Review Article

Dental management of patients receiving bisphosphonate therapy - A review

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Abstract

Bisphosphonates, synthetic (Non-biodegradable) analogues of pyrophosphate, were initially used in industry as water softening agents in irrigation systems and lateron discovered as bone loss inhibitors. Bisphosphonates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of the bone-resorbing osteoclasts. Thus, they have been proposed in the management of periodontal diseases by inhibiting the osteoclastic bone resorption and hence are used as a host modulating factor for prevention of bone loss. The other indications being Osteoporosis , Paget's disease, Malignant hypercalcemia , Bone metastasis, Multiple myeloma etc. Gastro intestinal intolerance, Renal and hepato-toxicity, Hypocalcaemia, Osteonecrosis of jaws seen especially after invasive dental treatment (called as Bisphosphonate related osteo-necrosis of jaw, BRONJ) are the main side effects of bisphosphonate therapy. To overcome such effects during dental management of patients, the recommendations focus on conservative surgical procedures, proper sterile technique, appropriate use of oral disinfectants and the principles of effective antibiotic therapy. The dentist should retain in his/her file the acknowledgment and consent for the treatment.

Key words

Bisphosphonate, BRONJ, Bone resorption, Osteonecrosis.

Introduction

Bisphosphonates are designed as synthetic (Non-biodegradable) analogues of pyrophosphate, initially used in industry as water softening agents in irrigation systems in the earlier 1920s and after that the medical use of the bisphosphonates came into existence. Etidronate was the first bisphosphonate for medical use. In 1969, bisphosphonates were discovered as bone loss inhibitors. Initial launch of Fosamax (alendronate) was done by Merck & Co. in 1990.

Structure

The long side-chain (R2 in the diagram) determines the chemical properties, the mode of action and the strength of bisphosphonate drugs. The short side-chain (R1), often called the 'hook', mainly influences chemical properties and pharmacokinetics.

Bio-Availibility

Chemical adsorption occurs onto the hydroxyapatite. Cellular uptake is by osteoclasts, macrophages, tumor cells, etc. Less than 1% of the oral dose is absorbed and GI absorption is suppressed by food intake. For a more rapid and effective action, bisphosphosphonates can be given by IV infusion. Pharmacokinetics is complex; bisphosphonates remain attached to bone for weeks to months [1].

It usually takes between 6-12 months for bisphosphonates to work, and they are normally taken for at least five years (some people take them for much longer). Always taken with a full glass of water on an empty stomach, and one must stand or sit upright for 30 minutes after it is taken because Oral bisphosphonates can cause upset stomach and inflammation and erosions of the esophagus, which is the main problem of oral N-containing preparations . Wait between 30 minutes and 2 hours before you eat any food or have any other drinks.

Classification

According to chemical structure:-

- Alkyl side chains (Etridonate)
- Amino side chains (Alendronate)
- Cyclic chains (Zelandronate)

They can also be classified as:

- Nitrogenous compounds which include Pamidronate, neridronate, Olpadronate
- Non-nitrogenous compounds which include Etidronate, Clodronate, Tiludronate.

Mechanism of Action

Bisphosphonates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of the bone-resorbing osteoclasts. Bisphosphonates are internalized by osteoclasts and interfere with specific biochemical processes. Bisphosphonates can be classified into at least two groups with different molecular modes of action. The simpler non-nitrogen-containing bisphosphonates (such as clodronate and etidronate) can be metabolically incorporated into non-hydrolyzable analogues of adenosine triphosphate (ATP) that may inhibit ATP-dependent intracellular enzymes. The more potent, nitrogen-containing bisphosphonates (such as pamidronate, alendronate, risedronate, ibandronate, and zoledronate) are not metabolized in this way but can inhibit enzymes of the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds that are essential for the post-translational modification of small GTP-binding proteins (which are also GTPases) such as rab, rho, and rac. The inhibition of protein prenylation and the disruption of the function of these key regulatory proteins explain the loss of osteoclast activity and induction of apoptosis. The key target for bisphosphonates is farnesyl pyrophosphate synthase (FPPS) within osteoclasts, and the recently elucidated crystal structure of this enzyme reveals how BPs bind to and inhibit at the active site via their critical N atoms [2].

Indications

FDA approved Indications of bisphosphonate therapy are:-

- Osteoporosis
- Paget's disease
- Malignant hypercalcemia
- Bone metastasis
- Multiple myeloma
- Primary hyperparathyroidism
- Osteogenesis imperfecta
- Carcinoma of breast.

Their use also has been proposed in the management of periodontal diseases by inhibiting the osteoclastic bone resorption and hence is used as a host modulating factor for prevention of bone loss [3].

Contraindications

Sensitivity to phosphate, GI upset, Parathyroid dysfunction, Pregnant or breast feeding mothers, Kidney or hepatic trouble, Hypocalcemia, Poor Oral Hygiene and Active Endodontic/ Periodontal Disease [4].

Side effects

- Gastro intestinal intolerance, e.g., drug induced oesophagitis
- Renal toxicity
- Hypocalcaemia caused by reduced bone resorption leading to reduced calcium efflux from bone
- Hepatotoxicity
- Acute phase reaction- transient and manageable
- Ocular inflammation
- Dermatologic reactions
- Osteonecrosis of jaws seen after tooth extraction because of over suppression of bone turnover
- Changes in White blood cell count
- Atrial fibrillation [5]

Osteo-Radio Necrosis Of Jaw - the main complication in dentistry-was first recognized in 2003 as a complication of bisphosphonate therapy, called as Bisphosphonate related osteo-necrosis of jaw (BRONJ) [6]. Higher frequency in the mandible (63%) than in the maxilla (38%) is observed. BRONJ can be related to dental treatment, dental pathology denture irritation or wear spontaneous with dental etiology or can be unrelated to any of the above or can be related to local trauma or can occur in a subgroup of oncological patients (multiple myeloma, breast, prostate, lung cancer bone metastases) receiving prolonged treatment with potent bisphosphonates (i.e. monthly IV administration) [7].

According to the updated 2009 BRONJ Position Paper published by the American Association of Oral and Maxillofacial Surgeons, both the potency of and the length of exposure to bisphosphonates are linked to the risk of developing bisphosphonate-associated osteonecrosis of the jaw [8].

Stages of Osteo-necrosis of jaw- Characterized by exposed bone that is asymptomatic with no evidence of significant soft tissue infection (**Stage - 1**), Exposed bone associated with pain, soft tissue and/or bone infection (**Stage - 2**), Exposed bone associated with soft tissue infection or pain that is not manageable with antibiotics due to the large volume of necrotic bone and pathological fracture (**Stage 3**).

Risk factors for Osteo-necrosis of jaw [9]- Poor oral hygiene, Dental procedures (tooth extractions, RCT, Periodontal surgery, implants), Chemotherapy, Corticosteroid use, Coagulopathies, Immunosuppression, Local cancerous invasion, Local radiation therapy, Heavy nicotine use, Oral herpes infection.

Dental Management of Patients Receiving Oral Bisphosphonate Therapy

The recommendations focus on conservative surgical procedures, proper sterile technique, appropriate use of oral disinfectants and the principles of effective antibiotic therapy. Because of a paucity of clinical data on the dental management of patients on oral bisphosphonate therapy, these recommendations primarily are based on expert opinion, intended to help dentists make clinical decisions.

General recommendations

Routine dental treatment generally should not be modified solely due to use of oral bisphosphonates. All patients should receive routine dental examinations. All patients taking the drug should be informed that:

- Oral bisphosphonate use places them at very low risk for developing BRONJ.
- The low risk for developing BRONJ may be minimized but not eliminated.
- An oral health program consisting of sound oral hygiene practices and regular dental care may be the optimal approach for lowering the risk for developing BRONJ.
- There is no validated diagnostic technique currently available to determine if patients are at increased risk for developing BRONJ.
- Discontinuing bisphosphonate therapy may not eliminate any risk for developing BRONJ.

The patient also should be informed of the dental treatment needed, alternative treatments, how any treatment relates to the risk of BRONJ and the patient should be encouraged to consult with his/her physician about health risks associated with discontinuation of bisphosphonate treatment. Since BRONJ can occur spontaneously, due to dental disease or secondary to dental therapy, therefore, patients taking oral bisphosphonates should be instructed to contact their dentist if any problem develops in the oral cavity. The dentist should retain in his/her file the acknowledgment and consent for the treatment.

Management of periodontal diseases

Bisphosphonate users who have active periodontal diseases should receive appropriate forms of non-surgical therapy, which should be combined with the commonly recommended re-evaluation at four to six weeks. If the disease fails to resolve, the goal of surgical treatment should be to obtain access to root surfaces. When necessary, modest bone re-contouring techniques should be used.

At this time, there is no evidence that, periodontal procedures such as guided tissue regeneration or bone replacement grafts increase or decrease the risk for BRONJ or success of implant treatment. Use of such techniques should be judiciously considered based on patient need. Primary soft tissue closure following periodontal surgical procedures is desirable, when feasible. Patients without periodontal disease should receive preventive therapy for periodontal disease. Patients should be regularly monitored.

Implant placement and maintenance

There is a paucity of data on the effects of implant placement in patients taking oral bisphosphonates [10]. Because implant placement requires the preparation of the osteotomy site, treatment plans should be carefully considered. The patient may be at increased risk for BRONJ when extensive implant placement or guided bone regeneration is necessary to augment the deficient alveolar ridge prior to implant placement. Before implant placement, the dentist and the patient should discuss the risks, benefits and treatment alternatives. Maintenance of implants should follow accepted mechanical and pharmaceutical methods to prevent peri-implantitis, with regular monitoring of the patient.

Oral and maxillofacial surgery

When treatment of dental and/or periodontal diseases has failed, surgical intervention may be the best alternative. Patients receiving oral bisphosphonates who are undergoing invasive surgical procedures should be informed of the risk, although small, of developing BRONJ. Alternative treatment plans should be discussed with the patient, which include:

- Endodontics (including endodontic treatment followed by removal of the clinical crown),
- Allowing the roots to exfoliate (instead of extraction),
- Bridges and partial dentures (instead of implant placement).

If extractions or bone surgery are necessary, conservative surgical technique with primary tissue closure, when feasible, should be considered. In addition, immediately before and after any surgical procedures involving bone, the patient should gently rinse with a chlorhexidine until healed. The regimen may be extended based on the patient's healing progress.

Periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis and active abscesses that already involve the medullary bone all may exacerbate osteonecrosis. These areas should be treated immediately. When dental pathoses are not evident, the trial sextant approach may be applicable. The sextant by sextant approach does not apply to emergency cases, even if multiple quadrants are involved.

Prophylactic antibiotics after a surgical procedure should be based on the risk of an infection and NOT because the patient is taking a bisphosphonate. There is no evidence that the use of antibiotics is effective in preventing BRONJ.

Endodontics

Endodontic treatment is preferable to surgical manipulation if a tooth is salvageable. Routine endodontic technique should be used. Manipulation beyond the apex is not recommended. In some situations, depending on risk, endodontic treatment of non-restored teeth after removal of the clinical crown, which allows passive exfoliation of the root tip, may be considered.

Restorative dentistry and Prosthodontics

There is no evidence that malocclusion or masticatory forces increase the risk for BRONJ. All routine restorative procedures may be conducted. Prosthodontic appliances in patients should be promptly adjusted for fit in order to avoid ulceration and possible bone exposure.

Orthodontics

There are no published studies examining the effect of bisphosphonates on orthodontia. Case reports have recounted inhibited tooth movement in patients taking bisphosphonates [11-13]. Patients should be advised of this potential complication.

CTX testing

Recently, the use of serum levels of the collagen breakdown product, C-terminal cross-linking telopeptide of type I collagen (CTX), has been advocated as a risk predictor for developing BON. Serum CTX and urinary N telopeptide of type I collagen (NTX) are considered markers for bone resorption. Higher levels of these markers are associated with active bone turnover. Reports suggest that dental treatment decisions should be based on the results of serum CTX/NTX levels [14, 15].

References

1. Ezra A, Golomb G. Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. Adv Drug Deliv Rev., 2000; 42: 175-95.
2. Hughes, et al., International Journal of Applied Biology and Pharmaceutical Technology 2012; 3(3): 103-108.
3. Maria Emanuel Ryan and Phillip M. Preshaw, Host Modulation, In Carranza's Clinical Periodontology, 10th Edition, 2007, p. 275-282.
4. Nase JB, Suzuki JB. Osteonecrosis of the jaw and oral bisphosphonate treatment. JADA, 2006; 137(8): 1115-9
5. DM Black, et al. Once-yearly Zoledronic acid for treatment of post -menopausal osteoporosis. N Engl J Med., 2007; 356(18): 1809–1822.
6. Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SK. Managing the care of patients with bisphosphonate associated necrosis. JADA, 2005; 136: 1658-68.
7. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of jaws associated with the use of

bisphosphonates: A review of 63 cases. J Oral Maxillofac Surg., 2004; 62: 527-34.
8. AAOMS Updates BRONJ Position Paper, January 23, 2009.
9. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-Induced Exposed Bone (Osteonecrosis/ Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment. J Oral Maxillofac Surg., 2005; 63: 1567-1575.
10. Wang HY, Weber D, McCauley LK. Effect of Long-Term Oral Bisphosphonates on Implant Wound Healing: literature Review and a case report. J Periodontol., 2007; 78(3): 584-94.
11. Schwartz JE. Ask us: Some drugs affect tooth movement. Am J Orthod Dentofacial Orthop., 2005; 127: 644.
12. Rinchuse DJ, Rinchuse DJ, Sosovicka MF, Robison JM, Pendleton R. Orthodontic treatment of patients using bisphosphonates: A report of 2 cases. Am J Orthod Dentofacial Orthop., 2007; 131: 321-6.
13. Adachi H, Igarashi K, Mitani H, Shinoda H. Effects of topical administration of a bisphosphonate (risedronate) on orthodontic tooth movements in rats. J Dent Res., 1994; 73: 148-184.
14. Marx RE. Oral & Intravenous Bisphosphonate–Induced Osteonecrosis of the Jaws: History, Etiology, Prevention, and Treatment. Hanover Park, IL: Quintessence; 2006.
15. Marx RE, Cillo JE, Ulloa JJ. Oral Bisphosphonate-Induced Osteonecrosis: Risk Factors, Prediction of Risk Using Serum CTX Testing, Prevention, and Treatment. J Oral Maxillofac Surg., 2007; 65: 2397-410.