Epidemiology, Pharmacology and Clinical Characterization of Bisphosphonate-related Osteonecrosis of the Jaw. A Retrospective Study of 70 Cases

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KEYWORDS
Osteonecrosis of the jaw; Bisphosphonates; Bone exposure

Abstract
Background and objectives: Bisphosphonates are widely prescribed drugs whose principal capacity is inhibiting the osteoclast function. In 2003 a complication related to their administration, bisphosphonate-related osteonecrosis of the jaw (BRONJ), was described. The objectives of this study were to identify diagnosed cases of BRONJ in a third-level hospital over 8 years, evaluating the main features in relation to the disease, the bisphosphonate and the presence of local or general risk factors that could trigger the BRONJ.

Methods: Patients diagnosed with BRONJ in a center of reference for a population of 1 100 000 inhabitants were selected. Variables analyzed were classified into 3 groups: patients, bisphosphonate (focusing on dose and weighting dose/potency) and osteonecrosis.

Results: Seventy cases were studied, 44 women and 26 men, with a mean age of 66.8 years. Eighteen patients received bisphosphonates orally and 52, intravenously. The mean time of administration was 26.53 months. In 67.1% of the patients it was possible to identify a local trigger, with the most common being tooth extraction (48.6%). Bone exposure was present in 89.2% of the cases, while 12 patients developed BRONJ without exposed bone, with only pain and/or chronic sinus tracts. Complete resolution was achieved in 58.6% of the patients, with a mean time of control of 16.28 months.


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Conclusions: 25% of the BRONJ cases were related to the administration of oral bisphosphonates, especially alendronate. Zoledronic acid was the bisphosphonate that required the fewest milligrams to induce osteonecrosis. Single bone exposure was the most common clinical finding, especially in the molar mandibular region in patients with metastatic disease.

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Resumen

Introducción y objetivos: Los bisfosfonatos son fármacos con un amplio espectro de indicaciones cuya principal capacidad es la inhibición de la función osteoclástica. En el año 2003 se ha descrito una complicación asociada a su empleo, la osteonecrosis de los maxilares por bisfosfonatos (ONMB). Los objetivos del presente estudio son identificar los casos recogidos de ONMB en un hospital de tercer nivel durante 8 años, evaluando las principales variables en relación con la enfermedad, el bisfosfonato empleado y los factores de riesgo locales o generales que pudieran actuar como desencadenante en la patogénesis de la ONMB.

Material y método: Se procedió a la selección de los pacientes diagnosticados de ONMB en un centro de referencia para una población de 1.100.000 habitantes. Las variables analizadas se dividieron tres grupos: pacientes, fármaco (incluyendo el análisis de la dosis aplicada y la ponderación dosis/potencia) y osteonecrosis.

Resultados: Se recogieron 70 casos, 44 mujeres y 26 varones, con una media de 66,8 años. Dieciocho pacientes habían recibido un aminobisfosfonato oral y 52 por vía intravenosa. El tiempo medio de administración fue de 26,53 meses. En un 67,1% de los pacientes se pudo identificar un factor local desencadenante, siendo el más frecuente la exodoncia (48,6%). Aunque la exposición ósea estaba presente en el 75,7% de los casos, ocho enfermos padecieron una osteonecrosis sin exposición, manifestando la presencia de dolor y/o fistula crónica. El 58,6% experimentaron una resolución completa con un tiempo medio de control de 16,28 meses.

Conclusiones: El 25% de las ONMB en nuestra serie se relacionaron con la administración de un bisfosfonato oral, especialmente el alendronato. El ácido zoledrónico es el agente que menos miligramos precisa para desarrollar la enfermedad. La exposición ósea solitaria fue el dato clínico más habitual, afectando especialmente a sectores posteriores mandibulares en pacientes con enfermedad metastásica.

Introduction

Since the first bibliographic data about Bisphosphonate-related Osteonecrosis of the Jaws (BRONJ) was published in September 2003 by Marx,1 several further studies have published their case series findings in worldwide publications.

Bagan et al.2 published the first case series in 2005 in Spain. This series collected epidemiological information from 10 patients, all of them oncology patients with bone metastases that had received different chemotherapeutic agents in conjunction with zoledronic acid and/or pamidronate. Despite previous information disclosed by Marx in 2003,1 the prudence of the authors took them to avoid using the term bisphosphonate as the title (“Avascular jaw osteonecrosis in association with cancer chemotherapy”). One year later the same author published in the journal Oral Oncology a letter to the editor in which he describes the experience from 20 cases of what already referred to as osteonecrosis associated with use of bisphosphonates.3

In 2007 an article was published in a Spanish magazine series highlighting 15 patients with BRONJ, two of whom had underlying disease osteoporosis and were treated with oral alendronate.4 In March 2008 another article was published with data from patients diagnosed between January 2004 and April 20075 in the Principality of Asturias (Spain). This paper detailed the information of 21 patients with chemical osteonecrosis, all except one with previous cancer history. In the same year a case series of 4 patients with multiple myeloma who developed BRONJ following the completion of dental extraction was also documented.6

Along the same line and more recently, two further BRONJ case series have been published in Spain, one of which contains clinical and epidemiological information from the northwest of Spain, the Galician provinces,7 and
the other from Canary Islands. Moreover, in 2012 Bagan et al. reported a case series of 126 patients with BRONJ and 19% of them had developed their disease in relation to oral intake of aminobisphosphonates.

The present study has three objectives: (1) Describe BRONJ cases listed in a reference hospital over a period of eight years, assessing the type, time and route of administration of the bisphosphonate. (2) Analyze the clinical presentation of BRONJ, describing in detail the location, stage, symptoms, characteristics of the bone exposure, underlying disease and chronic medications received by the patient. (3) Identify the existence of local and/or general risk factors that could act as a trigger in the pathogenesis of BRONJ.

Materials and Methods

Selection of Patients

We proceeded to select all the patients diagnosed with BRONJ in a reference center for a population of 1,100,000 inhabitants. The study period covered January 2004–December 2011.

Initially, a “case” of BRONJ (Figs. 1 and 2) was considered when the patient met diagnostic criteria established by the American Association of Oral and Maxillofacial Surgeons (AAOMS). However, throughout the study it was observed that in certain BRONJ patients the presence of bone exposure was not always presented as required clinical data.
Table 1  Main Characteristics of Bisphosphonates. Relative Potency, Mean Dose Administered and Mean Dose Deposited in the Bone Tissue of the Bisphosphonates in the Study.

<table>
<thead>
<tr>
<th>Bisphosphonate (oral/intravenous)</th>
<th>Relative potency</th>
<th>Average dose administered (mg)</th>
<th>Bone absorption rate</th>
<th>Average dose deposited in the bone tissue (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (oral)</td>
<td>1.000</td>
<td>1659.273</td>
<td>1%</td>
<td>16.593</td>
</tr>
<tr>
<td>Ibandronate (oral)</td>
<td>10.000</td>
<td>574.286</td>
<td>1%</td>
<td>57.43</td>
</tr>
<tr>
<td>Zoledronic acid (intravenous)</td>
<td>100.000</td>
<td>73.9</td>
<td>70%</td>
<td>51.73</td>
</tr>
<tr>
<td>Pamidronate (intravenous)</td>
<td>100</td>
<td>1575</td>
<td>70%</td>
<td>11.025</td>
</tr>
</tbody>
</table>

These patients were included in the study as a group initially named ‘‘Non-exposed Bisphosphate-Related Osteonecrosis of the Jaws’’. None of the patients in this study had a history of endocrine disorders related to parathyroid dysfunction.

Variables of the Study

The selection of the variables investigated was carried out in line with bibliographic information about the pathology and can be systematized in three groups: patients, bisphosphonate and osteonecrosis.

Patients

In the patients, the following were studied: age, sex, underlying disease and other previous antecedents, focusing on oral surgical history and traumatizing prosthesis. The interval of time (months) between the antecedent (if exist) and the onset of bone exposure was also recorded. Other investigated variables were: smoking and intake of anxiolytics. Although most of the patients had received different chemotherapics and/or corticosteroids concomitantly with aminobisphosphonates, the systematic collection of the first by lack of security in the dose, type and duration of the administration of the drug in many patients was was not undertaken.

Bisphosphonate

With regard to aminobisphosphonates the following variables were analyzed: type of bisphosphonate administered, duration of therapy until BRONJ diagnosis, route of administration, average dose administered in milligrams (mg), average dose deposited in bone tissue in milligrams and weighting dose/potency according to the bisphosphonate used.

For determining the average milligrams (mg.) deposited in bone tissue the following equation was applied: Average mg deposited in bone=Average mg administered×Deposit rate to the bone/100, where the percentage of the deposit of oral bisphosphonates is 1% and IV 70%. In order to determine the relative potency (RP) of the bisphosphonates, inhibition capacity on osteoclasts compared with etidronate (RP=1) was employed.

We proceed to weigh the dose deposited in the bone tissue adjusting to the RP (Table 1) of each bisphosphonate with the following formula: Weight dose deposited – RP= Average mg deposited in bone × relative potency.

Osteonecrosis

Finally, in relation to osteonecrosis the following variables were analyzed: previous history, clinical presentation and stage according to the criteria from Ruggiero et al. presence or absence of bone exposure, location (upper jaw/mandible; Anterior: incisive/premolar region, Posterior: distal to the premolar region), number of bone exposures, histology and microbiological findings, treatment applied following the recommendations of the AAOMS and evolution.

Data of the different variables were introduced into a Numbers spreadsheet (Numbers’09, Mac OS X, Version 2.3 2008–2012 Apple, Inc.) proceeding to obtain the descriptive information. The ‘‘Statistical Package for the Social Sciences’’ (SPSS for Mac OS X, version 20.0, 2011, SPSS Inc., Chicago, Illinois) was used for the subsequent analysis.

Results

Patients

In the time period of the study 70 patients were diagnosed with BRONJ, 44 women and 26 men, with a mean of 66.8 years (range: 35–89 years). Fig. 3 describes the underlying disease of the patients in the series. The most frequently disease observed was breast cancer (20 cases), followed by osteoporosis (18 cases) and multiple myeloma (16 cases).

The smoking habit was present in 45.7% of the patients and treatment with corticosteroids in 72%, mainly intermediate or long-acting corticosteroids, especially in relation to intravenous bisphosphonates. Furthermore, up to 55.7% of the patients were regular users of anxiolytics/antidepressants.

Bisphosphonate

Of the 70 patients studied, 18 patients (25.7%) had been treated with oral aminobisphosphate and 52 patients (74.3%) intravenously.

In 68.57% of the cases (48 patients) zoledronic acid (Zometa®, Novartis Pharmaceuticals, East Hanover, NJ) was the drug associated with the presentation of osteonecrosis.
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In two patients pamidronate (Aredia®, Novartis Pharmaceuticals, East Hanover, NJ) was the drug employed, and in two other cases pamidronate and zoledronic acid were administered at different times of the treatment.

Although intravenous administration of aminobisphosphonates was applied almost exclusively in patients with advanced cancer diseases (51 patients), at least one patient had a BRONJ osteonecrosis one month after receiving only a single dose of intravenous zoledronic acid 5 mg (Aclasta®, Novartis Pharmaceuticals, East Hanover, NJ).

Alendronate (15.71%) (Fosamax®, Merck, WhitehouseStation, NJ) and ibandronate (10%) (Bonviva®, Roche, Basel, Switzerland) were the oral aminobisphosphonates that induced BRONJ in eighteen patients. In nine patients, the condition was postmenopausal osteoporosis. In the nine remaining, the indication was motivated by the chronic use of corticosteroids in the context of rheumatoid arthritis (5 patients), sarcoidosis (1 patient), pemphigus (1 patient), Addison’s disease (1 patient) and Paget’s disease (1 patient).

The mean time of aminobisphosphonate administration was 26.53 months, underlining the osteonecrosis associated with oral bisphosphonates required higher induction time (48.44 months) than those associated with intravenous administration (19.94 months).

Unsurprisingly because of their greater dosage, lower relative potency and reduced volume of absorption, the average dose (Fig. 4) of oral bisphosphonates administered was higher both in the case of alendronate (16592.73 mg, range 12040 mg to 25480 mg) than in the ibandronate (5742.86 mg, range of 3600–7200 mg) compared to the mean doses administered intravenously.

The different dosage of zoledronic acid is the reason for which the observed dose (73.90 mg, range from 5 mg to 200 mg) is considerably lower even in comparison with pamidronate (1575 mg, range 540–2160 mg).

After the adjustment of average administered dose and dose deposited in the bone tissue, oral formulations showed to have a smaller deposit but the pamidronate is the drug which presented the highest deposits in the bone tissue (Table 1).

Finally, by weighting the mean dose deposited in bone tissue with the relative potency referenced to each bisphosphonate, we observed that the bisphosphonates most frequently related to osteonecrosis are those with the...
highest weight dose/strength; among them to highlight are ibandronate and especially, zoledronic acid (Table 2).

**Table 2 Microbiology Observed in BRONJ. Germs Isolated From Foci of Osteonecrosis From a Total of 34 Crops. In Several Cases, two or More Bacteria Were Isolated Simultaneously.**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomyces</td>
<td>23</td>
</tr>
<tr>
<td>Streptococci</td>
<td>9</td>
</tr>
<tr>
<td>Pseudomonas Aeruginosa</td>
<td>1</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
</tr>
<tr>
<td>Apergillus</td>
<td>1</td>
</tr>
<tr>
<td>Corynebacterium</td>
<td>1</td>
</tr>
<tr>
<td>Fusobacterium</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>1</td>
</tr>
<tr>
<td>Lactobacillus sp.</td>
<td>1</td>
</tr>
<tr>
<td>Prevotella</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 3 Antibiotic Administered. Eleven Patients did not Require Antibiotics.**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin–Clavulanic acid</td>
<td>2–4 g/day–125–250 mg/day</td>
<td>54</td>
<td>77.1%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1200 mg/day</td>
<td>3</td>
<td>4.3%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1 g/day</td>
<td>1</td>
<td>1.45%</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>300 mg/day</td>
<td>1</td>
<td>1.45%</td>
</tr>
</tbody>
</table>

Osteonecrosis

In 67.1% of the patients it was possible to identify the existence of a local triggering factor for osteonecrosis. Not only was there a history of dental extraction (48.6% of patients), but also a not insignificant association of osteonecrosis linkable to prosthetic trauma (15.7%) and other history of dental manipulations as endodontic teeth (2 patients) or implants (2 patients). In these cases, the average time between the triggering agent and the diagnosis of osteonecrosis was 5.7 months.

Bone exposure was the most common clinical manifestation of presentation (82.9%), but it should be emphasized that even in 12 patients (17.1%) the diagnosis of BRONJ was confirmed without the evidence of the existence of macroscopically exposed bone. Presence of pain and signs of infection with bleeding and halitosis were recognized in 48.6% of the patients, 21 of whom would end up creating chronic cutaneous or mucous fistulas. A woman who had BRONJ for more than 2 years of evolution developed left mandibular fracture. According to the classical classification of Ruggiero et al. 

The majority of the BRONJ were located in the mandible (74.3%). In 17 patients there was upper jaw involvement and one woman had symptoms affecting both jaws (left and right quadrants of the upper jaw and left mandible). Except in two patients, all the oral BRONJ were located in the mandible.

The most common clinical sign was the mandible of one single bone exposure (75.7%), but it is remarkable the number of patients with two areas of synchronous or metachronous exposed bone (12.9%). Topographically, the fourth quadrant was the anatomical region which presented the highest number of cases (20 cases), one more than the third quadrant. In addition, 67% of the osteonecrosis affected the posterior region of the jaws (distal to the premolar area).

The histopathological examination of thirty-five fragments of bone affected by the disease was characterized by the presence of necrotic osteitis. The presence of an inflammatory infiltrate consisting of lymphocytes and granulocytes in variable proportions could be recognized. The presence of different degrees of marrow fibrosis was also common and recognizable colonization by Actinomyces and other germs that are listed in Table 3.

The 50% of osteonecrosis required in their treatment the combination of oral antiseptics, antibiotics and surgery under local or general anesthesia. Amoxicillin (2.4 g/day)–clavulanic acid (125–250 mg/day) was administered to 77.1% of the patients. The scheduled antibiotic is detailed in Table 3.

In all cases the implemented surgery consisted in the removal of the bone sequestration and the curettage of the underlying bone until obtaining a profuse bleeding. Only in one patient a segmental mandibulectomy was performed after two previous failures with other surgeries. These developments allow us to affirm that 58.6% of the patients experimented a complete resolution in a control time of 16.28 months (range 1–54 months). Moreover, 30% of the patients reported an improvement in their symptomatology, limiting the disease to stage I of Ruggiero. 

**Discussion**

Since the recognition in late 2003 of the adverse effects that aminobisphosphonates administration induces on the jaws, numerous evidence based case series have been published in the international literature from whose analysis important evidence can be obtained. Between the years 2003 and 2005, there were five case series totaling 117 patients. The first publications in 2003 corresponded to Marx, Wang and Migliorati, and the most extensive series belonged to Ruggiero et al. in 2004.

A comparison with three important sources on the subject was developed in order to proceed to the critical review and the discussion of the results obtained. First is the systematic review of cases reported in the literature up to September 2009 by Filleul et al. This study includes the information from 2400 patients published in international journals in English, French, Spanish or Italian. Second is contrasting the results obtained with the information published by our group in 2009, which contained the characteristics of the
disease in our region from January 2004 until April 2007. Final step is assessing similarities or differences between our series and others with similar characteristics that gather information about BRONJ in other adjacent regions of Spain.

Regarding the systematic reviews, our results coincide with the variables of age, sex and location of bone exposure. Although multiple bone exposure is described in the literature in up to 27% of the cases, in the present study it is 12.9%. Concerning cases of oral BRONJ, the proportion observed in our study is high (25.7%) compared with systematic reviews (11%). Many authors coincide, and our results agree, the evolved neoplastic diseases, especially breast cancer, are the main group of patients who develop a chemical osteonecrosis. Second would be the multiple myeloma. While there are different points of view on the matter, in our opinion, the underlying disease with the highest risk of developing BRONJ is multiple myeloma.

Zoledronic acid is, by far, the most frequent intravenous drug associated with osteonecrosis. The great relative potency of zoledronic acid and its high degree of bone incorporation when it is administered parenterally justify this privileged position. On the other hand, alendronate (Fosamax®) is the main inducer of oral BRONJ because of its extensive use as historic first-choice bisphosphonate for the treatment of osteoporosis for years. But due to the increasing use of other bisphosphonates, we think alendronate will decrease as the leading cause of BRONJ associated with oral administration. It is interesting to see how the percentage of cases of BRONJ (67.1%) with evidence of local triggering factor in our study concurs with the information disclosed by Filleul et al.

According to the classic classification of Ruggiero the most frequent stage observed at the time of diagnosis is II. This point, common in the different studies reviewed, is justified because the “simple bone exposure” could go unnoticed in many patients and only the onset of pain and/or inflammatory signs motivate the patients to attend the specialist assessment.

In this series, 50% of the patients required any one type of surgery. The first diagnosed cases of BRONJ were usually operated under local anesthesia, and sequestrectomy was the most common surgery. The most recent cases are often subjected to general anesthesia and more extensive surgeries were performed, but only in one patient a segmental mandibulectomy was carried out. Filleul et al. describe that approximately 50% of the patients with chemical osteonecrosis will require a surgical treatment which they define as “conservative” (sequestrectomy) in 65% of the cases and as “aggressive” in 35% remaining.

The prognosis of this disease is fascinating, but its appropriate observation depends on establishing clearly the meaning of cure, improvement or treatment failure. In our study, “cured” was only considered in those patients who showed no symptoms or signs (no bone exposure) for more than twelve months after the treatment (Fig. 5). Under this premise we found that 58.6% of the patients achieved the status of healing. Cure rates range from 35% and 80% in the scientific literature indexed.

In the first study of BRONJ in our region the experience on 21 patients was detailed. Three main differences have to be highlighted with this recent study. First, the percentage of patients with BRONJ associated to oral administration increased from 4.7% in the first study to 25.7% in the current study. Although in most of the early studies the substantial weight of the pathology was attributable to the potent intravenous zoledronic acid, the prolonged use (over 3 years) of bisphosphonates in the treatment for osteoporosis has generated a large target population that, according to the classic Australian study from Mavrokokki et al. will undergo invasive dental treatment which further derive in BRONJ.

Second, in our first study, we observed that two patients (9.5%) had BONJ without bone exposure. In the current series, no bone exposure was objectified in 12 patients (17.1%). The publication of this work in 2008 generated a major controversy therefore assumed the three classic conditions according to the AAOMS should meet a patient to be diagnosed with the pathology, one of them (bone exposure) was not mandatory. On the other hand, and whether the proposal from our group is certain, the primitive classifications of the BRONJ should be revised.

In 2012, Patel et al. published a review on the subject and concluded that the available evidence must accept the existence of BRONJ without bone exposure. In the same vein, Fedele et al. on a European multicenter study of 332 patients grouped from five different hospitals, observed that 96 patients (29.8%) presented BRONJ without bone exposure. In these patients the most common clinical presentation were pain (91.6%) and oral fistulas (51%). At present, various attempts in the literature to include this clinical form of BRONJ in innovative classifications can be appreciated.

Finally, it may be interesting to discuss our results with those reported by other Spanish series. Bagan et al. published the largest series, 126 cases belonging the Valencian Community, 24 of them (19%) related to oral administration. Although the first series of this author were not observed in any cases of oral BRONJ, we also recognize that as in our region, the number of these cases has increased over time in the Valencian community.
For these authors, oral bisphosphonate-induced osteonecrosis is presented at lower stages and frequently include cases of "non-exposed bisphosphate-relate of the jaws". Our results do not coincide with these observations on the last two variables.

Furthermore, the experience corresponding to the northwest of Spain has been published in the year 2012 on 20 BRONJ patients (24 injuries) exclusively induced by oral bisphosphonates. We can emphasize two main differences: first, their not demonstrated association between osteonecrosis and hypertension (present in 68% of the cases) not observable in our study, and second, the lowest percentage of patients associating the ingestion of the bisphosphonates with corticosteroids (35%) compared with our percentage.

Finally, comparing our results with the data published in the Canary Islands in 2012 in 44 cases similar data for age, sex, location, primary oncological disease, history of oral surgery and type of aminobisphosphonate both oral (alendronate) and intravenous (zoledronic acid) are observed. This study differs from our results in the lower percentage of cases submitted to surgical treatment (39%) and surgically less "aggressive". Unfortunately, it is not possible to compare the evolution of the series because the information detailed by Bocanegra et al. only specifies that 45% of the patients remain stable after the treatment and 23% of them did not improve despite the treatment applied.

Conclusions

Seventy cases of chemical osteonecrosis were identified, 25% of them induced by oral administration of a bisphosphate, especially alendronate, but zoledronic acid was the agent most frequently associated with osteonecrosis. The most frequent clinical presentation was the single bone exposure in stages II and III, especially in the molar mandibular region in patients with metastatic disease. The main local trigger for BRONJ was the previous history of oral surgery, especially tooth extraction. Between the general factors a significant number of patients showed steroid use history.

References
