



Bisphosphonates in Periodontal Therapy

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ABSTRACT

Periodontitis is a multifactorial disease involving bacterial biofilms and the generation of an inflammatory response leading to the periodontal tissue breakdown. Alveolar bone resorption is a major component of the periodontal destruction observed in periodontitis. Various treatment modalities in recent times have tried to modulate the host response to bacterial assault. Although studies have shown that Bisphosphonates improve bone mineral density, reduce fracture risk, and reduce hypercalcaemia of malignancy, some patients develop Bisphosphonates-related osteonecrosis of the jaws. Drugs such as Bisphosphonates are proven anti-resorptive agents that can potentially inhibit the alveolar bone resorption. Various studies have been carried out on the improvement of clinical periodontal parameters after the administration of bisphosphonates. This article will try to represent the role of bisphosphonates in management of periodontal diseases.

Keywords : Bisphosphonates, Local Drug Delivery, Periodontitis.

INTRODUCTION:

The bisphosphonates are bone-seeking agents that inhibit bone resorption by disrupting osteoclast activity¹.

Bisphosphonates initially were used for softening the hard water in the water softening systems in the earlier 1920s. After that the medical use of the bisphosphonates came into existence.

Uses of bisphosphonates:

1. Systemically in treatment of osteoporosis², Paget's disease³, malignant hypercalcaemia⁴, bone metastasis⁵, multiple myeloma, primary hyperparathyroidism, osteogenesis imperfecta and carcinoma of breast.
2. Their use also has been proposed in the management of periodontal diseases, Bisphosphonates inhibit the osteoclastic bone resorption & hence are used as a host modulating factor for prevention of bone loss.⁶

CHEMICAL STRUCTURE:

All bisphosphonate drugs share a common P-C-P (phosphate-carbon-phosphate) that forms the "backbone" of the molecule. This makes them structurally related to pyrophosphates as they have P-O-P (phosphate-oxygen-phosphate) bond.

Pyrophosphates regulate bone mineralization by binding to hydroxyapatite. However the P-O-P bond is unstable and undergoes hydrolysis via pyrophosphatase activity. This instability is overcome by the stability of the P-C-P bond, which resists hydrolysis by pyrophosphatase and alkaline phos-

phatase, thus preventing the removal of the bisphosphonate molecule from bone surface.

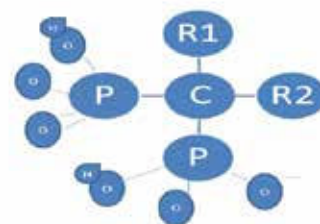


FIG1

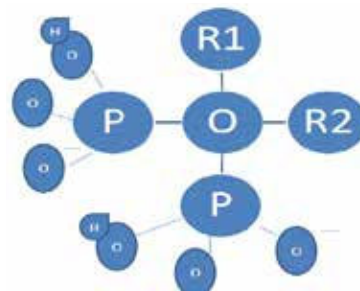


FIG2
 FIG 1 BISPHOSPHONATES
 FIG 2 PYROPHOSPHONATES

CLASSIFICATION: ⁷

According to chemical structure bisphosphonates are mainly classified into three categories:-

1. Alkyl side chains (Etridronate)
2. Amino side chains (Alendronate)
3. Cyclic chains (Zeladronate)

They can also be classified as:

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

MECHANISM OF ACTION: ⁸

A bisphosphonate group mimics pyrophosphate's structure, thereby inhibiting activation of enzymes that utilize pyrophosphate.

Bisphosphonate-based drugs' specificity comes from the two phosphonate groups (and possibly a hydroxyl at R1) that work together to coordinate calcium ions. Bisphosphonate molecules thus bind preferentially to calcium, and bones being the largest source of calcium in body. They accumulate maximum bisphosphonate molecules.

Bisphosphonates, when attached to bone tissue, are taken up by osteoclasts. There are two classes of bisphosphonates: the N-containing and non-N-containing bisphosphonates. The two types of bisphosphonates work differently in inhibiting osteoclastic activity.

Bisphosphonates affect both bone resorption and deposition by various mechanisms.

1. They bind to hydroxyapatite thus preventing its dissolution.
2. They inhibit osteoclast activation thus reducing the rate of bone resorption.
3. They increase osteoblast differentiation thus aiding in bone formation.

ANIMAL STUDIES:

AUTHORS	BP USED	ADMINISTRATION	EFFECT ON BONE RESORPTION	EFFECT ON PERIODONTAL HEALING
Reddy et al (1995)	Alendronate	oral route	↓alveolar bone resorption, ↑Bone mass	No clinical effect on clinical parameters
Alencar et al (2002)	Chlondronate	Subcutaneous route	↓alveolar bone resorption & osteoclast	↓PMNs
Buduneli et al (2004)	Alendronate	Intravenous route	↓alveolar bone resorption	↑Serum osteocalcin

HUMAN STUDIES:

AUTHOR	BP USED	ADMINISTRATION	EFFECT ON BONE RESORPTION	EFFECT ON PERIODONTAL HEALING
Rocha et al (2001)	Alendronate	oral route	↓alveolar bone resorption	↓Tooth mobility, ↓In clinical parameters
Lane et al (2005)	Alendronate OR Residronate	oral route	No effect on periodontal bone mass	↓Pocket probing depth, bop and clinical attachment level
Takaishi et al (2003)	Etridronate	oral route	↑alveolar bone deposition	↓Pocket probing depth and mobility

In spite of these improvements in periodontal status shown by bisphosphonates, they could never reach the stage of general periodontal use as host modulating agents. The reasons for the same are a multitude of adverse effects associated with systemic bisphosphonate therapy. These include –

1. Gastro intestinal intolerance, e.g., drug induced oesophagitis. This side effect is not seen in intravenous administration
2. Renal toxicity
3. Hypocalcaemia caused by reduced bone resorption leading to reduced calcium efflux from bone
4. Hepatotoxicity
5. Acute phase reaction

4. Their anti collagenase activity prevents degradation of the organic components of bone.

These actions of bisphosphonates have made them highly popular for the management of bone metabolic diseases like osteoporosis and other bone resorptive conditions like Paget's disease and malignant hypercalcaemia.

It is this bone sparing property of bisphosphonates that has attracted Periodontists towards the use of these drugs for prevention of alveolar bone loss that occurs in periodontal disease, thus opening a new chapter in periodontal host modulation therapy.

EFFECTS OF BISPHOSPHONATES: ⁸

At molecular level, bisphosphonates inhibit mevolanate pathway and post-translational prenylation of GTP- binding proteins. This causes changes at cellular level which include –

- Decrease osteoclastic activity as shown by the lack of ruffled border on osteoclast present in Howship's lacunae
- Decrease depth of resorption site
- Decrease release of cytokines
- Increase osteoblast differentiation and number

The cumulative effect of these cellular changes leads to changes at tissue level. These include –

- Decrease in bone turnover due to reduced bone resorption.
- Decrease in number of new bone multi-cellular units
- Increase net positive whole body bone balance
- Increase in bone mass since bone formation exceeds bone resorption.

ROLE IN PERIODONTAL THERAPY: ⁷

Early 1990's saw an increasing interest in application of bisphosphonates as host modulating agents for the treatment of periodontal disease. Many animal studies proved the high clinical efficacy of bisphosphonates in inhibiting the progression of experimentally induced periodontitis. These improvements in periodontal clinical parameters, especially alveolar bone gain, were also achieved in many human clinical trials.

6. Ocular inflammation
7. Dermatologic reactions
8. Osteonecrosis of jaws seen after tooth extraction because of over suppression of bone turnover.
9. Changes in White blood cell count.

To overcome these side effects, the local delivery of bisphosphonates has been proposed.

LOCAL DELIVERY ADMINISTRATION:

YAFFE A et al (2003)⁹ found that in local drug delivery of tetracycline in combination with alendronate showed significant reduction in alveolar bone loss.

A R PRADEEP et al (2012)^{10,11} in two different studies found significant reduction in PD and CAL and also more percentage of bone fill after using 1 % of Alendronate gel in the treatment of both chronic as well as aggressive periodontitis.

A Yaffe et al	Alendronate	Local drug delivery with tetracycline fibres	↓alveolar bone resorption	↓Pocket probing depth and clinical attachment level
Pradeep A R et al (2012)(chronic periodontitis)	Alendronate	Local drug delivery as 1% gel	↑% of bone fill	↓Pocket probing depth , clinical attachment level
Pradeep A R et al (2012) (aggressive periodontitis)	Alendronate	Local drug delivery as 1% gel in aggressive periodontitis patients	↑% of bone fill	↓Pocket probing depth , clinical attachment level

As these human studies indicate, local drug delivery of bisphosphonates show a ray of hope in the use of these drugs as local host modulating agents in periodontal therapy. This mode of application can overcome the adverse effects associated with systemic administration of bisphosphonates, while at the same time retaining the property of bone sparing.

CONCLUSION:

Several studies have shown that bisphosphonates have high potency to induce alveolar bone deposition but, long term

uses of bisphosphonates have their own disadvantages. Local administration of bisphosphonates have shown significant amount of gain in attachment levels and also alveolar bone level and can be an effective alternative to systemic administration. This new knowledge opens a new arena in the field of research on local use of bisphosphonates in periodontal therapy. However, considering the long list of adverse effects of these drugs, human clinical studies with long term follow up should be done to rule out any possible adverse effect of local delivery of bisphosphonates in periodontal pockets.

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