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Osteonecrosis of the Jaws Associated with Administration of Bisphosphonates

Martwica kości szczęk związana ze stosowaniem bisfosfonianów

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Abstract

Bisphosphonates (BPs) are pyrophosphate analogues with oxygen/carbon exchange in the basic chain and two additional substitutes by the central carbon atom. Their unique chemical structure determines their ability to inhibit bone resorption by selective adsorption to mineral surfaces, subsequent internalization in osteoclasts, and impairment of their function. BPs have been successfully used for several years to treat skeletal events in neoplasia, hypercalcemia of malignancy, osteoporosis, Paget’s disease, osteogenesis imperfecta, and fibrous dysplasia. Recently, bisphosphonate-related osteonecrosis of the jaws has been reported as a serious complication of therapy with these drugs; however, there is limited scientific understanding of this condition. This paper outlines current views on the etiology, pathogenesis, risk factors, and management strategies related to bisphosphonate-associated jaw bone osteonecrosis (Adv Clin Exp Med 2008, 17, 5, 575–581).

Key words: bisphosphonates, osteonecrosis, osteomyelitis, jaw.

Streszczenie


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

The jaws are especially subjected to infection due to close contact with the external environment, susceptibility to trauma, rich saprophytic flora, and the presence of teeth. However, the high regeneration rate of the oral epithelium and a very good blood supply constitute protective factors of these vulnerabilities. Potentially causative conditions such as open fractures, neglected teeth, periodontal abscesses, ill-fitting dentures, injuries of the mucosa, and infected facial wounds seldom trigger serious bone complications. Nevertheless, decreased immunity, blood supply, or cellular activity can destroy natural defenses and thereby contribute to the development of osteonecrosis of the jaws (ONJ). ONJ is determined by the death of bone as a consequence of a variety of systemic and local factors, such as trauma, corticosteroid therapy, chemotherapy of neoplasms, hemoglobinopathies, diabetes mellitus, anticardiolipin antibodies, intravascular coagulation, fat emboli, alcoholism, and systemic lupus erythematosus. Hypovascularity, hypocellularity, and hypoxia are
also well-recognized pathological conditions responsible for the development of ONJ in patients submitted to radiation for head and neck cancer [1−4]. Furthermore, since 2003 there have been increasing reports in the literature about the occurrence of large, therapy-resistant exposure of the maxilla and the mandible in patients receiving bisphosphonates (BPs). This issue is termed bisphosphate-related osteonecrosis of the jaws (BRONJ) [5–8]. Because of BPs’ unique ability to inhibit bone resorption, they have been used for several years to treat osteoporosis, Paget’s disease, osteogenesis imperfecta, and fibrous dysplasia. They have also become a part of the therapeutic protocol in the management of bone-invading tumors along with the treatment of hypercalcemia due to malignancy. The beneficial effect of BPs has resulted in a significant reduction in pain, pathological fractures, size of osteolytic lesions, the need for subsequent bone surgery, as well as in considerable improvement in the quality of patients’ lives [1, 4, 9]. Their strong specificity to bone and minimal metabolism made BPs remarkably efficacious drugs with notably few adverse effects until the first reports about BRONJ appeared. This review therefore outlines current views on the etiology, pathogenesis, risk factors, and management strategies related to BRONJ.

The Chemical Structure of Bisphosphonates and Their Molecular Mechanism of Action

The history of BPs dates back to the middle of the 19th century, when their use was mainly industrial [2]. The biological characteristics of BPs were first reported later, in the 1960s [1, 10]. BPs are pyrophosphate analogues in which the oxygen atom in the basic chain (P-O-P) is substituted by a carbon (P-C-P) (Fig. 1). As a consequence of the oxygen/carbon exchange, BPs are poorly metabolized by bone phosphatases, which makes them biologically stable [10−12]. There are two additional groups in the BP molecule attached to the central carbon atom termed R1 and R2. The presence of these groups allows for the introduction of numerous substitutions (Table 1). A hydroxyl R1 group increases BP binding to bone mineral due to the formation of tridentate bindings to calcium crystals. BPs lacking an R1 substitution or compounds with substitutions other than OH, such as H or Cl, present lower affinity to bone because they are able to form only bidentate connections [1, 13, 14]. The phosphate groups together with a group at the R1 position act as a “bone hook” which allows for rapid and efficient BP targeting to bone mineral surfaces. Once within the bone, the structure and three-dimensional conformation of the R2 side chain determine the biological activity of BPs and their molecular mechanism of action [15]. By lengthening the R2 side chain and incorporating amino groups, each successive BP has become more effective, giving the last generation a thousand-fold greater potency than the first [1, 4].

It is generally accepted that BPs act directly or indirectly on osteoclasts [10]. They are also able to cause bone dissolution in a purely physicochemical way. Non-nitrogen BPs (etidronate, clodronate, tiludronate) internalized by osteoclasts are metabolized to nonhydrolysable cytotoxic analogues of ATP. Intracellular accumulation of these products handicaps the mitochondrial function of osteoclasts and consequently leads to apoptosis of the cell [10, 11, 13, 14]. More recently synthesized and more potent nitrogen-containing BPs (alendronate, pamidronate, zoledronate, risedronate) are inhibitors of a specific biosynthetic way called the mevalonate pathway, responsible for the production of cholesterol and isoprenoid lipids such as isopentenylidiphosphate, (IPP), farnesylidiphosphate (FPP), and geranylgeranyldiphosphate (GGPP) [10]. FPP and GGPP are required for the posttranslational modification of small GTP-ases such as Ras, Rho, and Rac [10, 12]. Small GTP-ases are signaling proteins that regulate a variety of cell processes important for osteoclast function, including cell morphology, cytoskeletal arrangement, vesicle trafficking, and membrane ruffling [2, 12]. The “ruffled border” creates the “contact area” of an osteoclast with a bone and thus functions as a place of breaking down the bone tissue. When the ruffled border is compromised, the osteoclasts undergo apoptosis, netting a decrease in bone turnover [1].

A derivative of the structure of the nitrogen-containing BPs is that they are known to exert several beneficial anti-tumor effects such as apoptosis and inhibition of tumor cell adhesion and invasion. They also possess anti-angiogenic properties and can activate immunocompetent γδ T cells [4].

The Epidemiology of BRONJ

The association between BP administration and BRONJ was reported in a few studies on small groups and one Web-based review of 1203 cases [5, 7, 8, 16]. For the first time, BRONJ was recognized in patients treated for multiple myeloma, breast, and prostate carcinoma with the powerful
intravenously administrated nitrogen-containing BPs zoledronate and pamidronate. The incidence is estimated at 3.8% for multiple myeloma, 2.5% for breast carcinoma, and 2.9% for prostate cancer [9, 17]. Recently, 56 cases of BRONJ were reported in individuals taking long-term oral BPs (etidronate, alendronate, clodronate, ibandronate, risedronate) for osteoporosis, at present the most popular indication for therapy with this group of drugs [18-20]. All the above estimations were not based on prospective trials; consequently there are limited data from observational cohorts on incidence, time, course, and risk factors. BPs are the most widely used antiresorptive drugs, with the number of prescriptions exceeding 190 million yearly; therefore, the frequency of BRONJ in relation to the number of treated patients is vestigial [1, 2, 20]. Nevertheless, the seriousness of this complication and treatment difficulties make BRONJ a very important problem.

It is believed that both the duration of therapy and the cumulative dose of the drug correlate with the onset of symptoms and the severity of the clinical course. It is postulated that the probability of BRONJ increases by 3–10% with each year of BP continuation [17, 21]. The mean duration between the first application and the onset of symptoms was established at 15 months for patients taking pamidronate, 12 months in the case of switching from pamidronate to zoledronate, and 9 months in the patients taking zoledronate alone. For the oral prescriptions this interval was estimated at 3 years [4, 5].

It must be emphasized that the hypothetical role of BPs in BRONJ is based only on highly selected groups of patients who would have had a well-justified reason to develop ONJ because of cancer disease, anticancer therapy, or substantial osteoporosis [2, 6]. The affected patients suffered predominantly from multiple myeloma and breast or prostate carcinomas. These tumors are able to influence the skeletal system in a special manner. For example, multiple myeloma, which develops in the bone marrow, itself causes bone destruction and is able to form hybrids of normal osteoclasts with neoplastic cells possessing enormous activity to induce osteolysis [22]. Moreover, tumors such as breast, lung, or prostate carcinoma produce cytokines influencing the resorptive activity of osteoclasts. The humorally mediated bone degeneration is related to the secretion of parathyroid hormone-related peptide, receptor activator of NF-kappaB ligand, macrophage inflammatory peptide 1-α, interleukin-3, and interleukin-7 [23]. An ability of breast tumor cell lines to cause direct non-osteoclast-mediated bone resorption was documented in the early eighties [24]. What is more, cancer patients are usually submitted to an extremely burdening treatment with cytostatics, corticosteroids, and stem cell transplantation in different combinations. Each of these factors alone possesses an osteonecrotic potential. It can be seen in chemotherapy, which inhibits humoral and cellular immunological response and produces osteopenia, thus predisposing patients to ONJ. According to Tarassoff and Csermak, the incidence of ONJ in the cancer patient population is four times higher than in other cases [25]. Schwarz describes ONJ in his report as being a consequence of cancer chemotherapy in hemato-oncological patients [26]. Similar data were presented by Sung et al. [27]. Furthermore, steroid therapy is responsible for several negative effects in bone tissue in a way that osteopenia, fatty emboli in small bone marrow vessels, and decreased sinusoidal blood flow in combination with immunosuppressive action of corticosteroids contribute to an increased risk of inflammatory events [3]. In addition, reports by Tauchmanova et al. and Gahndi et al. confirm that stem cell transplantation in its own right results in the the development of either avascular osteonecrosis or bone dystrophy [28, 29].

Summarizing, a causal relationship between BP administration and ONJ has not been definitely proven and only the coexistence of BP therapy and ONJ has been evaluated so far [30].

Pathogenesis and Clinical Diagnosis

The mechanism that might underlie BRONJ is not fully understood. The current explanations include an infectious etiology, the loss of blood supply, or the suppression of bone turnover [9]. The most accepted theory suggests that impairment of the function of the osteoclasts is followed by impairment of osteoblastic activity due to feedback between these two cell groups. Osteoclastic resorption of the mineral bone matrix releases bone morphogenetic proteins, insulin-like growth factors, and other cytokines, thus recruiting local stem cells, inducing their osteoblastic differentiation, maintaining the capillary network, and making possible new bone formation. As a result, weakness of the osteoclast function is reflected in diminished bone resorption and reduced bone formation, which leads to decreased bone turnover and consequently to the bone necrosis [1, 2, 4]. BPs are also known to affect macrophage recruitment and differentiation as well as to shorten the life span of these cells [10].

Another concept puts emphasis on the disturbances in building the capillary network, which
would result in avascular bone necrosis followed by osteomyelitis. It has been shown both in vitro and in animal models that BPs inhibit angiogenesis, capillary tube formation, and vessel sprouting [2]. However, this theory is weakened by the fact that even stronger inhibitors of angiogenesis, for instance thalidomide, which are often included in the treatment protocols of multiple myeloma or instance thalidomide, which are often included in the treatment protocols of multiple myeloma or other tumors have not been proved to evoke ONJ.

Moreover, increased adhesion of *Staphylococcus aureus* to hydroxyapatite joint prostheses coated with clodronate or pamidronate is reported by Ganguli et al. [31]. This could contribute to the infectious theory of the condition. Indeed, rich bacterial colonization of the bony surface, predominantly by *Actinomyces*, Gram-positive cocci, and fungi has been well documented in pathological and microbiological reports concerning BRONJ [5, 7]. In this approach, exposure of the bone during surgery or tooth extraction would act as a trigger opening the door for bacterial invasion and could explain the existing strong correlation between BRONJ and dental surgical procedures.

BRONJ can occur spontaneously; however, it is mostly provoked by any kind of dental treatment. Many of the above patients reveal recent tooth extraction, root-tip resection, or cystectomy with subsequent osteonecrosis and dehiscence of the bone. Sometimes it arises as a result of local trauma, pressure from ill-fitting dentures, or periodontal infection. The most common clinical finding is an area of exposed, devitalized yellow-white bone [2, 5, 7]. Its surface is irregular and rough and does not bleed after scratching. The exposed bone is asymptomatic with either a cutaneous or mucosal fistula. The surrounding soft tissues are often inflamed and painful. The pain is a result of either a secondary infection or trauma to the surrounding soft tissue caused by the sharp edges of the necrotic bone. The patients often complain of swelling, pain, bleeding, paresthesia, and loose teeth [2, 5, 7].

The most common site of bone necrosis is the posterior/lingual mandible, the site of the thinnest epithelial lining; however, maxillary invasion is not unusual, in contrast to the other types of ONJ [4]. BRONJ can be diagnosed providing all the following conditions are present: current or previous treatment with BPs, exposed necrotic bone persisting for more than eight weeks, and no history of radiation therapy of the jaws [20].

The radiographic findings are variable and with no specific diagnostic characteristics. Conventional orthopantomographs usually demonstrate punched-out or “moth-eaten” lesions consistent with osteonecrosis and osteomyelitis. More advanced diagnostics with CT or MRI do not yield any characteristic picture [2, 6, 32].

Histologically, BRONJ resembles a rare hereditary bone disorder called osteopetrosis. The microscopic examination presents a “frozen bone” with a sclerotic cortical bone, compact and irregular laminations, the depletion of osteocytes of which lacunae are filled with amorphous substance, lack of bone remodeling, and loss of bone integrity. Such loss of integrity in an osteopetrotic bone is considered to be the primary reason for the microfractures and refractory osteomyelitis [6, 33].

**Treatment**

There is no consensus on the management in BRONJ. There are only treatment concepts available based on personal preferences or experience concerning small groups of patients. Different regimens of surgical, conservative, or combined methods have thus been recommended. As an illustration, there is often no living bone surface to be found during surgery; the entire bone is affected and therefore a viable margin cannot be established. Because of this, a classical decortication is of a little value in BRONJ. An invasive procedure is therefore mostly limited to wound debridement and bone shaving followed by coating of the dehiscence with soft tissues. In addition, surgery is often complicated by relapses. The high recurrence rate, usually exceeding 4–6 attempts at one site, persuades many doctors to look for conservative methods of treatment, i.e. a soft diet, intensive mouth hygiene, mouth rinsing with 0.12% chlorhexidine, 2% potassium iodine, and topical application of iodophor or zinc oxide. Administration of antibiotics has been recommended as well [2, 4, 5]. By reason of the specific flora, i.e. *Actinomyces*, Gram-positive cocci, and fungi, a long-term course of an oral penicillin is prescribed. Clindamycin alone is not recommended owing to its lack of activity against *Actinomyces*. In refractory or more symptomatic cases, metronidazole is added to this regimen. A severe course could require hospitalization and *i.v.* antibiotics. In the case of penicillin allergy, quinolones or erythromycin combined with metronidazole are advocated [5]. Hyperbaric oxygen therapy, in contrast to radiation-induced ONJ, has not manifested clinical efficacy in BRONJ [4, 5].

Discontinuation of BP therapy has as many supporters as opponents. The data show that once incorporated into bone, BPs remain there for months or years. Therefore, rejection of BPs offers no short-term benefit. Long-term discontinuation may be favorable in stabilizing BRONJ, reducing clinical symptoms and the development of new bone exposure. It should be especially considered
when the oncological indications for the BP therapy are resolved [1, 2, 15, 20].

According to the American Association of Oral and Maxillofacial Surgeons, three clinical stages of the condition are distinguished. The management recommendations for each group are displayed in Table 2 [20].

### Prevention

Prior to commencing BP treatment, the patients should be well versed in the potential adverse effects associated with this therapy. On the condition that the systemic conditions permit, the initiation of BP therapy should be delayed until dental health is optimized by means of conservative and invasive procedures in order to avoid future complications [2]. Moreover, these patients should not be considered candidates for dental implants because a lack of epithelial attachment around the implant could predispose to subsequent skeletal events [7]. Fully impacted teeth can be left undisturbed, but those with an oral communication should be removed. In this case a one-month healing period is advocated. Similarly, small lingual

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**Table 1.** Chemical structure, potency, and route of administration of different bisphosphonates

<table>
<thead>
<tr>
<th>Agent (Substancja)</th>
<th>R_1 side chain (Łańcuch boczny R_1)</th>
<th>R_2 side chain (Łańcuch boczny R_2)</th>
<th>Potency (Siła działania)</th>
<th>Administration (Droga podania)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>– OH</td>
<td>– CH₃</td>
<td>1</td>
<td>p.o.</td>
</tr>
<tr>
<td>Clodronate</td>
<td>– Cl</td>
<td>– Cl</td>
<td>10</td>
<td>p.o./i.v.</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>– H</td>
<td>– CH₂ – CH₃ – CH₂ – NH₂</td>
<td>100</td>
<td>i.v.</td>
</tr>
<tr>
<td>Risedronate</td>
<td>– OH</td>
<td>– CH₂ – CH₂ – CH₂ – CH₃ – NH₂ – CH₃</td>
<td>10 000</td>
<td>i.v.</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>– OH</td>
<td>– CH₂ – CH₂ – CH₂ – CH₃ – NH₂ – CH₃</td>
<td>10 000</td>
<td>i.v.</td>
</tr>
</tbody>
</table>

**Table 2.** Staging of BRONJ and treatment strategies according to the guidelines of the American Association of Oral and Maxillofacial Surgeons

<table>
<thead>
<tr>
<th>Stage (Stadium)</th>
<th>Description (Opis)</th>
<th>Treatment strategy (Sposób postępowania)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection</td>
<td>oral antimicrobial rinses (chlorhexidine 0.12%), no surgical treatment</td>
</tr>
<tr>
<td>II</td>
<td>exposed/necrotic bone in patients with pain and clinical evidence of infection</td>
<td>oral antimicrobial rinses in combination with antibiotic therapy, penicillins, quinolones, metronidazole, clindamycin, doxycycline, erythromycin</td>
</tr>
<tr>
<td>III</td>
<td>exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathological fracture, extra-oral fistula, or osteolysis extending to the inferior border</td>
<td>surgical debridement/resection in combination with antibiotic therapy</td>
</tr>
</tbody>
</table>

**Fig. 1.** Differences in chemical structure of pyrophosphates (a) and bisphosphonates (b)

**Ryc. 1.** Różnice w budowie chemicznej między pirofosforanami (a) i bisfosfonianami (b)
mandibular or palatal tori do not require removal, whereas large ones with thin overlying mucosa are recommended for removal [1].

Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease in asymptomatic patients receiving intravenous BPs. Moreover, invasive dental procedures should be avoided; if necessary, the patient should be referred to a maxillofacial surgeon. Antibiotic prophylaxis is recommended with a regimen similar to that of active BRONJ. In all patients treated with intravenous BPs, routine follow-up every three months is recommended to check for any signs of developing BRONJ [1, 4, 7]. Patients receiving oral BPs are at less risk of developing BRONJ [1, 2, 4, 7]. Patients with intravenous BPs, routine follow-up every three months is recommended to check for any signs of developing BRONJ [1, 4, 7]. Patients receiving oral BPs are at less risk of developing BRONJ [1, 2, 4, 7]. Patients with intravenous BPs, routine follow-up every three months is recommended to check for any signs of developing BRONJ [1, 4, 7]. Patients receiving oral BPs are at less risk of developing BRONJ [1, 2, 4, 7]. Patients with intravenous BPs, routine follow-up every three months is recommended to check for any signs of developing BRONJ [1, 4, 7]. Patients receiving oral BPs are at less risk of developing BRONJ.

Conclusions

The introduction of BPs to clinical practice diminished a number of skeletal events and considerably improved the quality of life of oncological patients as well as those with osteoporosis and inborn bone diseases. Unexpectedly, the drugs exerting so beneficial an effect became suspected of causing a serious complication in the form of jaw osteonecrosis. Opinions on both the etiology and management of BRONJ are divided. Nonetheless, for all healthcare professionals it is important to be aware of the potential complications associated with BPs use in order to assess deliberately the advantages and dangers connected with their administration.

References


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