Bisphosphonates: An update

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ABSTRACT

Bisphosphonates are used widely for variety of bone condition, most notably IV bisphosphonates in the treatment of metastic bone lesion and oral bisphosphonates for osteoporosis. They constitute a group of drugs capable of modulating bone turnover and reducing its remodeling when an excessive resorption occurs. In the last few years, due to their extensive use, many cases of complications associated with their use have been published. This paper provides recent knowledge on general characteristics of these drugs and their mechanism of action, pathogenesis, as well as their relevance to dentist.

KEY WORDS: Bisphosphonate-associated osteonecrosis, osteonecrosis, osteoporosis

Bisphosphonates constitute a group of drugs capable of modulating bone turnover and reducing its remodeling when excessive resorption occurs. They are increasingly being used in number of bone conditions, including osteoporosis, Paget's disease, and metastatic cancer. As a consequence, the reported cases of bisphosphonates related osteonecrosis of jaw (BONJ) have increased.[1]

In the last few years, there has been increasing awareness of the link between bisphosphonates and osteonecrosis of the jaw. (ONJ). As some dental practitioners may not be familiar with this family of drugs, it is important to discuss the growing range of bisphosphonates and their use so that patients who are of developing ONJ are identified.

Structure

Structurally, bisphosphonates are chemically stable derivatives of inorganic pyrophosphate, a naturally occurring compound in which two phosphate groups are linked by esterification. The short RI chain confers pharmacokinetics and longer R2 chain influences bisphosphonate potency. The resorption ability of the molecule can be increased by adding a chain containing cyclic nitrogen or an aminoterminal group on R2 side[2] [Figure 1]. In humans, inorganic pyrophosphate is released as a by-product of many of the body's synthetic reactions, and thus can be readily detected in many tissues including blood and urine. Pioneering studies have demonstrated that inorganic pyrophosphate is capable of inhibiting calcification by binding to hydroxyapatite crystal, leading to the hypothesis that regulation of pyrophosphate level could be the mechanism by which bone mineralization is regulated.

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Basic Structure

Classification

The newer classification differentiates bisphosphonates into the following groups [Table 1]: Nitrogen containing and non-nitrogen containing. Nitrogen containing bisphosphonates [Figure 2] are more widely used as they are extremely bone selective. For this reason, non-nitrogen containing bisphosphonates are now rarely used.[3]

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Mechanism of action

The mode of action of bisphosphonates is now more clearly understood. Bisphosphonates have high affinity for calcium ion and so they are strongly attracted to bone. In the resorptive process, bisphosphonates are released from the bone surface and are taken up by osteoclast. In fact, osteoclast can take large amount of bisphosphonates during natural bone resorption.

Protein prenylation is important in osteoclastic activities and for the osteoclast to survive. The mevalonate pathway is central to the prenylation process.

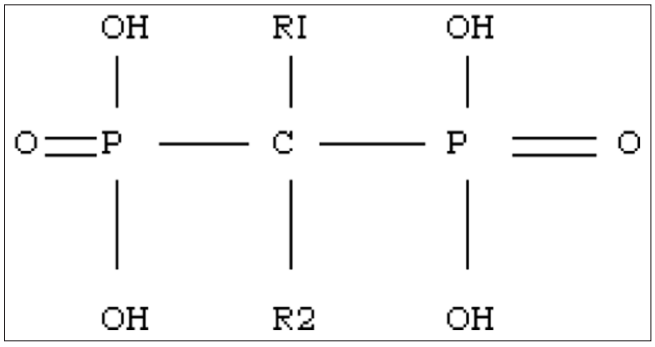


Figure 1: Basic structure of bisphosphonates Simple bisphosphonates Nitrogen-containing bisphosphonates

In this pathway, the action of enzyme farnesyl pyrophosphate synthase (FPPS) leads to the production of farnesyl pyrophosphate (FPP) which is necessary for the production of geranyl geranyl pyrophosphate (GGPP) by the action of the enzyme GGPP synthase. FPP and GGPP are both required for prenylation of GTPases.[4] which are signal proteins important for osteoclastic function and survival [Figures 3 and 4].

The bisphosphonate inhibits osteoclastic bone resorption via a mechanism that differs from that of other antiresorptive agents. Bisphosphonate attaches to hydroxyapatite binding site on bony surface, especially surface undergoing active resorption. When osteoclast begins to resorb the bone that is impregnated with bisphosphonate, the BisPhosphonate released during resorption

Table 1: Classification of bisphosphonates

Group	Drugs in group	Effect
Non-nitrogen bisphosphonates	Tiludronate Clodronate Etidronate	Incorporation into ATP results in osteoclast apoptosis
Alkyl-amino bisphosphonates	Pamidronate Alendronate Ibandronate	Inhibit the enzyme FPPS
Heterocyclic nitrogen bisphosphonates	Risedronate Zoledronate	Inhibit the enzyme FPPS

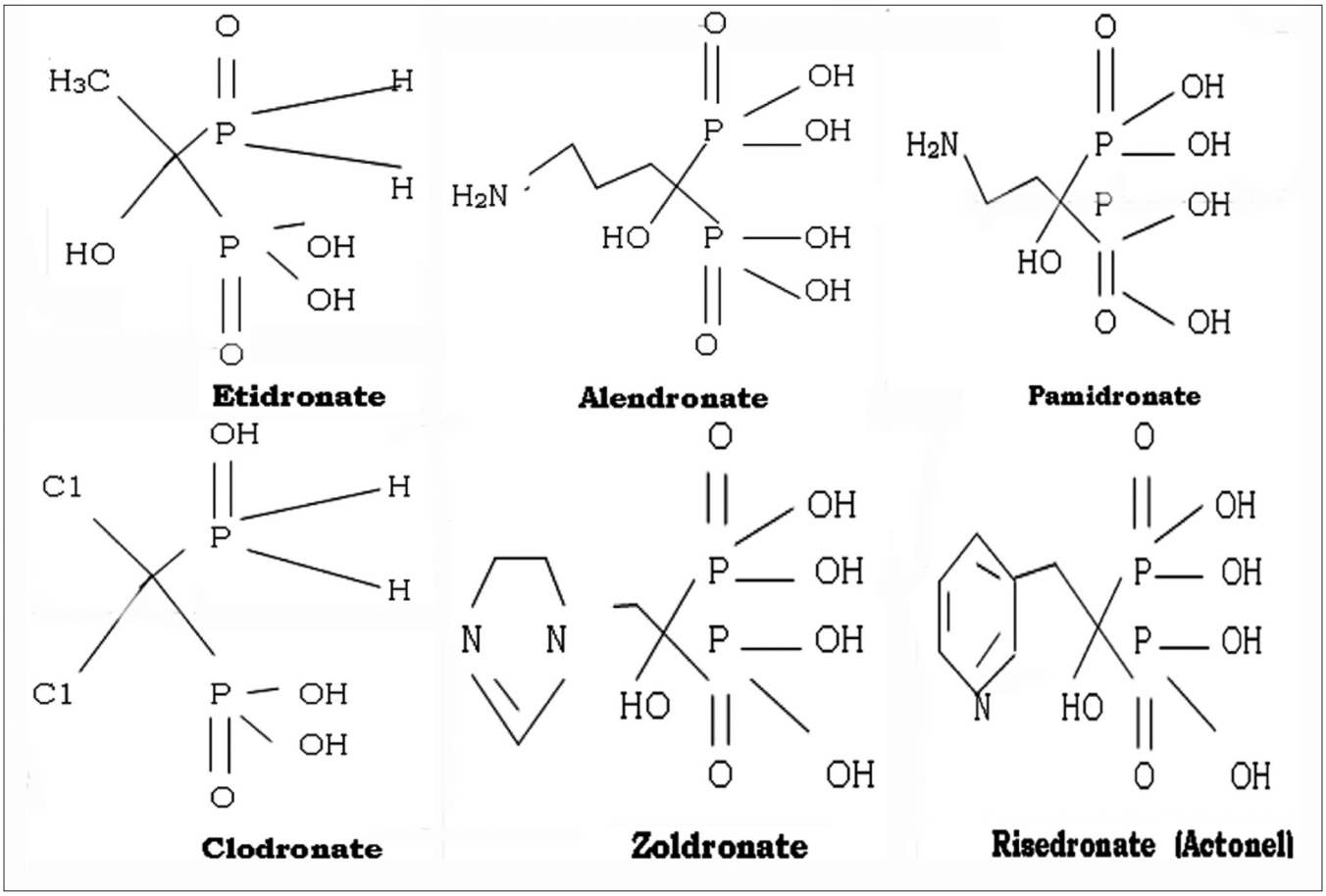


Figure 2: Chemical structure

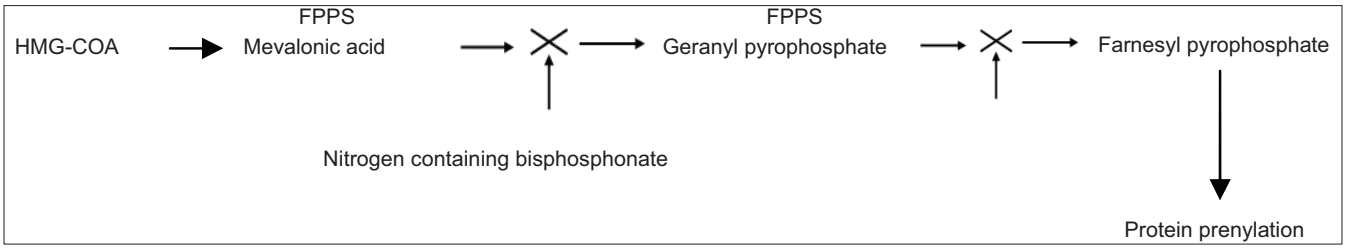


Figure 3: Prenylation process

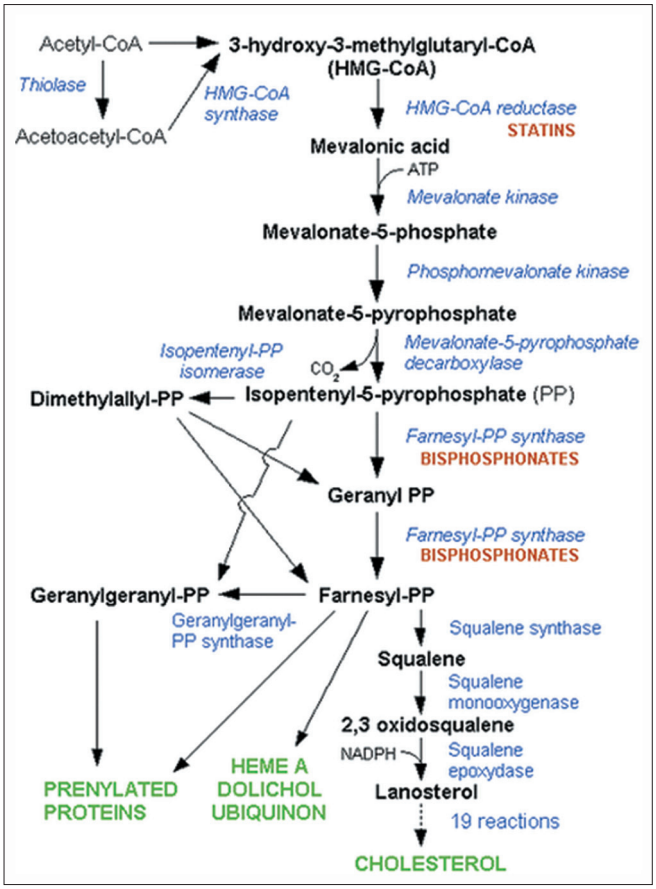


Figure 4: Action of bisphosphonate[5]

impairs the ability of osteoclast to form ruffled border, to adhere to the bony surface, and to produce the proton necessary for continued bone resorption.[6] Bisphosphonate also reduces osteoclastic activity by decreasing osteoclast progenitor development and recruitment and by promoting osteoclast apoptosis [Figure 5].

Diagnosis of ONJ

It is essential to refer ONJ suspected / diagnosed patients, together with a panoramic radiograph (if available) to a specialist. In general dental practice, the working party recommends taking a panoramic radiograph as a good baseline record. Conventional radiographs have limitations. When there are radiopaque sequestra, then radiographically metastatic lesions can be differentiated sufficiently from osteonecrosis. However, if the lesion is osteolytic, radiographs are not useful. Early lesions may also be missed.[7]

The suggested further specialist investigative procedures may include the following.

Bone imaging techniques

- Computed tomography (CT) used for differential diagnosis.
- Cone beam CT gives details on thickness of cortex, integrity, and marrow involvement, cancellous bone mineral density (BMD), and irregularities after tooth extraction.[8]

Soft tissue and bone marrow imaging technique

Magnetic resonance imaging (MRI) recognizes ischemic areas with the use of contrasting agents, but it may give false positives.

Functional/physiological tests

- Technetium-99 radioisotope scintigraphy: In patients with metastatic bone disease, where clinically indicated.
- Position emission tomography: Not very useful due to poor resolution with high radiation dose.
- Bone resorption markers such as the collagen telopeptide (CTX) may be of some value in assessing the risk of bisphosphonate-induced osteonecrosis by indicating oversuppression of bone turnover.[9]

Biopsy

In most cases, biopsy is not necessary and may even be detrimental to bone healing. However, when there is a history of parenteral bisphosphonate therapy for metastatic cancer, then the possibility of metastases to the jaw should be seriously considered and, if no biopsy is taken, the reason should be recorded in the patient's notes.[10]

However, there is a need for more research to develop further diagnostic procedures.

Prevention of ONJ

All patients with osteoporosis or other non-malignant disease need good oral hygiene and regular routine dental examinations. There are also important differences in the approach to patients taking bisphosphonates for osteoporosis and non-malignant disease compared to patients with malignancy who are starting or are already taking bisphosphonates.[11,12]

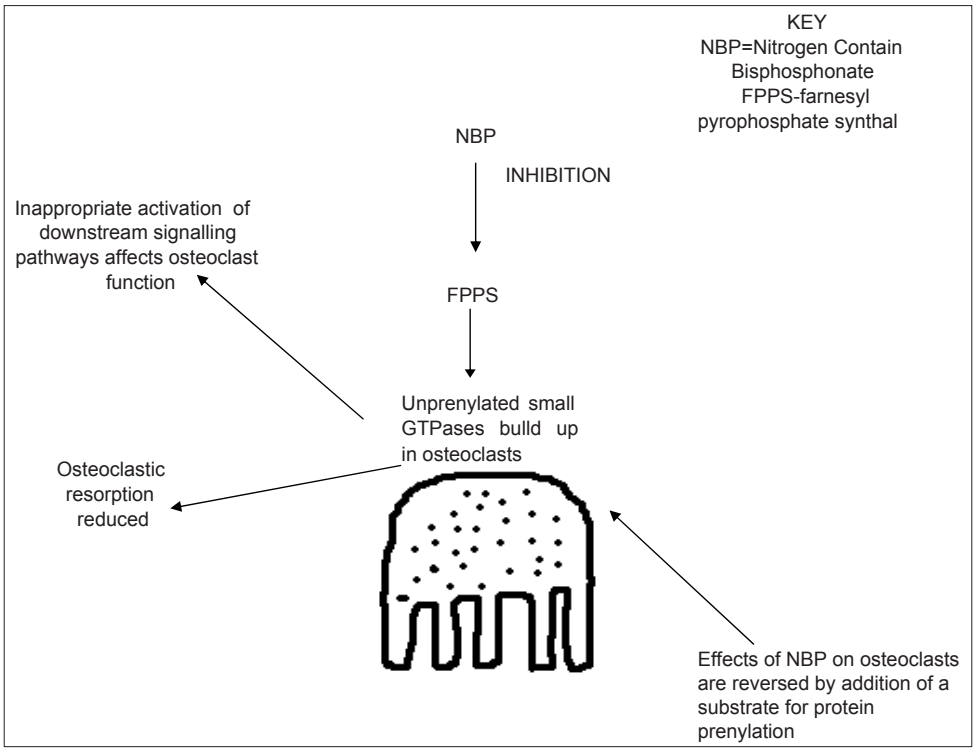


Figure 5: Action of nitrogen containing bisphosphonates on osteoclasts

Prevention, wherever possible, is therefore the key. This will have to start at primary care levels. Education and regular updated guidelines for general practitioners are important to limit the impact of ONJ.

References

1. Arrain Y, Masud T. Recent Recommendations on Bisphosphonate - Associated Osteonecrosis of the Jaw. Dent Update 2008;35:238-42.
2. Arrain Y, Masud T. Bisphosphonate and Osteonecrosis of the Jaw-Current Thought. Dent Update 2009;36:415-9.
3. Russell RG, Watts NB, Ebetino FH, Rogetrs MJ. Mechanisms of action of Bisphosphonates: Similarities and differences and their potential influence on clinical efficiency. Osteoporosis Int 2008;19:733-59.
4. Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, *et al.* Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation *in vitro*. Proc Natl Acad Sci USA 1999;96:133-8.
5. Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res 2006;12:6222-30.
6. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action an role in clinical practice. Mayo Clin Proc 2008;83:1032-45.
7. 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;63:1567-75.
8. Marx RE. Reconstruction of defects caused by bisphosphonate induced osteonecrosis of the jaws. J Oral Maxillofac Surg 2009;67(5 Suppl):107-19.
9. Marx RE. Oral and Intravenous bisphosphonate induced osteonecrosis of the jaws. History, Etiology, prevention and Treatment. Chicago: Quintessence Publishing Co Inc; 2007. p. 86.
10. Carlson ER, Basile JD. The role of bisphosphonate - related ostenoecrosis of the jaws. J Oral Maxillofac Surg 2009;67(5 Suppl): 85-95.
11. Brown JJ, Ramalingam L. Zacharin MR. Bisphosphonate - associated osteonecrosis of the Jaw: Does it occur in children. Clin Endocrinol 2008;68:863-7.
12. Nancollas GH, Tang R, Phipps RJ, Henneman Z, Gulde S, Wu W, *et al.* Novel insights into the actions of bisphosphonates on bone; differences in interactions with hydroxyapatite. Bone 2006;38: 617-27.

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