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Osteonecrosis of the jaw associated with the use of oral biphosphonates: apropos five cases

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Summary

Osteonecrosis of the jaw is a disease which needs to be taken into account whenever there is exposure of bone as a secondary result of any dental operation in a patient who has been taking biphosphonates over a long period of time. Unknown until the last few years, knowledge of such a pathology has increased due to the current increase in the taking of biphosphonates in the population, with most of the published cases being related to the taking of biphosphonates intravenously. We present 5 clinical cases of osteonecrosis of the jaw associated with the use of oral biphosphonates.

Key words: *osteonecrosis of the jaw, biphosphonates, alendronate, ibandronate.*

Introduction

Osteonecrosis of the jaw (ONJ) is characterised by an ulcerated lesion in the oral mucosa with exposure of bone for a period of longer than 8 weeks, located in the jaw and associated with the use of oral and intravenous bisphosphonates in the absence of cervicofacial radiotherapy¹⁻³.

Since 2003, with the appearance of the first clinical cases of ONJ in the literature, there have been numerous publications regarding the development of this pathology^{4,6}, the majority of these secondary to therapies with intravenous bisphosphonates, associated, in turn, with different chemotherapy and radiotherapy treatments.

In this article we bring together a series of 5 cases of ONJ related to the taking of oral bisphosphonates, and carry out a bibliographic review of the pathology and management of the patient taking oral bisphosphonates who is going to undergo oral surgery.

Clinical cases

We present 5 cases of ONJ in relation to the use of oral bisphosphonates seen in our service during the years between 2005 and 2008 (Table 1). They all have as common antecedents dental surgery and the taking of oral bisphosphonates at the time of the diagnosis of ONJ.

Case number 1. Woman of 70 years of age diagnosed with early osteoporosis due to an earlier hysterectomy which was treated with ibandronic acid over a period of 4 years. She developed a clinical picture characterised by pain and tumefaction in the submaxillary cells and inferior vestibule compatible with grade III ONJ. She was treated surgically by the elimination of the sequester, curettage and local advancement flaps to close the lesion, associated with intravenous antibiotic treatment with amoxicillin clavulanate 1g/200 mg every 8 hours for two weeks, plus 100 mg of doxycycline orally every 24 hours for 14 further days (Figures 1 & 2).

Case number 2. Patient with history of arthrosis of the knee (with knee prosthesis) recurrent polychondritis in treatment with corticoids and type II, or senile osteoporosis. The patient had received alendronate orally over a period of 4 years, developing grade II ONJ. She was subsequently treated with intravenous antibiotherapy consisting of amoxicillin clavulanate 1g/200 mg every 8 hours for a total of three weeks

Cases number 3, 4 and 5. The last three patients were women diagnosed with senile osteoporosis (one of them with history of rheumatoid arthritis treated with corticoids and immunosuppressants) and treated with oral alendronate (for three, five and four years, respectively), who developed ONJ grade III. They were treated by curettage of the lesion combined with intravenous antibiotherapy using amoxicillin clavulanate 1g/200 mg every 8 hours for a minimum period of 2 weeks.

All the patients had a complete remission of the lesions.

Discussion

ONJ was defined as such in the year 2007 by the American Society for Bone Mineral Research (ASBMR)¹ as an entity characterised by three requirements: previous taking of bisphosphonates, presence of exposed or necrotic bone in the maxillary region which has been developing or more than 8 weeks, and the absence of radiotherapy in this area.

Traditionally, ONJ has been related to the use of intravenous bisphosphonates in patients with history of neoplasms with metastasis, its secondary appearance related to the use of oral bisphosphonates being rare. In the last few years, the growth in the use of oral bisphosphonates in the treatment of osteoporosis has increased the number of cases of ONJ described⁷. In certain pathologies, such as rheumatoid arthritis, in which the development of serious osteoporosis has necessitated the initiation of treatment with oral bisphosphonates, the appearance of ONJ has also been observed⁸. It has been determined that the risk of ONJ due to oral bisphosphonates is related to the duration of treatment (above all, if it is greater than 3 years)⁹. In the cases described in this clinical note a period of approximately 3 or more years of treatment with bisphosphonates was observed before the appearance of ONJ.

Within the group of bisphosphonates associated with the development of ONJ, zoledronic acid is that which has resulted in most cases of ONJ^{10,11}. Woo et al.⁶, in a systematic review of 368 cases of ONJ observed that the oral bisphosphonate which most frequently produced ONJ was alendronate, which agrees with our review. If we compare oral bisphosphonates with intravenous it is seen that the intravenous administration develops ONJ more rapidly. Lazarovici et al., in 2011¹¹ studied 27 patients who had ONJ concluding that the average time for its appearance was 60 months for those who had taken alendronate, 13 for zoledronic acid and 35 months for pamidronate. Etiopathogenically, there is a series of factors which may explain the development of ONJ². These are: changes in immunity and the neoplasm repair mechanisms, vascular compromise (in the same way as happens in other areas such as the hip and half-moon bone, essentially), low bone turnover, and toxicity in the bone¹² and other soft tissues of the bisphosphonates themselves¹³.

ONJ is characterised clinically by areas of exposed bone accompanied by fistulation, pain, paresthesia, dental movement, and even fracture of the jaw. In 65% of cases we find mandibular affection, in 25%, affection of the upper jaw and in approximately 10% bimaxillary affection⁶.

In most cases the prognosis is favourable, with ONJ due to oral bisphosphonates having a better prognosis than those cases caused by intravenous bisphosphonates¹¹. The latter is aggravated by the deteriorated physical state of these patients (previous treatment with chemotherapy and/or radiotherapy).

The treatment for ONJ is based on the grade of ONJ which is diagnosed⁵ (Table 2). In ONJ grade I the treatment of choice is rinsing with 0.12%

chlorhexidine; in grade II the first treatment needs to be associated with oral or intravenous antibiotic therapy; and finally, in grade III, to those measures already mentioned should be added surgical treatment.

Therefore, the most important thing is to decide on how to manage the patient who is submitted for mouth surgery and who is being treated with oral bisphosphonates over a long period of time. For De Souza et al.¹⁴ it was necessary to postpone surgery and refer the patient to a specialist (rheumatologist or traumatologist) to evaluate the suspension of the bisphosphonate and, even to substitute it for another medicine for the treatment of osteoporosis before surgery.

On the other hand, the American Society, in 2009, developed a protocol for the management of patients taking oral bisphosphonates and who require a surgical intervention which involves the manipulation of the maxillary bones⁹:

- In patients whose treatment with oral bisphosphonates has lasted less than 3 years and with no risk factors, it is not necessary to take any special measures.

- In patients whose treatment with oral bisphosphonates has lasted for less than 3 years and who are taking corticoids concurrently it would be necessary to stop the oral bisphosphonate treatment at least 3 months before surgery, if the systemic conditions of the patients allow it. The oral bisphosphonates may be reintroduced once the bone is healed.

- In patients whose treatment with oral bisphosphonates lasts longer than 3 years, independently of having taken oral corticoids or not, the taking of bisphosphonates should be stopped at least 3 months before surgery if the systemic conditions of the patient permit. The administration of bisphosphonates would be restarted only when the bone had healed.

Similarly, the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) and the societies related to bone mineral metabolism have produced a document on the management of ONJ and the bisphosphonates used in the treatment of osteoporosis²:

- In patients taking bisphosphonates for less than 3 years and without risk factors it is not necessary to delay surgery

- In patients taking bisphosphonates for less than 3 years and associated corticotherapy the bisphosphonates should be discontinued three months before surgery, except where there is a high risk of fracture (age > 70 years, presence of earlier fracture, bone densitometry with a T-score of <-2.0). It would be reintroduced once the healing had occurred.

- With patients who are taking bisphosphonates for more than 3 years the bisphosphonates should be discontinued 3 months before surgery, except if there is a high risk of fracture (age > 70 years, presence of previous fracture, bone densitometry with a T-score <-3.0). It would be reintroduced once healing had taken place.

Figure 1. Orthopantomography and TAC which shows osteonecrosis in the right mandibular body

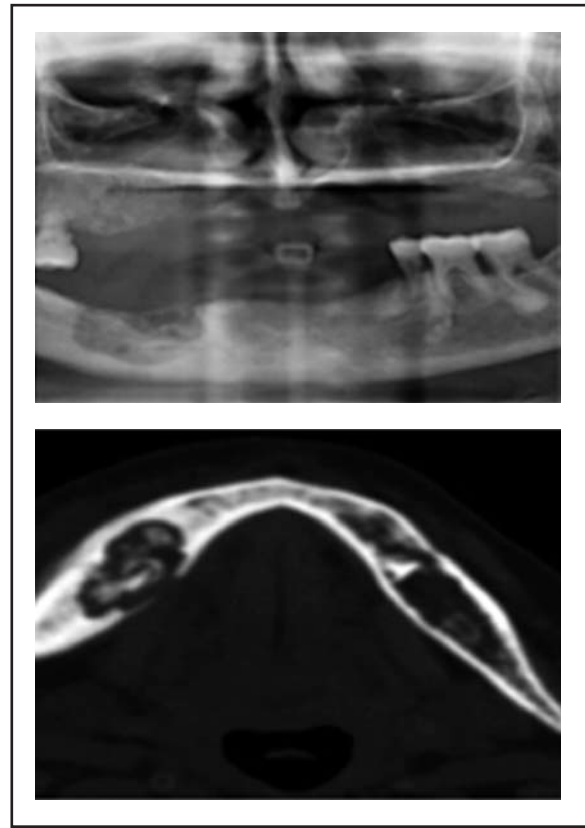
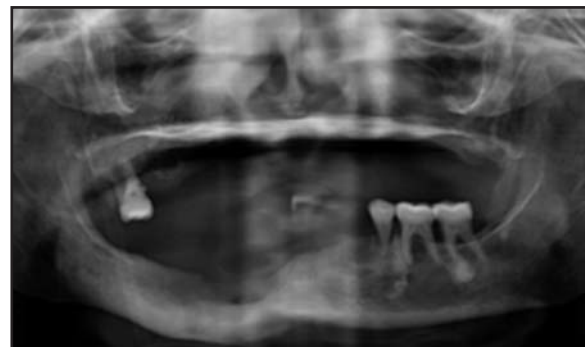


Figure 2. Control orthopantomography in which is seen the satisfactory development of bone re-ossification of the osteonecrosis in the mandible



Therefore, and in conclusion, ONJ is a little-understood but increasingly frequent pathology related to the taking of oral bisphosphonates. New protocols and consensuses around the activity in relation to a patient taking oral bisphosphonates over the long term and who is going to have oral surgery, will in future be the determining factor in avoiding, as much as possible, the development of ONJ.

None of the authors has a conflict of interest.

Table 1. Data from patients taking oral bisphosphonates who develop ONJ (iv: intravenous therapy)

	Sex	Age	History of interest	Bisphosphonate oral	Cause of treatment	Duration of treatment	Stadium ONJ	Treatment
Case 1	F	70	Bronchial asthma, dental extraction	Ibandronic acid (150 mg monthly)	Postmenopausal osteoporosis	4 years	III	Bone curettage + iv antibiotherapy
Case 2	F	75	Recurrent polychondritis, dental extraction	Alendronate (70 mg weekly)	Senile osteoporosis	4 years	II	iv antibiotherapy
Case 3	F	81	Bronchial asthma, dental manipulation	Alendronate (70 mg weekly)	Senile osteoporosis	3 years	III	Bone curettage and exodontia + iv antibiotherapy
Case 4	F	76	Rheumatoid arthritis, dental extraction	Alendronate (70 mg weekly)	Senile osteoporosis	5 years	III	Bone curettage + iv antibiotherapy
Case 5	F	74	Dental manipulation	Alendronate (70 mg weekly)	Senile osteoporosis	4 years	III	Bone curettage + iv antibiotherapy

Table 2. Stages of ONJ according to the American Society of Oral and Maxillofacial Surgery⁹

	Exposure of necrotic bone	Pain and signs of infection	Fistula and clinical or radiographical evidence of sequestered bone
Degree I	Yes	No	No
Degree II	Yes	Yes	No
Degree III	Yes	Yes	Yes

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