ejpmr, 2019,6(2), 588-593

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

DENTAL CONSIDERATIONS IN PATIENTS ON BISPHOSPHONATES- A REVIEW

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Article Received on 21/12/2018 **Article Revised on 11/01/2019** **Article Accepted on 01/02/2019**

INTRODUCTION

Bisphosphonates are the group of drugs that prevent bone resorption and hence are used to treat various diseases and conditions involving bone fragility like osteoporosis, Paget's disease, hypercalcaemia of malignancy and multiple myeloma.[1]The "bis" prefix is a term indicating two - phosphonate groups, attached to a common carbon atom. These are structurally similar to natural pyrophosphate (PP), which is a normal product of human metabolism that has a calcium chelating property.[2]

There are 2 types of bisphosphonates: nitrogen containing and non-nitrogen containing. Nitrogen-containing side chain increases potency and toxicity. Nitrogen containing bisphosphonates accumulate in maximum concentration in the matrix and osteoclasts.[3]

Bisphosphonates can be administrated intravenously (IV) and orally. With the oral administration only 1% of the dose is absorbed by gastrointestinal tract whereas with IV mode more than 50% of the dose administered is bio-available, which makes IV dose more potent.[4,5] The major uses of intravenous bisphosphonates are to reduce bone pain, Paget's disease, hypercalcaemia of malignancy, myeloma etc. Oral bisphosphonates are mainly used for treatment of osteoporosis, osteogenesis imperfecta.

The mechanism of action is due to the high affinity of bisphosphonates for bone minerals and strong binding to hydroxyapatite resulting in selective uptake to the target organ and high local concentration in bone, particularly at the sites of active bone remodelling. The major actions of bisphosphonates is to inhibit the osteoclast differentiation, reduce the osteoclastic activity, and induce osteoclast apoptosis.[6]

Bisphosphonates are divided into three generations. Their potency levels, mode of administration and main indications of drugs are described in Table 1.

Table 1: Bisphosphonates: Potency, administration, and main indications.

Generation	Potency	Administration	Main indication
Etidronate of bone	1	Oral	Osteoporosis, paget's disease
Clodronate	10	Oral/intravenous	Osteoporosis,paget's disease of bone
Second			
Pamidronate	100	Intravenous	Osteolytic bone metastasis of breast cancer and osteolytic lesions of multiple myloma, paget's disease of bone
Alendronate	500	Oral	Osteoporosis, paget's disease of bone
Ibandronate Third	1000	Oral/intravenous	Osteoporosis
Risedronate	2000	Oral/ intravenous	Osteoporosis, paget's disease of bone, osteolytic lesions of multiple myeloma, hypocalcemia of malignancy
Zoledronate	10000	Intravenous	osteolytic lesions of multiple myeloma, and metastases from solid tumors, hypocalcemia of malignancy.

And types and mode of action of bisphosphonates are described in Table 2.

Table 2: Bisphosphonates; types and mode of action.

Type	Example	Mode of action
NNBPs (non-nitrogen bisphosphonates)	Etidronate Clodronate Tiludronate	Formation of an ATP deivative that impairs osteoclast function and induces osteoclastic apoptosis
Aklyl- amino NBPs (nitrogencontaining bisphosphonates)	Pamidronate Alendronate Ibandronate olpadronate	Inhibits sterol synthesis via the mevalonate pathway, specifically inhibiting its famesyl diphosphate synthase enzyme
Heterocyclic NBPs(nitrogencontaining bisphosphonates)	Risedronate zoledronate	Inhibitsfarnesyldiphosphate enzyme and stabilize conformational changes

Adverse effects of bisphosphonates

GIT complications: Oral bisphosphonates may induce various adverse effects like recurrent ulcers with burning sensation and blisters in the oral cavity, erosive esophagitis, esophageal stenosis, stomach upset with ulceration, and abdominal pain. Alendronate may cause upper gastrointestinal upset due to gastro‑esophageal reflux and acidification of the esophagus. To avoid this patient should take alendronate with a glass of water at least half an hour before the meal and remain upright for an hour.[7,8]

Acute systemic inflammatory reactions: Intravenous infusion of bisphosphonates occasionally causes fever, myalgia, arthralgia, nausea, vomiting, and edema. Accompanying bone pain has also been seen in some patients.[9,10] Acute dyspnea and pneumonitis have also been reported with Pamidronate infusion in children with osteogenesis imperfecta, who have underlying pulmonary disease.[9,10] Supportive and symptomatic management with Non‑steroidal anti‑inflammatory drugs (NSAIDs) and acetaminophen is sufficient to resolve the symptoms completely in 24-48 hrs.[9,11]

Ocular complication: Orbital inflammation is most serious complication among the ocular effects followed by conjunctivitis, uveitis, scleritis, episcleritis and eyelid edema. In some cases, hypopyon, chemosis or proptosis indicating uveitis may also occur.[9,12,13] There may be periorbital edema and erythma causing orbital cellulitis. Vision can rapidly deteriorate due to oculomotor and trochlear nerve palsy.[9,12,13]

Renal complications: It has been reported that patients who are taking zoledronic acid and pamidronate are prone to acute and chronic renal failure. Renal failure is more common with zoledronic acid and hence is contraindicated in patients with severe renal impairment.[10] Pamidronate is basically associated with nehprotic syndrome, tubulo interstitial nephritis, and Fanconi's syndrome.[7] Discontinuation of bisphosphonates and other preventive measures like adequate hydration, avoiding concurrent nephrotoxic agents, reducing the dose for patients with mild renal insufficiency and with holding treatment in the presence of renal deterioration is the suggested treatment in such cases. Pamidronate can be safely used for short term treatment of hypocalcemia among patients already undergoing dialysis and zoledronic acid can be safely resumed when serum creatinine level returns within 10% of baseline but it should be stopped permanently if no improvement is seen after 4‑8 weeks.[7]

Electrolyte abnormalities: The incidence of hypocalcemia and hypophosphatemia increases in patients with multiple myeloma or those with bone metastases from breast cancer treated with pamidronate.[9] Signs and symptoms may include peri‑oral paresthesia, tetany, carpopedal spasm, and QT prolongation but non‑specific lethargy, shakiness, tingling or weakness can only be the presenting symptoms.[13] Daily calcium and vitamin D supplementation is recommended during treatment with zoledronic acid, but hypocalcemia can still occur.[13]

Anti‑angiogenesis: The serum levels of vascular endothelial growth factor (VEGF) levels and cytokines involved in angiogenesis have been found to decrease after administration of zoledronate and pamidronate.[14] Significant anti‑angiogenic effect with nitrogen containing bisphosphonates has been reported by some authors.

Bisphosphonate Related Osteonecrosis of Jaws (BRONJ)

Osteonecrosis of jaw was an endemic condition among the workers of phosphorus‑containing match factories in 1800s. The first case of bisphosphonate related osteonecrosis of jaws (BRONJ) was reported by Marx in 2003. He observed painful exposed bone in mandible, maxilla or both jaws in 36 patients who were treated with intravenous bisphosphonates. Many more reports on bisphosphonate associated osteonecrosis of jaws were published later on. **(Fig 1).**

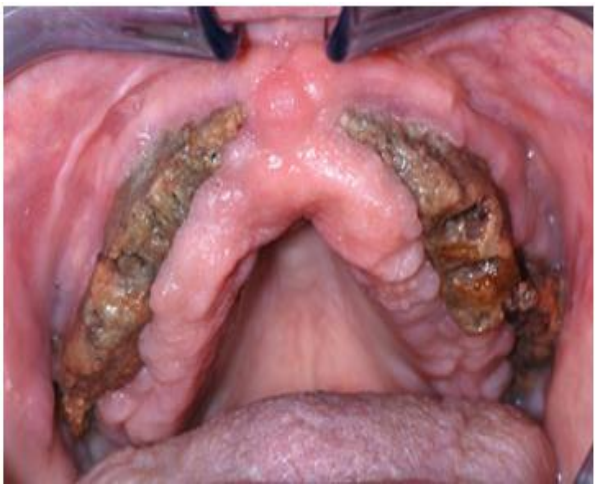

Fig. 1: Necrosis of Maxilla.

Pathogenesis of BRONJ

Bisphosphonates target osteoclasts and osteoclast mediated bone remodeling is suppressed through disruption of intracellular pathways leading to BRONJ. Suppression of bone vasculature due to the antiangiogenic effects of bisphosphonates contributes to BRONJ. Infection could contribute to BRONJ by enhancing osteoclast-independent bone resorption. Typically, the exposed bone is secondarily infected by Actinomyces species and other microflora in the oral cavity. Various other cofactors such as comorbidities (e.g. diabetes,[15]), lifestyle factors (e.g. smoking and obesity,[16]), interventions (e.g. dental extraction,[17]), and concurrent medications (e.g. corticosteroids) have all been associated with BRONJ. These cofactors individually do not cause bone necrosis of the jaws but in the presence of bisphosphonates play a significant role in the pathophysiology of BRONJ. Patients who are on oral bisphosphonate are considered safer than patients who are taking bisphosphonates intravenously. The incidence of BRONJ with intravenous bisphosphonate ranges from 0.8% to 12%.[18–25] Oral bisphosphonate is associated with lower incidence of BRONJ ranging from 0.01% to0.04%.[16] This increases to 0.09%–0.34% following extractions.

Radiologic Finding of BRONJ

The radiologic findings of BRONJ are not specific and mimic other conditions such as osteomyelitis, osteoradionecrosis, cancer metastasis and Paget's disease. Periapical radiograph and orthopantogram findings include thickening of the lamina dura, osteolysis, diffuse sclerosis, narrowing of the mandibular canal and poor healing or non-healing of extraction sites.[27–29] **(Fig 2,3).**

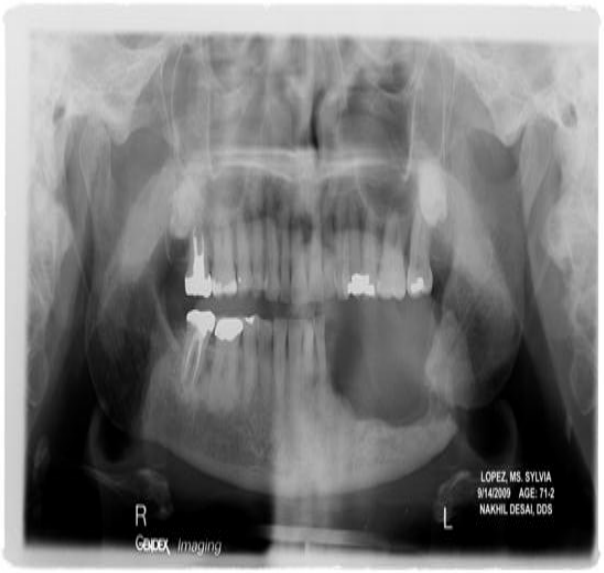

Fig. 2: Radiograph of Pathological Fracture In Mandible Due To Bronj.

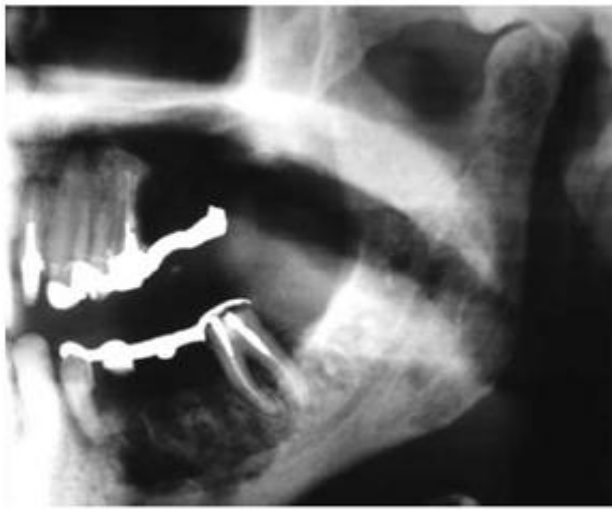

Fig. 3: Radiograph Showing Osteonecrosis In Mandible.

Definition and Staging of BRONJ

According to the definition proposed by the American Association of Oral and Maxillofacial surgeons, BRONJ is defined as the exposed necrotic bone in the maxillofacial region that has persisted for more than eight weeks in patients with current or previous treatment with a bisphosphonate and with no history of radiation therapy to the jaws.

There are four stages of BRONJ, which are as follows

Stage 0: Defines signs and symptoms short of exposed necrotic bone in patients that might indicate a histological necrosis or a prenecrotic state.

Stage 1: Defines exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.

Stage 2: Defines exposed/necrotic bone in patients with pain and clinical evidence of infection.

Stage 3: Defines exposed/necrotic bone in patients with pain, infection and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border.

Strategy for Management of Patients on Bisphosphonates

Routine dental treatment can be provided to low risk patients while high risk patients may be referred to an oral and maxillofacial surgeon or dental specialist who has experience in managing suchpatients.

High-risk patients include

- Cancer patients on intravenous bisphosphonate
- Patients on bisphosphonate therapy with exposure to chemotherapeutic agents (i.e. cyclophosphamide, erythropoietin, thalidomide and steroids)
- Patients on oral bisphosphonate for more than 3 years
- Patients on bisphosphonate and smoking
- Patients on bisphosphonate and other systemic medical conditions (i.e. cancer, diabetes, obesity, atherosclerotic heart disease.

Prevention of BRONJ

Patients planning to begin bisphosphonate therapy or have recently started therapy for osteoporosis:

- Eliminate oral infection and areas at high risk of infection (e.g. removal of partially impacted wisdom teeth, unsalvageable teeth, non-restorable teeth, teeth with substantial periodontal bone loss).
- Receive routine preventive and therapeutic care.
- Minimize periodontal inflammation.
- Baseline dental radiographs in forms of orthopantograms, bitewings, selective periapical radiographs are required for the detection of occult caries and any other pathology, such as cysts, buried teeth or roots.
- Removal of tori and bony exotosis are indicated especially when patients are wearing or will be wearing removable prostheses as these are sites at risk of bone exposure and initiation of BRONJ.
- Ill-fitting dentures are adjusted and fabrication of new dentures may be indicated if existing dentures are beyond salvage.
- Bisphosphonate therapy should be delayed, if systemic condition permits, until the extraction site has epithelialized (14–21 days) or until there is adequate osseous healing. Oral examination and dental cleaning shouid be performed six monthly.
- Oral hygiene in forms of tooth brushing, flossing and rinsing with fluoride containing mouth rinses, are reinforced.
- Diet counseling in patient with high caries risk, patient education and motivation are important to prevent future caries and periodontal diseases.

During bisphosphonate therapy

Patients on intravenous bisphosphonates

- Maintenance and conservative dental care are performed as far as possible to reduce the risk of BRONJ development.
- Nonrestorable teeth can be treated by decoronation and endodontic treatment.

Patients on oral bisphosphonates

- Elective dentoalveolar surgery and extractions are not contraindicated, provided the necessary precautions are taken.
- For patients on oral bisphosphonate therapy for more than 3 years with or without concomitant steroid medication, discontinuation of oral bisphosphonate 3 months prior to oral surgery should be considered in consultation with the prescribing physician if the systemic condition permits and resumed after osseous healing has occurred.
- For patients on oral bisphosphonate therapy less than 3 years without concomitant steroid medication and have no clinical risk factors, dentoalveolar surgery and extractions can proceed without any alterations.
- For patients on oral bisphosphonate therapy less than 3 years with concomitant steroid medication, a 3-month drug holiday should be considered, in consultation with the prescribing physician.

Biochemical test to assess risk for BRONJ inpatient on bisphosphonate

Serum C-terminal telopeptide (CTX) Biochemical bone turnover markers are released during bone remodeling and can provide a measure of the rate of bone metabolism. Serum CTX measures the serum level of the C-terminal telopeptide-related fragment from a cross-linking chain in type I collagen, which is cleaved by the osteoclast in bone resorption. CTX is a measure of the bone resorption activity and is used as a predictor of bone mineral density (BMD) response to bisphosphonatetherapy.[30] So by assessing the serum CTx levels risk assessment can be done.[31,32]

Management of BRONJ

Treatment of established BRONJ is targets to eliminate pain, control infection of the soft and hard tissues and minimise the progression or occurrence of bone necrosis.

Patient with BRONJ stage 0: The management of stage 0 patients is essentially preventive and avoids invasive oral surgical procedures and dental extractions as far as possible.

Patient with BRONJ stage 1: The management of stage 1 patients is mainly conservative. It includes oral antibacterial mouth rinse, adjustment of dentures to minimise soft tissue trauma or irritation, patient education, regular quarterly follow-up. Long-term discontinuation of bisphosphonate should be considered if the patient's systemic condition permits after discussing with prescribing physician.

Patient with BRONJ stage 2: The treatment of stage 2 patients includes the use of oral antibacterial mouth rinse, analgesia for pain control, superficial debridement and removal of loose sequestrum to relieve soft tissue irritation with minimal disruption to adjacent soft with the prescribing physician. The infection is usually treated with empirical broad-spectrum oral antibiotics such as penicillin V or amoxicillin. If patient is allergic to penicillin, clindamycin can be used. Other alternative antibiotics include erythromycin ethylsuccinate, doxycycline together with metronidazole, levofloxacin and moxifloxacin. Once the culture and sensitivity result is available, specific antibiotic therapy should be instituted.

Patient with BRONJ stage 3

The management of stage 3 patients is essentially similar to that of stage 2 patients. More aggressive surgical debridement or resection to achieve longer term palliation of infection and pain may be necessary. The effectiveness of hyperbaric oxygen therapy is still undetermined.

Bisphosphonates and Different Dental Procedures

Modification in dental treatment in patients on bisphosphonates is recommended and certain dental treatments are contraindicated in these patients to avoid adverse effects and to have a better dental treatment outcome **(Table 3).**

Table 3: Dental management of patients on bisphosphonates.

Speciality	Indicated procedures	Relative contraindication	Contra indication
Periodontics	Non surgical therapy (SRP)	Flap surgery with bone contouring consider drug holiday	GTR, Bone grafts
Oral and maxillofacial surgery	-Removal of crown and RCT for roots -If extractions or bone surgery are necessary -primary soft tissue closure -minimal manipulation of bone and periostium -prophylactic antibiotics -consider drug holiday for elective syrgical procedures		Reconstructive surgery
Endodontics	RCT- instrumentation	Periapical surgeries	Bone grafting
Restorative and prosthodontics	FPD'S and RPD'S without ill fitting margins		
Orthodontics	No scientific data reg BRONJ due to orthodontic Rx	Orthognathic surgery	
Implants	Consider RCT and FPD No scientific data	Consider drug holiday)3 to 6 months	Guided bone regeneration Bone augumentation

CONCLUSION

Patients on bisphosphonate therapy for various bone diseases are at the risk of developing BRONJ. BRONJ is a debilitating condition which is difficult to treat and patients may even require jaw resection to palliate the infection and pain. Hence prevention of BRONJ is more important in treating patients on bisphosphonates. It is better to avoid any dental surgery before or during bisphosphonate treatment. The dental practitioners should be aware of the risk factors for development of BRONJ and should also be aware of the latest approaches or guidelines to manage patients on bisphosphonates in collaboration with their medical colleagues. If dental extraction is mandatory, alternative treatments like endodontic treatment is a safer alternative to extraction of tooth.

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