

Osteonecrosis of the jaws and bisphosphonates. Report of three cases

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ABSTRACT

Bisphosphonates are recently acquiring increasing relevance in the treatment of several diseases.

In line with the increased use of these compounds, cases of mandibular osteonecrosis, and to a lesser extent, maxillary osteonecrosis, are being reported. This necrosis is difficult to treat in patients who usually have a previously limited quality of life.

A surgical performance carried out by oral and maxillofacial surgeons, stomatologists and odontologists might lead to bone exposure.

A treatment based on conservation and as harmless as possible seems to be the most advisable way of acting with these patients in order to minimize the incidence and treat the complications, once the lesions have been ascertained.

We report three cases treated in our service of osteonecrosis of the jaws after exodontics.

This side effect should be remembered before starting any surgical treatment in these patients.

Key words: *Bisphosphonates, osteonecrosis, side effects.*

RESUMEN

Los bisfosfonatos están adquiriendo una relevancia terapéutica cada vez mayor, dada su utilidad en el manejo de diversas patologías.

Con el incremento de su uso, se están documentando casos de necrosis ósea mandibular, y en menor medida maxilar, de difícil solución y con una importante afectación de la calidad de vida de los pacientes en tratamiento con estos fármacos.

El factor que con mayor frecuencia desencadena el proceso es la actuación de los profesionales: odontólogos, estomatólogos y cirujanos orales y maxilofaciales.

La previsión, las intervenciones atraumáticas y el tratamiento conservador, parecen ser los medios más adecuados para minimizar la incidencia o resolver las complicaciones.

Este artículo presenta tres casos, seguidos por nuestro servicio, de pacientes con necrosis ósea maxilar tras procedimientos dentales, fundamentalmente exodoncias.

El conocimiento de este posible efecto secundario de los bisfosfonatos debería ser tenido en cuenta antes de cualquier intervención en este tipo de pacientes.

Palabras clave: *Bisfosfonatos, osteonecrosis, efectos secundarios.*

INTRODUCTION

Bisphosphonates are recently acquiring increasing relevance with regard to the treatment of several pathologies such as lytic bone metastasis, malignant hypercalcemia, multiple myeloma, osteoporosis and Paget's disease. (1)

These compounds are pyrophosphate analogues where a carbon atom has replaced the oxygen between the phosphates, changing the lateral chains. They show great affinity with hydroxyapatite crystals and inhibit bone resorption. (2)

The effectiveness and power of bisphosphonates are common knowledge. In general, they show high tolerance, rarely occurring side effects of clinical significance. This last feature is caused by the accumulation of bisphosphonates on bone tissue, where their average life is longer than the time they spend in circulation. These features make bisphosphonates an effective and secure drug.

In line with the increased use of these compounds, cases of mandibular osteonecrosis, and to a lesser extent, maxillary osteonecrosis, are being recorded. These cases are associated with treatments with certain kinds of bisphosphonates: the aminobisphosphonates pamidronate disodium (Aredia®) and zoledronic acid (Zometa®), specially in oncologic patients in advanced stage. R.E. Marx's, S.L. Ruggiero's and J.V. Bagán's case reports are some of these studies. (3-6)

It is our intention to report a possible side effect produced by treatments with aminobisphosphonates, recently recorded in monographs, but of great clinical relevance due to the detriment in patients' quality of life.

CASE 1

67 year-old woman; smoker (6 cigarettes / day). She had been diagnosed as having breast cancer (T2 N0 M0) and treated with surgery combined with chemotherapy and radiotherapy. Due to the metastatic progression of the disease, the treatment with bisphosphonates was initiated (pamidronate 90 mg IV doses – 20 monthly cycles). It is after the first 9 cycles of pamidronate that the patient is remitted to our practice by her oncologist, suffering from burning sensation and diffuse gingival pain, regular gingival hemorrhages, and showing a very painful lesion (5mm in diameter) in the lateral edge of her right hemitongue.

The extraction of the molar which produced the lingual sore and of other four teeth without viability was prescribed. Approximately one month after such exodontics, bone exposure occurred where the extractions had been performed. (Figure 1) Limited curettages of the bone necrosis were made complemented with antibiotic therapy (amoxicilline, clarythromycin) and chlorhexidine gel application. The evolution was favourable in every area, except in the mandibular molar one, where the bone exposure maintained the lingual sore, requiring a more aggressive debridement. Although the exposure didn't disappear completely, control of the patient's pain was achieved with the resolution of the lingual lesion. (Figure 2)

CASE 2

49 year old woman; smoker (30 cigarettes / day). She had been diagnosed as having breast cancer (T1 N0 M0) and treated with

surgery, chemotherapy and radiotherapy. Given the metastatic evolution of the disease, she started treatment with zoledronate (4 mg IV doses – monthly cycles). She was sent to our practice by her stomatologist, as she showed mandibular nonhealing sockets after dental extractions, periodontal pain and paresthesia of the inferior dental nerve, without metastatic finding. (Figure 3) She had been previously diagnosed and treated as having dental abscess. She had improved with antibiotic treatment, but the process had not been completely solved. Nonsurgical treatment was prescribed, amoxicilline and clorhexidine, and the lesion healed.

CASE 3

71 year old man. He had been diagnosed as having multiple myeloma (III-A) and treated with chemotherapy, radiotherapy and medullar autotransplantation. He started treatment with bisphosphonates due to hypercalcemia (pamidronate 90 mg IV doses – monthly for three years and zoledronate 4 mg IV doses – monthly for one year). He was sent to our practice by his odontologist as he showed nonhealing sockets after mandibular exodontics. The axial computed tomography showed lytic lesions and the patologic studies bone necrosis and reactive osteitis. Surgical treatment was chosen, large debridement and a mucosal flap, complemented with antibiotic therapy and chlorhexidine rinses. Three weeks after surgery bone exposure was seen and conservative treatment precribed, clorhexidine gel, with favourable evolution.



Fig. 1. Case 1. Bone necrosis one month after nonviable tooth exodontic.

DISCUSSION

Pamidronate and zoledronate are synthetic analogues of endogenous pyrophosphate. Their clinical application involves a direct inhibition of the osteoclastic function.

Pamidronate disodium (Aredia®) and zoledronic acid (Zometa®) belong to the aminobisphosphonate group, nitrogen containing bisphosphonates with greater power and slower



Fig. 2. Case 1. Bone necrosis after molar extraction and lingual sore before debridement.



Fig. 3. Case 2. Osteonecrosis of the left jaw when the patient was sent to our practice.

metabolization compared to those synthesized earlier. The use of these bisphosphonates is increasing in the treatment of several diseases such as hypercalcemia associated with multiple myeloma or metastatic cancer, osteoporosis and Paget's disease. (1,2)

Some of the mechanisms for antiresorptive action and the subsequent low fragility of bone tissue are:

- Direct antiapoptotic effect on osteoblasts regardless of the proapoptotic common stimulation, in vitro and in vivo.
- Decreased osteoclast progenitor development and decreased mature osteoclasts recruitment in bone tissue.
- Promotion of apoptosis of mature osteoclasts blocking regulating proteins of mevalonate pathway. (7,8)
- Antiangiogenic properties reducing the circulating endothelial growth factor (EGF). (5)

Bisphosphonates have a direct effect on this dynamic unit which regulates the turn-over between bone formation and

resorption, increasing osteoblasts proliferation and decreasing osteoclasts average life, activity and adherence to the mineralized matrix. These effects have been also seen in the maxillofacial area. (9-11)

Through such metabolic changes, aminobisphosphonates reduce bone resorption decreasing skeletal morbidity in oncological patients with bone metastasis. They relieve bone pain, stabilize or even improve lytic bone lesions, decrease the incidence of pathologic fractures, spinal cord compression, hypercalcemia and the need of palliative radiation therapy, noticeably improving patients' quality of life. The median time to the first skeletal event is also lengthened and the development of new osteolytic lesions is prevented. As a long-term effect, they also decrease the need of subsequent orthopedic surgery although they don't lengthen survival. (12,13)

With the increasing use of pamidronate and zoledronate new cases of osteonecrosis are being reported, although sometimes there is no causal connection due to a lack of previous literature. (14) The three cases here described showed resistance to both medical and surgical treatments. They were oncological patients afflicted with metastatic breast cancer or multiple myeloma who had been treated with such drugs (Pamidronate 90 mg monthly IV, Zoledronate 4 mg monthly IV).

According to R.E. Marx, the incidence of avascular necrosis of the jaws induced by pamidronate and zoledronate is significant, especially in therapies involving corticosteroids. S.L. Ruggiero's and J.V. Bagán's cases reports are some of the studies which support this side effect. There is evidence of exposed necrotic bone, more frequently at the mylohyoid ridge and at the crestal mandible. Radiographic images might present a normal structure without visible lesions, because the bone density remains, inespecific changes or lytic lesions. Risk seems to be increased by long term treatments (longer than a year), and particularly when synchronic tumors, hypoprotei-nemia, steroids, renal failure or simultaneous chemotherapy treatments occur. (3-5)

At the beginning, the reported cases were diagnosed as different dental procedures such as odontalgia, dental abscess, osteomyelitis, etc... and extraction of the painful dental pieces always resulted in a new bone exposure. This might involve the physician as a possible worsening factor of the process, making it even more complex. (6)

Mandibular-maxillary occurrence of this pathology in the cases treated in our department and the absence of lesions in the rest of the bone tissues supports R.E. Marx's hypothesis, which suggests decisive influence of dental structures. (4) The bone, externally exposed through dental attachments, requires an adequate metabolism and blood supply. The normal turn-over modified by inhibition of osteoclastic resorption and vascular insufficiency could exceed bone vital capacity, resulting in avascular bone necrosis (5). This osteonecrosis is difficult to treat, having no established guidelines for the time being. We have obtained successful results from the treatment of medium size lesions. However, complete resolution has not been achieved in the case of the largest one, where the treatment was merely palliative. Each new extraction, as well as debridements, can cause a greater exposure. Direct closure over bone tissue could

fail and sometimes cause worsening, because it is difficult to be sure that the remaining bone is healthy. Surgery was reserved only for the areas which caused painful lesions on the tongue or soft tissue — more aggressive alternatives and hyperbaric oxygen cannot be dismissed as a therapeutic option. (3-6,14) From our own experience we agree with R.E. Marx that the antibiotic treatment (penicillin, erythromycin), together with limited debridements, is the best option to palliate, or even solve, this kind of lesions. (4,5) It is vital to maximize oral hygiene and the use of chlorhexidine containing gel and rinse, as well as the restriction of aggressive actions such as exodontics, unless they are unavoidable. If surgical treatment is required, R.E. Marx recommends a two months interruption of bisphosphonates. (3)

It is unquestionable that other well-known factors also contribute to the appearance of mandibular or maxillary osteonecrosis (radiation therapy, chemotherapy, corticoids, infections, anemia and vasoconstrictor local anesthetics). (15) From them all, radiation therapy remains the most influential, when it is used in the treatment of head and neck tumors. Our department has a population of reference of 560,000 and started giving assistance over 25 years ago; the incidence of malignant tumors in this population approaches the European average. The appearance of three similar cases, the only ones in our service which are not associated with head and neck radiation therapy and in less than six months, leads us to think of the appearance of a new factor.

Although a direct connection with the use of bisphosphonates in this pathology has not been established yet, the treatment with pamidronate and zoledronic acid, associated or not with other therapies, is common to all cases.

Until a further knowledge about the causes for this pathology is achieved, the best option seems to be a maximum control of the cases treated with pamidronate and zoledronate.

CONCLUSIONS

- Treatment with pamidronate and zoledronate might be a determining factor in oncological patients suffering from mandible and maxilla bone necrosis.
- A surgical performance carried out by oral and maxillofacial surgeons, stomatologists and odontologists might lead to bone exposure.
- It is a pathology difficult to treat, in patients who usually have a previously limited quality of life.
- A treatment based on conservation and as harmless as possible seems to be the most advisable way of acting with these patients.
- Further research will be essential to clarify the cause, minimize the incidence and register the treatment, once the lesions have been ascertained.

REFERENCES

1. Hillner BE, Ingle JN, Berenson JR, Janjan NA, Albain KS, Lipton A, et al. American Society of Clinical Oncology Guideline on the role of bisphosphonates in breast cancer. *J Clin Oncol* 2000;18:1378-91.
2. Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. *J Clin Invest* 1999;104:1373-4.
3. Marx RE, Stern D, eds. *Oral and Maxillofacial Pathology. A rationale for diagnosis and treatment.* Quintessence Publishing Co. Illinois; 2003. p. 36-8.
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. Ruggiero SL, 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.
6. Bagan JV, Murillo J, Jiménez Y, Poveda R, Milian MA, Sanchis JM et al. Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. *J Oral Pathol Med* 2005;34:120-3.
7. Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston RD. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *Br Med J* 2003; 327-469.
8. Oades GM, Senaratne SG, Clarke IA, Kirby RS, Colston KW. Nitrogen containing bisphosphonates induce apoptosis and inhibit the mevalonate pathway, impairing ras membrane localization in prostate cancer cells. *J Urol* 2003;170:246-52.
9. Fleisch H: Bisphosphonates. Mechanisms of action. *Endocrine Reviews* 1998;19:80-100.
10. Reinholz GG, Getz B, Pederson L, Sanders ES, Subramaniam M, Ingle JN et al. Bisphosphonates directly regulate cell proliferation, differentiation and gene expression in human osteoblasts. *Cancer Res* 2000;60:6001-7.
11. Altundal H, Guvener O. The effect of alendronate on resorption of the alveolar bone following tooth extraction. *Int J Oral Maxillofac Surg* 2004;33:286-93.
12. 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.
13. Gralow JR. Bisphosphonates as adjuvant treatment for breast cancer. *Br Med J* 2002;325:1051-2.
14. Wang J, Goodger NM, Pogrel MA. Osteonecrosis of the jaws associated with cancer chemotherapy. *J Oral Maxillofac Surg* 2003;61:1104-7.
15. Tarasoff P, Csermak K. Avascular necrosis of the jaws: risk factors in metastatic cancer patients. *J Oral Maxillofac Surg* 2003;61:1238-9.