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ORIGINAL ARTICLE

Bisphosphonate-associated osteonecrosis of the jaw: what do we currently know? A survey of knowledge given in the recent literature

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Abstract Increasing application of bisphosphonates for therapy of osteopathies has led to reports of the severe associated adverse effects of osteonecrosis of the jaw (ONJ). We reviewed recent literature to assess several aspects of bisphosphonate-associated ONJ, and to provide healthcare professionals with an overview of treatment and preventive options. Literature databases were searched using keywords. Information of 54 articles were discussed and completed by additional literature. High-risk factors were application of nitrogen-containing bisphosphonates, teeth extractions, and ill-fitting dentures. Treatment included non-surgical options and radical surgery. Success and failure were described for all treatment options; further studies investigating long-term recovery and recurrence are warranted. Paying attention to effective prevention of ONJ before, during, and after treatment is essential.

Keywords Bisphosphonate · Osteonecrosis · Osteomyelitis · Jaw · Adverse effect

Introduction

Bisphosphonates have been used in almost 2.5 million patients worldwide to improve bone architecture and mineralization and to solve osteopathies, particularly excessive bone resorption and osteoporosis, Paget's disease, and hypercalcemia of any cause [1–3]. Until now and despite various well-grounded studies, the exact biochemical mechanism of bisphosphonates remains, for the most part, unclear. This uncertainty did not result in a delay of clinical administration. In cancer patients in particular, the role of bisphosphonates in the prevention of skeletal-related events has been well established; these drugs have been incorporated in treatment guidelines for several common malignancies, e.g., breast cancer and multiple myeloma [4–7]. Cases with avascular necrosis of the femur have been successfully treated with bisphosphonates, and in vivo research suggests that they can block the resorption of necrotic bone during revascularization, preventing further collapse [8, 9].

Although serious side effects have been reported (including acute renal failure after intravenous administration or gastrointestinal toxicities, influenza-like illness, and myalgia), bisphosphonates are well tolerated [10, 11]. Several case series have recently documented patients who developed osteonecrosis of the jaw (ONJ) after receiving bisphosphonate therapy. This rare disorder has been associated with chemotherapy, but was not frequently reported before 2003 [12]. It is unclear whether this association is coincidental or causal. We reviewed recent studies in the literature, and discussed the effects of bisphosphonate administration with regard to risk factors, causality, therapy, and prevention of ONJ.

Methods

MEDLINE and PUBMED databases were searched using one or a combination of the following keywords in singular or plural: osteonecrosis, osteomyelitis, bisphosphonate, jaw

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necrosis, pathogenesis, dental extraction, and therapy. Search results were checked for relevance, and original publications were obtained. The reference list of each relevant publication was scanned to obtain further interesting contributions concerning the effect of bisphosphonates. For inclusion in the literature review, publications were analyzed if they matched the following data: information about the type and concentration of bisphosphonate used; primary disease being treated; duration of bisphosphonate treatment; comorbidities of patients suffering ONJ; potential causal factors such as previous dental extractions or dental trauma; location and symptoms of ONJ; therapeutic options; and preventive strategies. Information and observations of each article were extracted, summarized, and discussed with each other.

Results

Fifty-four publications presented relevant information. Thirty-two contributions dealt with bisphosphonate-associated ONJ in general, and gave two or more clinical examples. Six case reports described ONJ occurrence after therapy with one specific bisphosphonate. Eleven works described hypotheses of ONJ pathogenesis, of which two used animal models. Only five articles gave recommendations for the prevention and therapy of ONJ. None of the publications included the desired data in total, due to incomplete reporting of parameters or the lack of descriptive measures. For discussion, information from several articles were therefore sampled and supplemented by extracting information from additional retrieved literature.

Discussion

Chemical structure and effects of bisphosphonate therapy and their effect on the jaw

Evidence based on the structural configuration of bisphosphonates is accumulating. It links bisphosphonates with ONJ. The structure of bisphosphonates shows two phosphate groups bound to a carbon atom (P—C—P), which is responsible for their low bioavailability. Like pyrophosphates, bisphosphonates bind strongly to hydroxylapatite, which explains their affinity to, and therapeutic actions in, bone [13]. Bisphosphonates are released if bone reabsorption occurs, which would explain their long half-life [14]. This release is multi-phasic and, e.g., in the case of alendronate, persists 10.5 years. This would explain their persistent long-term effect in the bone [15]. The therapeutic effects of bisphosphonates depend on whether the side chains contain a nitrogen atom. Less potent non-nitrogen-containing bisphosphonates (e.g., etidronate, clodronate, tiludronate) induce the death of osteoclasts by the formation of cytotoxic metabolites of adenosine triphosphate (ATP) that accumulate and interfere with intracellular metabolic enzymes [16]. Potent nitrogen-containing bisphosphonates (e.g., pamidronate, alendronate, risedronate, ibandronate, zoledronic acid) inhibit the mevalonate pathway, leading to disturbances in the regulation of the morphology and activity of osteoclasts, resulting in poor cell functioning, apoptosis, and reduced turnover of bone [3, 17–22]. Table 1 displays a survey of the most commonly used bisphosphonates. Nitrogen-containing bisphosphonates are believed to inhibit the adhesion of neoplastic cells to bone, and to delay angiogenesis [23–25]. Following these possible actions of bisphosphonates, two hypotheses have been established to explain ONJ: (1) the action of bisphosphonates in bone turnover inhibiting osteoclasts (as described above); and (2) their anti-angiogenic action with reduced capillary formation and inhibition of endothelial and vascular growth factors, leading to avascular necrosis [21, 26–28]. However, for the latter hypothesis, there is no evidence in literature for this effect of bisphosphonates in bone; and furthermore, the angiogenesis during bone formation seems to be unaltered by bisphosphonates [29, 30]. In addition to these hypothetical mechanisms, another recent hypothesis stated that bisphosphonates accumulate in bone in concentrations sufficient to be directly toxic to the oral epithelium. This would result in the failure of healing

Table 1 Survey of bisphosphonates for clinical use approved by the "Food and Drug Administration" (FDA)

Generic name	Brand name	Formulation	Manufacturer	Nitrogen containing	FDA approval
Alendronate	Fosamax®	Oral	Merck & Co.	Yes	1995
Etidronate	Didronel®	Oral/IV	Procter & Gamble	No	1977
Ibandronate	Boniva®	Oral	Roche	Yes	2005
Pamidronate	Aredia®	IV	Novartis	Yes	1991
Risedronate	Actonel®	Oral	Procter & Gamble	Yes	1998
Tiludronate	Skelid®	Oral	Sanofi	No	1997
Zoledronic Acid	Zometa®	IV	Novartis	Yes	2001

Adapted from Ruggiero et al. [63] and Kumar et al. [64]

of soft tissue lesions affecting not only osteoclasts and osteoblasts but fibroblasts and macrophages leading to secondary infection of the underlying bone. This model would explain why bone resection is not always helpful in managing ONJ [31]. However, disrupted bone turnover and a critical vascular supply of any cause could affect the quality of bone during growth and healing, promoting the development of a non-healing wound and a necrotic jawbone as typical symptoms of ONJ, leaving the lesion prone to infection that could progress to widespread osteomyelitis (Fig. 1). The concentration of bisphosphonates may also play an important part. Naidu et al. [32] observed in primary rat osteoblasts in vitro that cell viability decreased significantly as drug concentration increased.

Prevalence, risk factors, and symptoms of bisphosphonate-associated ONJ

Local radiotherapy, chemotherapy, and chronic osteomyelitis have been identified as causes of ONJ [33]. It is also well known that long-term use of corticosteroids and allogeneic stem-cell transplantation (both frequently used in the treatment of multiple myeloma) can lead to avascular necrosis of the femoral head [34, 35]. The number of patients presenting with bisphosphonate-associated ONJ seems to be increasing, but the prevalence in cancer patients is difficult to estimate because many cases are isolated single cases or come from retrospective case series. The overall prevalence is believed to be 1.5–9% of patients receiving nitrogen-containing bisphosphonates, no matter whether oral or intravenous application is performed [36–42]. In contrast to the necrotic actions of nitrogen-containing bisphosphonates, an inhibition of ONJ is even attributed to non-nitrogen-containing bisphosphonates [43]. Of course, until now, ONJ induction using non-nitrogen-containing bisphosphonates cannot be totally ruled out [44], but in the referred works ONJ was almost associated with nitrogen-containing bisphosphonates. Further studies are needed for a profound clarification of this observation. Uncertainty concerning the time dependence of ONJ is another problem. With respect to the jaw, there are accounts of ONJ cases associated with bisphosphonate therapy in patients who have been on medication for years, and even for a few weeks [45, 46]. ONJ as a complication of bisphosphonate therapy was first described in 2003 [47] when thousands of patients had participated in clinical trials. This, in part, was because most ONJ cases had been described in patients with prolonged exposure to bisphosphonate. In a larger series of ONJ reported in 2005 [27], the mean induction time for ONJ was 9.4–14.3 months. In another study, longer exposure to bisphosphonate was the only significant factor, resulting in a prevalence of 1.5% among patients treated for <12 months, and 7.7% for those treated for 37–48 months [36].

The prevalence and time dependence of ONJ are controversial, but the relationship between surgical procedures in the oral cavity and ONJ is undisputable. About 60–70% of the ONJ cases described are related to a previous

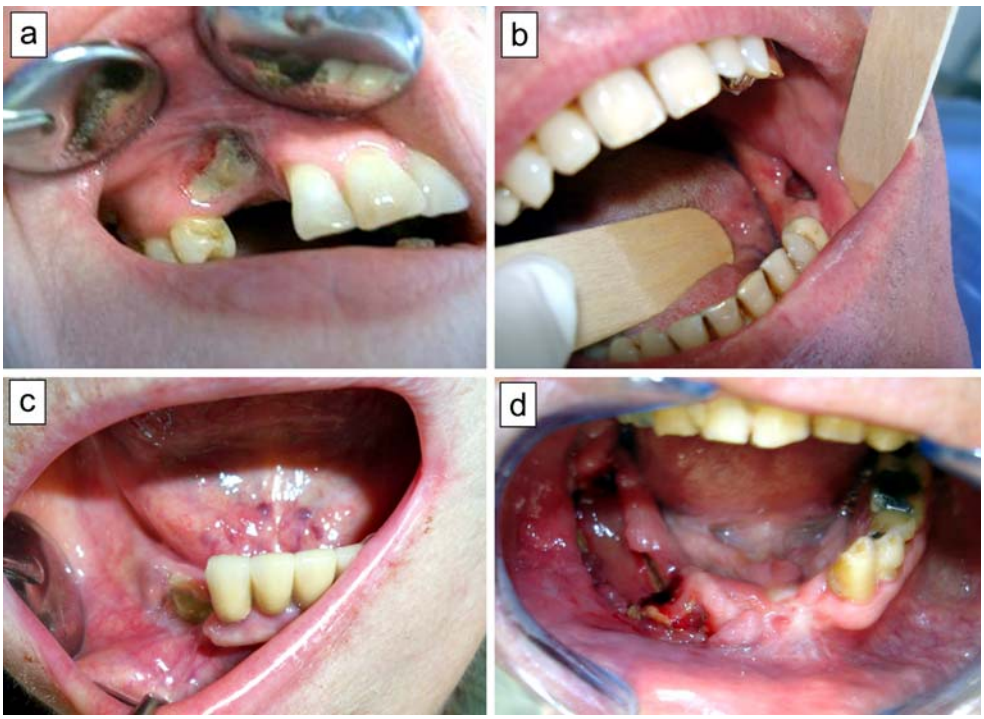

Fig. 1 Four aspects of bisphosphonate-associated ONJ. **a** ONJ of the right maxilla after tooth extraction with typical white-yellow appearance of the necrotic bone, only rare signs of inflammation. **b** Aspect of ONJ of the left mandible. Non-healing wound 4 weeks after tooth extraction. Thin vulnerable mucosa layer covering necrotic bone without further healing tendency. **c** ONJ affecting the neighboring tooth. **d** Wide ONJ of the right mandible with irritation of mucosa due to surrounding inflammation, necrotic bone visible anterior. Malignancy was ruled out by biopsies. All images referred to own cases

dental extraction [44, 48]. In a study of 119 ONJ cases [27], only 25.5% of patients had no previous apparent dental disease, treatment, or trauma. In another report [49], nine of 63 patients (14%) had no recent history of a dentoalveolar procedure. Only Aguiar-Bujanda and colleagues [50] detected an unexpectedly high prevalence of spontaneous ONJ (50%), but the number of patients in this study (six) was too small to provide significance. Dentures were found to be a significant risk factor for ONJ development. If they are ill fitting, they may injure the oral mucosa and dissolve the mechanical mucosal barrier, thereby permitting entry of oral flora into the bone. Root canal therapy was not significantly related to ONJ [7, 36]. Risk factors for ONJ were given by Abu-Id and colleagues [51]. They identified the use of pamidronate or zoledronat with prior chemotherapy or exogenous steroids as high-risk factors for ONJ. In a literature review, van den Wyngaert et al. [44] found that the commonest symptom of ONJ was pain (81.7%; although 12.2% of cases were asymptomatic), followed by purulent discharge, oroantral fistula, swelling, and fever. ONJ was located in most cases in the mandible (79.6%), followed by the maxilla, and cases in which both were affected. For diagnosis of ONJ, panoramic radiography and CT often revealed only mild findings, such as diffuse sclerosis of the cortical margins of the alveolar sockets along the area of the extraction sites without evidence of bone deposition, or trabecular pattern within the extraction sockets despite the length of time since extraction [52]. Staging according to severity and lesion size was therefore developed for ONJ [53] to find a uniform description for further assessment of ONJ for clinical purposes.

Treatment and prevention of bisphosphonate-associated ONJ

Treatment of necrotic bone in intraoral areas is problematic. This clinical quandary is similar to that seen in osteopetrosis and phosphorus poisoning ("phossy jaw") at the end of the nineteenth and the early twentieth century [51, 54]. Recommendations for treatment differ in the literature. Conservative treatment consisted of antibiotics, chlorhexidine rinse, narcotic medication, and hyperbaric oxygen therapy as well as surgery (including local debridement, sequestrectomy, or partial removal of the affected bone) [44, 51]. Unlike osteoradionecrosis, bisphosphonate-associated osteonecrosis is systemic rather than localized and, despite the hypothesis of anti-angiogenic actions, hyperbaric oxygen therapy (which has been shown to be helpful in treating osteoradionecrosis) may not be helpful in these cases [49]. There seems to be an association with bacterial infection in most patients with bisphosphonate-associated osteonecrosis. Most patients who develop ONJ are immunocompromised by virtue of metastatic cancer, and they are exposed to other medications known to be associated with ONJ (e.g., chemotherapeutic agents, corticosteroids) [52]. In recent studies, the oral surgeon is occasionally compelled to offer bony resection of osteonecrosis with primary or secondary placement of rigid plates if needed [42, 55]. In cases of single bony projections that cause soft-tissue irritation, debridement is not recommended. Instead, projections may be smoothed off and the patient placed on a course of antibiotics and 0.12% chlorhexidine. The protocol used by Migliorati et al. [56] consists of clindamycin 500 mg every 8 h, miconazole oral gel, and chlorhexidine mouthwashes. This approach is based on the identification of many pathogens, including actinomyces, as well as patients' positive clinical response to this regimen [57–59]. Radical treatment with segmental resection with loss of continuity of the mandible may become necessary in cases of non-response to minor surgery or non-invasive procedures to achieve curative outcome [51]. Total outcome of all treatment options was reported only for 40 cases, with healing of the lesions occurring in 11 patients (27.5%) and residual sites of necrosis remaining in 29 patients (72.5%) [44].

No single therapeutic method applies to every patient with ONJ, and many clinical factors must be taken into consideration during treatment planning. Remarkably, no improvement was seen in cases of interrupting bisphosphonate therapy due to the long half-life [60, 61].

Most patients underwent a dental extraction before the development of osteonecrosis. For prevention, it therefore makes sense to evaluate oral and dental status before initiation of bisphosphonate therapy. This consists of a complete clinical and radiographic exploration to identify infections and decayed teeth. If bisphosphonate therapy can be delayed, preventive surgery to eliminate potential sites of infection should be done. Oral treatment is aimed at eliminating infections and the need for invasive dental procedures in the near future, so preventive therapy should be aggressive and should include: tooth removal, periodontal surgery, root canal treatment, tooth decay control, dental restorations, and well-fitting prosthesis [62]. These patients are not candidates for dental implants because of the risk elements involved [27].

Bisphosphonates possess significant therapeutic benefits, and their use will continue to grow. ONJ complications can be expected to rise just as well until evidences could not be provided whether it is the dosing or the cumulative effect that is responsible for ONJ. The recent results of the FLEX study [57] contributed to the cumulative effect suggesting that discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk of women with postmenopausal osteoporosis compared with alendronate admission up to 10 years. Further studies are warranted to investigate this effect especially in cases of ONJ. The

preventive protocol supports the fundamental role of the odontologist in the effective prevention of this process before, during, and after treatment. Treatment of dental and periodontal infections and maintenance of good oral hygiene is absolutely essential before starting bisphosphonate therapy to help prevent ONJ.

Evidence-based therapeutic protocols for treating ONJ are not available. Diagnostic criteria are not well established; inclusion and exclusion criteria in reported cases are lacking, and no prospective studies have been conducted to characterize these conditions exactly. Significant research into ONJ is needed at the basic science and clinical level to elucidate the pathogenesis and provide more insight and a rationale for use of these agents.

Conflict of interest The authors declare they have no conflict of interest.

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