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Bisphosphonates: Do they prevent or cause bone fractures?

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abstract

Objective: to describe the effects of bisphosphonates with respect to whether they prevent or cause bone fractures. **Methods:** a review of the main short and long-term randomized clinical trials, long-term cohort studies and case reports of atypical fractures with bisphosphonates published in MEDLINE since 1965. **Results:** the effect of treatment with bisphosphonates versus placebo for short and long-term studies is described in absolute terms for the incidence of vertebral, hip and "non-vertebral" fractures. In addition, the current evidence on atypical femur fractures associated with bisphosphonate use is summarized. **Conclusions:** in the short-term, bisphosphonates show some effectiveness in preventing vertebral fractures demonstrated by x-ray. The efficacy with regard to preventing hip fractures is uncertain; for primary prevention hip fractures are not reduced and for secondary prevention the effect is of small magnitude and of questionable clinical relevance. In the long-term, there is an increased risk of atypical fractures affecting the subtrochanter and diaphysis of the femur. In addition, one cohort study suggests the incidence of hip fractures could be increased instead of reduced. Clarification of the long-term effects of bisphosphonates is therefore necessary and suspension of the use of these drugs for osteoporosis should be considered.

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Osteonecrosis of the jaw. A secondary effect or complication of bisphosphonate treatment

Short-term evidence (1-3 years)

Bisphosphonates are widely employed in the population to prevent bone fractures. The first most widely used drug was **alendronate**, which was approved by the FDA in September 1995 for the prevention and treatment of postmenopausal osteoporosis in relation to its capacity to increase bone density. Three years later **risedronate** was approved for the same indication and, in 2005, the same occured for **ibandronate**. The latter was also approved by the EMEA through a centralised procedure. When bisphosphonates came onto the market, they had demonstrated efficacy in the improvement of a surrogate endpoint, bone density, but there was no evidence for reduction of bone fractures. They were introduced on the theoretical assumption that the increase in bone density implied strengthening of the bone, and therefore a reduction in the risk of fracture.

Vertebral fractures

Subsequently pivotal clinical trials were conducted where the primary outcome was not bone density, but rather the prevention of morphological vertebral fractures determined by radiology. This was initially defined as a 20% reduction of the height of any vertebra in the case of the studies with alendronate[2,3] and ibandronate[4]. However, in the trials with risedronate and strontium ralenate the term "vertebral fracture", was arbitrarily re-defined, as a 15% reduction in the height of the vertebra, which led to an increase in the incidence of this outcome simply due to the change in criteria[5,6,7,8].

Bisphosphonates did show efficacy in reducing these vertebral height ("fractures") with a reduction in absolute risk between 1% and 8% (table 1). The absolute effect in reducing symptomatic events is much less given that only a third of people with radiologically demonstrated fractures have clinical symptoms[1,2].

The effects of these drugs on vertebral fractures are expected, given that the primary endpoint of the trials was the incidence of morphometric fractures and bisphosphonates deposit in and adhere to bone to a great extent. But regardless of whether they are deposited within bone structures, we need to ask ourselves... do bisphosphonates improve the micro-architecture in a way that bone becomes more resistant to fracture or do they, on the contrary, disrupt the micro-architecture and make the bone more prone to fracture?

Hip and non-vertebral fractures

The available clinical trials provide data on efficacy in the prevention of hip fracture and fractures not affecting the vertebral column. The concept "non-vertebral" is not the same in all clinical trials. In some cases, they include fractures presumably not related to osteoporosis and those caused by trauma[3,5,6,7,9], while, in other cases, the studies were limited to fractures associated with osteoporosis (table 1)[1,2,4,8].

The available evidence with regard to the use of these drugs in the prevention of hip fractures or non-vertebral fractures is very weak. Pivotal trials which gave way to approval of this indication for oral bisphosphonates only provided information on non-vertebral fractures as secondary endpoints.

Years later, a clinical trial whose primary endpoint was prevention of hip fracture[10] was carried out on another drug belonging to a different class, **strontium ranelate**. The results were not statistically significant vs placebo. However, a *post-hoc* analysis in a sub-group of women with a mean age of nearly 80 years, femoral bone density < -3.5 SD and prevalent fractures in 60% of the patients showed that the efficacy was close to statistical significance. With questionable evidence, the EMEA approved the indication for prevention of hip fractures. In the drug assessment report, the EMEA recognised that the indication was based on the results from a sub-group of patients *but given that bisphosphonates were approved in a similar fashion, there was no reason for a comparative grievance with regard to strontium ranelate*[11].

The evidence from the trials is inconsistent. In some studies no efficacy was observed in the prevention of hip fracture, but the drugs proved effective with regard to non-vertebral fractures. In other trials the opposite results were found. In the majority of cases there were no statistically significant differences vs placebo (table 1). Given this situation, various meta-analyses have been car-

ried out to study the effects of bisphosphonates in the prevention of hip fractures and non-vertebral fractures. Their results, however, do not guarantee any clear efficacy for these indications and the quality of the studies is questionable as will be explained in the following section.

It is not clear whether bisphosphonates are effective in the prevention of hip fractures and non-vertebral fractures

Alendronate

The first meta-analysis[12] included one pivotal study[3] and three other studies each with a low participation of patients (between 124 and 273 patients)[13,14,15]. One of them had a quality score of 2 on a scale of 0-5[15] and another was published only as an abstract[14]. The results of this meta-analysis showed that alendronate was not more effective than placebo in the prevention of hip fractures [HR = 0.46 (0.15-1.36)], but did statistically significantly reduce non-vertebral fractures from 4.45% for placebo to 3.26% for alendronate [HR = 0.71 (0.50-0.99)], absolute risk reduction, 1.2%.

Another older meta-analysis included three pivotal trials and no statistically significant differences were observed with respect to placebo in the prevention of hip fractures[16]. In this meta-analysis differences were found in favour of the drug with regard to non-vertebral fractures. In the analysis of non-vertebral fractures, the authors included two more trials than in the meta-analysis for hip fractures. Both were of low quality, one of them achieved a score of 2 out of 5[15], while the other was the only study in which data on non-vertebral fractures were not collected prospectively[13]. These two trials were the studies that showed more favourable data for the drug vs placebo.

Later another meta-analysis[17] on hip fractures was performed where differences in favour of alendronate were found. This analysis included the pivotal studies and another three studies of uncertain quality whose primary endpoint was the variation in bone density[18,19,20]. Two of them did not collect information on non-vertebral fractures prospectively[18,19]. In both cases the data was published as “fractures”, in a general fashion, with no specification on the site of fracture or on the origin whether associated with osteoporosis or not. In the last trial mentioned[20], the results were published in abstract form in 1998 and, up to now, the complete results have not been published. Of a total of 25,090 person-years evaluated in this meta-analysis, alendronate reduced the absolute risk of hip fracture when compared to placebo by 0.21% per year.

A meta-analysis first published in 2002[21] and updated as a Cochrane review in 2009[22] included clinical trials with a duration of more than one year. The outcomes were incidence of vertebral, non-vertebral, hip and wrist fractures. In this review a distinction was made between primary and secondary prevention of fractures. There was no proven effect on symptomatic fractures for primary prevention. For secondary prevention, alendronate given for 3 years reduced the absolute risk of hip fractures by 0.7% and non-vertebral fractures by 2.1%.

In addition to the low magnitude of the absolute benefits from the meta-analysis, there are methodological aspects of the analysis which make us question the validity of the data, for example the short duration of some of the trials, the absence of data on fractures and the small sample size. Of the eleven studies included, the majority did not comply with the inclusion criteria defined by the authors themselves. One of them lasted for only three months and did not report information on fractures[23], various others also did not report data on fractures[13,14,23,25,26] and many of them had a small sample size (various included between 30-50 women per group).

Risedronate

The case of risedronate is similar to that of alendronate. The VERT trial in Europe and Australia[5] found no statistically significant differences between risedronate and placebo in the prevention of non-vertebral fractures. The same trial design in the USA, did find statistical significance for the same endpoint[6]. The HIP trial concluded that there were significant differences in prevention of hip fractures but not so with respect to non-vertebral fractures. In this trial an incoherent finding was that the daily 2.5 mg dose showed statistically significant differences in hip fracture prevention, while the daily 5 mg dose was equal to placebo for the same outcome (table 1). An attempt to perform a meta-analysis of the effect of risedronate on hip fractures was frustrated. The problem preventing the meta-

Table 1. Data on the efficacy of alendronate, risedronate, ibandronate and zoledronate in pivotal clinical trials.

Clinical trial	Sponsor	Population	Intervention	Duration	Primary endpoint
ALENDRONATE					
Liberman, 1995[3]	Merck	Women 45-80 years (mean = 64 years) Postmenopausal > 5 years BMD < - 2,5 SD Previous vertebral fract : 20% Vertebral deformities: 55%	AL 5, 10 or 20 mg/d (20% per group) vs placebo (40%) n = 994	2 years (double blind) + 1 year (open)	BMD and morphometric vertebral fractures
Black (FIT 1), 1996[1]	Merck	Women 55-81 years (mean = 70 years) Postmenopausia > 2 años BMD < - 2,1 SD Previous vertebral fract: 70%	AL 10 mg/d vs placebo n = 2,027 n (AL) = 1,022 n (PL) = 1,005	3 years	New morphometric vertebral fractures
Bone, 1997[9]	Merck	Women 60-85 years (mean = 71 years) DMO < - 2.0 SD Previous vertebral fract: 35% ("no vertebral fract" as inclusión criteria)	AL 1; 2,5 or 5 mg/d vs placebo n = 359	2 years	BMD
Cummings (FIT 2), 1998[2]	Merck	Women 55-80 years (mean = 68 years) Postmenopausia > 2 years BMD < - 2.0 SD Previous vertebral fract: 35% ("no vertebral fract" as inclusión criteria)	AL 10 mg/d vs placebo n = 4,432 n (AL) = 2,214 n (PL) = 2,218	4 years	Clinical and morphometric vertebral fractures
RISEDRONATE					
Harris (VERT 1), 1999[6]	Procter & Gamble	Women < 85 years (mean = 69 years) BMD = - 2,4 SD Previous vertebral fract.: 80 % No previous vertebral fract = 2.5 Location = USA	RI 2.5 or 5 mg/d vs placebo n = 2,458 n (PL) = 815 n (RI 2,5) = 811 n (RI 5) = 324	3 years	BMD, morphometric vertebral fractures or non vertebrale fractures
Reginster (VERT 2), 2000[5]	Procter & Gamble	Women < 85 years (mean = 71 years) BMD = - 2.8 SD Previous vertebral fract: 98 % No previous vertebral frac. = 3 (PL) and 4 (RI 5 mg/d) Location = Europe and Australia	RI 2.5 or 5 mg/d vs placebo n = 1,226 n (PL) = 408 n (RI 2.5) = 410 n (RI 5) = 408	3 years	BMD, morphometric vertebral fractures or non-vertebral fractures
McClung (HIP), 2001[7]	Procter & Gamble y Aventis	**Sample 1:** Women 70-79 years (mean = 74 years) BMD = - 3.7 SD Previous vertebral fract: 40 % **Sample 2:** Women > 80 years (mean = 83 years) BMD < - 4 SD Previuos vertebral fract: 45 % ≥ 1 risk factor for hip fract.	RI 2.5 or 5 mg/d vs placebo n = 9,331 n sample 1=5,445 n sample 2=3,886 Dropouts: Sample 1 = 43% Sample 2 = 60%	3 years	Hip fractures
IBANDRONATE					
Chesnut (BONE), 2004[4]	Hoffmann / La Roche	Women 55-80 years (mean = 69 years) BMD < -2.0 SD with 1-4 previous vertebral fractures	· Ibandronate: 2.5 mg/d (n= 982) · Ibandronate: 20 mg/every other day/12 doses every 3 moths (n= 982) · Placebo (n= 982) n = 2,946	3 years	Morphometric vertebral fractures
ZOLEDRONATE					
Black, 2007[33]	Novartis	Women 65 -89 years (mean = 73 years) femoral BMD < -2.5 SD with or without vertebral fractures or femoral BMD < -1.5 SD and 2 verteb fract or 1 moderate	ZO 5 mg yearly (n = 3,889) vs PL (n = 3,876) n = 7,736	3 years	Morphometric vertebral fractures
Lyles, 2007[34]	Novartis	Women ≥ 50 years with low-impact hip fracture in the last 90 days	ZO 5 mg yearly (n = 1,065) vs PL (n = 1,062) n = 2,127	2 years	Any fracture

	Vertebral fractures (placebo vs drug)	Hip fractures (placebo vs drug)	Non-vertebrales fractures (placebo vs drug)	Definition non-vertebral fracture
	No data given on double-blind phase (2 years). Data on open extended year (third year) 6.2% *vs* 3.2% RRA = 3.0% HR = 0.52 (0.28-0.95)	No data given on double-blind phase (2 years). Data on open extended year (third year) 0.8% *vs* 0.2% **HR = n.s.**	N.s. differences double-blind phase (2 years). Data on open extended year (third year) included: 9.6% *vs* 7.5% **HR = n.s.**	Hip, pelvis, whist, forearm, arm, leg, ribs, ankle, foot, fingers, toes, clavicle, sternum, shoulder, face and skull. No traumatic fractures were excluded.
	15.0% *vs* 8.0% RRA = 7.0% HR = 0.53 (0.41-0.68)	2.2% *vs* 1.1% RRA = 1.1% HR = 0.49 (0.23-0.99)	14.7% *vs* 11.9% **HR = n.s.**	All except pathological (tumors), face and skull.
	6.6% *vs* 4.3% (PL vs AL 5 mg/d) HR = n.s.	**Data not published**	17.6% *vs* 9.7% **HR = n.s.**	Mainly extremities; also clavicle, ribs and nose.
	3.8% *vs* 2.1% HR = 0.56 (0.39-0.80) Clinical fractures: HR = n.s.	1.1% *vs* 0.9% **HR = n.s.**	13.3% *vs* 11.8% **HR = n.s.**	All except pathological (tumors), face and skull
	16.3% *vs* 11.3%) RRA = 5.0% (PL *vs* RI 5 mg/d) HR = 0.59 (0.43-0.82)	PL *vs* RI 5 mg/d: 1.8% *vs* 1.5% **HR = n.s.** (includes hip and/or pelvis)	PL *vs* RI 5 mg/d 8.4% *vs* 5.2% RRA = 3.2% HR = 0.60 (0.39-0.94)	Clavicle, humerus, wrist, pelvis, hip or leg whether traumatic or not.
	13.0% vs 5.6% RRA = 7.4% (PL *vs* RI 5 mg/d) HR = 0.51 (0.36-0.73)	PL vs RI 5 mg/d: 2.7% *vs* 2.2% **HR = n.s.** (includes only hip)	PL *vs* RI 5 mg/d: 16.0% *vs* 10.9% **HR = n.s.**	Clavicle, humerus, wrist, pelvis, hip or leg whether traumatic or not.
	Data not published	**Sample 1** 3.2% *vs* 1.9% RRA = 1.3% HR = 0.6 (0.4-0.9) RI 5; HR = n.s. RI 2.5; HR = 0.5 (0.3-0.9) **Sample 2** 9.7% *vs* 7.2% **HR = n.s.**	**Total population** 11.2% *vs* 9.4% **HR = n.s.** **No data according to each population**	Wrist, leg, humerus, hip or clavicle
	Daily IB vs IB interval vs PL 4.7% *vs* 4.9% vs 9.6% RRA placebo *vs*: ·daily IB = 4.9% ·IB inter = 4.7% HR (daily) = 0.38 (0.25-0.59) HR (inter) = 0.50 (0.34-0.74)	**Results not published**	8.2% *vs* 9.1% *vs* 8.9% **HR = n.s.**	All except: hand, foot, face and skull.
	10.9% *vs* 3.3% RRA = 7.6% (PL *vs* ZO) HR = 0.30 (0.24-0.38)	2.5% *vs* 1.4% RRA = 1.1% (PL *vs* ZO) HR = 0.59 (0.42-0.83)	10.7% *vs* 8.0% RRA = 2.7% (PL *vs* ZO) HR = 0.75 (0.64-0.87)	All except fingers, toes, face and traumatic fractures.
	9.6% *vs* 3.8% RRA = 5.8% (PL *vs* ZO) HR = 0.54 (0.32-0.92)	3.5% *vs* 2.0% (PL *vs* ZO) **HR = n.s.**	10.7% *vs* 7.6 % RRA = 3.1% HR = 0.73 (0.55-0.98)	All except face, fingers or skull.

There is increasing information that questions the long-term safety profile of bisphosphonates

analysis was that the authors discovered anomalous data in individual studies (partial submission of data proceeding from clinical trials by Procter and Gamble)[27,28].

In a meta-analysis by Cranney et al. there is no data offered on the prevention of hip fractures, whereas in the case of non-vertebral fractures, only relative risks are given with no data in absolute terms[29]. When this was updated in a Cochrane review[30] there was no statistically significant reduction of symptomatic fractures for primary prevention. For secondary prevention risedronate given for 3 years reduced the absolute risk of hip fractures by 0.7%, and non-vertebral fractures by 2.1%.

Ibandronate

Ibandronate has not shown any efficacy in preventing hip or non-vertebral fractures. Two meta-analyses claimed that on employing high doses (higher than doses used in clinical practice), the drug was effective for these indications[31,32]. However, both meta-analyses present important deficiencies in methodology, including the grouping of different doses and incorrect analysis.

For example, of the four clinical trials included in the second of the meta-analyses mentioned, two presented data of a 2-year period while the other two trials had data from a 3-year period of study. On carrying out the analysis of the four trials after a 2-year follow up, it was found that ibandronate did not show any differences when compared to placebo. By including data proceeding from the third year of the two trials, statistical significance was found in favour of ibandronate, given that a comparison is made between *two years* of follow up in the ibandronate group vs the *three years* of follow up with placebo. That is to say that the placebo group is deliberately penalised in order to obtain significant results in favour of the drug. This clearly puts in doubt the veracity of the claims.

Zoledronic acid

Zoledronic acid is a special class of bisphosphonate which is given intravenously in a single dose per year. The drug has been the object of study in two trials in which the primary endpoint was the incidence of hip fracture. In both trials statistically significant differences were observed in favour of the drug in the reduction of non-vertebral fractures (ARR = 3% in both). With respect to the prevention of hip fractures, in one significant differences were found (ARR = 1.1%)[33], while in the other, zoledronic acid was not different from placebo[34]. The latter trial was discontinued early when significant differences were found in favour of the drug in the prevention of vertebral fractures (table 1).

To conclude, the efficacy of bisphosphonates in the prevention of hip or non-vertebral fractures is unclear and, if there is a real effect its magnitude is of questionable clinical relevance. In table 1, it can be observed that after a considerable period of years, the clinical trials have searched for women with greater risks for fracture in order to demonstrate the efficacy of bisphosphonates (mainly older age, lower bone density, more previous fractures). However, despite the search for a very selective profile of the patients, the results have hardly been promising.

Long-term evidence (more than 3 years)

One of the controversial issues regarding this class of drugs is that while it is known that they reduce bone remodeling, there is a strong suspicion that this may lead to harmful effects in the bone structure. The EMEA recognised that *"with long-term treatment, loss of effect on fracture prevention due to altered bone structure or other changes is a matter of concern. The maintenance of effect after the second year (e.g. 3-5 years) should be studied, although data may be submitted after registration"*[35].

Osteonecrosis of the jaw was the first adverse effect described in patients treated with bisphosphonates. In 2005, the Spanish Drug Agency published a warning regarding the parenteral administration of bisphosphonates[36]. Soon after an update was published which also made reference to oral bisphosphonates[37]. In the notification, it was mentioned that the incidence of osteonecrosis ranged between 0.8-1.2% in the case of intravenous bisphosphonates, while a lower incidence was observed with the oral forms as lower doses were employed. In addition, the statement warned that it would be only a question of time before the incidence of these adverse effects increased "given

that the risk of osteonecrosis is associated with accumulated doses, and as the population with osteoporosis was increasing there would also be prolonged treatments with these drugs".

As more evidence became available with regard to the harmful effects of these drugs affecting the jaw, it was expected that more problems would arise in other areas of the skeleton.

In 2005, *Odvina CV et al* published the first paper warning on the potentially harmful effects of alendronate due to suppression of bone remodeling[38]. Spontaneous fractures were observed in 9 patients under long-term treatment with the drug (between 3-8 years). A hypothesis was made regarding the long-term use of bisphosphonates which could increase the risk of fracture and cause difficulties in repairing fractures in some patients.

Bisphosphonates induce apoptosis of the osteoclasts and inhibit bone resorption. However, during the normal process of bone remodeling the formation of bone produced by osteoblasts is induced by osteclasts, which implies that on reducing the resorptive activity, there is also an accompanying reduction in bone formation. The greater bone density observed after treatment with bisphosphonates could be understood as a greater bone weakness given the increase of mineral content in the bone. It should also be pointed out that these drugs weaken the collagen structure and produce an accumulation of microscopic injuries in bone structure. Biologically this makes the hypothesis presented by *Odvina CV et al* seem plausible.

In 2006, the FLEX trial was published[39]. This consisted of a follow up period of one of the pivotal trials with alendronate (FIT)[1,2]. The women treated with alendronate for five years were randomly assigned to continue with the drug for another five years or receive placebo. No significant differences between treatment groups were observed for all clinical fractures, alendronate 20% and placebo 21%, RR = 0.93 [0.71-1.21] or non-vertebral fractures, alendronate 19% and placebo 19%, RR = 1.00 [0.76-1.32]. The conclusion made by the authors was that there was no difference in the incidence of fractures between both groups and that "alendronate could be discontinued safely after five years of treatment." At no point was the effect of the drug compared to an authentic placebo, given that the women in the placebo group had previously received five years of treatment[40]. For this reason this trial does not offer information on comparative effects of alendronate and placebo in the long-term.

The bisphosphonates risk-benefit balance may be unfavourable for their use in osteoporosis

Between 2006 and 2007 three papers were published on atypical fractures due to alendronate[41,42,43]. Then Goh et al[44] decided to review the cases in the last ten years involving low impact subtrochanteric fractures. They identified 13 women, of which 9 had received long-term alendronate. The authors issued an alert regarding the severe adverse effects of long-term treatment with this drug.

During 2008 more cases of atypical fractures (diaphysis and subtrochanter) were published and the number of patients in the series increased[45,46,47,48,49,50] (15, 17 and 70 individuals in the three last references cited). The association between the use of bisphosphonates and the appearance of fractures was finally becoming consolidated.

During 2009 a well-designed case-control study was carried out to evaluate the association of low impact femur fractures and the long-term use of bisphosphonates[52]. A comparison was made between 41 subtrochanteric or diaphyseal fractures with 82 control patients with femoral or inter-trochanteric fractures. A strong association was found between the use of bisphosphonates and atypical fractures (OR = 4.4; 95%CI, 1.7-11.5). At the same time, a typical radiological pattern was described for the fractures related to bisphosphonates and a high association between the use of bisphosphonates and the appearance of this radiological pattern (OR = 15.3; 95%CI, 3.6-76.90).

During the same year more cases and series of cases of femur fractures associated with the use of bisphosphonates appeared in publications[53,54,55,56]. The capacity of bisphosphonates to weaken bone structure is reflected in an article that describes a series of seven cases of bilateral fractures or sequential cases of low impact fractures all associated with the treatment with alendronate for at least five years[57]. These included one patient with simultaneous bilateral femur fractures affecting the diaphysis, two patients with sequential subtrochanteric fractures and four patients in whom a contralateral subtrochanteric fracture was discovered after diagnosing the initial fracture.

The French journal *La Revue Prescrire* petitioned the EMEA to submit data available on atypical fractures related to alendronate. In response, the EMEA issued a public statement in February 2009 describing 115 reported cases of patients treated between 18 months and 10 years. Of these, 84 cases involved subtrochanteric fractures or affected the diaphysis. The majority occurred with no previous trauma and were preceded by pain for weeks or months. Continuation of treatment with alendronate in these cases apparently impeded or caused certain difficulty in healing of the fractures[58].

In 2008 a particularly relevant retrospective cohort study[51], in Danish women with no previous hip fracture was published. This 8-year study compared 5,187 women treated with alendronate and with at least one fracture at baseline with a control group of 10,374 women receiving no treatment matched for the same baseline fracture, age etc. Surprisingly, the women receiving alendronate were found to have a statistically significant higher incidence of hip fracture 18.23 per 1,000 women-years as compared to the controls 11.86 per 1,000 women-years [HR = 1.50 (1.26-1.79)]. The data obtained was consistent throughout the eight-year follow up period of the cohort. That is the risk of hip fracture increased in the group treated with alendronate by 50% in relative terms and by 6 cases per 1,000 women–year in absolute terms. No significant differences were observed in the incidence of subtrochanteric fractures or those affecting the diaphysis when comparing the groups treated with alendronate to the controls, however the study lacked the power to evaluate subtrochanteric or diaphyseal fractures given the low incidence of these cases.

Severe adverse effects of bisphosphonates

Initially one of the main adverse effects of these drugs was oesophagitis. In part this was resolved by new preparations for weekly, monthly and parenteral administration. Subsequently clinicians described other adverse effects for example jaw osteonecrosis, pain affecting the bone, joints or muscles produced by the bisphosphonates[59,60], atrial fibrillation[61,62,63] or renal toxicity (zoledronic acid)[64]. Recently it was discovered from FDA archives that deaths possibly related with the use of zoledronic and pamidronic acid in clinical trials, were not mentioned when the trials were published in scientific journals[65].

In the national database FEDRA, by the 28 September 2009 a total of 213 notifications of bisphosphonate related osteonecrosis were registered. In some of the cases, bone related pain and/or osteomyelitis were also associated. Of these, 177 cases were related to parenteral administration and 36 to the oral route (25 patients with alendronate, 9 with ibandronate, and 8 with risedronate). It is well known that the voluntary reporting of adverse reactions is much lower than what really happens in the population. Therefore it is worthwhile remembering the importance of notifying the centre for Drug Surveillance when there are suspicions of adverse reactions to drugs.

Conclusions

In the short-term bisphosphonates reduce radiologically determined morphometric vertebral fractures and modestly reduce clinical fractures.

The ability to prevent hip fractures in the short term is very uncertain. Even if there is some effect, it is small and of questionable clinical relevance.

In the long-term it seems that these agents increase the risk of atypical femoral fractures affecting the diaphysis and subtrochanteric region. They could also increase hip fractures rather than reducing them.

A specific radiological pattern has been described for the bone lesions produced by bisphosphonates in the long-term.

Given that bisphosphonates can cause severe adverse effects including fractures that they are meant to prevent, it is urgent that the overall benefits and harms of long-term treatment be clarified. The available evidence suggests that the benefit-harm balance may be unfavourable for their use in osteoporosis.

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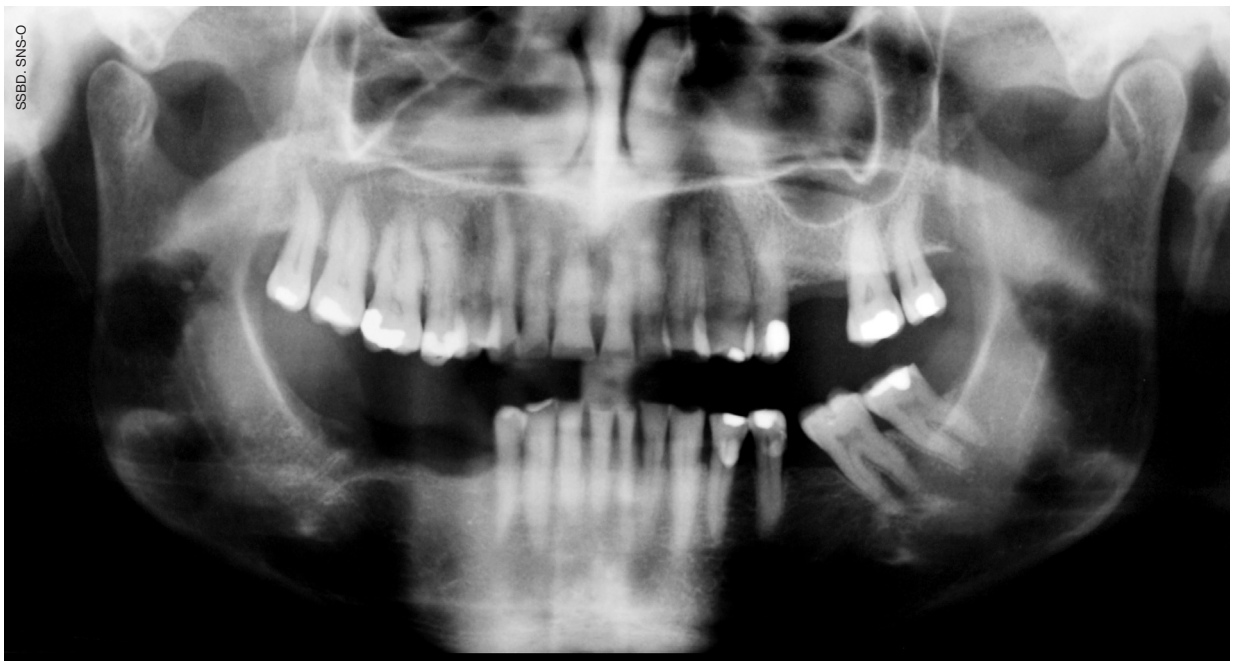
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Osteonecrosis of the jaw. A secondary effect or complication of bisphosphonate treatment

Objective: to describe the current evidence of osteonecrosis of the jaw associated with bisphosphonates and present a proposal regarding prevention and management. **Material and methods:** a selection was made of the main series of cases published in Medline since 1965 upto now and the recommendations offered by scientific societies and warning statements on the subject issued by the Spanish Drug Agency. **Results and conclusions:** osteonecrosis of the jaw is an important secondary effect or complication related to bisphosphonate treatment. It is associated mainly with the potency of the drug, the duration of treatment, and dental extractions or oral surgery that affects the bone. Serum levels of telopeptide C-terminal (CTX) do not possess any usefulness in predicting risk for osteonecrosis. Patients who will receive bisphosphonate treatment should be forewarned of this possible effect and a revision of their bucal cavity should be carried out to eliminate any irritative or infectious sources before treatment commences. Dentists and maxillofatial surgeons should be aware of this pathology and should take into account the medical history of their patients in order to minimize the incidence of osteonecrosis. In addition, patients should be warned of this complication with well documented information.

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Description

Bisphosphonates and natural pyrophosphates are very similar in structure, and both adhere strongly to bone hydroxyapatite. The difference lies in that bisphosphonates substitute the P-O-P structure of pyrophosphate for a P-C-P (carbon for oxygen atom), which confers them the characteristic of rendering them invulnerable to osteoclast degradation, thus reducing bone resorption[1]. The carbon atom possesses two more radicals than the oxygen atom and different elements depending on the bisphosphonates adhere to them. When nitrogen enters to form part of this structure, the power of the bisphosphonates, now denominated aminobisphosphonates is far greater than the simple bisphosphonates (ie, lacking nitrogen)[2].

Bisphosphonates have different mechanisms of action. Simple bisphosphonates accumulate in the interior of the osteoclasts and produce apoptosis. The aminobisphosphonates inhibit the mavelonate pathway[2], and it is also possible that they have an antiangiogenic effect[3]. The *in vitro* potency of the different bisphosphonates are shown in table 1, in addition to the presence or not of nitrogen and route of administration[4,5].

The most general use of bisphosphonates is, after all, to treat postmenopausal osteoporosis. It is generally administered orally, although intravenous presentations are also available for this indication. Adjuvant therapy in the treatment of some cancers represent the other main application of bisphosphonates and in which the intravenous route is employed. Authorization for the use of alendronate in the treatment of osteoporosis was approved in 1999 in the USA and the following year in Spain. The last drug of this class to be authorized is zolendronic acid which was indicated in cancer treatment in 2002 in the USA and the following year in Spain. Table 2 shows the diferent bisphosphonates in the Spanish market and their presentations[6].

Osteonecrosis of the jaw is a considerably important secondary effect or complication related to bisphosphonates

In 2003, cases of bisphosphonate associated osteonecrosis of the jaw (ONJ) began to appear. There were 36 cases in the first series by Marx[7]. This was followed by another series of 64 cases presented by Ruggieiro et al[8] in 2004 and in 2005, Bagán et al published the first Spanish and European series[9]. After this a few more series of cases have been published. Among others, in 2006 three cases were presented by the Maxillo-Facial Surgery Department of the Hospital Virgen del Camino (Pamplona, Spain)[10]. The ongoing incidence of cases probably influenced the Spanish Drug Agency to issue a couple of statements regarding treatment with bisphosphonates[11,12].

The continuous publication of cases produced interest in the issue and may have favoured the elaboration of multiple reviews carried out since. Of these it is worth mentioning Woo et al[13], who published their review in 2006, which is one of the most consulted references. In addition there is another shorter review, though more complete[3], and a recent review by Ruggiiero and Mehrotra available[14].

Bisphosphonate associated ONJ is a chronic osteomyelitis with a slow and torpid evolution and does not tend to healing. The authors who pre-

Table 1. Potency, nitrogen content and route of administration of bisphosphonates[4,5].

BISPHOSPHONATE	NITROGENATED	ROUTE OF ADMINISTRATION	POTENCY
Etidronate	No	Oral	1
Clodronate	No	Oral	10
Tiludronate	No	Oral	50
Alendronate	Yes	Oral	1,000
Risedronate	Yes	Oral	1,000
Ibandronate	Yes	Oral / I.V.	1,000
Pamidronate	Yes	I.V.	1,000-5,000
Zoledronate	Yes	I.V.	≥ 10,000

Table 2. Bisphosphonates available on the Spanish market[6].

GENERIC NAME	COMMERCIAL BRAND NAME
Alendronate	Alendronic acid EDIGEN 70 mg, 4 pills weekly treatment
	Alendronic acid ALMUS 70 mg, 4 pills weekly treatment
	Alendronic acid ALTER 70 mg, 4 pills weekly treatment
	Alendronic acid CINFA 70 mg, 4 pills weekly treatment
	Alendronic acid COMBIX 70 mg, 4 pills weekly treatment
	Alendronic acid CUVEFARMA 70 mg, 4 pills weekly treatment
	Alendronic acid DAVUR 70 mg, 4 pills weekly treatment
	Alendronic acid FARMALIDER 70 mg, 4 pills weekly treatment
	Alendronic acid KERN PHARMA 70 mg, 4 pills weekly treatment
	Alendronic acid KORHISPANA 70 mg, 4 pills weekly treatment
	Alendronic acid LAREQ 70 mg, 4 pills weekly treatment
	Alendronic acid MABO 70 mg, 4 pills weekly treatment
	Alendronic acid MYLAN 70 mg, 4 pills weekly treatment
	Alendronic acid NORMON 70 mg, 4 pills weekly treatment
	Alendronic acid PENSA 70 mg, 4 pills weekly treatment
	Alendronic acid PHARMAGENUS 70 mg, 4 pills weekly treatment
	Alendronic acid QUALIGEN 70 mg, 4 pills weekly treatment
	Alendronic acid RANBAXY 70 mg, 4 pills weekly treatment
	Alendronic acid RATIOPHARM 70 mg, 4 pills weekly treatment
	Alendronic acid RIMAFAR 70 mg, 4 pills weekly treatment
	Alendronic acid SANDOZ 70 mg 4 pills weekly treatment
	Alendronic acid STADA 70 mg4 pills weekly treatment
	Alendronic acid TECNIGEN 70 mg, 4 pills weekly treatment
	Alendronic acid VIR 70 mg, 4 pills weekly treatment
	Alendronic acid TEVA 10 mg, 28 pills
	Alendronic acid TEVA 70 mg, 4 pills
	ADELAN 70 mg, 4 weekly pills
	ADROVANCE 70 mg/2.800 UI, 4 weekly pills
	ADROVANCE 70 mg/5.600 UI, 4 weekly pills
	ALENDROCARE 70 mg, 4 weekly pills
	ALENDROFARM 70 mg, 4 weekly pills
	ALENDROGYN 70 mg, 4 weekly pills
	ALENVIR 70 mg, 4 weekly pills
	BIFOAL 70 mg, 4 weekly pills
	CALBION 70 mg, 4 weekly pills
	FOSAMAX 70 mg, 4 weekly pills
	FOSAMAX 10 mg, 28 pills
	FOSAVANCE 70 mg/2.800 UI, 4 weekly pills
	FOSAVANCE 70 mg/5.600 UI, 4 weekly pills
	LEFOSAN 70 mg, 4 weekly pills
	SEMANDROL 70 mg, 4 weekly pills
Clodronate	BONEFOS 400 mg, 60 capsules
	BONEFOS 400 mg, 120 capsules
Etidronate	OSTEUM 200 mg, 30 pills
	OSTEUM 200 mg, 60 pills
Ibandronate	BONDENZA 150 mg, 1 pill
	BONDRONAT 2 mg/2ml, 1 vial for i.v. perfusion
	BONDRONAT 50 mg, 28 pills
	BONDRONAT 6 mg/6 ml, 5 vials for i.v.perfusion
	BONVIVA 150 mg, 1 pill
	BONVIVA 3 mg, injectable solution
Pamidronate	AREDIA 15 mg, 4 injection 5 ml
	AREDIA 30 mg, 4 injection 10 ml
	AREDIA 90 mg, 1 injection 10 ml
	Pamidronate GENERIS 15 mg/ml, concentrate 1 ampoule 6 ml

	Pamidronate GENERIS 15 mg/ml, concentrate 1 ampoule 4 ml
	Pamidronate GENERIS 15 mg/ml, concentrate 4 ampoules 1 ml
	Pamidronate GENERIS 15 mg/ml, concentrate 4 ampoule s 2 ml
	Pamidronate HOSPIRA 6 mg/ml, concentrate, 1 vial
	Pamidronate HOSPIRA 3 mg/ml, concentrate, 1 vial
	Pamidronate HOSPIRA 3 mg/ml, concentrate , 5 vials
	Pamidronate HOSPIRA 9 mg/ml, concentrate, 1 vial
	Pamidronate STADA 3 mg/ml, concentrate, 4 vials 10 ml
	Pamidronate TEVA 3 mg/ml, concentrate, 1 vial 10 ml
	Pamidronate TEVA 3 mg/ml, concentrate, 1 vial 20 ml
	Pamidronate TEVA 3 mg/ml, concentrate , 1 vial 30 ml
	Pamidronate TEVA 3 mg/ml, concentrate, 1 vial 5 ml
	PAMIFOS 3mg/ml, concentrate, 1 vial 90 mg
Risedronate	ACREL semanal 35 mg, 4 pills
	ACREL 5 mg, 28 pills
	ACREL 75 mg, 2 pills
	ACTONEL semanal 35 mg, 4 pills
	ACTONEL 30 mg, 28 pills
	ACTONEL 5 mg, 28 pills
	ACTONEL 75 mg, 2 pills
	Risedronato semanal RATIOPHARM 35 mg, 4 cpills
	Risedronato semanal STADA 35 mg, 4 pills
Tiludronate	SKELID 200 mg, 28 pills
Zoledronate	ACLASTA 5 mg, one 100 ml bottle for perfusion
	ZOMETA 4 mg, 1 vial of 5 ml for perfusión

sented the first cases commented that they were attending to patients with a similar pathology to that of osteoradionecrosis or necrosis of the mandibula produced by radiotherapy.

However these patients presented a characteristic which was not present in those who underwent radiotherapy to the head or neck, though they were receiving bisphosphonates. These lesions presented a slow and insidious clinical evolution and were resistant to debridement and surgical intervention[8]. Shwartz commented in a letter to the editor that cases of osteonecrosis affecting the mandibula were seen 20 years ago in relation to chemotherapy[15]. These lesions were resolved after a brief interruption of chemotherapy and local debridement of the necrotic bone. It was not until 2002 that the first cases were observed in patients who, while not responding to surgery, were under treatment with bisphosphonates. This basically represents the difference between the lesions associated to chemotherapy, and those related to bisphosphonates.

To define the existence of ONJ associated with bisphosphonates, there are two requisites which were described by a panel of experts in 2008[16]:

· Patient who underwent therapy with bisphosphonates.

· Presence of one or various ulcerated lesions in the mucosa within the alveolar process, with exposure of the maxillar or mandibular bone.

· The exposed bone presents a necrotic aspect.

· The lesions occur spontaneously or, more frequently, after any dental or alveolar manipulation or surgery (especially exodontia).

· Absence of scarring during a period of at least 6 weeks.

It is also obvious that there is no history of radiotherapy in the mandicular area[17]. The clinical stages proceed from the contribution from Bagán et al[18] and are as follows:

Stage 0

Patients who have no clinical evidence of necrotic bone, but present symptoms or clinical or non-specific radiological findings (toothache with no real dental problem; dull pain in the mandibular area that may irradiate to the temporomandibular joint, sinus pain, abnormalities affecting neurosensorial functions, tooth loss with no periodontal cause; fistula with no pulpar necrosis due to caries; loss or alveolar bone resorption not related to the periodontial area; dense spongy bone; per-

Although it appears with oral administration and the incidence increases with the duration of treatment, it occurs at a faster rate when administered intravenously

sistence of bone with no remodelation in alveolar bone after exodontia; thickening of the lamina dura and reduction of the periodontal ligament space; or thinning of the mandibular canal).

Stage 1

Bone exposure with signs of necrosis or a small ulceration of the oral mucosa with no necrotic bone exposure. Both are asymptomatic.

Stage 2a

Bone exposure with necrosis or a small ulceration in the oral mucosa with no exposure of necrotic bone, but with symptoms: pain and infection of soft tissue / bone. Conservative management is sufficient and the ailment does not progress.

Stage 2b

Bone exposure with necrosis or a small ulceration of the oral mucosa with no necrotic bone exposure, but symptoms are present: pain and soft tissue and bone infection. Conservative treatments insufficient for management and there is progression to necrosis or signs of infection derived.

Stage 3

Bone exposure. Bone necrosis. Pain, infection and one or more of the following signs: pathological fracture, extra-oral fistulae or osteolysis that extends to the inferior border.

But why does this secondary effect or complication occur precisely in the jaw after treatment with bisphosphonates? According to Marx[7], this is due to the presence of teeth, which with frequent periodontal inflammatory processes, dental abscesses, endondontias and other diseases, increase the rate of bone resorption, allowing for greater deposits of bisphosphonates that debilitates the capacicty of this bone to respond to aggressive processes. According to Bagán et al[9], 77.7% of the cases of osteonecrosis had a history of one or various exondontias. Another important factor could be that the arteries irrigating the mandibular are terminal vessels.

The incidence of ONJ associated with bisphosphonates is very variable. The incidence is much greater in cases of intravenous administration when employed in patients suffering form cancer, varying between 0.8 and 1.2%[11]. This data is much more difficult to find in the cases of oral bisphosphonates or intravenous bisphosphonates employed in the management of osteoporosis. Here the incidence is lower than 1 case per 1,000 patients treated[12,19].

The different risk factors of bisphosphonate associated ONJ is summarised according to Khosla et al[20] in table 3. Some discrepancy exists concerning the possibility of predicting the incidence of osteonecrosis. Marx indicated in 2007 that the telopeptide C-terminal in serum (CTX) had predictive power[21], but other authors responded that this capacity could not be assigned to CTX and further ample studies and with control groups are necessary to reach this conclusion[22,23,24].

What approach should any doctor, irrespective of specialty, have before a patient who will receive treatment with bisphosphonates?

The adequate step would be to always inform the patient of the possibility of this secondary effect or complication. If bisphosphonates are to be prescribed for osteoporosis, or other pathologies other than cancer, (either oral or intravenous) then the patients should be advised to see their dentist. Dental management is recommendable to treat and maintain their teeth and oral cavity as healthy as possible.

If bisphosphonates are indicated or prescribed for oncological treatments, then insistence on dental revision should be made, either by a dentist or maxillo-facial surgeon. This is important to eliminate any sources of infection, extract any teeth that cannot be restored, or with considerable periodontal affectation. When possible, this revision should be carried out 4 or 5 weeks prior to commencing with bisphosphonate therapy. Afterwards, proper oral care should be maintained in the healthiest state possible. In the future, it would be expected that there should be less publications of cases[25,26] of ONJ in the group of patients that received oral cavity management before starting treatment with bisphosphonates.

What approach should dentists or maxilo-facial surgeons have before a patient who is about to commence treatment with bisphosphonates?

Whether they are oral or intravenous bisphosphonates for the treatment of osteoporosis or other pathologies other than cancer, dental management could be the same as with other patients who will not receive them[19]. In the case of cancer patients then all sources of infection should be eliminated, and teeth that cannot be restored and those affected by considerable periodontal disease. This treatment should be completed 4 or 5 weeks before introducing bisphosphonates[16 17 25].

And what approach should a dentist or maxillo-facial surgeon have when managing patients who already are taking bisphosphonates?

Although there is no scientific evidence on the issue, there are multiple consensus that offer recommendations on the steps to take[27,28]. Here the problem has different variants, which we will endeavor to outline below:

The patient is under either oral or intravenous bisphosphonate treatment for osteoporosis or other pathologies other than cancer.

Routine treatments can be offered with no problem[27]. Complications arise when surgical treatments (extractions, apical implants and periodontal surgery) or those interventions affecting the bone (grinding, root smoothening, orthodontia). At the least the patient should be informed and forewarned (Appendix 1) as, though only small, the risk of osteonecrosis exists[27]. Here the group is divided into three[17]:

Patients under bisphosphonates for less than 3 years and with no associated risk factors. Surgery may be performed with no delay.

Patients that have been under treatment with bisphosphonates for less than 3 years and are also taking systemic corticosteroids. It would be necessary to speak with the prescribing physician of the bisphosphonates to evaluate their possible withdrawal for 3 months before surgery except if the risk for fracture is high[28] (age >70 years, previous fracture, bone densitometry with a T score <-2.0 SD). Treatment may be continued after healing of the bone has occured.

Table 3. Risk factors for biphosphonate-associated osteonecrosis of the jaw (ONJ)[20].

1	Intravenous biphosphonates
2	Cancer treatment
3	Dental extraction, oral surgery affecting maxilla bones, maladjustment of dental prothesis, intraoral trauma
4	Duration of treatment with bisphosphonates
5	Treatment with glucocorticoids.
6	Co-morbidity factors (malign disease)
7	Alcohol abuse and/or smoking.
8	Pre-existing dental or periodontal disease.

Patients who have been taking bisphosphonates for over 3 years, with or without treatment with systemic corticosteroids. It would also be necessary to consult the prescribing physician of the bisphosphonates to consider suspending treatment for 3 months before surgery except if the risk for fracture is high[28] (age >70 years, previous fracture, bone densitometry with a T score <-3.0 SD). Treatment may be resumed once the bone has healed.

Treatment with bisphosphonates indicated in cancer patients.

No treatments that affect the bone should be carried out. It is advisable that endondontic treatments be avoided whenever possible, especially tooth extractions. Implants are not recommended in these patients. Dental and oral cavity hygiene is very important.

Management of ONJ is aimed at alleviating pain, controlling bone infection, and limiting the apparition or progression of bone necrosis. Surgical treatment should be delayed as far as possible[3,17].

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Annex 1. Informed Consent form of the Dental Health Section for patients under treatment with oral bisphosphonates.

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CONSENTIMIENTO INFORMADO PARA PACIENTES QUE TOMAN BISFOSFONATOS ORALES

APELLIDOS Y NOMBRE DEL/DE LA PACIENTE:

NOMBRE DEL DENTISTA QUE INFORMA:

FECHA (DÍA, MES Y AÑO):

Desde 2003, año en que apareció el primer caso descrito en la literatura científica, se han ido publicando cada vez más casos de **osteonecrosis de los maxilares**. Se trata de una enfermedad que afecta los huesos maxilares caracterizada por una infección que no acaba de curar, con exposición del hueso en la boca, supuración, dolor y otras manifestaciones. Esta enfermedad se ha asociado a:

1. El uso de bisfosfonatos:
   - en la inmensa mayoría de casos utilizados I.V. como tratamiento coadyuvante de distintos cánceres,
   - pero también se han observado algunos casos tras la utilización oral de estos medicamentos.
2. La realización de tratamientos dentales, como extracciones, implantes, cirugía oral y periodontal, en los pacientes que están tomando estos bisfosfonatos.

Usted, como paciente que está tomando bisfosfonatos orales debe saber que, aunque pequeño, existe el riesgo de que le aparezca tras la extracción, o la cirugía en la boca, una osteonecrosis de los maxilares, aunque se pongan en práctica (como evidentemente se va a hacer) todas las medidas y cuidados preventivos oportunos.

Por ello, tras ser informado y haber podido realizar las preguntas que he considerado oportunas, doy mi consentimiento para que se me realice:

.....

.....

.....

Si no me realizo este tratamiento las alternativas son:

.....

.....

.....

En Pamplona, a ..... de ..... de .....

Conclusions

Osteonecrosis of the jaw is an important secondary effect or complication resulting from the treatment with bisphosphonates. Its frequency oscillates between 0.8 and 1.2% in the intravenous form employed in cancer patients, while its incidence is notably inferior in patients treated for osteoporosis.

ONJ is related principally to the potency of the bisphosphonates, the duration of treatment and dental extractions or dental surgery that affects the bone. The levels of CTX in serum do not have any use in predicting the risk of suffering from maxilla osteonecrosis.

All patients who will undertake treatment with bisphosphonates should be warned of the existence of this secondary effect. They should also have a dental checkup to eliminate sources of infection or irritation before commencing treatment with bisphosphonates (especially those patients who will undergo intravenous treatment for example in cases of cancer). Patients should also receive adequate advice to maintain oral and dental health and carry out periodical dental checkups.

All dentists and maxillo-fatial surgeons should be aware of this complication and investigate the medical and pharmacological history of their patients to minimize the incidence of bisphosphonates associated osteonecrosis. They should warn patients of this complication with adequately documented information.

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