Special Article

Bisphosphonate-Related Osteonecrosis of the Jaws: A Call for Multidisciplinary Approaches

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Bisphosphonates have been prescribed for the treatments of oncologic and metabolic bone diseases to inhibit bone resorption of osteoclasts. However, in recent years, the increased numbers of cases diagnosed with exposed and necrotic bone localized in the jawbones associated with bisphosphonate use have been reported, mostly in patients with multiple myeloma or bone metastases who received long-term intravenous bisphosphonate treatments. The strong association between patients receiving dentoalveolar surgery and the incidence of this complication highlights the need for multidisciplinary approaches and necessitates the close attention from a team of health care personnel. The present review summarizes the current knowledge on etiology, risk factors, clinical presentations, and recommended preventive measures and managements for afflicted patients. In light of recent available data and because stanterdized management strategies have not been well established, prevention seems to be of paramount benefit to this group of patients.

Keywords: *Bisphosphonate, Osteonecrosis, Dentoalveolar surgery, Multiple myeloma, Bone metastases*

J Med Assoc Thai 2007; 90 (12): 2699-708
Full text. e-Journal: *http://www.medassocthai.org/journal*

In recent years, bisphosphonate-related osteonecrosis (BRON) of the jaws has been recognized as an adverse event of bisphosphonate therapy. Although the incidence of this complication is still very low and the use of bisphosphonates is not to be limited, this therapy resistant complication deserves attention from health care personnel.

Bisphosphonates: structure and mechanism of action

Bisphosphonates are the pyrophosphate analog with a carbon substitution. Both P-C-P structure of bisphosphonate and P-O-P structure of pyrophosphate have strong affinity with calcium phosphate crystal and their bindings inhibit further calcium phosphate accretion or dissolution[1]. Their molecular mechanisms of action are thought to be the inhibition of bone resorption by direct effects on osteoclasts[2-4]. When osteoclasts form their resorption lacunae during the bone resorption, bisphosphonates, which have been incorporated into mineral surfaces, would be simultaneously sequestered and endocytosed into cells through their ruffle borders[5]. Two additional covalently bounded groups (side chains) attached to the geminal carbon atom in P-C-P group, referred to, as R^1 and R^2, allow for variations in structure[4]. When R^1 is a hydroxyl (-OH) or primary amino ($-NH_2$) group, the affinity to hydroxyapatite is enhanced. R^2 is the determinant of antiresorptive potency. R^2 containing amino-nitrogen atom in an alkyl chain (as in pamidronate and aledronate) was found to be much more potent than non-nitrogen containing one (etidronate and clodronate) and the most potent forms were those containing a nitrogen atom within heterocyclic ring (as in risedronate and zoledronic acid)[4,6,7]. These findings led to the classification of bisphophonates into two main groups: nitrogen containing or non-nitrogen containing[7,8]. The more potent, nitrogen-containing bisphosphonates inhibit farnesyl diphosphate synthase, an enzyme in mevalonate pathway resulting in the reduction of geranylgeranyl diphosphate, which is required to prenylate GTP ases. Because of impaired prenylation, cytoskeletal organization and vesicular trafficking in osteoclast could not function properly, leading to osteoclast inactivation and induction of osteoclasts apoptosis[2,3].

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In contrast, non-nitrogen containing bisphosphonates are metabolized into non-hydrolysable cytotoxic molecules that resemble ATP, thus acting as a cytotoxic drug[3].

Several reports also suggested the antiangiogenic properties of bisphosphonates, as they significantly decreased circulating level of vascular endothelial growth factor (VEGF)[9-12], and inhibited matrix metalloproteinases[13]. In addition, their antineoplastic effects have been reported, though the underlying mechanism remains unclear[3,14].

Clinical use

Bisphosphonates have been used to treat a variety of diseases involving metabolic and oncologic bone disorders including osteoporosis[15,16], Paget's disease, multiple myeloma[17], hypercalcemia associated with malignancy, other metastatic bone diseases[18-20] and congenital pathologies, such as osteogenesis imperfecta[21]. Bisphosphonates can be administered orally, e.g. alendronate (fosamax), risedronate (actonel), ibandronate (bonviva), for the treatment of osteoporosis, and intravenously, e.g. pamidronate (aredia), zoledronic acid (zometa), second and third generation, respectively, as a more potent form for the treatment of bone pain, metastaic cancers, bone resorption defects in malignancy, osteogenesis imperfecta and recently-approved osteoporosis[22]. Generally, bisphosphonates are well tolerated. Their adverse effects related to anti-resorptive action, although infrequent, include osteomalacia, hypercalcmia bone pain and the newly described osteonecrosis of the jaws[8].

Osteonecrosis of the jaws and bisphosphonate use

Osteonecrosis is a term used to describe a microstructural failure with deformation of bone because of chronic inflammation in an area with insufficient blood supply. The most familiar type is osteoradionecrosis, a serious complication of radiotherapy in head and neck regions. BRON from intravenous (IV) bisphosphonates was first reported in 2003[23] and has since been increasingly reported. In September 2004, Novartis, the manufacturer of pamidronate and zoledronic acid notified the health care professionals of osteonecrosis of the jaws as a potential adverse effect[24]. United States Food and Drug Administration (USFDA) issued warning statements of this complication in 2005, covering broader drug class including oral preparations[25]. Recently, it has been reported that 10% of patients with osteonecrosis or osteomyelitis were associated with bisphosphonate use[26].

Etiology

Although the underlying etiology of BRON is still unclear, the profound anti-bone resorption of bisphosphonates has been suggested to be the primary cause. The osteonecrosis could result from the reduction or cessation of bone turnover and the conditions worsen when bone remodeling is required additionally, such as in healing after tooth extraction, and when the risk of infection increases. Osteoblasts and their progenitors may also be indirectly afflicted. If osteoclasts could not resorb the mineralized matrices which contain cytokines and growth factors involving in osteoblast proliferation and differentiation, the remodeling process would be arrested, leaving the bone acellular and necrotic[27]. A recent in vitro study reported an inhibition of bone healing by pamidronate in clavarial bony defect possibly due to a combination of the inhibition of angiogenesis and osteoclasts activity together with the cellular toxicity[28].

The unique structure of oral cavity may, in part, help explain the localized affected areas. The jaws have a relatively higher blood supply and a faster bone turnover rate when compared with other bones. This is due to the physiologic stress from daily activities and the presence of teeth, which results in bone remodeling around periodontal ligament. Thus, it might be possible that the bisphosphonate concentrations within the jaws are elevated selectively after the treatment, leading to a decreased remodeling activity of jaw bones, although no study has demonstrated a localized, high concentration of bisphosphonates in the jawbones[29]. When coupled with invasive dental treatments, osteonecrosis of compromised bone can occur as a result of the inability to repair and bacterial superinfection from oral flora. The dental comorbidities, including the presence of periodontitis, dental caries, and abscessed teeth, could also cause superinfection of the underlying bone through the infected periodontium or root canals[27]. Though infrequently reported, less severe dental procedures, such as root canal treatment and periodontal treatment as well as ulcers from ill-fitting dentures, could also trigger the development of BRON[8,27,30]. Despite the studies demonstrating that 20-40% of BRON cases occurred spontaneously, some authors suggested that at least one dental intervention, regardless of its severity, could be identified. Moreover, it has been suggested that the primary cause of BRON might be the setting that facilitates the oral microbial infiltration into the bone[30]. Further studies are clearly needed to understand the nature of these conditions.

Risk factors

Summary of known risk factors as proposed by the American Academy of Oral and Maxillofacial Surgeons (AAOMS) is presented in Table 1[31]. These factors have been classified into drug-related, local and systemic factors. Other potential risk factors that still need further investigations include corticosteroid therapy, smoking and alcohol use and chemotherapeutic drugs. Among multiple factors, potency and dosage of bisphosphonate seem to be a pivotal one. Zoledronic acid is more potent than pamidronate and pamidronate is more potent than oral bisphosphonates[29,32]. Moreover, the IV administration causes greater drug exposure than the oral administration[33,34]. Therefore, patients receiving oral bisphosphonates are considered at significantly lower risk for BRON[29,35]. The available incidence of developing BRON in patients treated with IV bisphosphonates was 0.8-13%[32,33,36,37]. It is much more difficult to obtain incidence of BRON from patients taking oral bisphosphonates. However, the estimated incidence of BRON in Australian patients receiving weekly alendronate was 0.01-0.04%. If the patients underwent tooth extraction, this incidence increased to 0.09-0.34%[38]. Among numerous BRON cases recently published[8,23,27,33-37,39-62], multiple myeloma is the most common reason for receiving bisphosphonates (approximately 53.4%), followed by breast cancer (30%), prostate cancer (6.1%), osteoporosis (5.8%) and other diseases, including other cancers and Paget's disease (4.7%). The mean induction time, the duration from when treatment was commenced until the first recognition of BRON, appears to be dependent on the type of bisphosphonates used. In patients receiving zoledronic acid, the mean induction time ranges from 9.4 to 28.6 months, whereas in patients receiving pamidronate, average induction time ranges from 14.3 to 72 months[27,30,36,63]. Though data regarding oral bisphosphonates are still limited, the reported induction time ranges from 24 to 60 months for patients receiving alendronate[27,30,38] and at least 15 months for patients receiving risedronate[55]. It has also been suggested that longer duration of treatments might increase the risk of having BRON[33,51].

The strong association of dental procedures especially dentoalveolar surgery prior to the development of BRON has been demonstrated. The risk of having BRON increased at least 7 folds in patients receiving IV bisphosphonates combined with dentoalveolar surgery, when compared with those without surgery[34]. The duration from the initial dental intervention to BRON diagnosis ranges from 3-12 months[8]. The oral diseases, such as periodontitis or dental caries have been proposed to be one of the key risk factors. The common anatomical sites of BRON appear to be the areas with bony prominence, such as tori, bony exostoses and the mylohyoid ridge[27,35,46]. Corticosteroid and adjuvant chemotherapy have also been proposed to be risk factors but unlikely to be the primary cause[31,64].

Diagnosis

Diagnosis of BRON can be made when patients are present with all of the following criteria[31,45]: 1) medical history of current or previous bisphosphonate treatment 2) bone exposure in maxillofacial region, persisting for more than eight weeks, which may be associated with pain, purulent secretion and swelling, and 3) no history of radiation therapy of the jaws. A suspected case of BRON has been defined[65] as a case with exposed bone in maxillofacial region for less than 8 weeks in patients receiving or had been exposed to bisphosphonates without history of head and neck radiotherapy. Such cases should receive follow-ups to confirm the definite diagnosis.

Table 1. Risk factors for the development of BRON[31]

I	Drug related factors
	A. Potency and route of administration of the bisphosphonate
	B. Duration of therapy
II	Local factors
	A. Dentoalveolar surgery e.g. extraction, periodontal surgery involving osseous injury, implant placement
	B. Local anatomy e.g. torus palatinus, torus mandibularis, mylohyoid ridge
	C. Concomitant inflammatory oral diseases e.g. periodontitis and dental abscesses
III	Systemic factors
	A. Age
	B. Cancer diagnosis
	C. Osteopenia/osteoporosis diagnosis concurrent with cancer diagnosis

Clinical findings

In patients with BRON, maxilla and mandible appear to be the only affected bone. The mandible, especially posterior part, was the most common area, (approximately 70%) followed by the posterior maxilla and a few cases (5-8%) that occurred simultaneously in both jaws[27,35]. The early stages of BRON usually are asymptomatic and no radiographic changes can be detected. Clinically, BRON symptoms can vary; the onset mostly presents as a failure to heal, or delay healing of bone with or without sequestration after tooth extraction or other oral surgery that insulted jawbones[29,45]. However, patients with asymptomatic exposed bone have also been reported[27]. Associated symptoms may encompass painful exposed avascular bone in which pain usually indicates a superimposed infection, paresthesia in the jaw or lower-lip, eating and speaking difficulties, halitosis, mucosal ulcerations, swelling, purulent mucosal or orocutaneous fistula and recurrent abscesses[27]. Ascending infection to paranasal sinuses from osteonecrosis of the maxilla has been reported[66]. Twenty to forty percent (20-40%) of BRON cases appear to occur spontaneously[27,49]. In these cases, patients initially experienced paresthesia and burning sensation in the mouth. Mucosal ulcerations that failed to heal arise next while pain is usually associated with super-infection of necrotic bone[45,49]. These signs and symptoms could herald the clinical manifestation of BRON; thus, early detection and prevention is indispensable for minimizing the progression of bone exposure and sequestration. Panoramic radiographs, CT scan and MRI demonstrated osteolysis or mottled bone. In some cases with the lesion extending into or beyond the inferior alveolar canal, paresthesia along the distribution of trigeminal branch could be observed[44].

Histopathological findings

Histological specimens obtained from biopsies usually demonstrated partially or completely necrotic bone with surrounding bacteria debris and granulation tissues. Intertrabecular fibrosis and inflammatory infiltrations of medullary spaces were also observed[30]. Moreover, cultures might be positive,

Table 2. Modified management strategies for patients receiving bisphosphonates[31,65]

Condition	Management strategies
Prior to IV Bisphosphonate treatment	Prevention A thorough oral examination All elective dentoalveolar surgery should be completed Dental prophylaxis, conservative restorative dentistry Oral hygiene instruction and optimization of oral health status
Asymptomatic Patients receiving IV bisphosphonates	Prevention Maintenance of optimum oral hygiene Dentoalveolar surgery should be avoided
Asymptomatic Patients receiving oral bisphosphonates	Prevention Maintenance of optimum oral hygiene Planned surgery can be performed in patient receiving short-term treatment Elective surgery is not a contraindication
Stage 1 Asymptomatic patients with exposed/necrotic bone and no evidence of infection	Treatment Antibacterial mouth rinse Oral hygiene instruction and reassessment of indications for continuing bisphosphonate therapy Clinical follow-up
Stage 2 exposed/necrotic bone associated with infection	Treatment Broad spectrum antibiotics Antibacterial mouth rinse Palliative treatment Superficial debridement to relieve soft tissue irritation
Stage 3 Exposed/necrotic bone with pain, infection and at least one of: pathologic fracture, extra-oral fistula or osteolysis extending to the border	Treatment Antibiotic therapy Antibacterial mouth rinse Palliative treatment Surgical debridement for infection control and relieve of pain

particularly for normal oral flora e.g. *Actinomyces*, *Enterococus*, *Streptococus Lactobacilli* and *Candida albicans*[30,53,66,67].

Prevention and treatments

Recommendations for BRON's management have been developed by several panels of experts[6,31,45,65,68] and are summarized in Table 2.

Prevention:

Prior to bisphosphonate treatment, prevention regimen (Fig. 1) should be performed. All patients should be informed of a potential, though low risk of developing BRON. An evaluation for systemic risk factors for developing BRON should be carried out. Thorough oral examination should be performed before starting an IV bisphosphonate and all invasive dental procedures should be completed while oral hygiene should be optimized and regular dental visits should be maintained. In patients undergoing the potent IV bisphosphonate treatment on a frequent schedule, any dental procedures involving direct osseous injury should be avoided and the less invasive procedures are preferable. Nonetheless, when tooth extraction is unavoidable (e.g. loosening teeth with periodontitis which increases risk of infection), removing the tooth and providing antibiotics seems to be the recourse[27]. Follow-ups should be done to ensure the complete healing[6]. In patients receiving oral bisphosphonates, elective dentoalveolar surgery appears not to be a contraindication, due to their lower potency. However, AAOMS recommends that the duration of treatment have to be taken into account. When duration of treatment is less than three years with no clinical risk factors, dentoalveolar surgery may be performed as in regular patients. When the treatment is less than three years but the patient has also taken corticosteroid concomitantly, or the treatment is more than three years whether or not corticosteroid has been taken, discontinuation of the oral bisphosphonates should be considered, given that systemic conditions allow, for at least three months prior to surgery[31]. However, it should be noted that there are no data supporting that discontinuation of bisphosphonates will improve dental outcomes[65]. In the cases that dosage of IV bisphosphonate is equivalent to oral dosage, it is believed that the risk of developing BRON should be comparable[31]; hence, the similar approaches are to be taken.

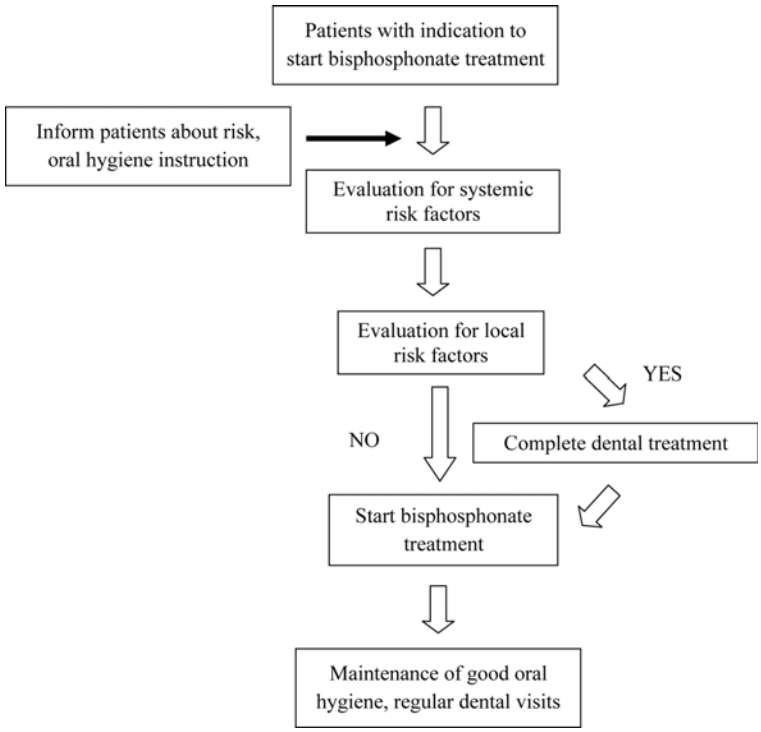

Fig. 1 Schematic diagram of recommended preventive regimen for patients about to start bisphophonate treatment

Therapy:

Once patients have been diagnosed with BRON, the treatment goals are palliative support, infection control of the soft and hard tissue and limitation of the progression of bone necrosis. Nevertheless, it appears that the established surgical treatment procedures for osteomyelitis or osteoradionecrosis do not result in a satisfactory outcome[69]. With the entire jaw bones exposed to bisphosphonate, obtaining the surgical margin with viable bleeding bone might pose a difficult task. The use of hyperbaric oxygen therapy in a few studies has not given an encouraging result; yet, its effectiveness remains to be determined[35,45].

AAOMS proposes classification of patients with BRON into three stages. Stage 1 represents exposed/necrotic bone in asymptomatic patients with no evidence of infection. Stage 2 represents exposed/necrotic bone in patients with pain and clinical evidence of infection, and stage 3 represents those as in stage 2 but with at least one of pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border. Treatments for stage 1 patients include the use of antimicrobial mouth rinse, such as chlorhexidine 0.12%. For stage 2 patients, antimicrobial mouth rinse in conjunction with antibiotic treatment has proved to be beneficial. The penicillin group is a preferable drug of choice while metronidazole, clindamycin and doxycyclin can be used for those who are allergic to penicillin with comparable therapeutic outcome. Long-term antibiotics or combination of antibiotics might be useful in some refractory cases. For stage 3 patients, surgical debridement combined with antibiotic therapy may be useful to help eliminate pain and control acute infection. Sequestrectomy to remove any mobile bone segments should be performed without exposing uninvolved bone. Since bisphosphonates have long half-life in skeleton, discontinuation of IV bisphosphonate treatments does not offer a short-term benefit, while long-term discontinuation may be useful in stabilizing the existing condition and reducing the incidence of new disease development[50]. Although it has been suggested that discontinuation of oral bisphosphonate appears to result in a resolution of disease condition[31], there is not enough evidence to support this concept[65,70]. The risks and benefits of continuing or modifying the treatments should be assessed, as per case basis, by the health care personnel and the patient. The treatments recommended could serve as a guideline and should, as more collective data will become available, be modified accordingly.

Conclusion

Although the incidence of BRON is still very low, the expanding indications for bisphosphonate treatment suggest that the increasing number of BRON may be expected in the future. It is obvious that awareness of healthcare professionals would aid in minimizing the risk of developing this potential complication. Since the standardized treatment plan has yet to be established, the preventive regimen involving consistent maintenance of good oral hygiene should be strongly emphasized and care must be taken to ensure the compliance from the patients.

This particular adverse effect would serve to remind the biomedical community that the seemingly unrelated causal relationship complications can occur unpredictably and it is within the biomedical community's responsibility to recognize and promptly respond to them.

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เนื้อกระดูกขากรรไกรตายจากการใช้ยาบิสฟอสโฟเนต การดูแลแบบสหวิทยาการ

เดือนพิมพ์ ปริสุทธิมาน

บิสฟอสโฟเนตเป็นยากลุ่มที่ใช้กันแพร่หลายในการรักษาโรคมะเร็งและโรคทางระบบเมตาบอลิสมของกระดูก เนื่องจากคุณสมบัติในการยับยั้งการสลายกระดูกของเซลล์ออสติโอคลาส ในปัจจุบันพบว่ามีรายงานของการเกิดกระดูกเนื้อตายที่บริเวณขากรรไกรจากการใช้บิสฟอสโฟเนตเพิ่มขึ้นอย่างต่อเนื่อง และมักพบในผู้ป่วยที่ได้รับยาทางเส้นเลือดเพื่อรักษามัลติเปิลมัยอีโลมา หรือ มะเร็งที่แพร่กระจายในกระดูกเป็นระยะเวลานาน ด้วยเหตุที่อุบัติการณ์ในการเกิดผลข้างเคียงที่ไม่พึงประสงค์นี้สัมพันธ์กับการผ่าตัดในช่องปาก การดูแลและให้การรักษาผู้ป่วยในแบบสหวิทยาการ จึงจำเป็นอย่างยิ่ง บทความนี้มีวัตถุประสงค์เพื่อรายงานถึงสาเหตุ ปัจจัยเสี่ยง อาการแสดง และคำแนะนำในการป้องกันและรักษาผู้ป่วย เนื่องจากยังไม่มีวิธีการรักษาที่เป็นมาตรฐาน การป้องกันโรคจึงเป็นมาตรการที่สำคัญที่สุดในปัจจุบัน