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Review Article

Bisphosphonates-Osteonecrosis of Jaw

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ABSTRACT
The recent recognition of bisphosphonate use came into use for pathological conditions which includes osteonecrosis of the jaw (ONJ) and other bone diseases. This article highlights about bisphosphonate and its effect and affect on ONJ. Jaw necrosis is a complication associated with conditions such as radiotherapy, severe fungal or bacterial infections, and sarcoidosis or after intravenous bisphosphonate therapy. The intravenous bisphosphonates - pamidronate (Aredia) and zoledronic acid (Zometa), are often used to treat cancer-related hypercalcemia, Paget's disease, symptoms from solid tumor bone metastasis and osteolytic lesions of multiple myeloma. Bisphosphonate related ONJ has been reported since 2003, in patients taking the drug, more often after dental procedures like extractions, minor surgeries, etc.

Key words: Bisphosphonates, Clinical practice, Mechanism, Osteonecrosis of jaw.

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INTRODUCTION

Osteonecrosis of Jaw (ONJ) is a painful condition characterized by avascular necrosis of bone in oral cavity that is commonly associated with localized swelling and in some cases, a purulent discharge[1]

In the mid 19th Century, the term "Phossyjaw" was coined to describe the maxillofacial necrosis that was seen in factory workers exposed to the white phosphorous used in matches[1].Subsequently, the development of safety matches, which use amorphous red phosphorus, led to decline in "Phossyjaw" from 1850[1]. Since 2003, a condition that bears some similarities to "phossyjaw" has been reported in patients with various cancers (reviewed by Woo et al.)[1].Bisphosphonate were synthesized in the 19th century and initially used for industrial purpose as antiscaling and anticorrosive agents in washing powders for prevention of depositon of calcium carbonate. 1960's Fleisch *et al* mentioned about the inhibition of quality of bone resorption qualities associated with of bisphosphonates along with both structural and functional development led to formation which in turn inhibits bone resorption without causing harm in mineraliztion.[2]

They are the drugs that are widely used in the management of metastatic bone diseases and in the treatment of osteoporosis[3], and in treating a wide variety of bone diseases (pagets' disease, osteosclerosis, hypercalcemia owing to immobilization or malignancy, fibrous dysplasia).[2]

The American Society of clinical oncology (ASCO) has mentioned clearly that the patients taking bisphosphonates for multiple myeloma and breast cancer it must be continuous. Osteonecrosis shows the characteristic feature of death of bone that is followed by many number of systemic and local factors along with the limited or compromised blood supply. Jaw bone necrosis is associated with both vascularisation of both maxilla or mandible. Usually present following head and neck radio therapy and/or oral surgical interventions.[4] Bone necrosis of jaws appear as an exposure of avascular bone in the mandible, maxilla or both.[4]

The correlation between the use of bishosphonates therapy in malignancy and the presence of jaw bone necrosis has been recently reported may be due to action of drug on bone vascularization and on osteoclastic activity.[4] Bisphosphonates medications have also become an essential part of treatment in patients with cancer and bone disease. Because of the evidence of clinical adverse effects that these medications have on maxilla and mandible investigations continue to be warranted to examine the effects on bone at cellular and molecular level.[5]

CHEMICAL STRUCTURES OF BIPHOSPHONATES

Bisphosphonates are synthetic analogues of pyrophosphates, an endogenous regulator of bone mineralization.[1] They consist of a pyrophoshate-carbon-phosphate(P-C-P) backbone and two covalently bonded groups attached to the central carbon atom, known as R_1 and R_2. The R1 chains has a hydroxyl group, which increases the affinity of bisphosphonates for bone hydroxyapetite. R_2 group the primary feature is to distinguish different bisphosphonates. The non-aminobisphosphonates etidronate and clodronate have-CH3 and a-Cl entity as their R_2 chain. Newer generation bisphosphonates-zolendronic acid,pamidronate,ibandronate and alendronate have nitrogen containing R_2 chain.[1]

Bisphophonates are mainly of two types, nitrogen containing and non –nitrogen containing with subgroups of either oral (or) intravenous administration. They are also divided into levels of potency: low (Alendronate, Risedronate), medium (pamidronate) and high (zoledronate). Pamidronate and zoledronate are administered intravenously and alendronate and riserdonate are given orally.[3]

BIPHOSPHONATES-OSTEONECROSIS OF JAW

Mechanism of action

They have such a high affinity for the hydroxyapetite in bone, they rapidly cleared from the systemic circulation and localize on bone mineral surfaces, particularly at sites of osteoclast activity.[1] When osteoclast are in their resorption phase, they are in a highly acidic microenvironment, which may facilitate release of the bisphosphonate from the bone surface, giving rise to high local bisphosphonate concentrations[6] The adverse effects depends on various factors such as whether or not they are an aminobisphosphonate, the route of administration, and the dose of frequency of administration.[11] Bisphosphonates bind avidly to exposed

bone mineral around resorbing osteoclast.Because they are not metabolized these high concentrations are maintained within bone for longer periods of time.[12] Bisphosphonates are stable analogues of pyrophosphate characterized by a p-c-p structure and two side chains attached to the carbon atom. The first chain controls the ability to bind to crystal in bone, the second chain determines the efficiency.[10] They are absorbed, stored and excreted unchanged from the body. The plasma half-life is, short (between 20 minutes and 2-3 hrs), while the bone half-life is very long, ranging from several months to years[4]. They also inhibit various metalloproteinases (MMPs) (such as MMP-2,9, 12) involved in cancer growth and metastasis *in vitro*[4]. A decrease of osteoclastic activity reduces bone resorption, and are therefore used for the treatment of multiple myeloma and controlling hypercalcemia in some malignancies and bone metastasis osteolysis.[7] The correct mechanism of Bisphosphonate mediated osteoclast inhibiton is not mentioned completely though, it has been established that these compounds affect bone turnover at various levels.At tissue level it inhibits bone resorption and decrease bone turnover as assessed by biochemical markers.[5] *On a cellular levels*, the bisphosphonates are clearly targeting the osteoclasts and may inhibit their function in several ways.[5] By inhibition of osteoclast recruitment, diminishing the osteoclast life span, and inhibition of osteoclastic activity at the bone surface.[5] *At a molecular level*, it has been postulated that bisphosphonates modulate osteoclast function by interacting with a cell surface receptor or an intracellular enzyme.[8] They have the ability to chelate calcium ions and bind to hydroxy–apetite on bone surfaces undergoing They are also known to affect expression of receptor activator of nuclear factor κB, Ligand (RANKL), an osteoclast differentiation factor[6] · RANKL, which is necessary for differentiation and activation of osteoclast and their fusion into multinucleated cells.[9] The effects of RANKL are blocked by osteoprotegerin, which acts as a receptor antagonist for RANKL and prevents bone resorption.

Biphosphonate Associated Osteonecrosis of Jaw

Bisphosphonate associated osteonecrosis of jaw can be defined as the unexpected development of necrosis in the oral cavity of a patient who has received bisphosphonates but not radiotherapy to the head and neck.[1] The first report of this painful and vascular necrosis of the bone in the mandible and maxilla in patients receiving the aminobisphosphonates pamidronate or zoledronic acid was published by Marx *et al* in 2005.[13]

Clinical Presentation

The typical clinical presentation of bisphosphonate associated Osteonecrosis of jaw has been concisely, described by Migliorati al.[1] Clinically BONJ presents as an area of exposed bone (alveolar) that occurs spontaneously or becomeclear followed by invasive surgical intervention like extraction of tooth,dental implant placement or even apicectomy.[2] The three most common site are (a) non-healing extraction sites (2)injured tori a developmental defect (palatal and/or mandibular) (3) exposed part of mylohyoid ridge.

A cumulative incidence for Bisphosphonates induced necrosis was noted of about 0.8-12%.An uncommon disease which is less aggressive and is moreresponsive to treatment is the Oral route of administration than intravenous. The American Association of oral and maxillofacial surgeons (AAOMS)classified the risk factors inclto three types 1. Drug related – depending on its potency and duration. Also include local factors and systemic factors which includes cancer diagnosis,bone disorders such as osteopororsis.[2] The nitrogen–containing bisphosphonates have been described as main culprits[7], Zervas *et al* and *Durie et al* showed the similar results having a risk factor of developing osteonecrosis which is 10 times more in zoledronic acid compared to that with pamidronate.[2]

Diagnosis of Biphosphonates induced Osteonecrosis of Jaws

The clinical picture does not show the real extent of BONJ. For early diagnosis of the disease the accurate estimation of its extent, imaging is important. However conventional radiographic methods-dental panaromic radiographs,are of limited use.[10] Computerized tomography(CT) scans and magnetic resonance imaging(MRI) have been shown to be better choices for the estimation of the extent of BONJ. Role of bone imaging with Tc-99 m diphosphonates and found to be more sensitive than CT and MRI. Recent studies have demonstrated that F-18 flouride is more accurate than 99 m-Tc disphosphonates single-photon emission CT for identifying both benign and malignant lesions.[10] Serum bone markers and other relevant endocrine assays were C-telopeptide, N-telopeptide, bone specific alkaline phosphates, osteocalcin, intact parathyroid hormone,T3,T4,TSH, Vitamin D25 hydroxy. They are signs of bone turnover process and may used to determine whether or not a patient may have bone disease and because the jaws have a greater blood supply than the other bones, and a high turnover of bone rate related to their daily activity, bisphosphonates are highly concentrated in jaws.[11]

Management and Prevention

Before initiating bisphosphonate therapy in cancer patients, all patients should undergo routine clinical dental examination and panoramic jaw radiography to detect potential periodontal and dental infection. The diagnostic value of bone scans by radioactive technetium in this situation are encouraging since 99 Tc (m)–MDP 3–phase bone scan was reported as the most sensitive tool for detecting osteonecrosis at an early stage. Patients must be educated regarding dental and oral hygiene, and they should have regular (every 3–4 months) scheduled oral assessments.[12]

MANAGEMENT RECOMMENDATIONS

- Prophylactic recommendation
- Routine oral examination and care to stabilize oral disease and prevent oral trauma/irritation before administering bisphosphonate therapy to the patient
- Management of acute symptoms: pain and infections
- Oral hygiene (brushing and flossing)
- Topical antibiotics (e.g., chlorexidine, tetracycline)
- Systemic antibiotics active against common oral/dental bacterial infections
- Pain medications
- Management of exposed bone
- Early: conservative removal of exposed bone, primary closure when possible
- Later: conservative protection of site, bone recontouring, prevention of infection
- Protective: covering of symptomatic (e.g., vinyl guards, stents)

CONCLUSION

The emergence of ONJ as a possible adverse effect of long-term, high-dose bisphosphonate therapy has raised serious concerns within the medical and dental communities. The direct relationship with bisphosphonates must undergo research into this phenomenon is prioritized to further characterize risk factors and inciting factors, and develop and test effective treatment strategies. In particular, it will be important to determine whether ONJ is predominantly observed in connection with the use of aminobisphosphonates. In the meantime, use of bisphosphonates

should be carefully planned in patients with risk for osteoradionecrosis of jaw and preventive measures must be carried out to avoid any further complications.

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