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

Correspondence: Ana Belén Marín Fernández - Calle Unis, 14 - Otura - 18630 Granada (Spain)
e-mail: anita1981@msn.com

Date of receipt: 02/01/2012
Date of acceptance: 27/01/2012

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 biphosphonates in the absence of cervicofacial radiotherapy. 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, the majority of these secondary to therapies with intravenous biphosphonates, 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 biphosphonates, and carry out a bibliographic review of the pathology and management of the patient taking oral biphosphonates who is going to undergo oral surgery.

Clinical cases
We present 5 cases of ONJ in relation to the use of oral biphosphonates 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 biphosphonates 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 antibiotic treatment 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 antibiotic treatment 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) as an entity characterised by three requirements: previous taking of biphosphonates, 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 biphosphonates in patients with history of neoplasms with metastasis, its secondary appearance related to the use of oral biphosphonates being rare. In the last few years, the growth in the use of oral biphosphonates in the treatment of osteoporosis has increased the number of cases of ONJ described. In certain pathologies, such as rheumatoid arthritis, in which the development of serious osteoporosis has necessitated the initiation of treatment with oral biphosphonates, the appearance of ONJ has also been observed. It has been determined that the risk of ONJ due to oral biphosphonates is related to the duration of treatment (above all, if it is greater than 3 years). In the cases described in this clinical note a period of approximately 3 or more years of treatment with biphosphonates was observed before the appearance of ONJ.

Within the group of biphosphonates associated with the development of ONJ, zoledronic acid is that which has resulted in most cases of ONJ. Woo et al., in a systematic review of 368 cases of ONJ observed that the oral biphosphonate which most frequently produced ONJ was alendronate, which agrees with our review. If we compare oral biphosphonates with intravenous it is seen that the intravenous administration develops ONJ more rapidly. Lazarovici et al., in 2011 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 ONJ. 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 bone and other soft tissues of the biphosphonates themselves.

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 affection.

In most cases the prognosis is favourable, with ONJ due to oral biphosphonates having a better prognosis than those cases caused by intravenous biphosphonates. 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 diagnosed (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 antibio-
therapy; and finally, in grade III, to those measure-
res already mentioned should be added surgical
treatment.

Therefore, the most important thing is to deci-
dede on how to manage the patient who is submit-
ted for mouth surgery and who is being treated
with oral biphosphonates over a long period of
time. For De Souza et al.14 it was necessary to pos-
tpone surgery and refer the patient to a specialist
(rheumatologist or traumatologist) to evaluate the
suspension of the biphosphonate 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 biphosphonates and who
require a surgical intervention which involves the
manipulation of the maxillary bones9:

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

- In patients whose treatment with oral biphos-
phonates lasts longer than 3 years, independently
of having taken oral corticoids or not, the taking
of biphosphonates should be stopped at least 3
months before surgery if the systemic conditions
of the patient permit. The administration of
biphosphonates 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 biphosphonates used in the treatment of
osteooporosis2:

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

- In patients taking biphosphonates for less
than 3 years and associated corticotherapy the
biphosphonates 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 hea-
ling had occurred.

- With patients who are taking biphosphonates
for more than 3 years the biphosphonates 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.

Therefore, and in conclusion, ONJ is a little-
understood but increasingly frequent pathology
related to the taking of oral biphosphonates. New
protocols and consensuses around the activity in
relation to a patient taking oral biphosphonates
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)

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

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

<table>
<thead>
<tr>
<th></th>
<th>Exposure of necrotic bone</th>
<th>Pain and signs of infection</th>
<th>Fistula and clinical or radiographical evidence of sequestered bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree I</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Degree II</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Degree III</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Bibliography

11. Lazarovici TS, Yahlom R, Taicher S, Schwartz-Adar D, Peleg O, Yarom N. Bisphosphonate-related osteone-