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REVIEW ARTICLE

Non-biological Antiresorptive: Bisphosphonates

Durairaj Arjunan[1] · Tushar Bhadada[2] · Subasri B Mohankumar[3] · Sanjay Kumar Bhadada[1,4]

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Abstract

Background Bisphosphonates, synthetic analogs of endogenous pyrophosphates, are pivotal in managing various bone disorders, primarily osteoporosis, which affects millions globally. While osteoporosis, especially postmenopausal osteoporosis, significantly benefits from bisphosphonate therapy, considerations arise regarding their administration and potential side effects.

Clinical application of Bisphosphonates Bisphosphonates, divided into nitrogen-containing and non-nitrogenous groups, exert their influence through distinct mechanisms, with the former being notably more potent. The role of bisphosphonates in other diseases, such as Paget's bone and skeletal metastasis disease is also discussed. Detailed information on the administration routes, dosage regimens, and considerations for drug holidays is provided. The article navigates through the chemical structure, generations, and mechanism of action of bisphosphonates. The article covers administration routes, dosage regimens, and drug holidays, in addition to discussing potential adverse effects and contraindications.

Conclusions Bisphosphonates hold an unrivaled legacy in the management of osteoporosis. The ubiquitous availability and the cost-effectiveness of these time-tested medications make them an invaluable asset in the osteoporosis treatment landscape, especially in developing nations like India.

Keywords Bisphosphonates · Osteoporosis · Fracture · Antiresorptive

Introduction

Bisphosphonates are an essential group of drugs used to manage various bone-related disorders, especially osteoporosis [1]. These drugs are synthetic analogs that resemble the naturally present pyrophosphate [2]. They are the most widely used antiresorptive drugs at present. They are not only used in the treatment of postmenopausal osteoporosis but also for the treatment of various other disorders such as secondary osteoporosis such as glucocorticoid-induced osteoporosis, treatment of hypercalcemia of malignancy, Paget's disease of bone, malignancy-related skeletal metastasis, multiple myeloma, osteogenesis imperfecta, etc. [1]. Initially synthesized in the nineteenth century for non-medical applications, bisphosphonates have transitioned from industrial use to the forefront of clinical osteology, particularly in treating osteoporosis and bone metastasis [3]. A class of drugs that prevent the loss of bone density, bisphosphonates act by inhibiting osteoclast-mediated bone resorption. This unique action mechanism has made them the mainstay in many bone-related pathologies where excessive bone resorption is a characteristic feature. We often encounter the debilitating impact of osteoporosis, especially postmenopausal osteoporosis and Paget's disease of bone. In these contexts, bisphosphonates have consistently demonstrated efficacy in reducing the risk of fractures.

Yet, as with all medications, bisphosphonates come with their own set of considerations. Their administration, be it oral or intravenous, requires a particular set of guidelines to maximize efficacy and minimize adverse events. Moreover, long-term use of these drugs leading on to atypical fractures,

✉ Sanjay Kumar Bhadada
bhadadask@rediffmail.com

[1] Department of Endocrinology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

[2] Department of Pharmacology, Government Medical College, Patiala, India

[3] Department of Pharmacology, Bangalore Medical College and Research Institute, Bangalore, India

[4] Department of Endocrinology, Postgraduate Institute of Medical Education and Research (PGIMER), Room No: 001, Nehru Hospital Extension, Chandigarh, India

and jaw osteonecrosis are significant concerns that have emerged over the years. This chapter is tailored to provide orthopedicians, especially those newly acquainted with the field, with a concise yet comprehensive insight into bisphosphonates. It aims to bridge the gap between basic pharmacology and its practical application in clinical orthopedics, ensuring that our patients benefit most from these agents.

Chemistry and Structure

The structure of bisphosphonates closely resembles pyrophosphate. Their system provides them with resilience against enzymatic degradation, leading to prolonged retention in the skeleton. They are classified into nitrogen-containing and non-nitrogenous groups depending on their side chains [4]. The nitrogen-containing bisphosphonates are more potent than the other group. Nitrogen-containing bisphosphonates: alendronate, risedronate, ibandronate, and zoledronic acid are nitrogen-containing bisphosphonates, and these molecules act by inhibiting the enzyme farnesyl pyrophosphate synthase, which leads to a reduction in the activity of osteoclasts resulting in inhibition of bone resorption. Non-nitrogen-containing bisphosphonates: these drugs are taken up by the osteoclast during bone resorption, and they finally lead to apoptosis of these cells. Examples are etidronate and clodronate. These drugs are in the older group and are currently less commonly used.

Bisphosphonates are characterized by two phosphonate (PO_3) groups bound to a single carbon atom, forming a P–C–P bond, which is central to their strong affinity for hydroxyapatite crystals in bone, while the pyrophosphates are rapidly degraded by enzymatic action in the body, the P–C–P bond in bisphosphonates makes them resistant to such hydrolysis, ensuring their longevity in bone tissues; moreover, the side chains attached to the central carbon of these compounds dictate their potency and mechanism of action, with non-nitrogenous bisphosphonates (like etidronate) being metabolically incorporated into non-hydrolysable analogs of ATP, ultimately leading to osteoclast apoptosis[1], whereas the more contemporary nitrogen-containing bisphosphonates (such as alendronate and zoledronate) interfere with the mevalonate pathway, impairing the function and survival of osteoclasts [1]; it is this structural distinction that not only impacts their antiresorptive potency–with nitrogen–containing variants being markedly more potent—but also influences their pharmacokinetic properties, as the latter tend to have a longer duration of action and are preferentially used in the current clinical settings; understanding this nuanced chemistry and structure is crucial for orthopedicians, as it directly informs the pharmacological basis of bisphosphonate efficacy, duration, and side-effect profile in bone pathologies.

Generations of Bisphosphonates

These drugs are chelating agents of divalent cations like calcium, and they have a strong affinity for bone.

First-Generation Drugs

Medronate, Clodronate, Etidronate, and Tiludronate.

The initial generation of compounds either consists of modified side chains or includes a chlorophenol group.

These agents are the least potent among the available drugs.

Second-Generation Drugs

This includes Alendronate and Pamidronate.

These drugs feature a nitrogen group within their side chains.

This makes them 10–100 times more powerful than the initial drug generation.

Third-Generation Drugs

Includes drugs like Risedronate and Zoledronate.

These drugs incorporate a nitrogen atom within a heterocyclic ring.

Hence, rendering them 10,000 times more potent than the first-generation counterparts.

Mechanism of Action

Bisphosphonates bind to the hydroxyapatite in bone avidly and, hence, are ingested by the osteoclasts during bone resorption. As mentioned earlier, the nitrogen-containing bisphosphonates lead to inhibition of the enzyme farnesyl pyrophosphate, and the non-nitrogen-containing bisphosphonates cause osteoclast apoptosis. These drugs also get incorporated into the matrix and prevent hydroxyapatite dissolution, but the major antiresorptive effect is due to the effect on osteoclast and also the inhibition of the enzyme farnesyl pyrophosphate synthase.

Pharmacokinetics and Pharmacodynamics

Oral bisphosphonates have very poor oral bioavailability ranging from 1 to 6%, and this is still less when taken along with calcium antacids or iron. Bisphosphonates do not undergo any hepatic clearance [5]. These drugs are eliminated without undergoing changes by the kidneys. The rate at which the drug is cleared from the body is directly linked to renal function, making it advisable to avoid bisphosphonates in individuals with a creatinine clearance of less than 30 ml/min [6].

Clinical Applications

Osteoporosis is the primary indication for the use of these drugs, and they are also used in many other disorders (Table 1).

Osteoporosis

In clinical practice, bisphosphonates are frequently prescribed for osteoporosis, a condition characterized by compromised bone strength, leading to an elevated fracture risk [7]. There is a disrupted equilibrium between the bone resorption mediated by osteoclasts and bone formation mediated by osteoblasts, resulting in heightened bone resorption in osteoporosis, decreased skeletal mass, degraded skeletal microarchitecture, and increased fracture risk [8]. Alendronate and risedronate are oral bisphosphonates that decrease vertebral and hip fractures [9–12]. Ibandronate is available in oral and intravenous formulations and is associated with reducing the risk of predominantly vertebral fractures [13, 14]. The US FDA approved both ibandronate and zoledronate for intravenous therapy for osteoporosis. Ibandronate is given quarterly intravenously, whereas zoledronate is given yearly once. Zoledronate reduces the incidence of vertebral (70%), hip (41%), and non-vertebral fractures (25%) [15]. Zoledronate also increases the BMD at the total hip, femoral neck, and lumbar spine [15]. Given the efficacy of zoledronate and ease of administration of the drug, it has become the mainstay of treatment of postmenopausal osteoporosis, especially in patients with poor adherence to treatment and intolerance to oral bisphosphonates. Combining selective estrogen receptor modulator raloxifene increases the BMD, but there are no clinical trial data on the risk of fractures in combination therapy [16, 17]. Prior bisphosphonate treatment tends to diminish the anabolic effects induced by teriparatide, with the most potent anabolic responses observed in patients initially treated with PTH, followed by maintenance with bisphosphonate therapy [18, 19].

Table 1 Indications of bisphosphonates

Post-menopausal osteoporosis
Secondary osteoporosis
Paget's disease of the bone
Hypercalcemia of malignancy
Skeletal metastasis
Multiple myeloma
Osteogenesis imperfecta
Fibrous dysplasia
Pachydermoperiostosis
Primary hyperparathyroidism
Giant cell tumor of bone

Glucocorticoid-Induced Osteoporosis (GIO)

Bisphosphonates are effective in mitigating bone loss in glucocorticoid-induced osteoporosis. Bisphosphonates are indicated in both the prevention and treatment of GIO. Also, multiple studies have demonstrated that bisphosphonates are effective in preventing bone loss in both hematopoietic stem cell transplant and solid organ transplantation. Bisphosphonates are recommended in patients who are receiving long-term glucocorticoids [20].

Paget Disease of Bone

Paget's disease of the bone is marked by localized areas of disorganized bone remodeling, where bone resorption by osteoclasts is succeeded by flawed bone deposition by osteoblasts [1, 21]. This leads to elevated alkaline phosphatase levels in these patients and alternative areas of lytic and sclerotic bone noted on radiology. The complications include bony pain, deformities, and increased fracture risk in these individuals [22]. Bisphosphonates reduced osteoclastic activity, leading to the normalization of alkaline phosphatase in these patients[23].

Fibrous Dysplasia

Paget's disease is a condition characterized by the abnormal remodeling of bone tissue. In this condition, the normal bone is replaced by abnormal fibrous tissue, leading to bone deformities, bony pain, and fractures. Both systemic bisphosphonates and also intralesional bisphosphonates have been tried for this condition [24].

Malignancy

Patients with advanced malignancy such as carcinoma breast, prostate, lung, or multiple myeloma may present with various skeletal metastases. This, in turn, results in hypercalcemia, bony pain, and fracture.

Administration of Bisphosphonates

Oral Alendronate and risedronate are the two currently available bisphosphonates.

Table 2 Dosage and frequency of common bisphosphonates

Bisphosphonates	Dosage	Frequency
Alendronate	10 mg PO	Daily
	70 mg PO	Weekly
Risedronate	5 mg PO	Daily
	35 mg PO	Weekly
	150 mg PO	Monthly
Ibandronate	150 mg PO	Monthly (Oral)
	3 mg IV	Every three months (IV)
Zoledronic acid	5 mg IV	Yearly (For osteoporosis)
	4 mg IV	Every 3–4 weeks (For cancer-related indications)
Etidronate	200–400 mg PO	Daily for 14 days in a 90-day cycle
Clodronate	1600 mg PO	Daily (Oral)
	300 mg IV	Daily (IV)

Intravenous For patients who are intolerant to oral bisphosphonates or non-compliant patients, intravenous bisphosphates are a better choice. Among the IV bisphosphonates, zoledronic acid is the most prescribed drug. Previous clinical trials have shown that all these drugs are efficacious in improving BMD in men and women with osteoporosis and reducing vertebral fractures, hip fractures, and non-vertebral fractures in patients with osteoporosis [25]. The various routes of administration and dose and frequency are shown in Table 2.

Instructions to be Given to Patients Who Take Oral Bisphosphonates

Oral bisphosphonates have very poor bioavailability, and hence, they should be taken on an empty stomach after an overnight fast. They must take oral bisphosphate with a full glass of water and stay upright for at least 30 min following drug intake. It is important to consume them with tap or filtered water, avoiding using mineral water. For individuals with an active upper gastrointestinal condition, oral bisphosphonates should be avoided, and intravenous formulations are the preferred choice in such cases. Oral drugs can be given daily, weekly, or even monthly, depending on the drugs (Table 2).

Palmidronate, ibandronate, and zoledronate are the drugs given intravenously. Ibandronate is given at a dose of 3 mg IV 3 monthly, whereas zoledronate is given at a dose of 5 mg once yearly (Table 3).

Table 3 Contraindications of bisphosphonates

Contraindication	Description
Hypocalcemia[1]	Bisphosphonates can further lower calcium levels
Esophageal abnormalities[2]	Risk of esophageal irritation or ulceration
Inability to stand or sit upright[3]	To prevent the medicine from causing esophageal irritation
Renal impairment[4]	Risk due to potential drug accumulation and adverse effects
Known allergy	Hypersensitivity to bisphosphonates or their components
Pregnancy and lactation	Potential fetal risk. Unknown if excreted in human milk
Atypical femur fractures[5]	Might need to discontinue therapy
Osteonecrosis of the jaw (ONJ)[6]	Rare risk associated with bisphosphonate use
Gastrointestinal issues[7]	Increased risk of esophageal side effects from oral bisphosphonates

[1]Ensure correction of calcium levels before initiating therapy

[2]Includes conditions like stricture or achalasia that delay esophageal emptying

[3]Patients should be able to stand or sit upright for at least 30 min after taking oral bisphosphonates

[4]Dosage adjustments and careful monitoring may be necessary depending on the degree of renal impairment

[5]Particularly relevant if the fracture is suspected to be linked to bisphosphonate therapy

[6]Recommended dental check-ups before initiating therapy, especially if invasive dental procedures are planned

[7]Patients with active gastritis or reflux might be more susceptible

For intravenous drugs, zoledronate is the most commonly prescribed drug, and it is administered intravenously for over 15 min. Antipyretics might be issued if the patient experiences flu-like symptoms or fever.

Side Effects

Mild Adverse Effects

Oral bisphosphonates Heartburn, esophageal irritation, esophagitis, rarely pain abdomen, and diarrhea. Oral bisphosphonates may cause reflux esophagitis; hence, they should be taken upright, and the patient should maintain this for at least 30 min [26].

Patients might encounter flu-like reactions after the initial dose of bisphosphonate therapy. This is the most common adverse effect of bisphosphonates. Skin flushing, muscle aches, nausea, vomiting, abdomen discomfort, and altered bowel habits (diarrhea or constipation) are more common at higher concentrations or when given rapidly, and they usually do not recur on repeated administration [27].

Severe Adverse Effects

Hypocalcemia and nephrotoxicity Side effects such as severe hypocalcemia is rare but can be caused by zoledronate.

It may cause nephrotoxicity. Hence, all patients should have renal function tests to be done before starting zoledronate [28, 29].

Atrial fibrillation All patients should be examined for an irregular pulse, and getting an ECG before administering the drug is a good practice [30].

Osteonecrosis of the jaw This is a severe adverse effect of bisphosphonates. The incidence is 2 in 100,000 patient-years. This adverse effect is more common in patients with malignancy who receive very high doses of bisphosphonates, with an incidence of 1–2% in these patients. However, this is rare in patients who are treated for osteoporosis. In our center, we routinely get dental evaluation for all patients before starting any bisphosphonate therapy [31].

Atypical femoral fractures can also be associated with bisphosphonates, most commonly with alendronate and rarely with zoledronate [32, 33].

Contraindications

Esophageal disorders: Oral bisphosphonates are contraindicated in esophageal conditions, such as achalasia cardia, Barret's esophagus, esophageal strictures, and esophageal varices.

Patients who underwent gastrointestinal tract surgery, like bariatric surgery.

Chronic kidney disease—contraindicated with eGFR < 30 to 35 ml/min.

Combination Therapy of Bisphosphonates with Teriparatide

Administration of teriparatide with bisphosphonates: teriparatide stimulates bone formation, and bisphosphonates prevent resorption; hence, it is hypothesized that combining both would have an additive effect. However, studies have shown that bisphosphonate provides no additional benefit in BMD or even prevents the increase in BMD by teriparatide. The data regarding fractures in combination therapy have yet to be made available [34].

Drug Holidays

While bisphosphonates stand as a cornerstone in osteoporosis treatment, the extended utilization of these drugs has raised concerns regarding possible long-term adverse outcomes, including osteonecrosis of the jaw and atypical femoral fractures. Consequently, the concept of a "drug holiday" has emerged for these patients, following a thorough risk assessment [35]. Also, these drugs accumulate within the bone matrix after years of administration, providing long-term anti-osteoporotic effects even after discontinuation. A drug holiday is recommended after 5–7 years of therapy with bisphosphonates. In the provision of drug holidays, the following factors are considered: duration of treatment, fracture risk, and other medical conditions. Bisphosphonates are resumed if the patient develops osteoporotic fractures or deterioration in bone health.

Conclusion

Bisphosphonates hold an unrivaled legacy in the management of osteoporosis. The ubiquitous availability and the cost-effectiveness of these time-tested medications make them an invaluable asset in the osteoporosis treatment landscape, especially in developing nations like India. While newer antiresorptive drugs, such as denosumab, show promising potential, bisphosphonates still anchor the therapeutic approach due to their accessibility and affordability. It is essential, however, to be aware of their side effects. While the most frequent adverse reaction is a flu-like febrile response, severe side effects, albeit rare, necessitate vigilant monitoring.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study informed consent is not required.

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