Bisphosphonates and osteonecrosis of the jaws: Science and rationale

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Bisphosphonates as a group of drugs were introduced for the management of various conditions such as osteoporosis, Paget’s disease, multiple myeloma, hypercalcemia of malignancy, breast cancer, prostate cancer, and other tumors. This group of drugs has improved the quality of life in many patients with proven efficacy in limiting pain and skeletal-related events. The controversy of osteonecrosis of the jaws and bisphosphonates is a recent and growing problem. Osteonecrosis of the jaws is recognized as a serious complication of bisphosphonate therapy, more commonly with the intravenous form of the drugs. However, there is limited scientific understanding about the association between osteonecrosis of the jaws and bisphosphonates. In the present article we discuss various mechanisms of action of bisphosphonates, the rationale for occurrence of osteonecrosis in the jaws, and treatment guidelines for the condition. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:186-93)

Osteonecrosis of the jaws (ONJ) is characterized by the death of bone as a natural consequence of a wide variety of systemic and local factors compromising the blood flow of the bone. Among these factors are hemoglobinopathies, anticardiolipin antibodies, defects in the thrombotic and fibrinolytic systems, fat emboli, alcoholism, systemic lupus erythematosus, and corticosteroids.1-3 Bisphosphonates (BPs) have recently been the subject of clinical controversies because of the increased incidence of ONJ.

The discovery of BPs as a major class of drugs has extended over a period of 3 decades, although the first synthesis of BP occurred in Germany in 1865.4 Originally, these drugs were exploited as inhibitors of bone resorption in humans.5 They have also been used as corrosion inhibitors and fertilizer and in the oil industry. However, their mechanism of action at the cellular and molecular levels remains enigmatic and continues to be investigated. An extensive review of the literature was performed with reference to BPs and ONJ and is summarized in the present paper.

DISCOVERY OF BISPHOSPHONATES AS INHIBITORS OF BONE RESORPTION

In the early 1960s Fleisch proved that inorganic pyrophosphates (PPI) prevent body fluid calcification by binding to hydroxyapatite crystals.6 They also revealed that the oral forms of PPI were inactivated by the phosphatases secreted by the gastrointestinal brush border.7 In an attempt to find stable analogs of PPI, diphosphonates (now called bisphosphonates) were among some of the drugs that were investigated during that time.7 The BPs tolerated the oral route very well without being inactivated, and this became the key element in their success. They also inhibited the dissolution of hydroxyapatite crystals.8 Further studies even proved that they prevented bone resorption by inhibiting osteoclast activity.9

Chemical structure

All bisphosphonates share a common “back bone.” Although they are analogous to PPI, structurally BPs differ in that they have a carbon atom bridging the 2 phosphate molecules. This morphology provides the stability for their action and withstands hydrolysis (Fig. 1).

The presence of a hydroxyl group at the R1 chain of the R1 and R2 side chains. Currently the amino-bisphosphonates are the most powerful drugs that are available (Table 1).

Pharmacology

The clinical pharmacology of intravenous (IV) BPs is characterized by low intestinal absorption but highly selective localization and deposition in bone. Oral BPs have a bioavailability of less than 5%.10 Once in the blood, BPs disappear very rapidly into the bone.11 After BPs are buried in the skeleton, they are released only when the bone is destroyed in the course of turnover. In humans, the skeletal half-lives of various BPs range from 3 months to as long as 10 years.12 The inhibition of bone resorption reaches a steady level even when the
compounds are given continuously, as has been reported in some animal studies.13

**Mechanism of action**

Different mechanisms have been reported to account for the action of BPs, including induction of apoptosis,14,15 and disruption of the cell cycle.16 They also have anti-invasive,17 antiangiogenic,18 and antimigration effects. To date, there is still no clear understanding of the molecular targets. Listed below are some of the proposed mechanisms of action of the bisphosphonates.

1. The first generation BPs, such as clodronate and etidronate, do not contain an amino group. They are metabolized to form cytotoxic adenosine triphosphate (ATP) analogs that accumulate intracellularly in osteoclasts and induce apoptosis.14,15

2. The potent groups of BPs (amino-BPs) are inhibitors of the mevalonate pathway, a biosynthetic pathway for isoprenoid proteins such as farnesyl-diphosphate and geranylgeranyl-diphosphate. The isoprenoid proteins are required for post-translational phrenylation of the guanosine triphosphates (GTPases), such as Ras, Rho, and Rac. The Ras group of proteins is responsible for cell proliferation and is activated by farnesylation.19 After internalization, BPs cause disruption of the cytoskeleton by inactivating GTPases such as Ras, Rho, and Rac. The Rho and Rac groups of proteins are responsible for cytoskeleton organization and cell membrane ruffling and are activated through geranylgeranylation.16,20,21 The cytoskeleton is essential to maintain the “ruffled border,” the area with which the osteoclast makes contact with bone and breaks down bone tissue. With the ruffled border compromised, the osteoclast initiates apoptosis, netting a decrease in bone turnover.

3. Bisphosphonates also inhibit various matrix metalloproteinases involved in cancer growth and metastasis.17,22

4. Although BPs are also known to have an antiangiogenesis effect, there have been some contradicting reports on this property based on histologic analysis of ONJ samples.23

5. There are some reports that BPs may inhibit bone resorption by stimulating osteoblasts to produce an osteoclast-inhibitory factor.24

6. Bisphosphonates are also reported to be powerful inhibitors of macrophage proliferation, cells that are of the same lineage as osteoclasts.25

7. Other mechanisms include inhibition of the osteoclast’s proton ATPase, phosphatases, and other lysozymal enzymes.26,27

The subcellular space beneath the osteoclast is acidified during the process of bone resorption by the proton-pumps in the ruffled border of the osteoclast membrane.28 This acidic environment causes dissolution of the hydroxyapatite mineral and releases more BPs, which are then internalized into the osteoclasts through the process of endocytosis.29 Apart from osteoclasts, some potent BPs, such as pamidronate and zoledronate, are also potent inducers of apoptosis in other cancer cells, such as multiple myeloma, breast cancer, pancreatic cancer, and intestinal epithelial cell lines.30-32 Many solid tumors cause hypercalcemia of malignancy, and the primary cause of this is often due to release of parathyroid hormone (PTH)–related peptide, which causes extensive bone destruction. Transforming growth factor, a bone-derived factor, also promotes increased production of PTH-related peptide by tumor cells, leading to a vicious cycle of progressive tumor growth and bone destruction. Bisphosphonates are known to interrupt this cycle by inducing osteoclast apoptosis.33

**Early clinical applications**

Etidronate was the first BP used to treat humans for myositis ossificans,34 and to prevent hypertrophic bone formation after total hip replacement surgery.35 They are also known to prevent dental calculus when used in toothpastes36-38 and to decrease periodontal bone destruction. However, BPs are predominantly used for osteoporosis, Paget’s disease, multiple myeloma, hypercalcemia of malignancy, and metastatic and osteolytic bone disease.39-42 BPs such as alendronate and tiludronate have been reported to prevent bone loss in healthy postmenopausal women.43,44 They have also been proven to decrease the accumulation of cholesterol, elastin, and collagen in the arteries.35

Bone metastases are common in patients with many types of cancer, particularly with breast and prostate cancer. These 2 combined account for more than 80% of metastatic bone disease. Others include multiple myeloma, lung cancer, and other solid tumors.46 This condition is associated with considerable skeletal morbidity, including severe bone pain, pathologic fracture,
spinal cord or nerve root compression, and hypercalce-
mia of malignancy. Among all of these types, breast
cancer has the highest incidence of skeletal complica-
tions and consequently BPs have become the standard
of treatment. Currently, zoledronate has been shown to
be significantly effective in patients with metastatic
breast, prostate, lung, renal, and other solid cancer
types. 47 Zoledronate resulted in a significantly lower
incidence of skeletal-related events in most cancer
types. A combination therapy with zoledronate and
pamidronate has been successfully used in patients with
breast cancer, lung cancer, multiple myeloma, lym-
phoma, and uterine sarcoma.

BP AND ONJ
Every year, an estimated 30 million BP prescriptions
are written in the U.S. alone. It is estimated that pam-
idronate and zoledronate have been used in over 2.5
million patients worldwide. 48 The first case report in
oral and maxillofacial surgery on BP was the failure of
osseointegrated dental implants. 49 The exact incidence
of ONJ is unknown. However, some reports have esti-
mated it to be about 1 in 10,000. 50 A single-center
study has reported 11% incidence of ONJ in patients
with multiple myeloma on BP therapy. In that study, it
was also concluded that zoledronic acid produced a
9.5-fold greater risk for developing ONJ than pamid-
ronate alone and 4.5-fold greater risk than subsequent
use of pamidronate + zoledronic acid. Use of thalido-
mide and a number of bisphosphonate infusions also
increased the risk for ONJ 2.4-fold and 4.9-fold, re-
spectively. 51 The incidence of developing ONJ in-
creases with time of exposure, and this risk increases
dramatically in patients using zoledronic acid. 52 It is
estimated that with each decade of life, there is a 9%
increased risk of developing ONJ in patients on BP
therapy for multiple myeloma. 53 In higher doses, BPs
are also known to affect the mineralization of enamel,
dentin, and cementum of the tooth. 54-56 In large doses,
etidronate or clodronate cause an increase in fracture
rate if given over a year. 57 Some oral forms of BPs
affect osteoclastic function with less severity, because
of their high intestinal absorption and poor bioavail-
ability. However, few oral BPs (alendronate, ibandr-
onate, and risedronate) are more potent than the IV
form of BP, such as pamidronate.

In 2003, the American Society of Clinical Oncology
recommended that once initiated, IV BPs be continued
until there is evidence of substantial decline in a pa-
tient’s general performance status. 58 At this time, we do
not have enough data to determine the long-term risks
of oral or IV BPs or which subset of the patient popu-
lation is at risk of developing ONJ. There are little data
on the activity of IV BPs beyond 2 years of adminis-
tration. In one report, there was an extremely low
incidence of skeletal-related events in a patient popu-
lation with bone metastasis that was followed for up to
10 years. 59 In a very interesting clinical study, Coleman
et al. 47 investigated the correlation between bone me-
tabolism and clinical outcome during BP therapy by
measuring urinary N-telopeptide. They estimated the
correlation between this bone resorption marker and the

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>R1 side chain</th>
<th>R2 side chain</th>
<th>Relative potency</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate (Didronel)</td>
<td>OH</td>
<td>-CH₃</td>
<td>×1</td>
<td>Oral</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Cl</td>
<td>-CL</td>
<td>×10</td>
<td>Oral/IV</td>
</tr>
<tr>
<td>Tiludronate (Skelid)</td>
<td>H</td>
<td>×10</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Pamidronate (Aredia)</td>
<td>OH</td>
<td>-(CH₃)₂-NH₂</td>
<td>×100</td>
<td>IV</td>
</tr>
<tr>
<td>Neridronate</td>
<td>OH</td>
<td>-(CH₂)₄-NH₂</td>
<td>×100</td>
<td>Oral</td>
</tr>
<tr>
<td>Olpadronate</td>
<td>OH</td>
<td>-(CH₃)₂-NH₂</td>
<td>×1,000</td>
<td>IV</td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>OH</td>
<td>-(CH₃)₂-NH₂</td>
<td>×1,000</td>
<td>Oral</td>
</tr>
<tr>
<td>Ibandronate (Boniva)</td>
<td>OH</td>
<td>×5,000</td>
<td>Oral/IV</td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
<td>OH</td>
<td>×5,000</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Zoledronate (Zometa)</td>
<td>OH</td>
<td>×10,000</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>
relative risks for negative clinical outcomes. Interestingly, N-telopeptide levels correlated with the risk of skeletal complications and disease progression. This serves as an excellent prognostic tool. This could lead to the selection of cancer patients who might benefit from therapy with BPs by evaluating urine or serum markers that predict who is at highest risk for skeletal complications and disease progression.46

**Importance of proper nomenclature**

Terms such as avascular necrosis of the jaws, bisphossy jaw, bisphosphonate osteomyelitis, bisphosphonate osteonecrosis, bisphosphonate osteochemonecrosis, and osteochemonecrosis have all been used in the literature. An analogy drawn to phossy jaw was also reported23: Osteonecrosis of the jaws caused by BPs was compared with the phossy jaw, more commonly seen in workers in the match industry in the 19th and early 20th centuries. Phossy jaw was caused by chronic exposure to white phosphorus, and the average period from first exposure to diagnosis was 5 years.60 Reports of phossy jaw were first reported in the literature as early as 1845.61 However, similar to phossy jaw necrosis, the bone morphology in ONJ is more like a pumice stone or of a moth-eaten appearance.

Some investigators have commented that ONJ is similar to osteoradionecrosis (ORN). However, there is a clear histologic difference between the 2 conditions. As reported by Hellstein and Marek,23 in ONJ there is relative paucity of Howship’s lacunae and sparse reversal lines. In contrast, there is a higher incidence of Howship’s lacunae and reversal lines in cases of ORN. Although there have been some reports in the literature about osteonecrosis caused by steroids, this form is different from ONJ in the sense that steroid-induced osteonecrosis does not cause bone exposure.62

**Scientific rationale for ONJ**

The oral cavity possesses some unique demands with constant bone remodeling. This requires adaptability and up-regulation of the osteoblast and osteoclast function. Osteoclasts have a life span of about 150 days, after which they resorb the mineral matrix of bone and release bone morphogenetic protein (BMP) and insulin-like growth factors, which in turn induce local stem cells to differentiate into osteoblasts and form new bone. This is a very critical cycle and remains in a tight temporal zone. If the osteoclast function is too severely impaired, dead and dying osteoclasts are not replaced and the capillary network in the bone is not maintained, resulting in bone necrosis. Besides resorption at the sites of bone turnover, formation is also decreased, as noted by a reduction in the bone formation surface.63,64

**Risk factors for developing ONJ**

The risk factors for developing ONJ include trauma, female gender, advanced age, edentulous regions, radiotherapy, chemotherapy, steroid therapy, blood dyscrasias/metastatic disease, anemia, coagulopathy, surgical dental procedures, alcohol or tobacco use, prior infection, and bisphosphonate therapy.65

**Clinical signs and symptoms**

Patients may remain asymptomatic for many weeks or months, and the condition may only be recognized by the presence of exposed bone in the oral cavity. These lesions are most frequently symptomatic when sites become secondarily infected or there is trauma to the soft tissues via the sharp edges of the exposed bone. Typical signs and symptoms include pain, bone exposure, soft-tissue swelling, infection, loosening of teeth, and drainage (Figs. 2-5).

**Treatment**

Based on the articles published to date, the following recommendations are made by the American Association of Oral and Maxillofacial Surgeons for management of patients on BP therapy and patients with proven ONJ.56

Management of patients receiving BP therapy without clinical symptoms

a. Individuals on IV BP therapy:
   i. Avoid procedures that involve direct osseous injury.
   ii. Nonrestorable teeth may be treated with endodontic therapy.
iii. Avoid placement of dental implants in patients on potent IV form of BPs.

b. Individuals on oral BP therapy:
   i. Elective dentoalveolar surgery is not contraindicated.
   ii. Patients should be adequately informed about the risk of compromised bone healing.
   iii. Alteration in surgical planning is not necessary in patients on oral BPs for less than 3 years and no other risk factors.
   iv. For a patient on oral BP and corticosteroids for less than 3 years, consider discontinuing the oral BP therapy for 3 months. Treatment may be resumed after bone healing is completed. This decision should be made after consulting the treating physician and only if systemic conditions permit. The same strategy applies for patients on oral BPs and steroids for more than 3 years.

Management of patients with proven ONJ based on staging of the condition

a. Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.
   c. Stage 3: Exposed/necrotic bone in patients with pain, infection, and 1 or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border.

Treatment of patients with established ONJ:

   i. Patients with stage 1 ONJ: Conservative management with oral rinse such as 0.12% chlorhexidine.
   ii. Patients with stage 2 ONJ: Manage with antibiotics and antimicrobial oral rinses.
   iii. Patients with stage 3 ONJ: Surgical debridement/resection in combination with antibiotic therapy. Extraction of symptomatic teeth can be performed without any additional risks of worsening the condition.

The International Myeloma Foundation recommends suppression of the drug for 2-4 months to facilitate recovery in patients with ONJ. They also advise discontinuing BP therapy if a patient must undergo any oral surgery. However, at this time it is unclear if this would have any beneficial effects. It has been reported that ONJ appears long after discontinuation of therapy, in some cases as long as 12 months.53

Prevention

Before initiating BP therapy, all medical and dental practitioners are encouraged to follow these guidelines:

1. All patients should undergo a routine dental exam to rule out any dental source of infection.
2. All medical practitioners also should perform a baseline oral exam.
3. Invasive dental or/and oral surgical procedures should be completed before initiating therapy.
4. Practice preventive dentistry, involving procedures such as oral prophylaxis, dental restorations, and endodontic therapy, and check dentures for irritational foci.
5. Schedule routine follow-up every 3 months to check for any signs of developing ONJ.
6. The risks associated with oral surgical procedures such as dental implants, extractions, and extensive periodontal surgeries must be discussed with the patient and weighted against the benefits.
7. Because the incidence of ONJ may vary between the oral and IV forms of BPs, procedures must be considered with caution especially for patients on the IV form of BPs.

CAN WE DESIGN SAFER COMPOUNDS?
It is possible to design BPs with activity against selective GTPases excluding the Rho and Ras groups of proteins. This will prevent the disruption of isoprenylation of the mevalonate pathway, thus sparing the osteoclastic activity. Based on the evidence that BPs act as inhibitors of farsenyldiphosphate and geranylgeranylphosphate, a later-generation aminobisphosphonate, NE10790, was developed. This has the specific ability to inhibit the activity of other proteins than the Ras and Rho groups. The NE10790 BP was able to inhibit bone resorption without affecting osteoclast number or the activity of osteoclasts. Also, agents such as stealth liposomes could be used as drug delivery systems for BPs. Doxorubicin is one of the first anticancer drugs encapsulated in pegylated liposomes and delivered to specific sites of action. This property could be used for BPs as well. Pegylated liposomes could be used as vehicles for BPs for specific accumulation in tumor sites rather than being accumulated in bone tissue. Currently, there are new compounds being added to this group of drugs. New-generation antibod-
ies, such as denosumab, have been developed to treat patients with bone metastasis, multiple myeloma, and osteoporosis. Denosumab is a human IgG2 molecule with long circulatory residence time that facilitates a rapid and sustained decrease in bone resorption. This drug does not have a direct inhibitory effect on osteoblasts, unlike the current generation bisphospho-
nates. Also, other issues, such as choice of regimen (continuous vs. intermittent dosing), oral route, combination therapy, and extension of use to other conditions, are all being considered.

CONCLUSION
It is important that all health professionals, especially dentists, oncologists, and oral surgeons, be aware of the possibility that patients being considered for dental extractions or other oral surgery may be undergoing BP therapy. Most medical practitioners are unaware of this serious and potentially permanent complication. Also, patients should be informed of the risk of ONJ, so that they have the opportunity to assess their need for dental treatment before starting therapy. All patients using BPs should be under vigilant surveillance.

REFERENCES


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