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

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

Heras-Rincón I, Zubillaga-Rodríguez I, Castrillo-Tambay M, Montalvo-Moreno JJ. Osteonecrosis of the jaws and bisphosphonates. Report of fifteen cases. Therapeutic recommendations. Med Oral Patol Oral Cir Bucal 2007;12:E267-71.

Indexed in:
-Index Medicus / MEDLINE / PubMed
-EMBASE, Excerpta Medica
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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 pacientes oncológicos que reciben tratamiento antineoplásico concomitante a largo plazo y muchos de ellos estaban sometidos a tratamiento intermitente con esteroides a corto plazo, junto a los bisfosfonatos vía endovenosa, para el tratamiento del cáncer y de los síntomas. Entre estos casos se encuentran los publicados por R.E. Marx (1), S.L. Ruggiero (2) y J. V. Bagán (3).

Este artículo presenta quince casos clínicos diagnosticados, tratados y seguidos por nuestro servicio y da una serie de recomendaciones para reducir su incidencia en pacientes con cáncer que van a recibir BF, así como en pacientes con ONM establecida en tratamiento con dichos fármacos y que puedan necesitar un tratamiento quirúrgico.

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.

Patient	Sex	Age	Diagnosis	Bisfosfonate	Localization	Treatment
1	F	74	Multiple Myeloma. Mts D-L column.	Zoledronic Acid.	Mandible and maxillary. Cutaneous fistula.	Clean, marginal mandibulectomy fistulectomy and closure.
2	F	75	Osteoporosis.	Alendronate.	Mandible.	Clean and sequestrectomy.
3	M	62	Multiple Myeloma.	Zoledronic Acid.	Mandible.	Bone contouring.
4	F	51	Breast Ca. Mts sacro and column	Zoledronic Acid.	Mandible. Pathologic fracture.	Curettage, bone contouring, segmentary mandibulectomy and EIMF .
5	M	66	Prostate Ca. Vertebral Mts.	Zoledronic Acid.	Mandible.	Curettage.
6	F	59	Breast Ca. Bone and lung Mts.	Zoledronic Acid.	Mandible and maxillary.	
7	F	72	Breast Ca.	Zoledronic Acid.	Maxillary Sinusitis.	Segmentary Maxilectomy, cleaning of sinus, drainage and bone contouring.
8	F	41	Breast Ca. Vertebral and liver Mts.	Zoledronic Acid.	Mandible and maxillary.	
9	M	61	Multiple Myeloma.	Zoledronic Acid.	Mandible.	
10	F	63	Multiple Myeloma.	Zoledronic Acid and Pamidronate.	Maxillary.	Remodelation of exposed bone and closure.
11	F	60	Breast Ca.	Zoledronic Acid.	Mandible.	Remodelation of exposed bone.
12	M	69	Prostate Ca.	Zoledronic Acid.	Mandíble.	
13	M	70	Prostate Ca.	Zoledronic Acid.	Mandible.	
14	F	73	Osteoporosis.	Alendronate.	Mandible.	
15	F	68	Multiple Myeloma.	Zoledronic Acid.	Mandible.	

* In all patients the first treatment was conservative (antibiotic therapy and mouth rinses of gluconate of clorohexidine). Ca.= Carcinoma. Mts.= Metastase. F.= Female. M.= Male. D-L.= Dorso-lumbar. EIMF.= Elastic Intermaxillary Fixation.

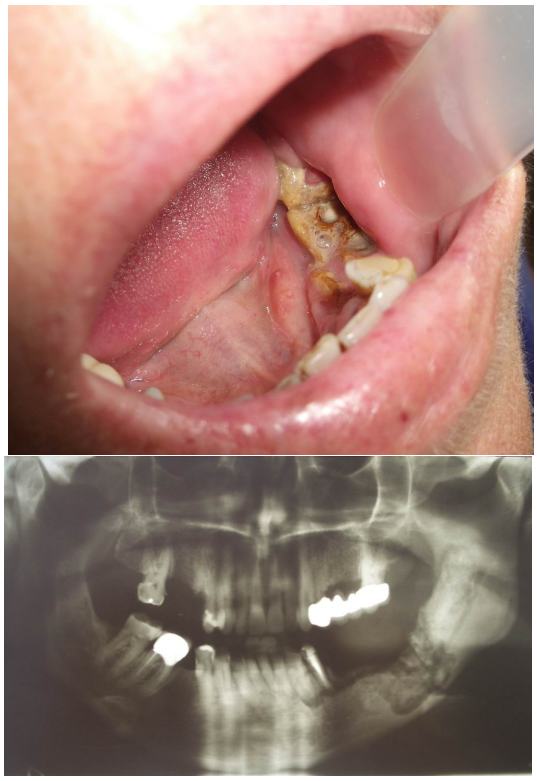

Fig. 1. Pathologic fracture of mandible.

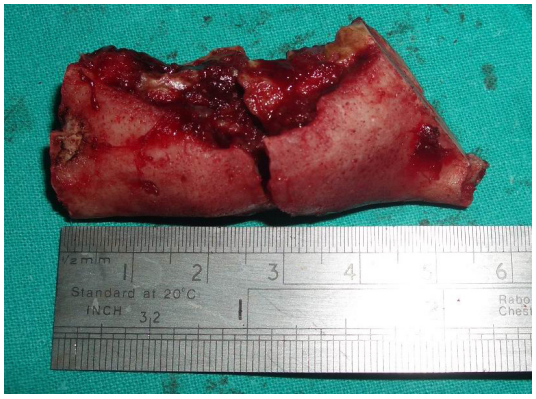

Fig. 2. Segmentary resection of mandible.

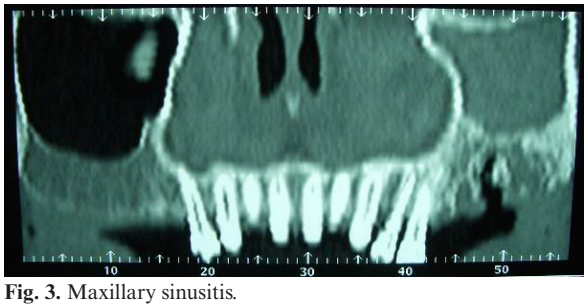

Fig. 3. Maxillary sinusitis.

Most of the study took place in oncology patients receiving antineoplasic 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

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 metastasic disease, multiple myeloma and hypercalcemy in metastasic 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 intracellulary 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 demostrate 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 litics bone metastase and preventing its appearance, reducing incidence of pathologic fractures, malignant hypercalcemy 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 (10, 11).

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 (12) 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 (13)). 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 (1, 14) 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 manbible 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 thomographic 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 Actynomices 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 semiinclude and nonrestorable tooth and functional rehabilitation of those that are restorable. According to other reports, rooth 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 systematic 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 continous antibiotic together with minimal surgical debridements 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 clorohexidina gels are almost as important (15). So far the duration of the antibiotic treatment and the beneficial effects of the antiseptical 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 clorohexidina at 0.12% (Peridex®) or periodontal bags of clorohidrate of minocicline (Arestín®) could be used.

Sometimes you can choose minimal surgical debridements 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 hypercalcemy 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

1. Marx RE, Sawatari Y, Fortín M, Broumand V. Biphosphonate-induced exponed bone (osteonecrosis-osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 2005;63:1567-75.
2. Ruggiero SI, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates. A review of 63 cases. J Oral Maxillofac Surg 2004;62:527-34.
3. Bagán JV, Murillo J, Jiménez Y, Poveda R, Milian MA, Sanchos JM et al. Avascular jaw osteonecrosis in association with cancer chemoterapy: series of 10 cases. J Oral Pathol Med 2005;34:120-3.
4. Marx RE. Pamidronate (Aredia) and Zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. J Oral Maxillofac Surg 2003;61:1115-7.
5. Migliorati CA. Biphosphonates and oral cavity avascular bone necrosis. J Clin Oncol 2003;21:4253-4.
6. Jimenez-Soriano Y, Bagan JV. Bisphosphonates, as a new cause of drug-induced jaw osteonecrosis: An update. Med Oral Patol Oral Cir Bucal 2005;10(Suppl2):E88–91.
7. Lugassy G, Shaham R, Nemets A, Ben-Dor D, Nahlieli O. severe osteomyelitis of the jaw in long-term survivors of multiple myeloma: a new clinical entity. American J Med 2004;15: 440-1.
8. Brian GM, Durie MD. Zometa and osteonecrosis of the jaws a new update Jul 2004. http://myeloma.org/main.jsp. aredia/
9. Migliorati CA. Bisphosphonate-associated oral osteonecrosis. Oral Surg Oral Med Oral Pathol Oral Radiology Endo 2005;99:135.
10. Hortobagyi GN, Theriault RL, Porter L, Blainey D, Lipton A, Sinoff C et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. N Engl J Med 1996;335:1785-92.
11. Gralow JR. Biphosphonates as adjuvant treatment for breast cancer. Br Med J 2002;325:1051-2.
12. McMahon RE, Bouquot JE, Glueck CJ, Spolnik KJ, Adams WR. Osteonecrosis: a multifactorial etiology. J Oral Maxillofac Surg. 2004;62:904–5.
13. Migliorati CA, Schubert MA, Peterson DE, Seneda ML. Biphosphonate-Associated osteonecrosis of mandibular and maxillary bone. Cancer 2005;104:83-93.
14. Ponte-Fernández N, Estefanía-Fresco R, Aguirre-Urizar JM. Bisphosphonates and Oral Pathology I. General and preventive aspects. Med Oral Patol Oral Cir Bucal 2006;11:226-30.
15. Pastor-Zuazaga D, Garatea-Crelgo J, Martino-Gorbea R, Etayo-Perez A, Sebastian-Lopez C. Osteonecrosis of the jaws and bisphosphonates. Report of three cases. Med Oral Patol Oral Cir Bucal 2006;11:E76-9.