BALKAN JOURNAL OF STOMATOLOGY

BaSS

ISSN 1107 - 1141

Biphosphonates: A Concern for Dental Practice - A Review of the Literature

SUMMARY

Objectives: *To review current knowledge of biphosphonates with respect to oral cavity pathology and dental procedures. The scope is the chemistry, properties, chemical uses and recommendations that refer to biphosphonates and are of oral and maxillofacial interest.*

Sources: *"PUBmed" and e-articles searched electronically with key words biphosphonates, oral cavity, oral pathology and manifestations.*

Conclusions: *Biphosphonates are analogues of pyrophosphate, comprising of 2 phosphate groups linked by a phospho-ether bond. This particular structure is responsible for their resistance to hydrolysis and their great variation in biological and therapeutic background. There are nitrogen and non-nitrogen containing biphosphonates of 4 generation types: I, II, III and IV. Etidronate is the main representative of the first type and zoledronic acid, pamidronate and ibandronate are some of the newer ones. Biphosphonates act almost exclusively on bone in proximity to the osteoclasts. They aren't metabolized and persist within the bone for long periods of time. The mechanisms that characterize their action are closely related to bone resorption and a decrease in bone turnover. Their action is explained on the basis of calcification, delay of the dissolution of calcium phosphate crystals, inhibition of formation and aggregation of calcium phosphate crystals. They are focused on the treatment of Paget's disease, hypercalcemia, bone metastases and present an anti-osteolytic effect, counteract bone loss in chronic periodontitis or play an anti-neoplastic role. Osteonecrosis, avascular necrosis of the jaws, renal toxicity, fever, bone pain, hypocalcemia, mild gastrointestinal complains and jaw fracture after extraction can follow biphosphonate therapy. All these underline the need of certain preventive measures and recommendations.*

Keywords: Bisphosphonates; Osteoclasts; Osteonecrosis; Prevention; Treatment

Petros Papadopoulos[1], Alexandros Kolokotronis[2]

[1]Private Practice
[2]Department of Oral Medicine and Maxillofacial Pathology, Dental School, Aristotle University Thessaloniki, Greece

REVIEW PAPER (RP)
Balk J Stom, 2009; 13:4-10

Introduction

Biphosphonates have been known to chemists since the middle of the 19th century, when the first synthesis in 1865 occurred in Germany[1]. Our knowledge of the biological characteristics of biphosphonates dates back 30 years[2].

They are a group of medication that have become increasingly and more widely used especially in the management of certain bone diseases, some of which are very common in our ageing population. However, daily clinical practice and research reveal the existence of several side-effects of biphosphonates, as well as an association between them and the implication or bone diseases that are able to put the success of dental procedures and not only.

These facts designate the need of special refers to the characteristics, properties of the medicine and their correlation with bone diseases and dental practice. This is the goal of this review.

Chemistry and Classification

Biphosphonates are synthetic compounds, analogues of pyrophosphate, an endogenous regulator of bone

mineralization. They are comprised of 2 phosphonate groups linked by phospho-ether bonds (P-C-P structure). This structure makes them resistant to hydrolysis in acid conditions or by pyrophosphatases. The P-C-P structure allows a great number of possible variations either by changing the 2 lateral chains on the carbon, or by esterifying the phosphate groups; therefore, the biological therapeutic and toxicological characteristics of different generations of biphosphonate vary dramatically[3-5].

Currently there are 2 main types of biphosphonates: nitrogen-containing and non-nitrogen containing. According to evolution, literature classifies them in 4 generation types: I, II, III and IV. Etidronate is the main representative of the first, and zolendronic acid, pamidronate and ibandronate are some of the newer ones.

Mechanism of Action

Biphosphonates act almost exclusively on bone when administered because of specific affinity to it where they deposit in newly formed bone and in proximity to the osteoclasts.

The half life of biphosphonates is quite short, ranging from 30 min to 2 hours. They are not metabolized and persist within bone for long periods of time[6,7]. They decrease both osteoclast activity and osteoclast numbers. The first is exemplified by internalization by osteoclasts causing disruption of osteoclast mediated bone resorption, the second by inhibiting osteoclast recruitment and apoptosis of them, thus reducing their number. The result is bone resorption and a decrease in bone turnover. However, once incorporated into bone tissue biphosphonates persist for up to 10 years depending on the skeletal turnover time.

The mechanisms of action of these medicines are described on the basis of several processes. The most important of these is calcification throughout which biphosphonates inhibit the formation and aggregation of calcium phosphate crystals, block the transformation of amorphous calcium phosphate into hydroxyapatite, and delay the aggregation of apatite crystals[8-10]. They delay the dissolution of calcium phosphate crystals and inhibit the formation and aggregation of calcium oxalate crystals. Biphosphonates' action is also taking place by bone resorption, which is performed by inhibition of mineral dissolution, on tissue level by reduction in bone turnover, on cellular level by inhibition of osteoclast recruitment and osteoclastic adhesion to mineralized matrix, and by shortening of life span of osteoclasts and inhibition of their activity as well. On the molecular level, various biphosphonates, especially clodranate, inhibit lysosomal enzymes and prostaglandin synthesis; prostaglandins are involved in bone resorption. They can also have several effects through other cells, such as osteoblast lineage cells, cells of mononuclear phagocyte and immune system, such as macrophages or tumour cells.

It is very important to mention that the 2 families of biphosphonates have different pathways of action. Nitrogen containing ones act through the mevalonate pathway, but non-nitrogen containing biphosphonates, such as etidronate, tiludronate and clodronate, are incorporated into phosphate chain of adenosine triphosphate (ATP) containing compounds, so that they become non-hydrolysable. The new P-C-P containing ATP analogues inhibit cell function and lead to cell death by apoptosis.

The cellular uptake of biphosphonates is mostly taking place in the cytosol, and the concentration expressed in terms of cellular water can be several folds higher than in the medium.

They have a very low bioavailability from a few % to 1% - mostly for the newer ones. This is explained by their low lipophilicity, which hampers trans-cellular transport and their negative change which hampers para-cellular transport. The absorption in the intestine mainly follows a para-cellular route[11].

The administration of ethylene-diaminotetraacetic acid, a strong Ca chelator, favours the absorption of biphosphonates and increased doses of them will lead to an increase in their own absorption[12]. Once in the blood, biphosphonates disappear very rapidly, mostly to bone[13]. This is due to the fact that they are characterized by a rapid and strong binding to hydroxyapatite crystals. Skeletal uptake might be determined above all by the vascularization of the bone.

The various biphosphonates display some differences in their affinity for the hydroxyapatite surface[14]. They were found to deposit under the osteoclasts besides those locations within the bone where new bone is formed[15]. The distribution of the amount deposited in bone formation and resorption sites depends upon the amount of medicine administered. Small quantities deposit mostly under the osteoclasts while bigger ones go to both forming and resorption sites. Soft tissues on the other hand are exposed to these compounds for only short periods, explaining their bone specific effects and their low toxicity. However, some biphosphonates, especially pamidronate, can at times deposit in other organs, such as stomach, liver and spleen[16-18].

Once the biphosphonates are buried in the skeleton, they will be released only when the bone is destroyed in the course of the turnover. The skeletal half-life of various biphosphonates is sometimes more than 10 years. They aren't metabolized *in vivo* due to the stability of their P-C-P bond to heat and most chemical reagents, as well as their resistance to hydrolysis by the enzymes found in the body. Biphosphonates are excreted renally[19].

Clinical Uses

Biphosphonates appear to play a multifactorial role in many kinds of clinical cases. One of the early clinical uses of biphosphonates was as bone scan imaging agent[3]. They are also used in the treatment of Paget's disease, hypercalcemia (the result of excessive bone resorption and release of Ca into circulation) related to malignancy, in the management of bone metastases by reducing skeletal tumour burden in patients with multiple myeloma and prostate cancer[20]. They play an extinguished role - reduce the incidence of new fractures in the management of osteoporosis characterized by abnormal rarefaction of bone, especially the third generation biphosphonates (riserdronate) in postmenopausal women[21]. They have an anti-osteolytic effect by inhibition of osteoclastic action[22]. They can be applied to counteract bone loss in chronic periodontitis[23]. Besides all these, they play an anti-neoplastic role by interacting with osteoclasts, osteoblasts, tumour cells, cytokine and growth factor production, leading to the interruption of bone destruction; by immunomodulating properties on γδ T cells (activate them), they have pre-apoptotic and anti-angiogenic potentials - their use as radiation sensitizers.

Properties

The first is inhibition of calcification when given at high doses and bone resorption[24,25]. Biphosphonates impair the mineralization of normal calcified tissues, such as bone and cartilage and dentine, enamel and cementum[2]. In the latter case, their administration can lead to a reduction of the extraction force. In addition to it, they decrease bone loss or actually increase bone mineral density. At the cellular level, biphosphonates increase proliferation of osteoblasts and cartilage cells, biosynthesis of collagen and osteocalcin by bone cells, and proteoglycans by cartilage cells. The effect on collagen may be due to impaired intracellular collagenolysis. It is very interesting to mention that bone that has been treated with biphosphonates is still able to show an anabolic response to intermittent parathyroid hormone although the effect is blunted[2]. They also exhibit anti-angiogenic properties by depriving tumour cells of adequate nutrient and blood supply. Biphosphonates alter the bone microenvironment making it less favourable for tumour cell proliferation[20].

Side-Effects

Biphosphonate therapy is presented by many scientists and case reports observations to be related with important adverse effects including renal toxicity, fever, bone pain, hypocalcemia and mild gastrointestinal complains[26-30]. In particular, the biphosphonate associated osteonecrosis of the jaws is a subject that draws the intense interest of the dental community. Osteonecrosis is characterized by the death of bone that results as a natural consequence of a wide variety of systemic and local factors compromising the blood flow of bone, such as haemoglobinopathies, anticardiolipin antibodies, defects of thrombotic and fibrinolytic systems, fat emboli, alcoholism, systemic lupus erythematosus (SLE) [31-34], corticosteroid administration and recently, as proven, biphosphonate therapy. Bone exposure caused by osteonecrosis has particular sites of establishment on the jaws: the posterior mandible in the molar area along the mylohyoid ridge is the most common one, followed by the posterior maxilla.

The complication of exposed bone jaws associated with biphosphonate therapy (osteonecrosis/osteopetrosis) is explained by 2 theories. The leading theory suggests that it is caused by cessation of bone remodelling and bone turnover by the basic osteoclast inhibiting effect of the drugs when given to reduce loss of bone density in osteoporosis, or to prevent cancer spread in bone. Since the jaws have a greater blood supply than other bones, and a faster turnover rate related both to their daily activity and the presence of teeth (which mandates daily bone remodelling around the periodontal ligament), biphosphonates are highly concentrated in the jaws. Coupled with chronic invasive dental diseases and treatments and the thin mucosa over bone, this anatomic concentration of biphosphonates causes this condition to be manifested exclusively in the jaws. Thus the exposed bone in the jaws is the direct result of the action of the drugs on the daily remodelling and replenishment of bone. Osteoblasts and osteocytes live for only about 150 days. If upon their death the mineral matrix is not resorbed by osteoclasts which release the cytokines of bone morphogenetic protein and insulin-like growth factors to induce new osteoblasts from the stem cell population, the osteon becomes acellular and necrotic. The small capillaries within the bone become involuted and the bone avascular. A spontaneous breakdown of the overlying mucosa, injury or invasive surgery in the jaws, usually cause this necrotic bone to expose. It then fails to heal.

According to the competing theory (based only on experimental evidence) biphosphonates, pamidronate and zoledronate, inhibit endothelial cell proliferation in the jaws thus leading to loss of blood vessels and avascular necrosis[35,36]. We must underline that osteonecrosis is actually a chemically induced form of osteopetrosis, an inherited autosomal dominant trait characterized by the loss of osteoclast development with 7 subtypes. In osteopetrosis, as in biphosphonate induced exposed bone, angiogenesis in the soft tissues is normal.

Moreover, the comparison between osteonecrosis and osteoradionecrosis is useful for the differential diagnosis of the first. Unlike osteoradionecrosis (ORN), biphosphonate associated osteonecrosis (BAO) doesn't appear to be amenable to hyperbaric oxygen therapy. In ORN, radiation induced tissue damage is characterized by hypoxia, hypocellularity and hypovascularity which are reversible or preventable to some degree with revascularization of bone. By contrast, in BAO the alteration in bone metabolism is such that revascularization alone is insufficient to alter the course of the lesions because biphosphonates are not metabolized appreciably and have the potential to remain in the bone indefinitely[37,38]. It has been reported that BAO is refractory to hyperbaric oxygen therapy and advised against using hyperbaric oxygen in the treatment of these patients.

A distinguished feature between the 2 situations is coming out from the observation that the maxilla is commonly involved in BAO, whereas this is sighted rarely in cases of ORN. It is critical to mention that BAO has substantial clinical implications because many patients fail to heal after dental surgical procedures, e.g. extraction.

Osteonecrosis is often related to a site of previous dental treatment but can also occur in regions without it. Jaw pain is present, as well as an infection secondary to bone exposure[26]. Extractions make the conditions worse with a non-healing socket sequestration, pain, offensive smell, soft tissue infections and deformity[3]. The class of biphosphonates that is mostly related with osteonecrosis is the nitrogen-containing (zolendronate, pamidronate).

Besides osteonecrosis and exposed bone lesions, biphosphonate therapy is being associated with avascular necrosis although our current knowledge of the related process is limited, showing that these drugs are a direct factor in a multifactorial aetiology leading to avascular necrosis in the jaws. They are suggested to produce ischemic changes in the maxilla and mandible[3].

Finally dental implant failure attributable to oral biphosphonate therapy has been reported in patients with osteoporosis[39].

Preventive Measures and Recommendation

The whole description of the implications of the biphosphonate therapy reflects the critical value of several preventive measures and recommendations in order to avoid them. Generally, impacted teeth that are completely covered by bone or soft tissue should be left undisturbed, but those with an oral communication are recommended to be removed and given a month healing period. Prophylactic antibiotic coverage for invasive dental procedures is necessary and thus penicillin remains the drug of choice[19]. In case of penicillin allergy, combination of guinolones and metronidazole would be appropriate.

Before initiating biphosphonate therapy and for non invasive dental care, biphosphonate therapy need not to be delayed. In case of invasive procedures, such as extractions, commencement of biphosphonate therapy should be delayed for a month to allow sufficient time for home recovery and healing. Once the regimen of biphosphonate therapy has begun, surveillance schedule of once every 4 months is recommended[40].

While receiving biphosphonate therapy, tooth extractions should be avoided as well as selective surgery within the jaws, replaced by alternatives including root canal treatment and amputation of the crown. Patients with dentures should have well maintained soft liners to minimise trauma of the oral mucosa, or leave their dentures out. Pain control is important Fluoride and possibly 0.12% chlorhexidine may be considered to decrease the possibility of tooth extraction[26]. Placing implants should be strictly avoided[41].

Treatment of Patients with Osteonecrosis/ Established Avascular Necrosis of the Jaws

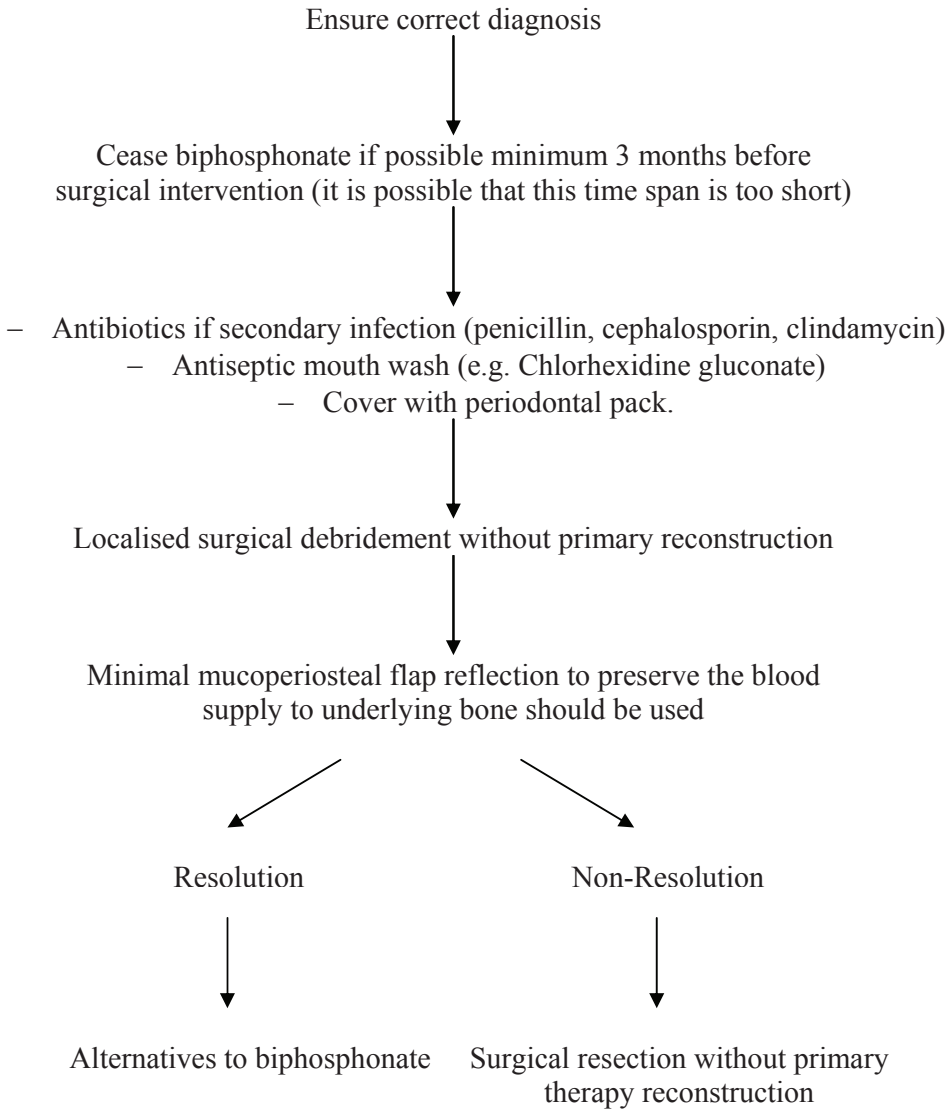
Attempts to accomplish debridement, cover the exposed bone with flaps, or bone contouring procedures are being considered only in cases refractory to non-surgical management, and in the face of continuing symptoms[19]. This model of therapy is suitable for avascular necrosis of the jaws being shown by table 1.

Bone grafting either as a free graft or by microvascular transfer involves affected bone. There is a risk that there could be 2 problem areas, the donor graft site as well as the recipient jaw site. Major resection surgery should be avoided[5].

In osteonecrosis, treatment should be directed towards eliminating or controlling pain, preventing progression of the exposed bone .The necrotic exposed bone itself is not painful and will remain structurally sound to support normal jaw function. Once secondarily infected, it will become painful and may lead to cellulitis and fistula formation[42, 43]. Pathologic fractures do not usually occur unless debridement surgeries have reduced the structural integrity of the mandible.

Therefore, aside from rounding off sharp bony projections that produce soft tissue inflammation, and a long term course of penicillin V-K 500 mg, 4 times a day, and 0.12% chlorhexidine[44] is prescribed. Occasionally, severe cellulitis will warrant hospital care using IV antibiotics (ampicillin).

Table 1: Therapeutic management of the established avascular necrosis of the jaws



Conclusions

Summarising the main points concerning biphosphonates, on the basis of dental interest, we should mention that they are used in the treatment of Paget's disease, multiple myeloma and in chronic periodontitis by counteracting bone loss. However, it is critical to notice that biphosphonate therapy needs to be stopped 6 months before the attempt of any surgical or invasive method in the mouth, including tooth extraction, thus minimising the danger of osteonecrosis.

There are many unknown facts regarding the process of biphosphonate related osteonecrosis of the jaws. The incidence is currently low, 0.1-1% of all patients on biphosphonates, and may differ among different bone pathologies, biphosphonates and dosage regiments. The most important question, however, is whether this is a cumulative problem.

Moreover, biphosphonate therapy has become a standard of care for patients with malignant bone disease. Preclinical and preliminary clinical data suggest that biphosphonates may prevent cancer-treatment induced bone loss in patients with breast or prostate cancer receiving oestrogen/androgen therapies. In addition to it, biphosphonates have demonstrated anti-tumour activity in preclinical models and clinical evidence supports the fact that biphosphonates may slow the progression of bone lesions or prevent bone metastases[45]. Therefore, trials to determine the anti-tumour effects of these drugs in patients with early stage breast and prostate cancer, non-small

cell lung cancer and renal cell carcinoma will provide important insight into the optimal timing and modality of biphosphonate therapy in those patient populations. The clinical applications of these medicines are likely to expand further in oncology as these trials mature. This whole concept reveals a part of the new horizons in biphosphonate therapy research[45].

References

1. *Menschutkin M*. Ueber die Einwirkung des Chloracetyls auf phosphorige Saüre. *Annals of Chemical Pharmaracology*, 1865; 133:317-320.
2. *Von Baeyer H, Hofmann KA*. Acetodiphosphorige Saure. *Berichte der Deutschen Chemischen Gesellschaft*, 1897; 30:973-1978.
3. *Cheng A, Marrokokki A, Carter G, Stein B*. The dental implications of biphosphonates and bone disease. *Australian Dental Journal - Medications Supplement*, 2005; 50:4.
4. *Sparidans RW, Twiss IM, Talbot S*. Biphosphonates in bone diseases. *Pharmacology World Science*, 1998; 20:206-213.
5. *Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, Frith JC*. Cellular and molecular mechanisms of action of biphosphonates. *Journal of Cancer*, 2000; 88:2961-2978.
6. *Martin TJ, Grin V*. Biphosphonates-mechanisms of action. *Australian Prescriber*, 2000; 23:130-132.
7. *Carter GD, Goss AN*. Letter to the editor. Biphosphonates and avascular necrosis of the jaws. *Aus Dent J*, 2003; 48:268.
8. *Francis MD, Russel RGG, Fleisch H*. Biphosphonates inhibit formation of calcium phosphate crystals in vitro and pathological calcification in vivo. *Journal of Science*, 1969; 165:1264-1266.
9. *Hansen NM, Felix R, Bisaz S, Fleisch H*. Aggregation of hydroxyapatite crystals. *Biochimica et Biophysica Acta*, 1976; 451:549-559.
10. *Francis MD*. The inhibition of calcium hydroxyapatite crystal growth by polyphosphonates and polyphosphates. *Calcified Tissue Research*, 1969; 3:151-162.
11. *Boulenc X, Marti E, Joyeux H, Roques C, Berger Y, Fabre G*. Importance of the paracellular pathway for the transport of a new biphosphonate using the human CACO-2 monolayers model. *Biochemical Pharmacology*, 1993; 46:1591-1600.
12. *Boulenc X, Roques C, Joyeux, Berger Y, Fabre G*. Biphosphonates increase tight junction permeability in the human intestinal epithelial (Caco-2) model. *Int J Pharmacol*, 1995; 123:13-24.
13. *Fleisch H*. Bisphosphonates: Mechanisms of action. *Endocrine Reviews*, 2006; 19:80-100.
14. *Bisaz S, Jung A, Fleisch H*. Uptake by bone of pyrophosphate, biphosphonates and their technetium derivatives. *J Clin Sci Mol Med*, 1978; 54:265-272.
15. *Sato M, Grasser W, Endo N, Akins R, Simmons H, Thompson DD, et al*. Biphosphonate action. Alendronate localization in rat bone and effects on osteoclast ultrastructure. *J Clin Invest*, 1991; 88:2095-2105.
16. *Larsson A, Rohlin M*. In vivo distribution of C-labelled ethylene-1- hydroxy-1, 1-diphosphonate in normal and treated young rats. An autoradiographic and ultrastructural study. *Toxicology and Applied Pharmacology*, 1980; 52:391-399.
17. *Wingen F, Schmahl D*. Distribution of 3- amino-1-hydroxypropane-1, 1-diphosphonic acid in rats and effects on rat osteosarcoma. *Arzneimittelforschung*, 1985; 35:1565-1571.
18. *Monkkonen J, Koponen HM, Ylitalo P*. Comparison of the distribution of three bisphosphonates in mice. *Pharmacol Toxicol*, 1990; 66:294-298.
19. The Endocrine Society. Editorial Long-Term Safety of Biphosphonates. *The Journal of Clinical Endocrinology & Metabolism*, 2005; 90:1897-1899.
20. *Melo DM, Obeid G*. Osteonecrosis of the Maxilla in a Patient with a History of Biphosphonate Therapy. *J Can Dent Assoc*, 2005; 71:111-1113.
21. *Woodward J, Coleman R, Holen I*. Preclinical evidence for the effects of biphosphonates and cytotoxic drugs on tumour cell invasion. *Anticancer Drugs*, 2005; 16:11-19.
22. *Hughes DE, Wright KR, Uy HL, Sasaki A, Yoneda T, Roodman GD, Mundy GR, Boyce BF*. Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. *Journal of Bone and Mineral Research*, 1995; 10:1478-1487.
23. *Figara G, Beninati F, Rubino I, Vannucchi A, Longo G, Tonelli P, Pini Prato G*. Osteonecrosis of the jaws in periodontal patients with a history of biphosphonates treatment. *J Clin Periodont*, 2005; 141:4793-4796.
24. King WR, Francis MD, Michael WR. Effect of disodium ethane-1-hydroxy-1,1-biphosphonate on bone formation. *Clinical Orthopaedics and Related Research*, 1971; 78:251-270.
25. *Flora L, Hassing GS, Parfitt AM, Villanueva AR*. Comparative skeletal effects of two biphosphonates in dogs. *Metabolic Bone Disease & Related Research*, 1980; 2:389-407.
26. *Bukowski JF, Dascher CC, Das H*. Alternative biphosphonate targets and mechanisms of action. *Biochemical and Biophysical Research Communications*, 2005; 328:746-750.
27. *Pavlakis N, Schmidt R, Stockler M*. Bisphosphonates for breast cancer. *The Cochrane Database of Systematic Reviews*, 2005; CD003474
28. *Smetana S, Michlin A, Rosenman E, Biro A, Boaz M, Katzir Z*. Pamidronate-induced nephrotoxic tubular necrosis:a case report. *Clinical Nephrology*, 2004; 61:63-67.
29. *Dicuonzo G, Vincenzi B, Santini D, Avvisati G, Rocci L, Battistoni F, et al*. Fever after zoledronic acid administration is due to increase in TNF-alpha and IL-6. *Journal of Interferon and Cytokine Research*, 2003; 23:649-654.
30. *Teramoto S, Matsuse T, Ouchi Y*. Increased cytokines and pamidronate-induced bone pain in adults with cystic fibrosis. *Lancet*, 1999; 353:750.
31. *Merigo E, Manfredi M, Meleti M, Corradi D, Vescovi P*. Jaw bone necrosis without previous dental extractions associated with the use of biphosphonates (pamidronate and zoledronate): a four-case report. *J Oral Pathol Med*, 2005; 34:613-617.
32. *Bouquot JE, McMahon RE*. Neuropathic pain in maxillofacial osteonecrosis. *J Oral Maxillofac Surg*, 2000; 58:1003-1020.

33. *Assouline-Dayan Y,Chang C, Greenspan A, Shoenfeld Y, Gershwin ME*. Pathogenesis and natural history of osteonecrosis. *Seminars in Arthritis and Rheumatism*, 2002; 32:94-124.
34. *Gruppo R, Glueck CJ, McMahon RE, Bouquot J, Rabinovich BA, Becker A, et al*. The pathophysiology of alveolar osteonecrosis of the jaw: anticardiolipin antibodies thrombophilia and hypofibrinolysis. *J Lab Clin Med*, 1996; 127:481-488.
35. *Zigic TM, Marcous C, Hungerford DS, Dansereau JV, Stevens MB*. Corticosteroid therapy associated with ischemic necrosis of bone in systemic lupus erythematosis. *Am J Med*, 1985; 79:596.
36. *Marx ER, Sawatari Y, Fortin M, Broumand V*. Biphosphonate-induced exposed bone (Osteonecrosis/ Osteopetrosis) of the jaws: Risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg*, 2005; 63:1567-1575.
37. *Melo DM, Obeid G*. Osteonecrosis of the jaws in patients with a history of receiving biphosphonate therapy. Strategies for prevention and early recognition. *J Am Dent Assoc*, 2005; 136:1675-1681.
38. *Russel RG, Rogers MJ, Frith JC, Luckman SP, Coxon FP, Benford HL, et al*. The pharmacology of biphosphonates and new insights into their mechanisms of action. *J Bone Miner Res*, 1999; 14:53-65.
39. *Ruggiero LS, Mehrotra B, Rosenberg JT, Engroff SL*. Osteonecrosis of the Jaws Associated with the Use of Biphosphonates: A Review of 63 Cases. *J Oral Maxillofac Surg*, 2004; 62:527-534.
40. *Schwartz HC*. Osteonecrosis and biphosphonates: correlation versus causation. *J Oral Maxillofac Surg*, 2004; 62:763-764.
41. *Carter GD, Goss AN, Doecke C*. Bisphosphonates and avascular necrosis of the jaw: a possible association. *Medical Journal of Australia*, 2005; 182:413-415.
42. *Marx RE*. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*, 2003; 61:1115-1117.
43. *Migliorati CA*. Biphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol*, 2003; 21:4253-4254.
44. *Dimitrakopoulos I, Magopoulos C, Karakasis D*. Biphosphonates-induced avascular osteonecrosis of the jaws: a clinical report of 11 cases. *J Oral Maxillofac Surg*, 2006; 35:588-593.
45. *Lipton A*. Towards New Horizons. The Future of Biphosphonate Therapy. *The Oncologist*, 2004; 9:38-47.

Correspondence and request for offprints to:

Petros Papadopoulos
542 48, Thessaloniki
Greece
E-mail: peterpap77@yahoo.gr