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# Osteonecrosis of the jaw induced by clodronate, an alkylbiphosphonate: case report and literature review

Sabrina Crépin · Marie-Laure Laroche ·  
Bernard Sarry · Louis Merle

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## Abstract

**Purpose** To report on a case of osteonecrosis of the jaw (ONJ) in a patient treated with clodronate, an alkylbiphosphonate, and to draw attention to the risk of ONJ following treatment with all biphosphonates, whether they are alkyl- or amino-biphosphonates.

**Case report** Beginning at age 58 years, a female patient took clodronate for almost 13 years for a metastatic bone cancer. She also underwent chemotherapy and radiotherapy. Three months after the end of biphosphonate therapy, she suffered from toothache, and tooth 27 (left maxillary second molar) was extracted. A maxillary focus of osteitis with an oral sinus communication was discovered, and a maxillofacial denture prosthesis was grafted in September 2006. Some days later, the patient consulted her dentist for an ulceration of the oral cavity floor in front of tooth 33 (left mandibular canine) extending to the left inferior side of the lip. In October 2006, teeth 33 and 34 (left mandibular first premolar) were extracted. No secondary infection occurred. A complete healing was only observed 3 months

after the last extraction. ONJ due to alkylbiphosphonate treatment was diagnosed as bone reconstruction and mucous cicatrisation were delayed.

**Methods** A systematic review was carried out to identify all cases of alkylbiphosphonate-induced ONJ by searching the Medline and Cochrane databases using ‘osteonecrosis of the jaw’, ‘jaw diseases’, ‘osteonecrosis’, ‘diphosphonate’, ‘biphosphonate’ (amino-, alkyl- or the international non-proprietary name) as the main search items. The search was limited to English- and French-language articles published between 1966 and February 2010.

**Results** Our search identified 27 cases of alkylbiphosphonate-induced ONJ in the literature. Among these cases, only ten patients were on alkylbiphosphonate monotherapy; in the other cases, aminobiphosphonates had also been used. The clinical presentation of the alkylbiphosphonate-induced ONJ was similar to that most often encountered with aminobiphosphonate treatment. The duration of exposure before onset was higher with alkylbiphosphonates than with aminobiphosphonates, and dental procedures before ONJ were frequent.

**Conclusion** Osteonecrosis of the jaw has been widely reported with various aminobiphosphonates, but data on the role of alkylbiphosphonates are scarce. As these latter drugs are less potent, a high cumulative dose through long-term exposure would appear to be necessary and would favour ONJ. Although the degree of risk for ONJ occurrence in patients on alkylbiphosphonates remains uncertain, it would be wise to reconsider carefully the indications for using these agents and to apply preventive measures as is currently done for aminobiphosphonates.

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S. Crépin (✉) · M.-L. Laroche · L. Merle  
Service de Toxicologie-Pharmacologie, Pharmacovigilance,  
CHU Limoges,  
2 avenue ML King,  
87042 Limoges, Cedex France  
e-mail: sabrina.crepin@chu-limoges.fr

S. Crépin  
Department of Toxicology-Pharmacology, Pharmacovigilance,  
CHU Limoges,  
Limoges, France

B. Sarry  
Service d’Odontologie, CHU Limoges,  
Limoges, France

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## Introduction

Biphosphonates are synthetic analogues of pyrophosphate, an endogenous regulator of bone mineralization. In this heterogeneous family, two types of biphosphonates share a common phosphorus–carbon–phosphorus backbone: (1) alkylbiphosphonates, also called first-generation biphosphonates (clodronate, etidronate and tiludronate), which are devoid of amine function on the lateral chain; (2) aminobiphosphonates, which are considered to be second- (alendronate, pamidronate) or third-generation biphosphonates (zoledronate, risedronate, ibandronate) (Table 1). The amine function is responsible for the increased potency of the biphosphonates: the inhibition of bone resorption is greater with aminobiphosphonate than with alkylbiphosphonates [1, 2]. Biphosphonates are used to treat numerous disorders that affect bone, such as osteoporosis, bone metastases, hypercalcaemia of malignancy and multiple myeloma (Table 1). Since aminobiphosphonates have much stronger activities than alkylbiphosphonates, the former are more widely used.

Unfortunately, biphosphonates induce a serious adverse effect—osteonecrosis of the jaw (ONJ). Osteonecrosis is a necrotic lesion of bone tissue characterized by a slow progression and by failure to heal spontaneously. It manifests itself by pain, soft-tissue swelling, gingival bleeding, exposed bone and non-healing extraction socket, and it induces serious sequelae. These lesions can develop into an osteomyelitis with purulent material often containing *Actinomyces*. Radiographs may show regions of mottled bone [3, 4]. A differential diagnosis of biphosphonate related-ONJ can be considered if all of the following three characteristics are present: (1) patient is currently undergoing or has previously received treatment with a

biphosphonate; (2) patient has an exposed bone in the maxillofacial region that has persisted for >8 weeks; (3) patient has no history of radiotherapy to the jaw [5].

The first ONJ cases due to aminobiphosphonate treatment were reported in 2003–2004 by Marx et al. [6] and Ruggiero et al. [7]. Since then, more than 3,000 cases have been published [8], almost all of which have been linked to aminobiphosphonate treatments. Risk factors such as administration route, indication, duration of treatment and administered cumulative dose of biphosphonates have already been described. Several other factors also seem to favour ONJ occurrence, including dental risk factors (tooth extraction, periodontal disease, other surgical or invasive dental procedure), which were present in nearly 70% of reported cases, cancer and anti-cancer therapy (local radiotherapy, chemotherapy etc), corticosteroids and various comorbidities (diabetes, anaemia, among others) [9–12]. Only a few cases have been reported with alkylbiphosphonates.

We report here on a case of ONJ in a patient who received an alkylbiphosphonate, clodronate, for treatment of bone metastasis from breast cancer. After a systematic review to identify all published cases of alkylbiphosphonate-induced ONJ, we discuss the risk factors of biphosphonate-induced ONJ.

## Case report

In March 1987, the patient, then a 58-year-old woman, was operated on for cancer of the right breast and subsequently underwent locoregional irradiation. Six years later, she had bone metastasis (sternum and L4) and was treated with chemotherapy (5-fluorouracile, carboplatin, vinorelbine, mitoxantrone), hormone therapy (aminogluthetimide, leu-

**Table 1** Description of available biphosphonates

Type of biphosphonate	Molecule	Indications	Relative potency relative to etidronate	Route
Alkylbiphosphonate (first-generation biphosphonate)	Etidronate	Paget disease, malignancy-related hypercalcaemia	1	oral
	Clodronate	Malignancy-related hypercalcaemia	10	oral/IV
	Tiludronate	Paget disease	10	oral
Aminobiphosphonate				
Second-generation biphosphonate	Pamidronate	Malignancy-related hypercalcaemia, bone metastasis, multiple myeloma	100	IV
	Alendronate	Osteoporosis	1,000	oral
Third-generation biphosphonate	Ibandronate	Bone metastasis, malignancy-related hypercalcaemia, osteoporosis	5,000	oral/IV
	Risedronate	Osteoporosis	5,000	oral
	Zoledronate	Osteoporosis, Paget disease	10,000	IV

IV, Intravenous

proreline), steroids and irradiation of the lower spine (L2–L5 for 1 year). She was also given clodronate by the oral route from August 1993 onwards. Bisphosphonate treatment was stopped after the discovery of renal failure in March 2006. The cumulative dose of clodronate amounted to 6.8 kg within a 151-month period (almost 13 years).

In May 2006, the patient consulted a dentist for the occurrence of pain near tooth 27 (left maxillary second molar). One month later, this infected tooth was extracted, and a maxillary focus of osteitis with an oral sinus communication was discovered. A maxillofacial denture prosthesis was grafted in September 2006. Some days later, the patient again consulted her dentist, this time for an ulceration of the oral cavity floor in front of tooth 33 (left mandibular canine) extending to the left inferior side of the lip. In October 2006, teeth 33 and 34 (left mandibular first premolar) were extracted. No secondary infection occurred. A complete healing was only observed 3 months after the last extraction. Based on the delayed bone reconstruction and mucous cicatrisation, we diagnosed ONJ.

Analysis using the Naranjo probability scale revealed that an association between clodronate and ONJ was probable [13].

### Case reports of alkylbiphosphonate-induced ONJ

A systematic review of the literature was performed by searching the Medline and Cochrane databases using Mesh and non-Mesh terms. The main search terms were ‘osteonecrosis of the jaw’, ‘jaw diseases’, ‘osteonecrosis’, ‘diphosphonate’ and ‘biphosphonate’ (amino-, alkyl- or international nonproprietary name). The search was limited to English- and French-language articles published between 1966 and February 2010. Titles and available abstracts were scanned for relevance in order to identify paper requiring further consideration. The literature review was completed by a search done by hand accessing the references cited in all relevant publications. Among the 1,211 references identified, nine articles were selected in which cases of ONJ were identified as being induced by alkylbiphosphonate treatment.

The results of the search are shown in Table 2. Twenty-seven cases were identified: 25 with clodronate and two with etidronate [10, 14–21]. Among these 27 cases, clodronate was used alone in eight cases and etidronate alone in two cases. Indications of bisphosphonates were varied: six patients had multiple myeloma, 12 had solid cancers, five had osteoporosis, one had solid cancer associated with osteoporosis and two patients required orthopedic surgery (one indication was unknown). Eighteen (67%) of the patients had required dental procedures. The mean duration of exposure before onset of ONJ was 35 months when clodronate or etidronate was used alone.

### Discussion

Reported cases of ONJ have been less frequently associated with alkylbiphosphonate treatments (27 cases to date plus the one discussed here) than with aminobiphosphonate treatments (>3,000). Our patient showed characteristics similar to those reported in earlier cases of alkylbiphosphonate-induced ONJ, namely, an indication of malignant disease and long period of alkylbiphosphonate treatment [in our case, almost 13 years (151 months) with a cumulative amount of close to 7 kg]. Other risk factors of ONJ are chemotherapy and dental procedure.

The main risk factors for developing ONJ linked to bisphosphonate use are administration route, indication and duration of exposure.

Bisphosphonates given intravenously are usually considered to be more potent than those administered by the oral route and, therefore, more of a risk factor for inducing ONJ, as evidenced by the higher estimated incidence of ONJ (0–10%) in patients receiving intravenous bisphosphonates than in patients on oral therapy (<1%) [22]. The risk depends on the specific bisphosphonate given, the dose, the duration of treatment and the dental history of the patient. However, the incidence rate also depends on the reporting source. Manufacturer-sponsored epidemiological studies have reported incidence estimates of ONJ of 0.1–1.8% [23, 24], while independent epidemiological studies from clinicians and the International Myeloma Foundation report somewhat higher incidence estimates of between 5 and 10%. The fairly low incidence of ONJ with oral bisphosphonates could also be related to a poor bioavailability and to poor treatment compliance. As ONJ is now a well-known adverse effect of intravenous bisphosphonates, one can be falsely reassuring about the safety of oral bisphosphonates. According to Yarom et al., of all the ONJ patients in case series reported in the literature, the relative proportion of orally administered bisphosphonate-induced ONJ ranges from 2.5 to 27.3% [25]. In most cases, alendronate, an aminobiphosphonate, was the oral bisphosphonate mentioned because it is the most widely used oral bisphosphonate. These authors reported on a personal series of 11 female patients (8.9% of their ONJ patients on bisphosphonates) who developed ONJ after monotherapy with oral bisphosphonate. The extent of the relative risk with oral bisphosphonate treatment is still being debated. In a case-control study nested within a cardiovascular cohort, Etminan et al. determined the adjusted relative risk for the occurrence of ONJ among oral bisphosphonate users to be 2.9 [95% confidence interval (CI) 1.7–5.1] [26]. In contrast, in another study, Jeffcoat found no increased risk of ONJ with oral bisphosphonates in 335 patients treated with alendronate for 2 years [27]. Khan et al. also reported that low-dose bisphosphonate use in patients with osteoporosis

**Table 2** Review of cases of osteonecrosis of the jaw induced by alkylbiphosphonate treatment

Molecule (number of patients)	Authors	Sex (number of patients) <sup>a</sup>	Age (years) [mean; min-max]	Underlying condition (number of patients)	Presentation (number of patients)	Duration of treatment [mean; min-max]	Time of onset [mean; min-max]	Outcome	Associated drugs or risk factors (number of patients)
Clodronate + pamidronate (1)	[16]	M	64	Multiple myeloma	Chronic nasal infection/sinusitis. Computed tomography scan: maxillary sclerosis, sequestrum and mucosal thickening in the right maxillary sinus	Unknown	Unknown	Unknown	Unknown
Clodronate (1)	[15]	M	41	Multiple myeloma	Unsatisfactorily healing socket after dental extraction. Biopsy: necrotic bone fragment + acute and chronic inflammatory changes in soft tissue + Actinomyces	4 years	40 months	Healing after alveoplasty and antibiotherapy	Chemotherapy
Clodronate (1)	[17]	F	72	Multiple myeloma	Exposed alveolar bone after tooth extraction. Biopsy: necrotic bone + dense infiltration of plasma cells + lymphocytes/leukocytes + Actinomyces	5 years	5 years	Healing after alveoplasty and antibiotherapy	Chemotherapy
Clodronate + zoledronate (9)	[19]	F(11) M(3)	[63; 41–81]	Solid cancer breast cancer (11) Multiple myeloma (2) Unknown (1)	In ten cases, after tooth extraction	Zoledronate: [23; 2-52] <sup>c</sup> Clodronate [17; 4-45] <sup>c</sup> Pamidronate: [39; 29-48] <sup>c</sup>	Zoledronate: [23; 2-52] <sup>c</sup> Clodronate: [29; 7-73] <sup>c</sup> Pamidronate: [48; 29-67] <sup>c</sup>	Six healing Five not healing Three unknown	Chemotherapy (6) Radiotherapy (3) Corticosteroids (1) Unknown (4)
Clodronate + pamidronate + zoledronate (3)	[14]	U	60	Multiple myeloma	Mandibular localization Spontaneous onset	Zoledronate: 11 months, pamidronate: 11 months, clodronate: 2 days	Zoledronate: 11 months, pamidronate: 44 months, clodronate: 33 months Unknown	Unknown	Radiotherapy
Clodronate + pamidronate + zoledronate (1)	[10]	U	U	Breast cancer	Tooth extraction for periodontitis. Maxilla	Pamidronate: 27 cycles, Zoledronate: 19 cycles, Clodronate: unknown	Pamidronate: 27 cycles, Zoledronate: 19 cycles, Clodronate: unknown	Unknown	Chemotherapy with corticosteroids
Etidronate (1)	[18]	U	U	Osteoporosis	Failure of restored dental implants	6 months	6 months	Unknown	Unknown

Etidronate (1)	[19]	M	52	Osteoporosis	Necrosis of two sinuses + Aspergillus colonias	2 years	2 years	Healing after antifungus therapy	Corticoids Diabetes
Clodronate (3)	[20]	U	[73; 72–73]	Osteoporosis (1) Orthopedic surgery (2)	Periodontal disease, implant surgery, tooth extraction Mandible (2), maxilla (1)	Unknown	[19; 16–22] <sup>c</sup>	Healing after surgery	Unknown
Clodronate + alendronate (1)	[20]	U	82	Osteoporosis	Tooth extraction, mandible	Unknown	18 months	Healing after surgery	Unknown
Clodronate + risedronate (1)	[20]	U	79	Osteoporosis	Tooth extraction, mandible	Unknown	40 months	Unknown	Unknown
Clodronate, (1)	[21]	F	53	Breast cancer, osteoporosis	Maxilla	Unknown	12 months	Unknown	Chemotherapy

<sup>a</sup> F, Female; M, male; U, unknown

<sup>b</sup> Time of onset after the beginning of the bisphosphonates therapy

<sup>c</sup> Months

or other metabolic diseases was not causally linked to the development of ONJ [28]

The administration route seen previously as a risk is in fact linked to the indication. ONJ is more often reported in patients with cancer, with the most frequently reported cancers being multiple myeloma, breast, prostate and lung cancers and all cases with bone metastasis. However, the type of malignant disease does not seem to be associated with an increased ONJ incidence [11, 29–31]. In a recent meta-analysis performed on bisphosphonates used in breast cancer treatment, ONJ occurred in 13 of the 5,312 patients receiving bisphosphonates (0.24%) versus one of the 5,382 patients (0.018%) who were on placebo. In all cases, zoledronate, an aminobisphosphonate, was used. Treatment with zoledronate was significantly associated to the occurrence of ONJ [odds ratio (OR) 3.23, 95% CI 1.7–8] compared with no use [32]. ONJ has also been reported in patients with non-malignant conditions, such as osteoporosis [20, 33]. In a retrospective survey, the frequency of ONJ in osteoporotic patients was 0.01–0.04% (mainly on weekly oral alendronate), and if a tooth extraction was carried out, the frequency increased up to 0.09–0.34% [12]. In a review on ONJ in patients with osteoporosis treated with bisphosphonates, the authors identified 26 cases in 11 publications. The bisphosphonates prescribed were alendronate (23 patients), risedronate, pamidronate and alendronate and zoledronate (1 patient each); all of these are aminobisphosphonates [34]. The most recent case series reported on 24 non-oncologic patients with ONJ who were treated with bisphosphonates: 15 patients with alendronate, two with risedronate, two with ibandronate, three with clodronate, one with clodronate+alendronate and one with clodronate+risedronate. Five of these cases involved the use of alkylbisphosphonates. The indication was osteoporosis in 20 of the 24 patients [20].

Drug exposure is also an important risk factor. In one study, the median duration of exposure to bisphosphonates was 39.3 months for patients with ONJ compared with 19 months for patients with no ONJ ( $p=0.001$ ) [30]. When bisphosphonates are administered by the intravenous route to treat skeletal complications of malignancy, the annual doses of pamidronate or zoledronate (two aminobisphosphonates), are four- to tenfold higher than those used to treat osteoporosis [35]. The mean time from first drug exposure to occurrence of ONJ is variable according to the drug used: 9.4–18 months for zoledronate, 14.3–24 months for pamidronate and 12.1 months for pamidronate+zoledronate [6, 7, 12, 36, 37]. The estimated cumulative hazard rate of developing ONJ has been reported to be 1% at 1 year and 21% at 3 years or 15% at 4 years [30, 38] with zoledronate and 7% at 3 years with pamidronate [30]. In cases of oral use, patients in some studies received bisphosphonate for a mean duration of 24–40 months before the occurrence of ONJ [12,



34], while in other case series, the mean duration was 4.6 and 5.6 years, respectively [37, 39]. Based on these results, it would appear that long-term treatment and high doses of bisphosphonate are probable risk factors of ONJ onset.

To date, only a relatively few cases of alkylbisphosphonate-induced ONJ have been reported (etidronate, tiludronate and clodronate), including 25 cases of ONJ with clodronate and two cases with etidronate [10, 14–21]; no case has been found with tiludronate. The clinical presentation of alkylbisphosphonate-induced ONJ is very similar to that of aminobisphosphonate-induced ONJ. In the reported cases, the patients underwent dental procedures at the same frequency as those receiving aminobisphosphonates (67 vs. 70%) [11, 12]. The duration of exposure before the onset of ONJ seemed to be longer with alkylbisphosphonates than with aminobisphosphonates: 35 months when clodronate or etidronate were used alone versus 9–18 months for zoledronate and 14–24 months for pamidronate, both used alone [6, 7, 12, 15, 18–21, 36].

Of the bisphosphonates, the ones most likely to induce ONJ are aminobisphosphonates [33, 40, 41], possibly because they are more potent than alkylbisphosphonates. Indeed, pamidronate, alendronate and zoledronate are respectively 10-, 100- and 1,000-fold more potent than clodronate. The exact mechanism involved in the occurrence of ONJ with bisphosphonate is unknown. Different pharmacological mechanisms of bisphosphonate activity have been reported, and mechanisms also seem to differ according to the bisphosphonate generation. Osteoclasts metabolize alkylbisphosphonates into cytotoxic adenosine triphosphate analogues that accumulate in osteoclasts and induce apoptosis. Aminobisphosphonates inhibit the mevalonate pathway implicated in cytoskeleton organization [40]. The cortical bone of the mandible has a much higher turnover than appendicular sites. Therefore, bisphosphonates will be selectively concentrated into the jaw, thereby changing the balance of bone resorption and bone formation and resulting in reduced bone turnover. The bisphosphonate concentration in the bone of the jaw may be sufficient to be directly toxic to the oral epithelium [42]. Bisphosphonates inhibit proliferation, differentiation and migration of osteoclast precursors. Aminobisphosphonates also inhibit various proteins involved in cancer growth and metastasis and have an antiangiogenic effect [43].

Bone necrosis is considered to be time and dose dependant because of the long half-life of bisphosphonates in bones [33], which can amount to 10 years. Although the activity of clodronate is weaker than that of aminobisphosphonates, the osteoclast-inhibiting action of such a huge cumulated dose (7 kg in our case) was probably marked and protracted. We therefore conclude that it is essential to obtain a complete history for every patient treated with bisphosphonates in whom ONJ is suspected.

Finally, it should be noted that as the action mechanisms of alkylbisphosphonates and aminobisphosphonates are slightly different and as aminobisphosphonates are more potent, these latter drugs tend to be prescribed more often.

## Conclusion

The occurrence of ONJ is now a well-known adverse event associated with relatively long bisphosphonate treatment. The intravenous route, duration of exposure, cumulative dose and aminobisphosphonates are recognized risk factors. Bisphosphonates—seldom alkylbisphosphonates—are more likely to be involved in ONJ. The risk profile of patients treated with alkylbisphosphonates was similar to that of patients receiving aminobisphosphonate treatments (patients with malignant disease and history of recent dental procedures). As alkylbisphosphonates are less potent, long-term exposure seems to be necessary for a high cumulative dose and the development of ONJ. Two hypotheses could be advanced to explain the small numbers of case-reports with alkylbisphosphonates:

- alkylbisphosphonates are prescribed less often than aminobisphosphonates;
- as the duration of treatment before ONJ occurrence is longer with alkylbisphosphonates, the relationship between ONJ and alkylbisphosphonate intake is more difficult to assess; however, in most of the cases reported with alkylbisphosphonates, aminobisphosphonates were also used.

Finally, there is probably a trend towards a moderate over-risk with alkylbisphosphonates, but data are still insufficient to quantitate this relationship with ONJ as we found only 28 cases of alkylbisphosphonate-induced ONJ (27 in the literature plus our case). Among these cases, only 40% of the patients were administered alkylbisphosphonates alone.

A Mayo Clinic consensus-statement for the use of bisphosphonates in multiple myeloma has recently been published. The statement recommends that the duration of bisphosphonate therapy should no longer be indefinite and that pamidronate is the bisphosphonate of choice [44] among the aminobisphosphonates. The International Myeloma Working Group recommends clodronate [45].

Physicians should be alerted to the risk of ONJ occurrence in patients on alkylbisphosphonates (clodronate, etidronate, tiludronate). As there is no effective therapy for bisphosphonate-associated ONJ, specific measures should be taken, such as dental care before the initiation of therapy, communication between professionals prescribing bisphosphonates and dental professionals and careful choice of the indications for use.

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