Bisphosphonates and Oral Pathology II. Osteonecrosis of the jaws: Review of the literature before 2005

Ruth Estefanía Fresco, Nerea Ponte Fernández, José Manuel Aguirre Urizar

Medicina Bucal. Departamento de Estomatología. Unidad de Patología Oral y Maxilofacial. Servicio Clínica Odontológica. Universidad del País Vasco EHU

Correspondence:
Prof. José Manuel Aguirre Urízar
Medicina Bucal. Departamento de Estomatología.
Universidad del País Vasco EHU
Barrio Sarriena s/n
Leioa 48940. Vizcaya
E-mail:otpagurj@lg.ehu.es

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ABSTRACT
Bisphosphonates are bone-turnover modulating drugs which are used in the management of a number of bone diseases ranging from osteoporosis to neoplasic pathology-associated osteolysis. In the last years a number of cases of osteonecrosis of the jaws associated with these drugs have been reported. In this review we analyze the cases published in the literature indexed from 2003 to December 2005. During this period 246 cases were reported, being more frequently associated with women in the sixth decade of life. More frequently associated bisphosphonates were the nitrogenated bisphosphonates (pamidronate, zolendronic acid) and the most common oral antecedent was a dental extraction. Nevertheless more than 25% of the cases were spontaneous. The most frequent site was the mandible and most of the cases presented clinical evidence of bone exposure and pain. Different treatments have been proposed with different antibiotic therapies with or without surgery, showing in general terms an uncertain prognosis with low healing rates.

Key words: *Bisphosphonates, osteonecrosis, jaws, review.*

RESUMEN
Los bisfosfonatos son fármacos moduladores del recambio óseo que están indicados en numerosas patologías óseas desde la osteoporosis a la osteolisis asociada a patología neoplásica. En los últimos años se han ido publicando numerosos casos de osteonecrosis de los maxilares asociada a la toma de estos medicamentos. En esta revisión se analizan los casos publicados en la literatura indexada desde el inicial del 2003 hasta diciembre del 2005. Durante este periodo se han publicado 246 casos, afectando más a las mujeres y sobre todo en la sexta década de vida. Los bisfosfonatos más frecuentemente asociados han sido los nitrogenados (pamidronato-ácido zoledrónico) y el antecedente oral más común la exodoncia. No obstante, más del 25% correspondieron a casos "espontáneos". La localización mas frecuente fue la mandíbula y clínicamente la mayoría de los casos mostraban exposición ósea y dolor asociado. La terapéutica ha sido muy diversa con diferentes pautas antibióticas con o sin cirugía, mostrando en general un pronóstico incierto con bajos índices de curación.

Palabras clave: *Bisfosfonatos, osteonecrosis, maxilar, revisión.*

INTRODUCTION

The first case of osteonecrosis of the jaws (ONJ) associated with bisphosphonate (BPP)-therapy was reported by Marx in 2003 (1). Since then a number of new cases have been reported, isolated or in series, which has now become a "growing epidemic" (1).

In the present review we have gathered the cases indexed in MEDLINE database, from the first one in 2003 made by Wang et al (2) to the one made at the end of 2005 by Merigo et al (3) which makes a total of 246 cases.

The first author to associate ONJ with BPP was Marx (1). However, the first description of BPP associated ONJ was made by Wang et al (2), but was initially attributed to chemotherapy received by these patients. At a later time, when similar cases were reported, it was concluded that the osteonecrosis could be caused by BPP. (4)

Last year 2005, Marx et al. (5) published a review on this subject with a wide number of cases in which his own case as well as those derived by colleagues were analyzed, including also cases that had already been published.

In this review we have gathered 246 cases of scientific literature indexed and have divided them into Group A with 127 cases obtained from different studies (2, 3, 6-16) and Group B with the 119 cases reported by Marx et al. (5). In each of the sections, both groups were analyzed separately as it was not possible to form one group due to lack of important data in some of the articles.

REVIEW

1.- In relation to the age and sex

In Group A (N=127) 85 cases (66.9%) corresponded to female and 42 (33.1%) to male patients. In this group the relationship female-male was almost 2:1.

The average age in Group A at the moment of diagnosis of the ONJ was 65.6 years, with a minimum of 36 and a maximum of 89 years. The average age of female patients was 65.3 years (range 36-89) and 66.1 years (range 45-85) for the male patients.

Surprisingly in the review presented by Marx et al. (Group B) (5) no references appear related to sex or the age of the patients.

2.- In relation to the type of BPP and the previous pathology

From the different types of BPP associated with ONJ in Group A (N=127), the most common was pamidronate in 54 patients (42.5%), followed by the combination of pamidronate and zolendronic acid in 31 (24.4%) and zolendronic acid in 29 (22.8%). Alendronate was associated with 9 patients (7.1%) and ibandronate and risedronate in 1 patient (0.8%) respectively. The combination of alendronate and zolendronic acid was used in 2 patients (1.6%).

The main data concerning patients of Group A who took alendronate are shown in Table 1.

In Group B (5) the most frequently associated BPP was zolendronic acid in 40.3% of the patients, followed by those who started their treatment with pamidronate and then changed to zolendronic acid in 30.2%, 26% of the patients with pamidronate and 2.5% with alendronate.

Table 1. Characteristics of ONJ patients associated to alendronate therapy.

ONJ-Alendronate (N=9)		
Sex	8 female: 1 male	
Middle age	71.6 years (range 58-84)	
Pathology associated	Osteoporosis	7 (77.8%)
	Breast cancer	1 (11.1%)
	Paget´s disease	1 (11.1%)
Time therapy BPP >ONJ	Middle time	44.2 months (range 25-60)
Localization ONJ	Mandible	6 (66.7%)
	Upper maxillary	3 (33.3%)
	Bilateral	1 (12.5%)*
	Unilateral	7 (87.5%)*

(References: 6, 11, 12, 14)
ONJ: osteonecrosis of the jawsr/BPP: bisphosphonate
* (N=8)

Table 2. Characteristics of the group of patients with breast cancer and ONJ associated to BPP therapy.
ONJ-BPP breast cancer
(N=50)

ONJ-BPP breast cancer (N=50)		
Sex	50 female (100%)	
Middle age	61.7 years (range 36-89).	
Type of BPP	Pamidronate	25 (50%)
	Zoledronic acid	13 (26%)
	Pamidronate & zolendronic	10 (20%)
	Ibandronate	1 (2%)
	Alendronate	1 (2%)
Time of therapy BPP>ONJ	Middle time	18.3 months (range 5-48)
Localization ONJ	Mandible	24 (48%)
	Upper maxillary	15 (30%)
	Mandible & Maxillary	11 (22%)
Previous oral intervention (N=27)	Nine	14 (51.9)
	Dental extraction	13 (48.1%)

ONJ: osteonecrosis of the jaws/BPP: bisphosphonate

Table 3. Characteristics of the group of patients with multiple myeloma and ONJ associated to BPP therapy.

ONJ-BFF multiple myeloma (N=53)		
Sex	23 female: 30 male	
Middle age	66.2 years (range 40-87).	
Type of BPP	Pamidronate	22 (41.5%)
	Zoledronic acid	11 (20.7%)
	Pamidronate+Zoledronic	19 (35.8%)
	Alendronate+Zoledronic	1 (1.9%)
Time therapy BPP>ONJ	Middle time	19.3 months (range 12-72)
Localization ONJ	Mandible	33 (62.3%)
	Upper maxillary	12 (22.6%)
	Mandible & Maxillary	8 (15.1%)
Previous oral intervention (N=21)	Nine	7 (33.3%)
	Dental extraction	14 (66.7%)

ONJ: osteonecrosis of the jaws/BPP: bisphosphonate

Table 4. Characteristics of the group of patients with osteoporosis and ONJ associated to BPP therapy.

ONJ-BPP osteoporosis (N=10)		
Sex	8 female: 2 male	
Middle age	71 years (range 45-82).	
Type of BPP	Alendronate	7 (70%)
	Alendronate+zoledronic	1 (10%)
	Pamidronate+zoledronic	1 (10%)
	Risedronate	1 (10%)
Time therapy BPP>ONJ (N=4)	Middle time	40 months (range 12-79)
Localization	Mandible	8 (80%)
	Upper maxillary	2 (20%)
Previous oral intervention (N=3)	Nine	1
	Dental extraction	1
	Oral surgery	1

ONJ: osteonecrosis of the jaws/BPP: bisphosphonate

In Group A (N=127) therapy with BPP was used in the management of multiple myeloma in 53 patients (41.7%) and breast cancer in 50 (39.4%). It was also used in osteoporosis in 10 patients (7.9%),in prostate cancer in 8 cases (6.3%), Paget's disease in 3 patients (2.4%), in 2 patients with metastatic lung cancer (1.6%) and in 1 case of uterine sarcoma (0.8%).

The main data concerning the characteristics of the groups of patients with breast cancer, multiple myeloma and osteoporosis in Group A are shown in Tables 2, 3 and 4.

In Group B (5) the most frequent pathologies were multiple myeloma (52.1%) and breast cancer (42%) followed by prostate cancer (3.4%) and osteoporosis (2.5%).

3.- In relation to treatment duration before the ONJ appeared

In Group A (N=100) the average time of treatment with BPP before the appearance of the ONJ was 19.9 months (range 5-79). In those patients under treatment with the combination of zolendronic acid and pamidronate (27 cases), the average time of the therapy was 25.8 months (range 9-79), for zolendronic acid (24 cases) 16.9 months (range 5-36) and for pamidronate (45 cases) 15.5 months (range 6-72). In the patients taking alendronate the time was only specified in 4 cases, the average being 44.2 months (range 25-60).

In Group B (5) the average time in patients taking zolendronic acid was 9.4 months. In those patients who began their therapy with pamidronate and then changed to zolendronic acid it was 12.1 months, 14.3 months for those treated with pamidronate and 36 months for the patients taking alendronate.

4.- In relation to the odontologic antecedent and the location

In Group A (N=124) the ONJ appeared in 87 cases after a dental extraction (71.3%), without a known oral antecedent ("spontaneous") in 35 cases (28.7%), caused by a denture in 1 case (0.8%) and after the surgical removal of implants in another case (0.8%).

In Group B (5) the most frequent antecedent was a dental extraction (37.8%), followed by periodontal disease (28.6%) and was spontaneous in 25.2% of the cases. Other antecedents named were periodontal surgery (4.2%), implantation surgery (3.4%) and 1 case associated with apicectomy (0.8%).

As to the site of the lesions in Group A (N=127) in 69 cases (54.3%) they appeared in the mandible, in 37 cases in the maxilla (29.1%) and in 21 patients (16.5%) both jaws were affected. In 94 cases when specified, the ONJ was unilateral in 86 cases (91.5%) and bilateral in 8 (8.5%).

In Group B (5) 68.1% of ONJ developed in the lower jaw, 27.7% in the upper jaw and only in 4.2% of the patients were both jaws affected.

5.- In relation to clinical aspects

The clinical forms of presentation of ONJ associated with BPP described in literature are diverse and in each case there are different clinical items combined, sometimes very extensively and some other times not so extensively.

In the analysis of Group A we excluded 58 of the 63 cases

from the article of Ruggiero et al (11) as the form of presentation of the pathology was not clearly specified.

In Group A (N=69) the most common data was the presence of an exposed area of bone which appeared in 52 cases (75.4%), followed by pain in 22 patients (31.9%). Other clinical manifestations were pathologic fractures in 8 cases (7.2%), non-healing sockets in 6 (8.7%), suppuration in 4 (5.8%), NOS ulcers (inespecific) in 6 (8.7%), swelling in 3 (4.3%) and maxillar sinusitis in 1 case (1.4%). In 15 other cases (21.7%) other signs were described such as: oroantral fistula, bone sequestrum, soft tissue lesions, osteolytic lesions, paresthesia, infection and skin fistula.

In Group B (5), the most frequent clinical manifestation was bone exposition associated with pain in 68.9% of the patients. Nevertheless, Marx et al. (5) noted that in 31.1% of the cases the exposed bone was asymptomatic and was a casual finding in a routine oral exploration. In this group 23.5% of the patients presented one or more mobile teeth and in 17.6% there was skin or mucosa fistula and even exposed bone through the skin.

6.- In relation to the treatment and the prognosis

In Group A the treatment was completely specified in 102 cases, explaining the procedures and the drugs used. In this group 80 cases (78.4%) were treated with antibiotics and minor oral surgery and 22 (21.6%) with antibiotic therapy and radical oral surgery. In 3 cases (2.9%) only antibiotic therapy was given and in 4 cases hiperbaric oxygen was also administered (3.9%).

In relation to the type of antibiotic used, some authors (6) advised penicillin, while others used amoxicillin exclusively (7) either in combination with clavulanic acid (9) or metronidazol (12). In allergic patients the alternative to amoxicillin was clindamicin (7, 9). On the other hand, Merigo et al (3) combined cefallosporines and metronidazol in conjunction with antifungic drugs (fluconazol), as in 2 patients *Candida albicans* was found. Throndson et al (13) used different antibiotic therapies with penicillin and other betalactamics, tetraciclines, doxicicline and/or eritromicine.

Regarding surgery, among the minor surgey to be included are sequestrectomy, practiced in 59 cases (73.7%), debridement or local resection in 17 cases (21.2%) and curetage in 6 cases (7.5%).

More radical surgery consisted of: mandibular decortication in 1 case (4.5%), marginal mandibulectomy in 4 cases (18.2%), segmentary or partial maxilectomy or mandibulectomy in 13 cases (59.1%) and total maxillectomy in 4 cases (18.2%).

In Group B Marx et al. (5) expounds as a general therapy the administration of a long-term or even a permanent antibiotic therapy, based on penicillin V-K (500 mg oral, 4 times a day) as well as mouthwashes with clorhexidine 0.12%. In refractory cases or those with a more serious symptomatology, metronidazol (500 mg oral 3 times a day) should be added. If a severe celulitis develops hospitalization it's necessary and intravenous ampicillin with metronidazol should be given. In patients with penicillin allergy metronidazol should be given (500 mg oral 3 times a day), combined with ciprofloxacin (500 mg oral twice a day) or combined with eritromicine (400 mg oral 3 times a day). This author (5) does not recommend surgery in the treatment of these cases.

In Group A the results of the treatment used were only shown in 14 cases. In 5 patients (35.7%) a total success was obtained, in 5 (35.7%) a partial success was obtained and in the 4 last cases (28.6%) the treatment failed. In 3 cases treatment with minor surgery was a total success and in the other 2 cases with major surgery. The cases of partial success were treated with antibiotics in 2 cases, minor surgery in 2 cases and minor surgery combined with hiperbaric oxygen in 1 case. The patients where treatment failed had been managed with minor surgery in 2 cases, hiperbaric oxygen in 1 case and major surgery combined with hiperbaric oxygen in another case.

In the review presented by Marx et al. (5) of the 91 cases treated only with antibiotics, in 9 (9.9%) an intermittent pain persisted; that required dose adjustments or the adding more antibiotics. However, in the other 82 cases (90.1%) the patients had no pain and a change in antibiotherapy was not necessary. None of the patients had jaw fractures.

DISCUSSION

The ONJ has become over the last years a frequent and important pathology in patients with diverse bone systemic disorders treated with BPP therapies. (1, 5, 8, 9, 11, 17).

In the review of the cases which appeared in the literature indexed between 2003 and 2005 ONJ associated with BPP is much more frequent in female patients. This could be explained by the fact that these drugs are used more frequently in women as is the case with postmenopausic osteoporosis and breast cancer.

Also, the fact that this group of patients had a higher average age would be related to the age at which this disease, in which the BPP are more frequently used, appear which usually corresponds to people with more than 55 years. Nevertheless, there are cases of ONJ-BPP described in young people (<40 years), which would indicate this pathology is not age-dependent (8, 9).

In the analysis of the literature it is clearly recognized that the nitrogenated BPP, of parenteral administration and high activity (pamidronate and zolendronic acid), are the BPP most commonly associated with ONJ. However, there are also cases associated with other BPP of oral administration, including alendronate, but of a scarce frequency (6, 11, 12, 14).

The pathologies most frequently associated with ONJ-BPP were multiple myeloma and breast cancer, that together represent more than 80%. This would not be unexpected because these two diseases usually receive treatment with parenteral high activity BPP, preferentially pamidronate and zolendronic acid.

The ONJ appears earlier in patients treated with parenteral BPP such as zolendronic acid and pamidronate than in others such as alendronate. Also, it can be concluded from the review that as the treatment time increases, the possibility

of suffering this disorder increase as well. However we think that the ONJ apparition is related preferentially to the time when the predisposing oral lesion is produced, for example a tooth extraction, than with the real treatment time.

In both groups it can be seen that even though the dental extraction is the most frequent cause of oral antecedent, other odontologic factors can cause the development of ONJ. Also, it should be noticed that in both groups 25% of the cases were diagnosed with no confirmed oral antecedent, that is, they were "spontaneous cases". Nevertheless, the oral cavity is constantly exposed to traumatic situations, subjectively imperceptible, which in a normal mouth would not give rise to any disorder but that in this anormal condition any tisular laceration can become the initiating factor of ONJ.

As would be expected, the jaw has been the most frequent location of ONJ in both groups of patients. It is known that mandibular bone has anatomic and physiologic features that would give rise to the apparition of osteonecrotic pathology (18).

We do not know why in Group A there are more cases of ONJ affecting both jaws than in Group B, although it could be because the diagnosis was made later, giving time for more serious lesions to develop.

Regarding antibiotic therapy there is no agreement concerning the cases described in the literature and different therapies have been used, usually with long-term wide spectrum antibiotics such as: amoxicillin with or without clavulanic acid, cefallosporins, metronidazol, macrolids, etc., alone or combined. Marx et al. (5) advocated the use of oral amoxicillin combined with clorhexidine mouthwashes, a therapy with good results. However, this antibiotic therapy needs to be strictly followed and sometimes it is very difficult to finish the treatment. The most common alternative to penicillin derived drugs is clindamicine (7, 9). Nevertheless, some authors (5) are against the use of clindamicine as its low activity versus *Actynomices, Eikenella corrodens* and other similar species that appear in these cases.

Regarding surgical treatment, Marx et al. (5) does not recommend surgery in the treatment of ONJ-BPP, because he considers that attempts to make debridements, covering exposed areas with flaps or remodelation of bone usually are counter-productive. For this author (5), these procedures can lead to a greater amount of exposed bone with a worsening of symptoms and a greater risk of a jaw fracture. He only recommends surgery in those refractory cases to non-surgical treatment and if sypmtoms continue. He considers that in BPP-induced bone exposures, the whole bone is affected thus it is not possible to find a viable bone margin. For Marx et al. (5), these patients can and must live with some exposed bone and treatment should be aimed at eliminating or controlling pain and preventing the progression of lesions. The exposed necrotic bone itself is not painful and will maintain its structure for normal jaw function. However if it becomes infected secondary pain starts and celulitis and fistula formation could appear. Pathologic fractures are not common unless debridement surgery has reduced the jaw's structural integrity. For this author (5), debridement surgery is not to be recommended except where there is softening of bony sharp projections causing inflammation and pain.

Concerning the prognosis, only in Marx's et al. review (5) can we see good results if we consider that 90% of the patients were controlled only with antibiotic therapy. In the rest of the cases, the scarce data do not show that surgery or the use of other techniques such as hiperbaric oxygen are the main elements in the prognosis.

All this supports the fact of the need to establish preventive measures in all the patients treated with BPP to prevent this osteonecrotic pathology of the jaws.

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