Bisphosphonates in Orthopedics: Evidence-based Review of Indications and Adverse Effects

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ABSTRACT

Bisphosphonates (BPs) are clinically the most important class of antiresorptive agents available to treat diseases characterized by osteoclast-mediated bone resorption. These agents have a potent effect on the skeleton and are in common use for treatment of osteoporosis, Paget’s disease, and metastatic bone disease in adults as well as in the treatment of pediatric disorders, such as osteogenesis imperfecta, Perthes’ disease, and fibrous dysplasia. Although initial investigations had demonstrated an acceptable safety profile of bisphosphonate drugs, but recently this has been questioned by some authors. In this article, we review the chemistry, pharmacokinetics, and pharmacodynamics of these agents in brief and the orthopedic applications as well as adverse effects in detail.

Keywords: Adverse effects, Bisphosphonates, Indications, Review.

INTRODUCTION

Bisphosphonates (BPs) are synthetic, pyrophosphate analogs containing two phosphonate groups attached to a central carbon atom that replaces the oxygen in pyrophosphate (the P-O-P bond has been replaced with a nonhydrolysable P-C-P bond (Fig. 1). They are metabolically stable analogs of inorganic pyrophosphate and have a strong affinity for bone, especially areas of high turnover.

The BPs can be grouped into three generations according to their side chains:

1. First-generation BPs contain minimally modified side chains (e.g., medronate, clodronate, and etidronate) or a chlorophenyl group (e.g., tiludronate).

2. Second-generation BPs or amino-BPs contain an N-atom in the side chain (e.g., Pamidronate, Alendronate, and Ibandronate). These are 10 to 100 times more potent than the first-generation drugs.

3. Third-generation BPs contain an N-atom within a heterocyclic ring (e.g., Risedronate and Zoledronate). These are up to 10,000 times more potent than the first-generation drugs.

MECHANISM OF ACTION OF BPs

Bisphosphonates are antiresorptive agents; they inhibit bone resorption by acting directly on osteoclasts. They reduce the rate of excessive turnover and slow or arrest the progressive deterioration of micro-architecture and loss of bone tissue, and may in fact partially reverse these changes. Bisphosphonates act preferentially over the active bone remodeling sites on the bones by binding to exposed bone minerals, thus rapidly and specifically inhibiting bone resorption mediated by osteoclasts in a dose-dependent manner. This improves the existing bone micro-architecture and mineralization and slows or prevents the progressive loss of structural elements. Continuous (daily or weekly) treatment with nitrogen-containing BPs causes a rapid and sustained improvement in bone micro-architecture, together with an increase in bone mass, leading to improved mechanical strength and reduced fracture risk. Newer nitrogen-containing BPs also inhibit components of the intracellular mevalonate pathway of cholesterol biosynthesis and protein prenylation thus affecting GTPase formation. The latter causes disruption of integrin signaling, altered membrane-protein trafficking, loss of membrane ruffling, cytoskeleton disruption, and induction of apoptosis of osteoclasts.

Binding affinity and antiresorptive potency differ among the compounds. The side chains (Fig. 1) influence the binding affinity (R1 side chain) and the antiresorptive...
potency (R2 side chain). Both oral and parental preparations are available for clinical use. Only about 1% of an orally administered dose is absorbed in ideal conditions and taking a BPs with food or anything containing divalent cations will completely block its absorption. They are not metabolized systemically and the half-life in plasma is short. Half of the absorbed dose binds to bone surfaces, most avidly at the sites of active remodeling and the rest is excreted rapidly by kidneys. The skeletal capacity is large and the binding sites are virtually unsaturable. In the acidic environment with enzymes beneath an active osteoclast, BPs are released from the bone and enter the osteoclasts. This causes loss of resorptive function and accelerates apoptosis of these cells, thus reducing the osteoclast-mediated bone resorption and bone turnover. Maximum effect is noted in 3-6 months and with continued treatment and is maintained in a steady state for 10 years or more.

**CLINICAL USES OF BPs IN ORTHOPEDICS**

Till date, eight BPs have been approved for clinical use by US-Food and Drugs Administration (FDA). These are pamidronate, clodronate, etidronate, tiludronate, alendronate, ibandronate, risedronate, and zolindronic acid. Last four are freely available in India. The primary indication is to increase the bone mass and reduce the fracture risk in patients with osteoporosis. Other common indications are Paget’s disease and bone metastases. They are also useful in lowering the elevated levels of blood calcium in patients with cancer (multiple myeloma, hypercalcemia of malignancy). Other indications and contraindications for their use are listed in Table 1.

**Osteoporosis**

Use of BPs for treatment of osteoporosis is now well-established. They can be used in postmenopausal osteoporosis as well as in idiopathic osteoporosis in men, in glucocorticoid-induced osteoporosis, and in secondary osteoporosis with various diseases and drugs. Weekly and monthly oral formulations are available for prevention and treatment. Intravenous (IV) formulation can be used in patients with low gastrointestinal (GI) tolerance and noncompliant patients. Black et al. found a significant reduction in vertebral fracture risk (70%) and vertebral fractures (40%) with use of an annual infusion of 5 mg zolendronic acid over a period of 3 years. Bisphosphonates also reduced the mortality rate following hip fractures by 28% over 3 years. Similar data are also presented by Kanis et al. This is a common belief that BPs therapy should not be continued beyond 3 to 5 years. Many studies claim that BPs given over a period of 2–3 years will cause brittle bones. But the same has not been proven in larger longitudinal studies. Current studies are unable to support the earlier concept of basic conversion of the bone into “frozen bone” with administration of BPs and have proven rising bone density (about 1% or more annually) even 10 years after BPs treatment. The differentiation of bone turnover in osteoporosis as “high turnover” and “low turnover” is currently not relevant to the choice of BPs. After discontinuation of BP therapy, fracture reduction can be expected with positive after-effects of several years.

Watts and Diab in his review on long-term use of BPs in osteoporosis recommends a drug holiday after 5 to 10 years of BP treatment. The duration of treatment and length of the holiday are based on fracture risk and pharmacokinetics of the BP used. Patients at mild risk might stop treatment after 5 years and remain off as long as the bone mineral density is stable and no fractures occur. Higher risk patients should be treated for 10 years, with a holiday of no more than a year or two. He also recommended non-BP treatment for osteoporosis during this holiday period.

**Antitumor Activity—Solid Tumors and Metastasis**

Bone metastasis is probably the most symptomatic metastatic disease. It has a tremendous impact on the quality of life, mobility, and independence. Bone metastases eventually develop in >80% of patients with...
breast, prostate, or kidney malignancies. This may present as hypercalcemia, bone pain, pathologic fracture, and spinal cord compression. The invasion of malignant cells into the bone microenvironment causes a breakdown in the normal, tightly controlled bone-remodeling process, leading to an uncoupling of cellular function and an excess of osteoclastic over osteoblastic activity. This disruption of bone homeostasis leads to osteolysis, skeletal destruction, and a risk of pathologic fractures.23 There is a growing body of evidence that BPs possess direct antitumor activity against a variety of cancers as well as act synergistically when combined with other anticancer agents.24,25 Bisphosphonates work by several different mechanisms to reduce bone resorption and bone formation in cancers.26-28 They are effective in cancer treatment by making the bone marrow a less favorable environment for cancer cell colonization by inhibiting the release of bone-derived growth factors and prostaglandins during bone resorption. They also interfere with the functions of bone marrow derived cells (mesenchymal cells, monocytes, macrophages, and progenitor cells)29 that have an important role in priming distant tissues for tumor metastasis. They have also been shown to improve immune surveillance against neoplastic cells. Some authors suggested that BPs exhibit direct antitumor effects, especially when administered with cytotoxic agents.8 Bisphosphonates reduce the breast cancer incidence in postmenopausal women by 30%.30 In vitro work by Mundy et al31 has shown that BPs may have a direct action on tumor cells by inducing apoptosis, inhibiting matrix metalloproteinase-1, and inhibiting adhesion of tumor cells within the bone.

Consensus guidelines indicate that all patients with multiple myeloma and radiologically confirmed bone metastases from breast cancer should receive BPs from the time of diagnosis and continued indefinitely.32 The beneficial effect of BPs in patients with bone metastases secondary to other cancers including prostate cancer33 and a broad range of other solid tumors including lung cancer34 has also been demonstrated. Zoledronic acid, however, has proven effective across the range of solid tumors, whereas the efficacy of the other agents is restricted to breast cancer and myeloma.35,36

Hypercalcemia

Hypercalcemia is not a very common condition in orthopedic practice. It is usually seen in patients with metastatic bone disease, multiple myeloma, and primary hyperparathyroidism.8 Mostly, it is due to calcium release from the bone by osteoclasts or metastatic tumor cells. Bisphosphonates are very effective in controlling osteoclast-mediated calcium release and hypercalcemia. A single infusion of zoledronic acid normalizes serum calcium level in 88% of cases in an average of 10 days.37 The duration of the normocalcemic phase depends on the underlying disease, about 2 weeks in most cases. A second infusion may be required if serum calcium level rises again. For rapid normalization of hypercalcemia in life-threatening conditions, a combination of BPs with calcitonin is effective. It lowers the calcium level within hours by increasing renal calcium excretion.

Fibrous Dysplasia

Fibrous dysplasia is characterized by the production of fibrous tissue and woven bone that replaces the normal cortical bone. This abnormal bone leaves the skeleton weak and prone to fractures. In this disease, the fundamental defect is somatic mutation in the gene coding for the alpha subunit of Gs protein (the G protein that stimulates cAMP formation). This overproduction of cAMP in turn causes overexpression of c-fos, which plays an important role in regulating the interplay of osteoblastic and osteoclastic proliferation and differentiation, resulting in excessive osteoclastic activity. Bisphosphonates lead to thickening and progressive ossification radiologically and, improvement in pain and N-telopeptide levels. Most workers have used IV pamidronate,38-44 with sporadic reports of use of combined pamidronate and oral alendronate35 and only oral alendronate.46

Arthroplasty

Main objective of BPs in arthroplasty is to prevent aseptic loosening, periprosthetic osteoporosis, and fractures so as to reduce the frequency of further revision surgeries. Common reasons for revision are aseptic loosening, periprosthetic osteoporosis (stress shielding), wear debris-induced osteolysis, and periprosthetic fracture.47 Initially, it was thought that by inhibiting the bone remodeling, BPs will affect the bone in-growth in uncemented prosthesis and thus may affect implant-bonding. In clinical studies, however, many authors noted an improved periprosthetic bone density and reduced stress shielding after oral or local use of BPs. Many of them also found decreased rate of migration of the implants.48-52 Bisphosphonates are also supposed to reduce osteoclastic activation and osteolysis induced by wear debris. Wang et al52 reported that oral administration of alendronate for 6 months postoperatively significantly improved the bone mineral density in total knee arthroplasty (TKA) patients.

Heterotopic Calcification and Ossification

For the prophylaxis and treatment of heterotopic ossification, indomethacin is most commonly used and
found to be effective. Other modality that has shown good result is radiotherapy, but it is not commonly used. Bisphosphonates experimentally inhibit the mineralization of soft tissues and heterotopic ossification, but in clinical use, mixed results have been reported. Mavrogenis et al found that BPs are prophylactically effective if started shortly after the trauma, but mineralization of the bone matrix resumes after drug discontinuation. Etidronate is considered to be as effective as indomethacin but not cost-effective. Other BPs under trial are alendronate, pamidronate, and risendronate.

**Paget’s Disease**

In the present times, normalization of bone turnover is possible in almost all patients with the potent BPs available for clinical use. Modern BPs normalize the bone turnover and bone histology as well as lead to healing of lytic radiologic lesions. Long-term follow-up data from the zoledronate demonstrate high response rates and very long durations of biochemical remission. Patient treated with this drug is unlikely to experience disease progression for greater than 6 years and therefore require less often follow-ups thus making therapy cost-effective and has beneficial effects on quality of life.

**Complex Regional Pain Syndrome**

The reflex sympathetic dystrophy (RSD) or complex regional pain syndrome-I (CRPS-I) is associated with increased bone resorption and patchy osteoporosis, which might benefit from treatment with BPs, powerful inhibitors of bone resorption. Due to still unknown etiology, multiple modalities have been used till date for treatment of RSD, including BPs. The role of BPs in treatment of RSD has been proven by clinical response with diminution in spontaneous pain, tenderness, swelling (circumference of the affected limb), and improvement in motion by reducing local acceleration of bone remodeling in many clinical studies. Tran de et al reviewed 41 randomized controlled trials and found that only BPs (oral alendronate and IV pamidronate) appear to offer clear benefits for patients with CRPS-I as compared with other treatments.

**Avascular Necrosis of Femoral Head (AVNFH)**

Use of BPs in AVNFH is still controversial. Bisphosphonates, especially alendronate, have been shown to decrease rate of progression of AVN lesions, but the benefit is mostly in the pre-collapse stages. Hence, most authors recommend that therapy should be initiated in the early phases of AVN, as later stages appear to be less responsive to medication.

**Bone Marrow Edema Syndrome**

This is also known as idiopathic transient osteoporosis of the hip. It is most often seen in middle-aged men, but sometimes occurs in women (usually in late pregnancy) and is bilateral in one-third of the patients. It presents as increasing pain and limp with local muscle wasting. It is usually diagnosed by an abnormal bone scan and in later stage by radiologically visible osteoporosis in the region of femoral head and neck. Demineralization may not be apparent on plain radiographs for 6 weeks after onset of symptoms. Intravenous ibandronate combined with physical therapy and calcium, vitamin D supplementation have shown a significant improvement in hip score before and after treatment of these patients.

**Stress Fractures in Athletes**

Stress fractures are a major problem for athletic and military populations. Reported incidences are 1.4% in collegiate athletes and 8.4% among infantry units of the Finnish Army. Till date, there is still no conclusive evidence to prove any effect of BPs on stress fracture healing in humans. Alendronate and pamidronate have shown some promise in initial studies, but larger studies need to be done to accept BPs as a treatment modality for stress fractures.

**Perthe’s Disease**

Legg Calvé Perthes disease is a childhood form of osteonecrosis of the femoral head with a reported incidence of 8.5–21 per 100,000 children per year. Little et al showed that zoledronic acid improves femoral head sphericity in Perthes’s disease in rats. McQuade et al also found it useful in children with Perthe’s disease. Recently, Fanord et al proved that BPs (alendronate) modified gold nanoparticles as a useful vehicle to study the treatment of osteonecrosis of the femoral head in *in vitro* models of Perthe’s disease.

**Adverse Effects**

**Gastrointestinal Side Effects**

These side effects are predominantly seen with oral formulations (Table 2). Bisphosphonates affect all levels of the GI tract from the lower esophagus to the colon. Common side effects are mucositis, flatulence, and diarrhea. Less common side effects are erosion and ulceration in the esophagus, stomach, and duodenum. These side effects may be avoided by adhering to dosing instructions. Biswas et al in their observational study in 11,916 postmenopausal women found that the most common reasons for stopping alendronate therapy are...
Bisphosphonates in Orthopedics

Acute Phase Reaction and Musculoskeletal Pain

This side effect is basically a spectrum of various flu-like signs and symptoms, particularly mild fever (up to 38°C), weakness and exhaustion, leukocytosis, myalgia, and bone pain. These symptoms are reported commonly with use of IV formulations of amino-BPs and after the first infusion. They generally resolve within 48 hours and respond well to nonsteroidal anti-inflammatory drugs (NSAIDs) and antipyretic measures. Most authors relate this with transient release of pyrogenic cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α). The frequency and severity of acute-phase reactions to different BPs reported in clinical trials appear to vary markedly. Acute-phase reactions occur only with IV amino-BPs and may be more common with zoledronic acid. These are thought to occur because of their potential to activate human T cells. Notably, these symptoms do not recur with subsequent infusions.

Bisphosphonates-related Osteonecrosis of the Jaw (BRONJ)

This condition was reported first by Marx (2003) in 36 patients, soon after the introduction of zoledronic acid. All patients had received high doses of IV BPs for skeletal complications of malignancy. Subsequently, this condition was also reported with use of lower doses of BPs as in osteoporosis, but even in these series, 90% of cases were cancer patients. As per the working definition of BRONJ, following criteria should be fulfilled: Current or previous exposure to BPs; exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and no history of radiotherapy to the jaws.

The exact incidence of BRONJ is still unknown. The estimated incidence of BRONJ is from 0.8 to 12% with IV BPs. Other studies also indicate that nearly 95% of patients diagnosed with BRONJ are cancer patients who received more potent nitrogen-substituted IV BPs. Ruggiero et al in their retrospective analysis of patients with BRONJ found that only 11% of all patients were treated with chronic oral BPs and the rest received IV BPs. Dental interventions, such as tooth extractions, dental implants, or trauma from dentures along with poor periodontal status increase the risk of developing BRONJ.

Most of the reports of BRONJ are associated with malignancies, such as multiple myeloma or breast cancer. Durie et al reported the incidence of jaw osteonecrosis in myeloma patient as 3% with pamidronate and 10% with zolendronic acid at 36 months of therapy.

This is very surprising that BRONJ was identified mostly in individual case reports and case series and also in retrospective studies but not identified in any prospective clinical trials. In prospective clinical trials for osteoporosis or Paget’s disease with more than 60,000 patient-years, Bilezikian et al were unable to find BRONJ. The HORIZON trial by Black et al with IV zoledronic acid for osteoporosis found only two patients of osteonecrosis on retrospective review, one in the treatment group, and another in the placebo group. Recently, Borromeo et al in their case–control study found significant association of osteonecrosis of jaw with BPs treatment.

Atrial Fibrillation (AF)

The first report of increased chances of AF came from fracture intervention trial (FIT) by Merck et al in 1997. They found 47 (1.5%) serious AF adverse events among...
patients receiving alendronate vs 31 (1.0%) among those receiving placebo during an average of 4 years. This was not statistically significant and alendronate was considered to be safe from this point of view. In year 2007, a randomized controlled trial by Black et al19 demonstrated a significant risk of serious AF with IV zolindronic acid. Other studies either showed a nonsignificant trend112 or even contradictory results.20 Recently, a meta-analysis of RCTs by Mak et al113 revealed only a trend of higher AF risk in BP users than in patients on placebo. They concluded that there is no evidence of a higher risk of AF associated with BP use, but there is a probability of development of AF (this is 0.484 if the risk of AF was estimated to be more than 20%). Lewiecki et al114 in their pooled analysis of four ibandronate pivotal trials found that ibandronate is not associated with an increased incidence of AF. Similarly, many other authors were also unable to find any a significant correlation between BPs and AF.115-122

**Esophageal Cancer**

There is lot of confusion in literature regarding this side effect. Green et al123 found an increased risk (almost double) of esophageal cancers with BPs use for more than 3 years (in most cases 5 years). They found that the risk increased to 2/1000 from 1/1000 in a control population of age 60 to 79 years. In another study from the same population, Cardwell et al124 were unable to find this increased risk. They reported a combined incidence of 0.7 per 1000 person-years of risk for esophageal and gastric cancer in both the BP and control cohorts; the incidence of esophageal cancer alone in the BP and control cohorts was 0.48 and 0.44 per 1000 person-years of risk, respectively. There was no difference in the risk of esophageal and gastric cancer combined between the cohorts for any BP use or risk of esophageal cancer only. Recently, Wysowski125 addressed this issue and opined that the major difference in the two studies was the length of follow-up, with the negative study having 4.5 years and the positive one 7.7 years. The positive study also had an adequate sample size, control group, and adjustment for covariates (age; sex; smoking status; alcohol drinking; body mass index; diagnosis of osteoporosis; previous fracture; upper GI disease; and prescription of NSAIDs, corticosteroids, or acid suppressants). However, neither study validated diagnoses by medical records nor provided information on whether drugs were taken according to directions. It is now general consensus that further studies are needed on this area to confirm any of the results.126-128

**Renal Safety**

Renal side effects of BPs are mostly dose dependent. When BPs are given to patients either orally or parenterally, part of the drug is taken up by the tissues and the rest is excreted unchanged via the kidneys. Increasing the BP dose leads to an increase in the amount of drug measured in the urine. This linear relation is maintained only up to a certain point, after which further dose escalation leads to a relative decrease in the renal excretion.93 Most of the reports of this side effect come from more frequent IV doses of BPs as used in cancer treatment (zoledronic acid >> pamidronate), not seen with standard oral doses used in prevention of osteoporosis.129-138 The renal safety profile of IV ibandronate and all oral BP’s is similar to that of placebo.93,139,140

**Atypical Fractures**

On literature review, we found numerous case reports describing unusual low-energy subtrochanteric femoral fractures and pelvic insufficiency fractures in patients with long-term BP treatment. These reports are presumed to be because of the prolonged suppression of bone metabolism and problems with bone healing.141-152 These fractures are typically associated with prodromal pain in the region of the fracture and have characteristic radiographic findings, including cortical hypertrophy, a transverse and low oblique fracture pattern with medial cortical spiking. Sometimes, these fractures are bilateral.151-155 These patients usually show severe suppression of bone turnover on bone biopsy,154-161 though normal biopsy has also been reported.11 Similar conclusions have also been drawn by Tucci et al,162 Schilcher et al,163 Gunawardena et al,164 and Giusti et al.165 Czerwinski has estimated these fractures to be very rare (2.3 per 10,000 patient-years). Other authors also suggest that the number of fractures prevented by BP therapy far exceeds the number of atypical femoral fractures potentially related to BPs; so, there is no rationale in stopping the therapy.22,166,167

**SUMMARY AND CONCLUSION**

Newer BPs available for clinical use are very potent in their action and have fewer side effects. These can be given orally on daily, weekly, and monthly basis or intravenously on quarterly and yearly basis. These agents have been proven safe and effective for the prevention and treatment of osteoporosis with broad spectrum of action in fracture-risk reduction (i.e., spine, hip, and nonvertebral fractures). They are also very effective in Paget’s disease and fibrous dysplasia. Now increasing evidences are available for their use in CRPS I, AVNHF, stress fractures, and many other conditions. These agents have a special place in the treatment of solid cancers, metastatic bone diseases, and hypercalcemia of malignancy. There are ongoing studies to prove their effectiveness in childhood diseases such as Perthe’s
disease and in heterotropic calcification. There is some evidence for their effectiveness in prevention of bone collapse following AVNFH and in enhancing implant fixation with a decreased rate of osteolysis following arthroplasty.

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Bisphosphonates in Orthopedics