 3b Area of bone exposure>3 cm or areas with clinical signs of osteolysis or oral cutaneous fistula, or pathological fracture [Table 1][4]

Table 1: Clinical staging of BRONJ and the treatment proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS)

BRONJ staging and treatment strategies		
Staging	**Clinical presentation**	**Management**
At risk	No exposed bone	Patient education
1	Asymptomatic exposed bone with little inflammation of soft tissues	Patient education, antibacterial mouth rinse, and careful follow-up
2	Exposed bone, inflammation or infection of adjacent soft tissues	Patient education, antibacterial mouth rinse, antibiotic therapy, superficial bone debridement, and careful follow-up
3	Exposed bone with pain, inflammation or infection of adjacent soft tissues, possible osteolysis extending to the inferior border of the mandible, pathologic fractures and extra-oral fistula	Patient education, antibacterial mouth rinse, palliative surgeries, and careful follow-up

Etiopathogenesis

So far, the etiopathogenesis of ONJ remains uncertain. It is worth noting that BPs act at the following levels: physicalchemical, tissue, cellular, and molecular.Studies have reported that ONJ is secondary to the mechanisms of action of BPs involving anti-osteoclastic and anti-angiogenic activities, which alter bone metabolism, inhibiting bone resorption and reducing bone turnover. In addition, it is worth noting the anatomical peculiarities of the maxillary and mandibular bones, separated from the oral cavity by a thin mucosa, a barrier that can be easily broken by physiological activities, such as mastication.[5]
These peculiarities are more marked in the mandible than in the maxilla, which could explain the higher prevalence of ONJ in the former. The

mouth is colonized by a large number of bacteria, and the maxillary bones are frequently involved in septic processes of periodontal or pulpar origin. In the presence of BP accumulation capable of decreasing bone metabolism, tissue repair following an induced or a physiological trauma does not occur properly, leading to the exposure of a necrotic bone area to the oral environment. Thus, the hypothesis that best explains the development of ONJ would be an alteration in bone turnover associated with the particular characteristics of the maxillary bones, such as their mucosal coating, frequent risk of infection, and constant potential for trauma.[6]

Some authors have discussed the appearance of ONJ and infection by Actinomyces, and have reported several cases associating bone necrosis and osteomyelitis caused by that microorganism.[7]

The following predisposing factors for the development of BRONJ have been reported: BP type, BP administration route, BP use duration, concomitant administration of other drugs (mainly corticosteroids, chemotherapeutic drugs, and estrogen) and invasive dental procedures.

Anti-angiogenic and chemotherapeutic drugs, such as thalidomide or bevacizumab, have been suggested as factors that can predispose to ONJ or increase the risk of developing ONJ.

Some studies have reported that, when using zoledronic acid for controlling bone metastases, approximately six doses of intravenous BP per month are associated with the risk of developing ONJ. For BPs orally administered, such as alendronate, three years or 156 week doses would be required for the development of ONJ. According to the authors, such difference is due to the low lipid solubility of BPs orally administered, which results in an intestinal absorption of only 0.63% of the drug. Orally administered BPs are accumulated slowly in the bones, and the clinical exposure of the necrotic bone does not occur before three years of BP administration, its incidence and severity increasing with each additional year of BP use.

The BP administration route can be associated with the occurrence of BRONJ. In patients using the intravenous route, the prevalence is of 1%–10%, while in those using the oral route the prevalence is of 0.00007%–0.04%. There is no doubt that the risk of BP users developing BRONJ is greater when the drug is intravenously administered as compared with the oral route. Both the American Dental Association (ADA) and AAOMS have confirmed that such risk is dose/time dependent.

This fact, however, is based only on the clinical observations of the authors.

The concomitant use of other drugs, such as corticosteroids and chemotherapeutic drugs, can potentiate the risk for developing ONJ.[8]

Duration of BP use, concomitant use of estrogen and age over 65 years can also potentiate the risk of ONJ.[9]

A multicenter retrospective study22 involving 78 patients with BRONJ has reported that most patients were on intravenous BPs for oncological treatment for over a year, and had received previous treatment with chemotherapy or steroids. Some theories try to explain that the lack of epithelial repair of intraoral exposed bone secondary to the use of BPs can be attributed to the toxicity of BPs on the epithelial tissue caused by the high concentrations of those drugs in the bone tissue.[10]

Diagnosis

Standardization of diagnostic criteria for this new clinical entity is important in order to facilitate future clinical and epidemiological research. In addition, a uniform definition for BRONJ will serve to distinguish this new clinical entity from other delayed intraoral healing conditions. Various organizations have proposed clinical definitions for BRONJ, all of which are analogous to each other. The AAOMS established a working definition for BRONJ that is fairly concise and specific. Patients may be considered to have BRONJ if all of the following three characteristics are present:

1. Current or previous treatment with a bisphosphonate;
2. Exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaws.[5]

Table 2: Imaging characterstics of ONJ[11]

Imaging Characteristics of ONJ	
Imaging Modalities	Imaging Characteristics
Radiography, CT	Osteolysis, sclerotic lesions, periosteal reaction, narrowing of the marrow space, involvement of the inferior alveolar canal, fractures
MR imaging	
T1-weighted	Typically decreased signal intensity
T2-weighted*	Variable: intermediate or slightly increased signal intensity in early disease; increased or decreased signal intensity in later stages of disease
Contrast material–enhanced	Variable: may correlate with the degree of signal intensity decrease on T1-weighted images; typically spares the low T2 signal bony sequestrum
Technetium 99m bone scintigraphy†	Areas of decreased uptake may be present in early disease; in later stages of disease, there is increased uptake with possible decreased central uptake

*Little information is available on the imaging features of early disease. Signal intensity changes may correlate with overlying exposed bone, chronicity of disease, and viability of bone.
†The ability to identify areas of decreased central uptake may depend on the size of the lesion and the camera type.

Treatment and Prevention

The microorganisms most frequently found in exposed bone are: Actinomyces, Veillonella, Eikenella, Moraxella, Fusobacterium, Bacillus, Staphylococcus, Streptococcus, and Selenomonas. All of them are sensitive to penicillin, which is, thus, the drug of choice for the non-surgical treatment of ONJ.[12]

The major goal of prevention for patients at risk for BRONJ or of treatment for those who have BRONJ is to preserve their quality of life, controlling pain and infections, and avoiding the development of new necrotic areas.[5]

The risk is associated with the accumulation of drug doses during years of treatment. Patients should undergo careful dental evaluation, including

radiographic exams, and be instructed about the possibility of developing ONJ.

Whenever any surgical procedure is required, some authors have suggested that the patients should sign a written informed consent. The treatment of patients receiving intravenous BPs should be focused on reducing the risk for ONJ, minimizing the need for surgical procedures. In such cases, they should be carefully instructed about oral hygiene practices.

Preferentially, prior to beginning BPs therapy, patients should be assessed clinically and radiographically. Dental treatment including dental restorations, endodontic treatment and surgical procedures should be performed prior to initiating BPs therapy.[5]

ONJ's treatment comprises the following: pain control, antibiotic therapy, mouth rinse, BP discontinuation, hyperbaric chamber therapy, lasertherapy,and surgical debridement.[13]

Such measures, however, do not always achieve the resolution of the clinical findings – prevention is always the best option.

The serum CTx test (C-terminal telopeptide of type I collagen, or ITCP), a marker of bone resorption that assesses the elimination of specific c fragments produced by type I collagen hydrolysis, can be used as a parameter to assess the risk of developing ONJ.

There is a direct exponential relation between the duration of BPs use and the exposed bone size. Patients with CTx levels lower than 150 pg/mL should contact the attending physician and consider discontinuation of the BP (drug holiday) for a period of 4–6 months. After that period, the test should be repeated, and, if the CTx level is still lower than 150 pg/mL, the literature recommends extending the "drug holiday" for a period of 6–9 months. When CTx levels are not greater than 150 pg/mL and a "drug holiday" is not possible, the instructions to patients about the risk of developing ONJ should be emphasized. The search for a non-invasive form of treatment should always be recommended.

It is important to distinguish and emphasize that ONJ due to orally administered BPs seems to be less frequent, less severe, and responds better to a "drug holiday" and surgical debridement.Patients receiving oral BPs seem to have a better chance of improvement with a "drug holiday".[14]

The statement that the discontinuation of BP for three months prior to surgery, as recommended by the AAOMS and ADA, could either modify or not the risk of a patient developing BRONJ is controversial. The half-life of BPs is approximately 10 years, and their prolonged use results in their substantial accumulation in the skeleton. Thus, a long "drug holiday" would be required to eliminate the drug from the body. This "drug holiday" is not always possible, because of the benefits BPs provide for the prevention of osteoporosis and treatment of bone metastases.

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