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# OSTEONECROSIS OF THE JAW INDUCED BY BIPHOSPHONATES: ABOUT 2 CLINICAL CASES WITH LITERATURE REVIEW

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## ABSTRACT

Biphospohonates are a class of drugs used to treat multiple disorders of calcium metabolism. Since 2003, patients receiving therapies concomitants with biphosphonates have suffered new complications associated with osteonecrosis of the jaw. Bone necrosis of the maxilla is rare but potentially dramatic. It manifests by a wound of the gum, lesion exposing necrotic bone and episode of clinical infections. These complications may be caused by trauma or dental surgery, but it can be also spontaneous.
We report two cases of osteonecrosis of the jaw. The first case is a mandibular osteonecrosis occurring after tooth extraction in a patient receiving intravenous bisphosphonate. Medical and surgical management has been undertaken with a regular clinical follow up. The second case is a sequestered maxillary osteonecrosis induced by bisphosphonate, that fall down after medical treatment, leading to an oro-antral communication.
The management of this complication remains problematic and the surgical treatment is difficult as for the result is uncertain. Emphasis should therefore be placed on preventive and conservative measures for all patients treated with bisphosphonates, as their therapeutic efficacy seems indisputable. The best attitude remains preventive management of these patients prior to initiation of biphosphonate therapy.

**Keywords:**biphosphonates; jaw; osteonecrosis.

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## INTRODUCTION

Biphosphonates (BPs) are structural analogues of pyrophosphates inorganic compounds discovered in the 1960s and used for the treatment of pathologies accompanied by a rate of bone resorption abnormally high. [1]
In three decades, indications for BPs are gradually broadened. After having been initially used in bone disease Paget, they are now prescribed for treatment and prevention of osteoporosis, of malignant hypercalcemia and bone tumors of haematological origin or metastasis, which are accompanied by osteolysis and, more recently, for the treatment of aseptic necrosis of the hip, SAPHO, besides certain fibrous dysplasias of bone and osteogenesis imperfecta [2,3,4].
The BPs represent a class of highly active drugs on resorption bone by direct action on osteoclasts [5, 6]. Depending on the existence or not of the nitrogen atom, we distinguish the first BPs generation without amine and the second generation and third generation called amino- bisphosphonates [1, 7].
Although BPs are a key element to help patients recover of these ailments including its undeniable therapeutic benefits and a considerable gain in terms of life's quality. Recently, reports are describing osteonecrosis of the jaw (ONJ) in patients receiving BPs [8, 9].
An ONJ can be defined by four characteristics:

- Lesion of the mucosa in the maxillofacial region responsible for exposing the bone necrotic and it's persistence for more than 8 weeks,
- Previous or ongoing BPs treatment,
- Absence of a history of radiotherapy in the region maxillary,

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- Absence of metastatic localization in the ONJ objectified by the histopathological exam [1, 10, 11].

These diagnostic criteria are currently being international consensus. However, the only difficulty for the diagnosis resides in the long delay between the onset of and the occurrence of the ONJ (sometimes several years).

This article presents a synthesis of the current state of knowledge related to the maxillary osteonecrosis associated with biphosphonates throughout 2 cases.

## CLINICAL CASES

### Case1

A 69-year-old patient was consulting for pulsatile pains and delayed healing at the site of extraction of 44 and 45 performed 3 months ago. The interrogatory revealed that the patient was treated monthly with Zometa ® IV courses for more than one year for prostate neoplasm. No allergies or intake of alcohol or tobacco is noted.

The exo-buccal examination presents no particularity. The endo-buccal examination showed the exposure of a necrotic bone (yellowish white) of hard consistency at the extraction site associated with suppuration. (**Figure 1**).

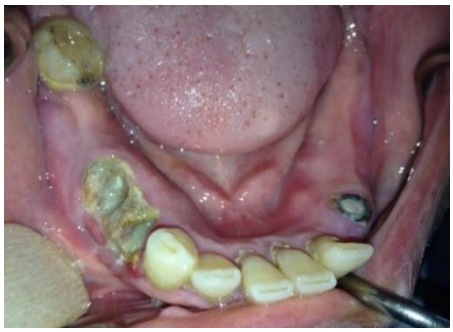

**Fig 1 :** Intraoral view showing a bone denudation with a diameter of 3 cm, surrounded by an ulcerated mucosa in the site of extraction.

Radiological examination (Panoramic radiography) showed no particularity a part from the unhealed of the socket of 44 and 45(Fig. 2).

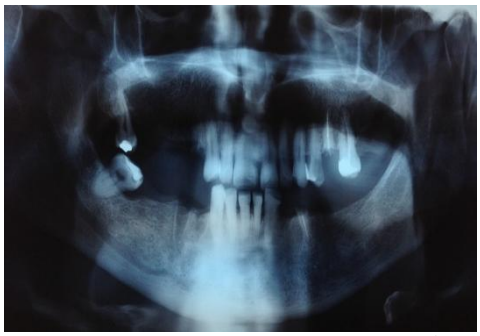

**Fig 2 :** Panoramic radiography showing the absence of osseous healing after 3 months of extraction at the site of 44 and 45.

The diagnosis of osteonecrosis induced by biphosphonates was raised

The patient was treated with antibiotic therapy with a combination of Amoxicillin + Clavulanic Acid and Metronidazole due to 2g / day and 1500 mg / day for a month until supination disappears.

Curettage with elimination of the avascular bone is carried out under local anesthesia with the bone rongeurs and with a bone cutter at low speed and under irrigation until partial bleeding of the bone. The surgical specimens were sent to histological examination.(Fig. 3).

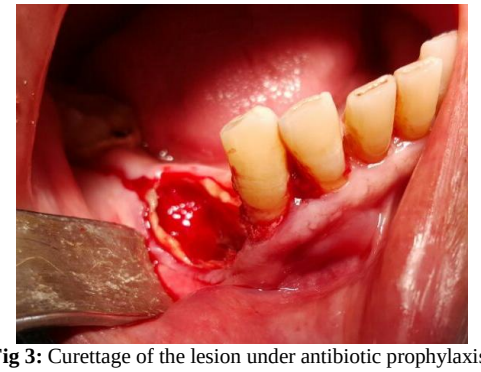

**Fig 3:** Curettage of the lesion under antibiotic prophylaxis, which has eliminated a soft bone, avascular, yellowish white in color, surrounded by a granulation tissue

Histopathology report indicated that it was necrosis bone without histological signs of malignancy.(Fig. 4).

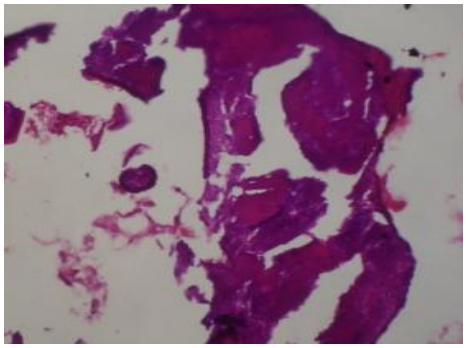

**Fig 4:** Histopathological picture showing bone necrosis (osteocytes empty cavities) (HES, x 100).

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Control at 1-monthshows that there is no formation of sequestration within the usual time limits and without any tendency to spontaneous healing**.** But there is a beginning of budding and proliferation of the mucosa within the necrotic bone. (Figure 5)
Given the general medical context, the age of the patient and the absence of functional impairment, it is decided not to intervene surgically and to set up a clinical follow-up regular.

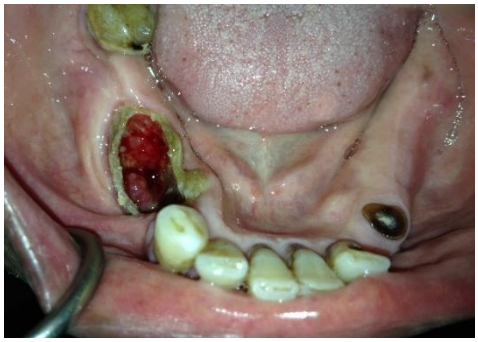

**Fig 5:** Control showing persistent exposed bone after the intervention**.** Budding and proliferation of the mucosa within the necrotic bone

**Case 2**

A woman of 61yearsold consulting for the absence of wound healing with bone exposed, after the extraction of 13 performed 4 months ago. Immediate follow-up was carried out without pain or local infection, but it was found in the following weeks an unhealing of the site of extraction.
In her antecedents, she received monthly infusions of BPs for correction of hypercalcemia due to myeloma between 2010 and 2012.
The clinical examination showed a denaturation of maxillary bone on 3 cm long, between 13 and 16 with mobile sequestration. (Figure 6)

**Fig 6:** Extensive right maxillary osteonecrosis with bone sequestrumappeared after canine extraction.

Radiological examination (Panoramic radiography) presents a well-defined osteolytic image of the right premolar area. (Figure 7)

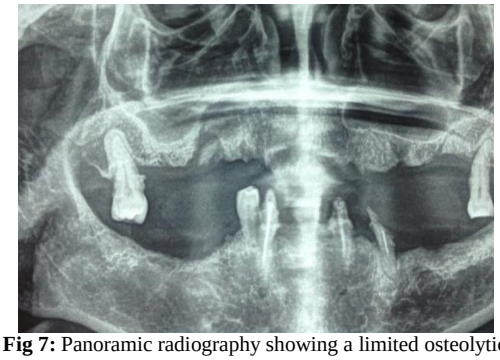

**Fig 7:** Panoramic radiography showing a limited osteolytic image in relation to the maxillary sinus

The patient was allergic to Amoxicillin; she is placed under Spiramycin and Metronidazole due to 3 Cp/day for 2 weeks.
The **Figure 8** shows an oro-antral communication after fragment has been fallen after few days.

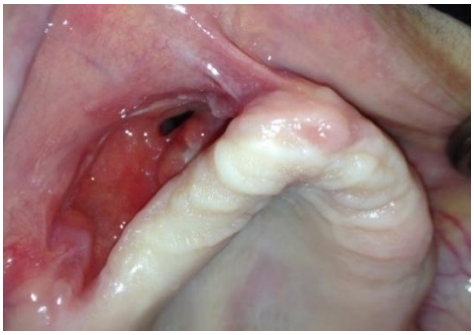

**Fig 8 :**Aspect after the fall of the sequestrum: healing occurred in the area and a large oral-antral communication is visible.

No surgery was performed to close the communication, a strict oral hygiene was recommended. The oro-antral communication persisted but had decreased in size and a follow-up schedule has been established. (**Figure 9**).

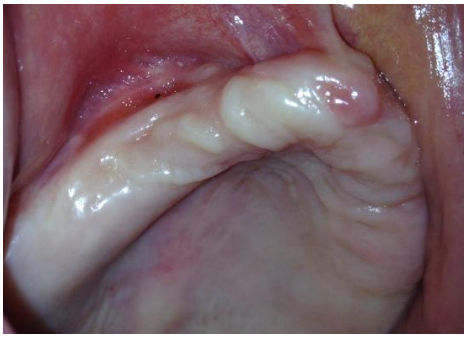

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**Fig 9 :** Control showing the healing of the mucosa achieved 8 months after bone exposure. Notice the smallest size of the oral-antral communication.

## DISCUSSION

In 2003, Marx and al. described a new type of ONJ resistant to conventional therapeutics. Their patients had in common a very specific type of drugs: BPs. The authors discovered a potential relation between this class of drugs and the occurrence of ONJ [12].
Indeed, patients with ONJ had many factors risk that may be responsible for an increase in the incidence of ONJ (radiotherapy, chemotherapy, corticosteroids, dental and / or sinus infections, interventions invasive dental, anemia, local anesthesia with vasoconstrictors, etc.) [13]
However, as of April 2005, the ONJ was added to the list of adverse reactions of the following BPs taken by intravenous (IV): Zoledronate, Pamidronate.[1]
In July 2005, the Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM) informed prescribers of the risk of ONJ and recommendations concerning the limitation period of BP administered by IV [14]. These recommendations were completed in 2007 by a letter to the professionals for the management of patients treated with BP. [10]
In 2014 the American Association of Oral Maxillofacial Surgeons (AAOMS)gives an update. This update contains revisions to diagnosis, staging, and management strategies, and highlights of the current research status [15].
The mechanisms of BP studied in vitro and in vivo have shown that inhibition of bone resorption is the major cause of effect of BPs. [16-18] This effect is observed both in healthy subjects and in subjects with an osteolytic condition. The BPs are selectively attached to the crystal structure of hydroxyapatite in the mineral phase of bone tissue: they are absorbed by osteoclasts which disrupts their functioning and induces their apoptosis. [19]
Osteoclasts drops due to BPs, lead to a decreasment of bone remodeling's level.
The BPs are not metabolized: approximately half of the dose is fixed on the bone, the other half is eliminated by the kidney, without any change in their structure.[2]
The half-life of BP is long because of their retention in the skeletal level. The molecules integrated on the surface of the bone are slowly liberated after bone remodeling. [20, 21] For several years, it has been known that urinary excretion of Pamidronate can be recovered up to 8 yearsafter discontinuation of treatment. There appears to be no correlation between the cumulative dose of BP and its urinary excretion although it's tending to decrease over time. This prolonged release of BP raises the question of theiractivity and their unknown long-term consequences during the period of growth, and effects of persistence in the body years after the treatment cut-off. [20,22]
The etiopathogenesis of ONJ remains unclear and many theories were proposed, including:

- The theory of hypocellularity: this theory is based on the apoptosis of bone cells induced by amino-BP which would lead to a reduction in bone remodeling and reduce the ability to repair and heal tissue bone mass. [23,24]
  Bone incorporation of BPs is proportional to the intensity of bone remodeling at when they are used, their concentration is therefore higher in growth areas, bone sites in the process of healing, sites tumors and those with naturally greater physiological remodeling rate as the alveolar bone of the maxilla. [25] This is probably why osteonecrosis associated with BPs relate more often to the maxilla and exceptionally to other sites. [26,27]
  In the oral cavity, the maxilla are subdued, during function (chewing) and parafunctions (bruxism), to regular stress which leads straight to important incorporation of BPs.
  As a consequence, it becomes responsible for serious remodeling reduction that generates bone necrosis.[28]
- The theory of hypovascularization: anti-angiogenic effects of certain BPs, in particular zoledronate, would lead to a fatal decrease of bone vascularization with avascular osteonecrosis [23,29].
- Infectious theory: trauma can alter the buccal mucosa causing exposure of the underlying bone tissue hypovascularized; the contact of the bone with the oral environment sepsis may lead to superinfection. [23]
- The theory of toxicity specific to BPs: the BPs would have a toxic effect on the buccal epithelium due to their concentration in the underlying bone ; it decreases in epithelial cell proliferation by apoptosis, which explains the appearance of a dehiscence of mucous membrane, bacterial contamination of the bone from the environment leading to the development of osteonecrosis and compromising the healing of soft tissue andulteriorly the hard tissue.[30,31]

Several risk factors are responsible for the development of ONJ :

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**Oral factors:**

- Oral hygiene: a good oral hygiene level allows significantly reduce the incidence of ONJ [32]
- Pathological factors [33]:
  - Dental infections including periapical infections and periodontal [34]
  - Dental caries, presence of residual roots,
  - Compromised teeth for periodontal reasons (Pocket depth greater than or equal to 5 mm, Mobility 2 or 3, furcation involvement, loss of attachment greater than 50%) [33]
- Anatomical factors: bony reliefs covered with mucosa of fine thickness [35] (mylohyoid line, exostosis, mandibular torus [33])

**Risk factors for oral treatment**

This concerns invasive dental care: dental extractions, apical resection, implant procedures, periodontal surgery, etc. [12, 29] For Bamiasand al., 88% of patients with ONJ had benefited from dental extractions in the 12 months before the discovery of ONJ. [35] Many studies show that surgical procedures would be the triggering factor of an ONJ in 50-80% of cases. [36, 37, 38] This means, however, that about20% of ONJ appears spontaneously. [39, 40] For the AAOMS,the risk of occurrence of an ONJ is multiplied by average of seven in the case of dental surgical gestures. [11] The average delay between the implementation of invasive oral and dental the appearance of an ONJ is 6.6 months. [41]

**BPs Risk Factors**

**Type of molecule**

Almost all ONJ occur with amino-BPs more potent, such as zoledronic acid. [11,42]According to the American Society of Clinical Oncology, zoledronate is among the most powerful inhibitors of bone resorption, a property that causes a high incidence of ONJ [43].
Not all BPs carry the same risk of ONJ [5]. The intensity of bone-related effects associated with the presence of nitrogen function could explain that BPs of third generation are mainly involved in the occurrence of ONJ. The second-generation of BPs are 100 to500 times more potent than non-nitrogenated BPs. Those of third generation additionally have a methylation of the amine, which makes them 10 to 20 times more potent than BPsof second generation. [5] Zoledronic acid in addition to itsanti-resorbentaction, also has an anti-angiogenic effect which could constitute an etiopathogenic co-factor important for the development of the ONJ. [44] For Zervasandal. Zoledronate alone would cause an ONJ risk 9.5 times higher than pamidronate alone and 4.5 times higher than the subsequent association pamidronate and zoledronate. [45]

**Duration exposure and cumulative dose:**

The risk of ONJ grows exponentially with the exposure time to BP. [8] Average cumulative risk is 1% after 12 months of treatment to nearly 11% after 48 months.[23] The half-life of BPs in bone is very long(approximately 10 years) and long term use of these substantial augments their accumulations in the skeleton, but the risk of developing ONJ is proportional to the cumulative dose.[44,46] In patients treated with amino- BP by IV, the risk of occurrence of an ONJ appears during the first few months of treatment and increases significantly after 18 to 24 months of treatment with zoledronate and 60 months with pamidronate. [35, 47] The average time between the start treatment of BPs and the appearance of anONJ varies according to the molecules: ONJ occur more frequently in treatment related to zoledronate than topamidronate. [26,44,45]
Clinically, the aspect of necrosis is bone exposure, with a yellowish white or white bone greyish appearance, associated with peripheral inflammation of the mucous membrane bleeding at contact. The bone is often coated with a coating and the contact, often painless, remains of hard consistency brings small-sized bone sequestrates size (a few mm).The evolution of osteonecrosismaybeaccompanied by the appearance of an important bonesequestration, antral or nasal communication as it's the case of our patient , and sometimescutaneousfistulaorpathological fracture of the mandible. [29,48,49].
The mandible is the preferred location : 65% of cases involving the mandible, 26% of the cases in the maxillary and 9% in both. [50] The mandibular posterior areas seem to be more concerned than the symphyseal regions and mandibular parasymphysis. [26]
The radiologicalsigns are verydiscreet.The signs are often absent at the beginning of the evolution: osteonecrosis is clinically visible while there is no evidence of bone damage in conventional x-rays (Retro-alveolar, panoramic radiography). [2]
The aspect is usually the resultof a moderateosseousrearrangement, enlargement of the periodontalspace or persistence of the alveolusaftertooth extraction. [51,52] At an advanced stage, osteonecrosisappears as a poorly

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defined radiocaly image, associated or not with a radiopaque bone sequestrum. This radiological aspect is non-specific and should be differentiated from chronic osteomyelitis, infectedosteo-radionecrosis, primary bone tumor (myeloma) or metastatic disease and pathological fracture of the maxilla. [51]

On the radiological level, the Cone beam would perform better in early diagnosis of osteonecrosis than the denta-scanner. [53]

Histopathological examination shows bone necrosis associated with bacterial superinfection and granulation tissue. [51] Osteonecrosis therefore seems to have different evolutionary phases. In the initial phase, the bone is still alive but it is the site of a moderate inflammatory infiltrate, associated with vasodilation and medullary fibrosis. In the intermediate phase, there are areas of live bone and foci of necrosis, and the inflammatory infiltrate is very abundant. In the terminal phase, the fully necrotic bone is the site of a large saprophytic bacterial colonization [44]. The literature reports some cases of maxillary metastases of malignant tumors able to mimic osteonecrosis associated with bisphosphonates [54, 55], If a tumor bone metastasis is suspected, a bone biopsy should be performed [48].

In prevention, before the start of a BPs treatment, a complete oral dental check-up must be carried out by the dental surgeon. The search for infectious foci is systematic and must be done by means of a long-cone retro-alveolar radiographic assessment and a panoramic snapshot. These infectious foci should be eliminated, the tooth with poor prognosis extracted and the peri- odontium should be cleaned. Removable prostheses must be adjusted and made atraumatic. The oral hygiene instructions are given to the patient and he should be thoroughly informed about the risk of maxillary osteonecrosis due to BPs in order to increase his motivation for perfect oral hygiene and regular care [56].

The treatment of osteonecrosis associated with the bisphosphonate depends on clinical and radiological aspects of the lesion. The AAOMS defines 4 stages of osteonecrosis, with a recommended treatment for each stage [15]

- -Stage 0 includes patients exposed to bisphosphonates without clinical signs of bone necrosis.
- Stage 1 charcterized by an asymptomatic bone exposure and without evidence of infection, this is should lead to the establishment of a local treatment (baths of antiseptic mouth) and quarterly clinical follow-up; the patient should be informed and continued treatment with BPs should be re-evaluated.
- -Stage 2 combines pain and clinical signs (Soft tissue inflammation, edema and / or suppuration) to bone exposure; The AAOMS recommends the least invasive (surface debridement to relieve irritation mucosal) and the use of oral antibiotics, analgesics and antiseptic mouthwashes.
- Stage 3 is characterized by the existence of extension's signs of the lesion (bone involvement beyond the alveolar bone, pathological fracture, extra-oral fistula, communication oro-sinusian/ oro-nasal or osteolysis extended to the edge lower mandible or sinusal floor); debridement surgical or bone resection should allow, over a longer period of time, to alleviate pain and infection.

At any stage, oral care should be regular: one control every 6 months for BPs oral treatment or every 4 months for intravenous BPs therapy. Infectious foci should be treated if possible using non-invasive techniques. Extractions should be avoided except in the case of infections that cannot be treated otherwise and in case of periodontal involvement with stage 3 mobility. If extraction is necessary, it must be the least traumatic possible without flapor irregularization of the bone contours. The fibrin glue placed in the alveolus seems to be a favorable factor for healing. [7] A suture aims at bringing the bankscloser may be practiced to optimize the healing. An antibiotic prescription to frame the gestureuntil complete healing was initially advocated. Mouth washes with 0.12% chlorhexidine twice daily is recommended until the mucosa closes. [23]

The recommendations of the AAOMS for the management of osteonecrosis associated with taking BPsare based on expert advice and make it possible to orient the therapeutic decision. The management has always allowed at least to slow down the evolution and to control the symptoms thus ensuring a correct quality of life to the patients. There is no international consensus. However, several recent articles show higher rates of osteonecrosis healing after surgical treatment only after conservative treatment, even in early stages of development for which interventional therapies have long been discouraged.[57,58,59] Some authors evoke complementary therapies such as oxygen therapy hyperbaric [60] but its efficacy is not proven. It is also reported that laser treatment (Er-YAG or Nd-YAG) would improve healing, in particular because of the better vascular perfusion [61, 62]

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## CONCLUSION

Treatment of an outbreak of osteonecrosis is very complex. Primary prevention is a key element in limiting the appearance of this complication. It is up to the prescribers, in close collaboration with dental surgeons, to direct patients in appropriate structures for complete oral health assessment, allowing the screening of threserved prognosisteethsin short and medium term, eradication of oral infections and the rehabilitation of the oral cavity, preferably before any administration of bisphosphonate when the patient's condition permits.
If all BP-treated patients do not developosteonecrosis, they are all likely to do so.
The risk persists even after discontinuation of treatment because the half-life of the molecule is very long. Faced with an aging population, the probability of caring for a patient with an antecedent of bisphosphonates is increasing.

The authors declare that there is no conflict of interests regarding the publication of this article.

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