

# REVIEWS

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## Bisphosphonates – Risk Assessment of Osteonecrosis of the Jaw and Potential Benefits for Periodontal Therapy

### Bisfosfoniany – ocena ryzyka martwicy kości szczęk i potencjalnych korzyści w leczeniu periodontologicznym

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A – koncepcja i projekt badania; B – gromadzenie i/lub zestawianie danych; C – opracowanie statystyczne; D – interpretacja danych; E – przygotowanie tekstu; F – zebranie piśmiennictwa

#### Abstract

Bisphosphonates (BPs) are a class of drugs commonly used for the treatment and prevention of increased bone resorption associated with diseases such as osteoporosis, osteopenia, hypercalcemia of malignancy, multiple myeloma, Paget's disease. BPs are known to inhibit osteoclastic bone resorption and stimulate the formation of osteoblast precursors to promote osteoblastogenesis. Since 2003 cases of bisphosphonate-related osteonecrosis of the jaws (BRONJ) have been reported. On the basis of the available data, a significantly increased risk of this complication is observed in patients receiving intravenous BPs compared to those receiving oral BPs. Other risk factors for the development of BRONJ include: duration of therapy, dentoalveolar surgery, age, concomitant oral disease, demographic and systemic factors. Preventive dental interventions before initiating bisphosphonate therapy can reduce the risk of BRONJ. Antiresorptive and anti-inflammatory properties of BPs can play a potentially important role in treatment of periodontitis. The results of the recent studies showed that the local delivery of alendronate in treatment of chronic and aggressive periodontitis was more effective in improving clinical and radiographic parameters compared to placebo (*Dent. Med. Probl.* 2012, 49, 4, 576–582).

**Key words:** bisphosphonates, osteonecrosis of the jaws, periodontitis.

#### Streszczenie

Bisfosfoniany to grupa leków powszechnie stosowanych w leczeniu i zapobieganiu nasilonej resorpcji kości związanej z takimi chorobami, jak: osteoporoza, osteopenia, hiperkalcemia nowotworowa, szpiczak mnogi, choroba Pageta. Bisfosfoniany hamują zależną od osteoklastów resorpcję kości i przyspieszają formowanie prekursorów osteoblastów, pobudzając tym samym osteoblastogenezę. W 2003 r. pojawiły się doniesienia o przypadkach martwicy kości szczęk związanej z terapią bisfosfonianami. Na podstawie dostępnych danych stwierdza się znacząco większe ryzyko tego powikłania u pacjentów otrzymujących bisfosfoniany drogą dożylną niż doustną. Inne czynniki ryzyka rozwoju martwicy kości związanej z bisfosfonianami to: długość trwania terapii, zabiegi chirurgii stomatologicznej, wiek, współistniejące choroby w jamie ustnej, czynniki demograficzne i ogólnoustrojowe. Profilaktyczne zabiegi stomatologiczne przed rozpoczęciem terapii bisfosfonianami mogą przyczynić się do minimalizacji ryzyka martwicy kości. Antyresorpcyjne i przeciwzapalne właściwości bisfosfonianów mogą mieć potencjalnie ważną rolę w leczeniu zapaleń przyzębia. Wyniki najnowszych badań wykazały, że miejscowe zastosowanie alendronatu w leczeniu przewlekłego i agresywnego zapalenia przyzębia było bardziej skuteczne w porównaniu z placebo (*Dent. Med. Probl.* 2012, 49, 4, 576–582).

**Słowa kluczowe:** bisfosfoniany, martwica kości szczęk, zapalenie przyzębia.

Bisphosphonates are a group of drugs used in the treatment of diseases with excessive bone resorption. Their chemical structure resembles that

of inorganic pyrophosphate where an oxygen atom is replaced by a carbon atom. Due to the presence of two phosphonate bonds at the carbon at-

om, the compounds are characterized by high resistance to degradation. The R1 side chain ensures affinity for calcium, and the other side chain, R2, determines the antiresorptive strength [1].

## Characteristics of Bisphosphonates

The mechanism of bisphosphonate action is multidirectional. Generally BPs inhibit bone resorption and increase the bone's mineral density, positively changing the metabolic balance of the bone (towards ossification), inducing an increase in bone mass [1]. These compounds are permanently incorporated in the mineralized bone structure— they combine with hydroxyapatite to form complexes not amenable to enzymatic, chemical, physical hydrolysis, while inhibiting the synthesis of new hydroxyapatite crystals. In bone tissue they remain active for a long time. Bisphosphonates impair the function of osteoclasts on several levels. They inhibit maturation of osteoclast precursors, recruitment and adhesion of mature cells, they slow down intracellular metabolism and activate the path for osteoclast apoptosis [2, 3]. On the other hand, bisphosphonates can stimulate osteoblast activity and osteoblastogenesis, as well as synthesis of osteoclast recruitment inhibitor by these cells [4, 5]. These mechanisms contribute to the increase of anabolic processes in the bone tissue and to inhibition of catabolic processes.

## Indications for Bisphosphonate Use and Side Effects

The main routes of bisphosphonate administration are intravenous and oral. Intravenous administration is used in hypercalcemia of malignancy, metastatic cancer of solid tumors to the bone (breast cancer, lung cancer, prostate cancer), plasma-cell myeloma [6–9]. These drugs used in cancer cases do not increase the survival rate of patients, but significantly improve the quality of life. Gnani et al. [10] found that the addition of zoledronic acid to adjuvant endocrine therapy increased disease-free survival in premenopausal patients with estrogen-responsive early breast cancer. A relative risk reduction of disease progression was estimated at 36%. However, later studies did not confirm those results [11]. This may be due to the multidirectional mechanism of bisphosphonate action. Moreover, the reproductive hormones may be an important treatment modifier.

Bisphosphonates are administered orally for the prevention and treatment of osteoporosis (postmenopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis), osteopenia, Paget's disease, osteogenesis imperfecta in children [12–14]. Bisphosphonates are characterized by very low absorption from the gastrointestinal tract, reduced further by taking them with food. Therefore, they should be taken on an empty stomach with plenty of boiled water. These drugs are irritating to esophageal mucosa, thus they should not be chewed, and the patient should remain upright (standing or sitting) for 30 minutes after swallowing the tablet.

Bisphosphonates in most cases are well tolerated; however, in some cases they can cause adverse bone remodeling (in the case of antiresorptive overdose, mineralization suppression occurs in the inhibition mechanism of hydroxyapatite formation), esophageal mucosal inflammation, nephrotoxicity, muscle pain, hypocalcemia, and in rare cases, jaw bone necrosis [15, 16]. There were no reported cases of osteonecrosis of the jaw in any trial of intravenous bisphosphonates before US Food and Drug Administration approval. This side effect was observed later, a few years after bisphosphonate's therapy had been commonly carried.

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) resembles osteonecrosis after treatment of the head and neck by radiant energy [17]. The etiology of this disease is not fully understood; it appears that it may be associated with inhibition of angiogenesis, which leads to a local disturbance of blood supply and osteoclast dysfunction. Bisphosphonates lead to the accumulation of bone microdamage by inhibiting bone turnover [18]. Tissue remnants are removed by osteoclasts in physiological conditions. The mandible is characterized by faster, when compared with the other bones, bone metabolism, which may explain the increased incidence of necrosis in this area.

The highest risk of developing BRONJ occurs in the case of intravenous administration of bisphosphonates in the treatment of patients with oncological problems and is rated at 0.8–12% [19–21]. Intravenous administration of bisphosphonates in the treatment of osteoporosis bears a lower risk of BRONJ [22]. The risk of developing BRONJ resulting from oral therapy of osteoporosis equals 0.01–0.06% [22, 23]. According to the American Dental Association, in the group of patients diagnosed with bisphosphonate-related osteonecrosis, 94% were treated with intravenous therapy, and 6% with oral therapy [24]. In conclusion, the risk of developing BRONJ is significantly higher in patients treated with intravenous bisphosphonates than in those treated with oral BPs.

## Risk Factors for the Development of Bisphosphonate-Related Osteonecrosis

American Association of Oral and Maxillofacial Surgeons (AAOMS) identifies five main groups of BRONJ risk factors:

- I. Drug-related factors:
  - b) potency of drug, route of administration;
  - c) period of treatment.
- II. Local factors:
  - a) dental surgery procedures;
  - b) anatomical factors;
  - c) oral diseases.
- III. Demographic and systemic factors.
- IV. Genetic factors.
- V. Preventive factors [24].

The risk of developing osteonecrosis of the jaw increases with the period of the administration of bisphosphonate (over 3 years) and its potency [19]. Zoledronic acid is more potent than pamidronate, and pamidronate is more potent than the oral bisphosphonates, such as alendronate, risedronate, ibandronate [24]. The risk of BRONJ is higher for patients taking zoledronic acid and increases over time, probably because of the long half-life of this drug, its more potent inhibitory effect on bone turnover and a stronger anti-resorptive activity compared with pamidronate [8, 16]. The possible explanation for zoledronic acid being responsible for the majority of BRONJ cases is the fact that zoledronic acid is the most commonly used drug to reduce skeletal-related events in patients with bone involvement from multiple myeloma and solid tumors (particularly in the USA).

The intravenous route combined with recommended oncologic doses (up to twelve times greater than for non-oncologic purposes) is associated with a higher risk of BRONJ than the oral therapy [15]. The study results indicated that patients with oncological problems who receive intravenous bisphosphonates are 2.7–4.2 times more likely to develop BRONJ, compared to patients not treated with this form of pharmacotherapy [26, 27].

The risk factors for osteonecrosis of the jaws include dental surgery procedures (e.g. tooth extraction, apicoectomy, implant placement, periostomy). Patients taking bisphosphonates intravenously after surgery are 5–21 times more likely to develop BRONJ than patients in whom surgical intervention has not been implemented [26, 28, 29]. In the study by Yamazaki et al. [30] the risk of BRONJ after tooth extraction was higher in patients with bisphosphonates therapy, compared to those without it. Among patients aged

65 years or older with an intravenous route of bisphosphonates administration risk ratio equaled 200.2 (95% CI: 23.8–1679.4;  $P < 0.001$ ). A significant association was found between alveolar bone loss score and the incidence of BRONJ. Unsatisfactory oral hygiene and the presence of inflammation in the oral cavity, such as periodontitis or odontogenic abscesses also increases the risk of BRONJ. Aghaloo et al. [31] proved that periodontitis and bisphosphonate therapy were sufficient for BRONJ development in the rat. The authors induced periodontitis in rats by ligature placement around the crown of the right maxillary first molar and observed osteonecrosis in the rats treated with zoledronic acid. Histologic examination confirmed that those lesions were similar to those of BRONJ patients.

Necrotic lesions are more common within the bones of the mandible (mandible to maxilla ratio is 2:1), which is associated with faster bone turnover and increased metabolic activity of the mandible [32]. The lesions are mostly related to areas of bone eminence covered with a thin layer of mucous membrane (lingual ridge and mylohyoid ridge within the mandible, palatal ridge within the maxilla).

Demographic and systemic factors that predispose to BRONJ include: age, Caucasian race, cancer, dialysis therapy, diabetes, obesity, coagulopathy, peripheral vascular disease, other types of treatment in combination with bisphosphonates (radiotherapy, chemotherapy, steroid therapy) [19, 20, 27–29, 33, 34]. More recently, genetic polymorphism has also been considered in assessing the risk of developing BRONJ [35].

The results of scientific research indicate that the most important predisposing factors for the development of BRONJ are: long-term administration of intravenous bisphosphonates and dental surgery intervention. Dental examination and oral cavity sanitation before implementation of treatment with bisphosphonates may affect the reduction of this risk.

## Dental Prophylaxis

Before implementing bisphosphonate therapy, dental examination and appropriate dental treatment should be performed. All invasive procedures should be completed before the initiation of pharmacotherapy, while marginal periodontal tissues should be devoid of inflammation. Such procedures reduce the risk of osteonecrosis of the jaws [36, 37]. Patients during treatment with bisphosphonates should be subjected to conservative treatment of teeth [38]. If there is a need for sur-

gery, most authors recommend discontinuation of their administration for three months prior to the intervention, which allows the osteoclast function to be restored [39]. This procedure is usually recommended for patients taking bisphosphonates intravenously, orally over 3 years, orally less than 3 years, but together with steroids [40]. The treatment must be performed in antibiotic cover [41]. Because the half-life of bisphosphonates is long and reaches up to 10 years, the issue of withdrawal of bisphosphonates in patients taking them orally for less than three years is debatable [40, 42].

## Classification of Bisphosphonate-Related Osteonecrosis of the Jaws and Its Treatment

There are many classifications of BRONJ [25, 43, 44]. However, the classification proposed by Mignogna et al. [44] appears to be the most accessible one. This classification distinguishes three classes, and each class is assigned appropriate treatment.

### Class I

Radiological symptoms (osteosclerosis, alveolus lasting more than 6 months after tooth extraction, foci with increased and reduced saturation, bone sequesters) or clinical symptoms without subjective ailments, with or without exposure of the bone surface. Treatment: mouth rinsing with 0.2% chlorhexidine solution three times a day for 3–4 weeks.

### Class II

Radiological symptoms (as in Class I) or clinical symptoms with subjective ailments, signifying an active process (fistula, purulent exudate, pain, mucositis) with or without exposure of the bone surface. Treatment: amoxicillin/clavulanate 500 mg orally three times daily for two weeks, mouth rinsing with 0.2% chlorhexidine solution three times a day for 3–4 weeks.

### Class III

Radiological symptoms (as in Class I) or clinical symptoms (as in Class II) and the presence of clinical complications (pathological fracture of the bone, extraoral fistula, paresthesia, oronasal fistula) with or without exposure of the bone surface. Treatment: ampicillin/sulbactam 1.0 g intramus-

cularly two times a day for 10 days, mouth rinsing with 0.2% chlorhexidine solution three times a day for 3–4 weeks. If the patient does not respond to treatment proposed for Class III, surgical treatment to remove the pathological bone area should be considered.

## Bisphosphonates – a Chance for Use in Periodontal Therapy

Bisphosphonates are characterized by a high affinity for bone tissue, they reduce hydroxyapatite solubility, inhibit osteoclast activity and stimulate differentiation of osteoblasts [2, 3]. In recent years, there have been reports of attempts to use the anti-resorptive and anti-inflammatory action of bisphosphonates in the treatment of periodontitis.

In studies on rats subjected to orthodontic therapy, it was demonstrated that local application of clodronate causes a significant reduction in movement of teeth. A reduction in the number of osteoclasts at the site of clodronate administration, as well as limitation of the scope of root resorption have also been proven [45]. Binderman et al. [46] demonstrated in studies on rats that intraprocedural, local application of alendronate reduces the risk of alveolar bone loss following periodontal surgery.

In clinical trials of topical application of bisphosphonates in periodontal treatment, a higher effectiveness of therapy with 1% alendronate gel (ALN) compared with placebo was demonstrated [47, 48]. Intraosseous defects in patients with chronic and aggressive periodontitis were treated with 1% alendronate gel or placebo after scaling and root planning (SRP). Clinical parameters were recorded at baseline and after two and six months of therapy, whereas radiological controls were performed before treatment and after six months. A significantly greater reduction in PD, CAL gain and filling of bone defects was observed in patients treated with 1% ALN compared to those treated with placebo gel.

Veena et al. [49] used alendronate as adjunctive therapy in surgical treatment of periodontitis. They obtained greater filling of bone defects after application of the drug compared to the control group, treated only with flap operation. Alendronate was well-tolerated; there were no side-effects. Rocha et al. [50] observed greater improvement in periodontal clinical parameters and radiographic parameters after the administration of alendronate compared to the control group, also in patients with type 2 diabetes mellitus.

In recent studies on rats with diabetes and periodontitis, it was demonstrated that the use of mono and combined clodronate and low-dose doxycycline (LDD) administration may decrease the levels of proinflammatory mediators and destructive enzymes in gingival tissues, such as matrix metalloproteinase-9 (MMP-9) and interleukin-1 $\beta$  (Il-1 $\beta$ ) [51]. During the study period, drug administration did not affect alveolar bone levels.

The results of the research performed to date on the outcome of local therapy with bisphosphonates may indicate a new direction in the treatment of periodontitis. Undoubtedly, however, only longitudinal studies could confirm the clinical, histological and radiological effects of bisphosphonates on bone regeneration in patients with periodontitis and to determine the optimal dose of these drugs, route and method of administration, possible side effects.

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