Dental Care in the Patients with Bisphosphonates Therapy
M.B. Mishra, Shanu Mishra, Ranu Mishra

Abstract:
Bisphosphonates for the treatment of osteoporosis has widely been practiced in developed countries. Many individuals with injectable bisphosphonates therapy have been found to suffer osteonecrosis of the jaw bones in presence of infection, surgical manipulations etc. This paper reviews the various aspects of bisphosphonate therapy in dental care.
Key Words: Osteoporosis; Pyrophosphates, Hydroxyapatite; Microdamage; Remodeling.

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Introduction
Bisphosphonates (Bps) are synthetic non-degradable analogues of naturally occurring inorganic pyrophosphates, and are also known as bone sparing drugs.(1) Structurally bisphosphonates are similar to pyrophosphates and perform similar biochemical effects. Pyrophosphates are formed by hydroxylation of ATP into AMP in the cells. It is understood that the parachlorophenol moiety central to chemical structure of Bps is essential for binding to hydroxyapatite and for affinity to the skeleton.(2) Bps have great affinity for calcium phosphate crystal. They bind with bone mineral and concentrate selectively in the bone. Though Bps is rapidly eliminated from circulation in urine,(3) however depending on the duration of treatment, and the specific type of Bps prescribed, the drug may remain in the body for years. (4) Bisphosphonates are used to treat Paget’s disease of bone, multiple myeloma, hypercalcemia of malignancy and osteoporosis induced due to senile changes, female hormone therapy, prolonged use of steroids, post chemotherapy, celiac disease etc.
Bio-pathology
Once bone has been formed, the new mineralized tissue starts to be reshaped and renewed by process of resorption and apposition, i.e. through modeling and remodeling. Modeling represents a process that allows a change in the initial bone architecture. It has been suggested that external demands such as load on the bone tissue may initiate modeling. Remodeling on the other hand represents a change that occurs within the mineralized bone without a concomitant alteration of the architecture of the tissue. The process of remodeling is important during bone formation and old bone is replaced with new bone.(2, 3) During the bone resorption, Bps are released from bone and may be either reincorporated into newly formed bone or phagocytized by osteoclasts, subsequently these osteoclasts lose its ability of bone resorption, and promote apoptosis or programmed cell death.(5) Recent evidence suggested that Bps interfere with osteoblasts metabolism and secretion of lysozyme enzyme.(6) Nakaya et al. have suggested that Bps possess anticollagenase property.(7) Many research works suggest that Bps are inhibitors of osteoclastic activity.(8) Physiologic bone remodeling and deposition are severely compromised in patients receiving Bps therapy, because during the process of bone resorption, the drug is phagocytized by the osteoclast. The Bps engulfed by the osteoclast loses its ability of bone resorption. (8) Osteonecrosis literary means death, or necrosis of bone. According to the National Osteonecrosis Foundation (NOF), many risk factors for osteonecrosis can be divided into two categories: definite and probable (Table 1).(9)

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<th>Definitive</th>
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<td>Arterial Disease</td>
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<td>Bone metastasis</td>
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<td>Caisson Disease</td>
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<td>Sickle cell disease</td>
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The Food and Drug Administration (FDA) USA; recognizes additional risk factors associated with the development of osteonecrosis (not limited to jaw) in cancer patients such as female sex, advanced age, edentulous regions, combination cancer therapy, blood dyscrasias / metastatic disease, anemia, coagulopathy,
surgical dental procedure, and prior infection.(10) Odvina et al. have suggested that estrogen may increase the risk of developing BON.(9) Markievicz et al. have reported, being older over 65 years also may increase the risk of BON.(10) Bisphosphonates have anti-angiogenic ability which is tumoricidal, making the drug an important agent for cancer therapy.(11) BPs appears to have fast and slow elimination rates from the bone, which may support drug holidays as being advantageous.

Bisphosphonates retard bone loss and by virtue of its affinity for calcium it increases the bone density, subsequently decreasing risk of pathologic bone fracture. In addition, emerging research is exploring the ability of intravenous BPs therapy to inhibit the spread of some cancers to the bone. In cancer patients receiving IV BPs therapy, the median time for starting therapy to develop BON was 25 months, reported by Green JR et al.(12)

Osteoporosis: “Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of the bone scaffold that results in increased bone fragility and susceptibility to fracture”. (13) Modeling of bone represents a process that allows a change in the initial bone architecture. It has been suggested that external demands such as load on bone tissue may initiate modeling. Remodeling on the other hand represents a change that occurs within the mineralized bone without a concomitant alteration of the architecture of the tissue. The process of remodeling is important during bone formation and old bone is replaced with new bone.(3, 4) In osteoporosis bone mineral density (BMD) is reduced, bone micro-architecture is disrupted and the amount and variety of non-collagenous proteins in bone is altered. Dual energy x-ray absorptiometry (DXA, formerly DEXA) is considered gold standard for diagnosis of osteoporosis. Diagnosis is made when BMD is less than or equal to 2.5 SDs below that of young adult reference population. This is translated as a T-score, WHO has established diagnostic guidelines as T-score -1.0 or greater is “normal”, T-score between -1.0 and -2.5 or below as osteoporosis (WHO Study Group 1994).

Normal bone undergoes physiologic remodeling. Micro-damaged bone is removed and replaced by new elastic osseous tissue. This process of removal and replacement takes place within small compartments called “bone multicellular units” (BMUs). (14)

These BMUs are composed of osteoblasts (pre-bone–producing cells), osteoclasts, and blood vessels and pericytes. Bisphosphonates bind to bone and incorporate within the osseous matrix. During the process of remodeling, the BPs are taken up by the osteoclast and are internalized within the cytoplasm of the cell, thereby, resulting the osteoclasts to lose the bone resorptive function and subsequently undergoes apoptotic cell death. Bisphosphonates also inhibit osteoblasts-mediated osteoclastic resorption. Along with these features, the BPs are anti-angiogenic; as a result, bone turnover becomes profoundly suppressed and over times physiologic remodeling of bone is diminished. The bone becomes brittle and unable to repair the microresorption which occurs during daily activity. Oral bone loss has been shown to have association with osteoporosis and low skeletal BMD. For the jaw bones to measure bone mass, the measures include single and dual photon absorptiometry, DXA, Quantitative computer tomography (QCT), and film densitometry.(10)

Influence on the jaw bones: In oral cavity maxilla and mandible are subjected to constant stress from masticatory forces. Probably in the jaws, the microdamage is not repaired in the patient taking bisphosphonates and is likely to result in osteonecrosis. During the infection of maxilla or mandible, the need for repair and remodeling increases greatly. Extractions performed in the patients taking bisphosphonates, the bone unable to meet these needs, because of inhibited remodel capability and hypo vascularity, and subsequently results in osteonecrosis. Therefore, bisphosphonates associated osteonecrosis (BON) results from a complex interplay of bone metabolism, local trauma, and increased demand for bone repair, infection and hypo vascularity. Osteoporosis has been suggested as risk factor for periodontitis. Study by von Wower et al. reported that the women with osteoporosis had greater loss of attachment than the control subjects.(15, 16) Although osteonecrosis has been of great concern, the routine BPs effects on bone, of decreased bone healing and tooth movement should be noted. Bisphosphonates are administered orally or intravenous. Among oral Bps Alendronate, Pamidronate and Zoledronic acid are commonly prescribed. Patients receiving intravenous Bps are clearly more susceptible to BON than are those receiving BPs orally. As early as 2006 cases of bisphosphonates associated osteonecrosis (BON)
in individuals taking orally administered nitrogen-containing bisphosphonates, used for the treatment of osteoporosis. Patients on intravenous therapy of Bps suffering from BON were documented in 2003. (17) There are comorbid factors which may play a role but the extent of their influence is not clearly determined. These systemic factors are diabetes mellitus, overall tumor burden and stage of disease, extent of skeletal involvement, the patients overall systemic health, degree of immunosuppression, the patients history of stem cell transplantation, and patients current and historical use of drugs like chemotherapeutic agents or corticosteroids.

Dental procedures that require optimal bone resorption and formation surrounding periodontics ligament (PDL), such as extraction, bone augmentations and orthodontic tooth movement, should be monitored for decreased success. Radiographic records should be evaluated for decreased function or sclerotic or radiolucent changes surrounding the PDL. (17) Local comorbid factors include oral health status, presence of infection (acute or chronic), history of radiation therapy, and presence of myeloma or metastatic cancer at BON site. The typical clinical presentation of BON includes pain, soft tissue swelling, and infection, loosening of teeth, drainage and exposed bone. Symptoms may occur spontaneously in the bone or, at the site of previous extraction. However the bone remains asymptomatic for weeks or months, and may become evident only after the finding of exposed bone in the jaw during a routine examination. In some cases, the symptoms of BON can mimic dental or periodontal disease.

Dental treatment of patients taking bisphosphonates: Routine dental treatment of patients taking Bps is a challenging task. In an internet survey study conducted by Durie BGM et al. evaluated the incidence of BON in 1,203 patients receiving intravenous Bps therapy for the treatment of multiple Myeloma (904), breast cancer (299). (18) The patients were assessed on age, sex, diagnosis, duration and type of Bps treatment, presence of variety of dental problems and dental treatment. Of 904 patients with myeloma 62 had been diagnosed BON and 54 had suspicious findings. Of the breast cancer patients, 13 had been diagnosed BON and 23 had suspicious findings. This research after 36 months also evaluated that 10 % of patients were taking Zoledronic acid and 4 % taking Pamidronate developed BON. This study showed that 81 percent of the patients with myeloma and 69 percent of the patients with breast cancer who developed BON had underlying dental disease like infection, or had had a dental extraction done.

Rehabilitation of edentulous area, in recent years is preferred to be done by implant placement, and have been considered successful. Patient on Bps therapy for implant placement should be considered very carefully, the procedure requires osteotomy site. Therefore patient may be at increased risk of developing BON when implant placement or guided bone regeneration to augment the deficient alveolar ridge. (1)

Preventive measures of jaw bone necrosis: American Association of Oral and Maxillofacial Surgeons (AAOMS) suggests a three month oral Bps drug holiday before and after dental procedures if a patient has been taking Bps continuously for three years, or less than three years concurrent Glucocorticoids, such as prednisone. The treatment of patient receiving oral or intravenous bisphosphonates therapy is principally preventive in nature.

Needed dental treatment should be provided to these patients before the risk of developing BON increases. Patients who have been given oral Bps within last three months also should undergo a dental evaluation. Recent literature reported various types of cancers receiving intravenous bisphosphonates to control and treat metastatic bone disease. (17)

It is unknown how much lengthy duration of use (more than five years) will contribute to adverse dental effects from Bps accumulation within the bone. However three month oral drug holiday before and after dental procedures if a patient has been taking Bps continuously for three years, or less than three years concurrent Glucocorticoids, such as prednisone. The treatment of patient receiving oral or intravenous bisphosphonates therapy is principally preventive in nature. The treatment of patient receiving oral or intravenous bisphosphonates therapy is principally preventive in nature. The treatment of patient receiving oral or intravenous bisphosphonates therapy is principally preventive in nature. The treatment of patient receiving oral or intravenous bisphosphonates therapy is principally preventive in nature. The treatment of patient receiving oral or intravenous bisphosphonates therapy is principally preventive in nature.
hygiene appointments will be necessary in the consultation, the following should occur.

- A comprehensive extra oral and intraoral examination should be performed. A full mouth radiographic series and panoramic radiograph will be useful in diagnosis of caries and periodontal disease and in the identification of metastasis cancer and other bony pathology.

- Periodontal health status should be determined and appropriate therapy provided. Pocket must be eliminated to reduce bacterial plaque accumulation. Minimize acute and chronic periodontal infections.

- Extraction of indicated teeth should be done as soon as possible.

- Restoration of all carious teeth should be performed, including less extensive crown and bridge work.

- Prophylaxis and necessary oral hygiene instruction be given.

- Patient should be given information about BON and made aware of early signs of developing this condition.

- Periodic follow-up visits should be scheduled to reinforce the importance of oral hygiene and conduct re-examination of the oral cavity.

Conclusion

Bps has its significant affinity for binding with calcium. The drug has acquired an important place in the treatment of osteoporosis and several other conditions discussed above. Greater than 65 years age group, oral corticosteroid use for chronic conditions, periodontitis, and prolonged use of Bps have been associated with an increased risk of developing BON. No patient should ever discontinue Bps use without a physician’s consultation. Medical benefits of decreased morbidity and mortality from hip and vertebral fractures outweigh possible dental risks. It is unknown how much lengthy Bps use will contribute to adverse dental effects from Bps accumulation within the bone. However after three to five years of Bps use, the physician may decide that Bps is still to be continued or not needed for the treatment of osteoporosis. These patients have to undergo BMD check before discontinuation of the drug.

In the patients taking Bps, routine dental treatment should be carefully executed which may include, restorative care and oral prophylaxis doneatraumatically as possible with gentle soft tissue management, extraction should be avoided, or if necessary then atraumatically as possible. Antibiotic cover may reduce the possibility of infection. And teeth those can be preserved by endodontic procedures should be carried out. BON can occur spontaneously but is more commonly associated with dental procedures that traumatize bone, such as dental extractions.

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