Osteonecrosis of the jaws and bisphosphonates. 
Report of fifteen cases. Therapeutic recommendations

Ignacio Heras Rincón 1, Ignacio Zubillaga Rodriguez 2, Manuel Castrillo Tambay 3, Juan José Montalvo Moreno 4

(1) Resident. Oral and Maxillofacial Surgery Department, 12 de octubre University Hospital. Madrid 
(2) Staff. Oral and Maxillofacial Surgery Department, 12 de octubre University Hospital. Madrid 
(3) Staff. Oral and Maxillofacial Surgery Department, General Hospital. Ciudad Real 
(4) Head. Oral and Maxillofacial Surgery Department 12 de octubre University Hospital. Madrid

Correspondence:
Dr. Ignacio Heras Rincón 
Servicio de Cirugía Oral y Maxilofacial. 
Hospital Universitario 12 de octubre. 
Avenida de Córdoba sn 28041 Madrid 
E-mail: nachohr1@hotmail.com

Received: 30-10-2006 
Accepted: 4-05-2007

ABSTRACT
Recently there have been reports of osteonecrosis of the jaw (ONJ) in patients with chronic therapy with bisphosphonates (Bps). So far three drugs have been linked: Pamidronate of disodium, Zoledronic acid and Alendronate of sodium. It is due to a non detected side effect in clinical trials before commercialization, and reverberates significantly in the quality of life of these patients. 

Most of the cases are seen in oncology patients that have received long term concurrent antineoplasic therapy and were treated sporadically with steroids, together with Bps endovenous, for treatment of cancer and its symptoms. Among these cases we find the reported by R.E. Marx (1), S.L. Ruggiero (2) and J. V. Bagán (3). 

In this report fifteen cases diagnosed, treated and followed up at the author`s surgery department are presented and some suggestions are given in order to reduce the incidence in patients with cancer who are going to receive Bps, as well as in patients with established ONJ being treated with these drugs who may need a surgical intervention.

Key words: Bisphosphonates, osteonecrosis of the jaw, recommendations.

RESUMEN
Recientemente se han descrito casos de osteonecrosis mandibular y maxilar (ONM) en pacientes sometidos a tratamiento crónico con bisfosfonatos (BF). Hasta el momento tres han sido los fármacos implicados: Pamidronato de disodio, Ácido Zoledrónico y Alendronato de sodio. Se trata de un efecto secundario muy poco frecuente, no detectado en ensayos clínicos precomercialización, que repercute de forma significativa en la calidad de vida de estos pacientes.

La mayoría de los casos se dan en oncology patients that have received long term concurrent antineoplasic therapy and were treated sporadically with steroids, together with Bps endovenous, for treatment of cancer and its symptoms. Among these cases we find the reported by R.E. Marx (1), S.L. Ruggiero (2) and J. V. Bagán (3).

In this report fifteen cases diagnosed, treated and followed up at the author`s surgery department are presented and some suggestions are given in order to reduce the incidence in patients with cancer who are going to receive Bps, as well as in patients with established ONM being treated with these drugs who may need a surgical intervention.

Palabras clave: Bisfosfonatos, osteonecrosis maxilar, recomendaciones.
BACKGROUND
ONJ induced by BPs appears as a side effect. Most of the cases are seen in oncology patients that, besides intravenous BPs, have received chemotherapy in the long term for their base disease with or without intermittent cycles of steroids (3-5). Its incidence remains unknown in patients with cancer although current estimations suggest that it is low, daily more cases are being detected so it is expected that this tendency will increase (has been called “growing epidemic” (4,6,7)). Its appearance has been associated with various risk factors like cancer diagnosis, concurrent treatments (systemic chemotherapy, radiotherapy of head and neck or steroids) and medical comorbidities (anaemia, coagulation disorders, infection, dental disease comorbidity). ONJ has also been observed though less often in patients receiving less powerful BPs for management of osteoporosis during a long period of time.

It is not clear its time-dependency, Brian et al. (8), found in a evaluation of 812 patients with multiple myeloma in treatment with Bps that the risk of osteonecrosis is significant after 12 months (p=0.03), with a further increase after 36 months (p=0.004). On the other hand, cases exist in patients that have used the drugs for only a few weeks. (9).

Mechanism of action begins to be recognized, these drugs are analogues of pyrophosphate and present high affinity to hidroxiapatita crystals and inhibit bone resorption. They inhibit osteoclastes activity too and therefore decrease bone remodelling.

CLINICAL CASES
A retrospective study of 15 cases of ONJ in patients receiving Bps was performed in our department from October 2005 to February 2006 (Table 1).

Table 1. Relation of clinical cases.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Bisphosphonate</th>
<th>Localization</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>M</td>
<td>61</td>
<td>Multiple Myeloma.</td>
<td>Zoledronic Acid.</td>
<td>Mandible.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>70</td>
<td>Prostate Ca.</td>
<td>Zoledronic Acid.</td>
<td>Mandible.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>68</td>
<td>Multiple Myeloma.</td>
<td>Zoledronic Acid.</td>
<td>Mandible.</td>
<td></td>
</tr>
</tbody>
</table>

Most of the study took place in oncology patients receiving antineoplastic therapy, often in addition to intermittent cycles of steroids. A total of 10 women (66.6%) and 5 men (33.3%) were included in this report with an average age of 64 years (41-75). Both, multiple myeloma and breast cancer were the most common indication for BP with 5 cases (33.3% every one), followed by 3 cases for prostate cancer (20%) and 2 cases for osteoporosis (13.3%). Bp administrated was zoledronic acid (Zometa®) in 13 cases, alendronate of sodium (Fosamax®) oral route in 2 cases (13.3%), and pamidronate of disodium (Aredia®) in addition to zoledronic acid only in one case. Tooth removal was found in 6 cases (40%). The most common site of bone exposure was the mandible with 13 cases (86.6%), 3 of them had involved the maxillary bone (20%). Only 2 patients were affected in the maxillary bone exclusively. 14 patients presented with exposed bone in the oral cavity (93.3%), the only patient that didn’t, presented a gingival granuloma in the 48 (6.7%) and paresthesia in dental nerve territory. 3 patients (20%) presented with anesthesia, disesthesia, hipoesthesia or paresthesia. 3 cases of cutaneous fistula (20%), 2 of oro-antral communication and maxillary sinusitis associated (13.3%) and 1 pathologic fracture of mandible were seen (6.6) (figure 1). Biopsy was performed on 9 patients (60%): the result was non specific inflammation in 3 cases and osteomyelitis in 6, in 5 of them Actinomyces could be detected.

A conservative attitude was supported for initial stage of treatment (intermittent-continous cycles of systemic antibiotic therapy and mouth rinsing with 0.12% gluconate of clorohexidine), resulting successfully in 7 cases (46.6%). Besides exposed bone ulcerating soft tissues (33,3%) was remodelled in 5 cases. Among 2 patients with oro-antral communication and maxillary sinusitis associated: the first one presented a basal condition that advised cleaning of the maxillary sinus, bone contouring and covering the exposed bone with mucous flap; on the second one segmentary maxillectomy, extirpation of mucosa of the maxillary sinus, drainage, contouring bone and closure with mucous flap was performed without new exposed-bone appearance. The only patient without exposed bone had a gingival granuloma in 48 and evolved satisfactorily after curettage, local debridement and closure with mucous flap. Finally, in 2 cases with chronic suppuration and cutaneous fistula by ONJ in the third quadrant (13.3%) marginal mandibulectomy, preserving mandibular basal in the first one and contouring bone in the second one, followed by closure with mucous flap and fistulectomy in both of them was performed. The first one evolved successfully and the second one developed a pathologic fracture of mandible few months later, treated by radical resection of necrotic bone (figure2) and elastic intermaxillary fixation in order to organize a bone reconstruction, in the short term.

**DISCUSSION**

Although controlled, randomized, prospective, double blinded study with p<0.05% would be necessary to prove the specific causal relationship between Bps therapy and
Osteonecrosis of the jaws and bisphosphonates

Exposed bone, many times painful in oral cavity, the drugs pamidronate, zoledronic acid and alendronate have shown a direct correlation that cannot be ignored. BPs are inhibitors of osteoclastic bone resorption with high affinity for bone mineral and are used in the treatment of skeletal disorders like osteoporosis, Paget’s disease, bone metastatic disease, multiple myeloma and hypercalcemia in metastatic cancer. The molecular mechanism of action depends on the presence of a nitrogen atom in the alkyl chain of the molecule. Non–nitrogen-containing BPs (nNBps) are converted intracellularly to nonhydrolyzable analogues of ATP, which are toxic for the cells. Nitrogen-containing BPs (NBps), however, are taken up by mature osteoclasts losing their cytoeskeletal integrity and shape, become inactive and undergo apoptosis. Although there are studies that demonstrate antiangiogenic effect of BPs like pamidronate and zoledronic acid, it doesn’t seem to be responsible for the production of ONJ. This mechanism of action justifies their properties: helping to control bone pain, stabilizing lentic bone metastasis and preventing its appearance, reducing incidence of pathologic fractures, malignant hypercalcemia and need for palliative radiotherapy, improving quality of life of these patients. Delay the first skeletal complication and the need for orthopaedic intervention due to skeletal pathology, but they do not improve the patient’s survival.

However, if BPs are used for the management and prevention of skeletal events, why is there an association between, BPs therapy and ONJ?, may be attributable to the fact that the bones of the jaws have a faster bone turnover and to the fact that they are in direct contact with a septic environment (bacterial products have been shown to increase bone resorption and to decrease bone formation). It is a strange and contradictory fact of which more research would be needed.

ONJ can remain asymptomatic for weeks or months and be recognized only by the presence of exposed bone in oral cavity, sometimes painless. As soon as the oncologist prescribes BPs therapy, the patient should be referred to a dentist or oral and maxillofacial surgeon for a complete examination of the oral cavity that includes an orthopantograph in every case and dental radiograph of the necessary teeth. In the orthopantograph it is frequent to find zones of osteolysis, sometimes in combination with osteosclerosis as well as periodontal disturbances (it is characteristic bone loss between the roots of the third molar). Biopsy is only indicated if you suspect bone metastasis in the mandible or the maxillary. If you perform it, microbiological cultures (aerobic and anaerobic) are useful in the detection of pathogenic microorganisms causers of a secondary infection. Finally, you can take tomographic images to establish the extent of bone necrosis and for a more accurate diagnosis of the complications (maxillary sinusitis (figure 3), oro-nasal or oro-antral communication, pathologic fracture of mandible...).

In the case that you have to perform dental treatments, if they are non invasive they will not need to delay the beginning of the BPs therapy. However, invasive dental procedures like tooth removals, root canal therapy and periodontal surgery force the start of BPs therapy to be deferred by at least one month and require prophylactic antibiotic coverage with penicillin (for individuals with a penicillin allergy, combination therapy using quinolones and metronidazol should be employed because clindamycin alone does not cover either Actinomycetes or Eikenella corrodens, microorganisms that frequently colonize exposed bone) (1). In our hands it is necessary to support an attitude as conservative as possible, performing removal of semiincludem and nonrestorable tooth and functional rehabilitation of those that are restorable. According to other reports, root canal therapy and amputation of the crown is better than extraction in nonrestorable tooth. (14).

An exam of the prosthesis would be suitable to confirm correct adjustment and to remove them at night, teaching the patient about good dental hygiene and performing systemic reviews of the oral cavity every 3 or 4 months (hard and soft tissues) by the oncologist to notify the oral and maxillofacial surgeon every symptom. In patients with established ONJ, intermittent or continuous antibiotic together with minimal surgical debride-ments can be beneficial to palliate this kind of injuries. The goal of the treatment is to prevent a secondary infection in the soft tissues and an osteomyelitis and therefore to prevent the pain. Good dental hygiene and the use of mouth rinses and cloroxhexidina gels are almost as important (15). So far the duration of the antibiotic treatment and the beneficial effects of the antisep-tical mouth rinses have not been defined although relief of the pain and control of the progression of the exposed bone have been seen. The antibiotic of choice is still penicillin. With regard to antiseptic mouth rinses gluconate of cloroxhexidina at 0.12% (Peridex®) or periodontal bags of clorohidrate of minocycline (Arestin®) could be used.

Sometimes you can choose minimal surgical debride-ments and regulate the acute edge of the exposed bone and closure with mucous flaps although it does not ensure the absence of new exposed bone, the recurrence of osteonecrosis or of the osteomyelitis. Instead of this removable devices, similar to prosthesis, can be used to cover the exposed bone. Also correct adjustment of dentures and their removal at night are important to reduce irritation and traumatism on the soft tissues.

Interruption of BPs therapy is a controversial issue. Due to its molecular structure (analogue to pirofosfates), BPs are accumulated in high levels inside the bone matrix, therefore, although we interrupt BPs therapy they stay in the organism for a long time. On the other hand, cessation of BPs therapy can produce worse consequences, like hypercalcemia associated with tumour or skeletal complications in metastatic cancer. The oncologist, who is in charge of the treatment, will decide discontinuation of the therapy in collaboration with an oral and maxillofacial surgeon or other specialist. Hyperbaric oxygen has no proven efficiency and therefore is not recommended.
Any dental care not strictly necessary wouldn’t be performed with BPs therapy and always under the authorization of the oncologist. Therefore osteointegrated implants and any invasive dental treatment related to aesthetic dental would be contraindicated.

REFERENCES