Beyond ONJ – A review of the potential uses of bisphosphonates in dentistry

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In brief

The aim of this paper is to increase dentists' awareness of other potential benefits of these drugs.

This paper reviews, and gives the reader an insight to, past and current research on these potential benefits within dentistry.

Bisphosphonates need to be recognised outside of the context of osteonecrosis of the jaws (ONJ).

There is evidence, although limited, for beneficial effects of bisphophonates (BPs) across multiple dental specialties. Within implant dentistry BP coatings have been shown to significantly increase pull out forces and bone density in animal models, and significantly increase implant stability whilst reducing marginal bone loss in humans. Adjunctive topical and systemic application of BPs during conventional periodontal treatment have shown significant improvements in probing depth and clinical attachment level in various forms of periodontal disease. Within orthodontics, BPs have been shown to significantly reduce root resorption and have benefits with respect to anchorage maintenance. Case reports have suggested the use of BPs in the management of diffuse sclerosing osteomylitis. Whilst this review highlights these potential benefits and acknowledges there are no reported cases of osteonecrosis of the jaw associated with locally applied BP, there remains a paucity of human and long-term studies exploring BPs in the context of significant clinical benefit. Further human studies are required to understand the long-term clinical outcomes of these drugs when used as primary therapeutic agents, or adjuncts to conventional treatment.

Introduction

Most commonly used in the treatment of osteoporosis in post-menopausal women, or for oncology patients with metastatic disease, bisphosphonates (BPs) are implicated in osteonecrosis of the jaws (ONJ), a condition which has received extensive attention in the dental literature. The incidence of ONJ in patients receiving oral BPs for osteoporosis varies, but is generally reported as less than 0.5% in most studies.[1] The incidence of medication-related ONJ (MRONJ) in cancer patients exposed to zolendronate is higher (up to 6.7%), but when limited to studies of level 1 evidence, the risk approximates 1%.[1] This association has overshadowed any potential benefits of BPs in relation to implant dentistry, orthodontics, periodontal health and pathology of the jaws. This article will highlight beneficial effects BPs may have across a range of specialties within dentistry.

References cited in this literature review were identified through searches of publications listed by PubMed and Medline. Our search terms included 'bisphosphonate', and names of each individual subject, such as 'implant' or 'periodontal disease'. References were also identified from relevant review articles if thought to be of value. Both animal and human studies were included in our search criteria, providing they were published in English.

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The role of bisphosphonates

Bisphosphonates are used in the management of osteoporosis, where an imbalance of bone remodelling results in bone of lower density and quality; administered orally (daily, weekly, or monthly) or intravenously (every three months or annually) to reduce fracture risk. Within oncology, BPs are used as adjuncts to anti-neoplastic therapy to manage complications of bony metastatic spread including: pain, hypercalcemia and pathological fracture.

Mechanism of action

In general, bisphosphonates are inhibitors of osteoclast-mediated bone resorption. Nitrogen-containing BPs such as alendronate and risedronate attach to hydroxyapatite on bony surfaces, which in turn undergoes osteoclast-mediated resorption. The BP taken up by osteoclasts during bone resorption inhibits the enzyme farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway. Metabolites produced in this pathway are important regulatory proteins to the cell membrane required for osteoclast function. Earlier BPs (that do not have a nitrogen-containing side chain) such as etidronate and clodronate are incorporated into adenosine triphosphate (ATP) causing it to be resistant to hyrolysis.[2] Accumulation of this nonhydrolyzable adenine-containing metabolite eventually leads to cell death of the osteoclast.[3] The effects of bisphosphonates on bone resorption may not be due to their direct action on osteoclasts

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alone, there is some evidence they stimulate proliferation of osteoblast precursor cells[4] and the production of osteoprotegerin by osteoblasts[5] (an anti-resorptive protein), however the mechanisms involving osteoblasts are not as well understood.

Implants

Placement of dental implants is a traumatic procedure involving bony removal at the osteotomy site, with subsequent 'healing' through osseointegration. Osseointegration is characterised by formation of a union between the bone and implant, relying on remodelling of early woven bone to form mature bone in close apposition to the implant surface. Perhaps unsurprisingly, there are reports of systemic oral BPs associated with delayed wound healing,[6] failure of osseointegration[7] and failure post osseointegration,[8–10] but it is notable that a systematic review of the literature concluded that there was no significant difference in short-term implant survival between patients taking oral BPs compared with control groups.[11] The American Association of Oral and Maxillofacial Surgeons (2014) does not suggest prohibition of placement of dental implants in patients taking oral BPs but does specifically advise clinicians against procedures involving direct osseous injury in patients receiving intravenous BPs or anti-angiogenic therapy for cancer.[1]

There is some evidence that bisphosphonates may have a positive effect on osseointegration of dental implants when used as a surface coating, specifically improving early fixation of implants. The rationale behind use of BPs in implant placement is to prevent resorption of bone at the osteotomy site. Modifications to the dental implant surface texture (for example, sandblasting and acid etching) and chemical composition (for example, surface coating), by plasma spraying or electrochemical techniques, have been studied as potential methods to aid peri-implant bone formation. Surface coatings that have been researched include hydroxyapatite (HA), tricalcium phosphate (TCP), bioglass and more recently bisphosphonates.[12] Bisphosphonate coated implants are prepared by covalently bonding a fibrinogen matrix to the metal onto which BPs, specifically pamidronate and ibandronate, are bound and adsorbed to the matrix.[13–16] Most studies are based on animal models, however, some limited human trials have also been performed.[13] It is acknowledged, however, that lack of standardisation in methods and variable primary and secondary outcome measures render these studies difficult to compare directly.

Animal studies

Rat model studies using BP coated implants have shown significantly increased pull out forces and pull out energies using stainless steel screws[14] and titanium screws[15] after two weeks of insertion. Another rat model study compared the bone density around BP coated screws, fibrinogen coated screws and uncoated screws at one and eight weeks.[16] Bone area density in the screw thread at eight weeks was 40% higher for the BP screws compared to uncoated and fibrinogen coated ones ($P = 0.01$), and was more than double in comparison to the uncoated screws (120% higher) at a distance of 250 μm from the screw ($P = 0.00$). The authors have suggested that the increase in the bone density in close proximity to the screw could explain the improved mechanical fixation seen in previous studies. In another study comparing BP coated, HA coated, and control screws, the authors concluded that BP coated screws showed a significantly increased pull out force compared to controls, and bisphosphonates improved fixation by increasing the amount of surrounding bone (demonstrated by a significant increase in bone volume around the screw) whereas HA mainly improves bone to implant attachment.[17] However, changes in bone quality, significantly lower bone-implant contact (%BIC) and significantly lower removal torque have been reported when sodium alendronate (ALN) gel was applied onto titanium implant surfaces versus a control of sterile saline.[18]

Human studies

Published studies on the use of BP coated implants in humans are limited to a few small studies.[13,19,20] One report included 16 patients each receiving a BP coated implant (pamidronate and ibandronate) and a control implant.[19] Implant fixation was evaluated by measurement of resonance frequency (implant stability quotient; ISQ). At six months, the average increase in ISQ was significantly greater for the coated implants group, suggesting improved implant fixation. The authors also compared periapical radiographs of the experimental and control implants, finding significantly less marginal bone loss in the BP group at six months, 18 months (one year after loading the implants) and five years. At five years the median difference in marginal bone loss within each pair of implants was 0.34 mm (95% confidence interval 0.00–0.75 mm; $P = 0.04$). A split-mouth study[20] of 39 patients also demonstrated a 100% survival rate at five years in the test group of implants, where the implant osteotomy site and implant surface were exposed to 3% clodronate solution mixed with surfactant. This study showed a reduction in marginal bone loss in the test sites, however this was not statistically significant. In both studies there were no reported cases of ONJ, nor failure of osseointegration in the test implants. In support of this, McKenzie *et al.* found the BPs eluted from implants remained mainly localised to the implant, with minimal systemic distribution,[21] suggesting that should ONJ develop it might be resolved by removing the implant with the intimately related bone.

These studies demonstrate potential clinical benefits of BPs in implant dentistry, however, they are relatively short in duration, small in size, mostly in animals, and thus the extent of clinical benefit is uncertain at this stage.

Periodontal disease

Bisphosphonates have been investigated as potential inhibitors of alveolar bone resorption in the treatment of periodontitis for over two decades.[22–29] Recently, this hypothesis has been developed to combine bisphosphonate with platelet rich fibrin (PRF) to create a synergistic approach in the management of this chronic disease.[30]

Local application

Local delivery of these drugs to sites of periodontal disease has been examined by a few investigators.[22–25,30] For example, subgingival injection of 1% ALN gel as an adjunct to scaling and root planing (for class II furcation defects, intrabony defects in chronic disease, aggressive disease, and intrabony defects in patients with diabetes mellitus) was compared to control groups receiving scaling, root planning and a placebo gel. The RCTs showed significant improvements in probing depth (PD) reduction, clinical attachment level (CAL) gain and improved bone infill compared to the control groups at six months, with the first study showing similar results at 12 months. It is suggested that subgingival injection of the gel offers an advantage over raising the mucoperiostium to apply the gel, reducing both the number of clinical stages and the risk of bone loss following flap elevation.[24] The potential benefits of subgingival

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injection over systemic administration of ALN in the context of adverse reactions and patient compliance are also suggested.[31]

The use of PRF as a growth factor providing agent, aimed to encourage bone regeneration in periodontal disease has shown significantly positive clinical outcomes at nine months.[32] Further application of this technique has been trialled in a more recent study combining PRF with 1% ALN gel (1:1) to treat intra-bony defects in chronic periodontitis.[30] The RCT showed promising results at nine months with significantly greater reduction in PD and CAL gain and defect depth reduction compared to the control group receiving conventional surgical periodontal therapy only and another group receiving surgical periodontal therapy and PRF.

A summary of the results of these respective trials are outlined in Table 1. ONJ was not reported as a complication of ALN gel application during the trial periods of the mentioned studies, however, longer study periods and multi-centre trials are required to further investigate clinical benefits and possible adverse effects on the surrounding tissues. To date there have been no studies comparing other locally applied adjuncts (such as antimicrobials) to BPs.

Systemic application

The host modulating effect of systemic bisphosphonate adjunct with the treatment of chronic periodontitis has also been studied.[26–28] ALN has been trialled as a systemic adjunctive drug therapy in preventing bone loss in patients with type 2 diabetes mellitus and periodontal disease.[27] A double blind RCT including 40 patients with established periodontitis, randomly allocated either alendronate (10 mg/daily) or a placebo treatment for six months. Following six months of scaling and root planing, by the same operator, the ALN group showed a significant decrease in a biochemical marker of bone resorption (urine N-telopeptide) compared to the control group. Whereas the distance between the alveolar bone border and the cemento-enamel-junction increased in the control group, a significant decrease was seen in the experimental group, indicating bone gain. The short duration of the study meant the authors could only make observations at six months, with uncertainty as to whether the bone gained in the treatment group was maintained or resorbed upon ALN cessation. A similar study carried out over 12 months showed daily bisphosphonate treatment in conjunction with initial scaling and root planing followed by maintenance care at three month intervals improved CAL, PD, and BOP, relative to the placebo group, during the 612 month period in sites of mild and moderate periodontal disease, but not in sites of severe disease.[26] The authors discuss the confounding factor of more challenging debridement for teeth with deeper periodontal pockets. Bhavsar *et al.* evaluated the effect of risedronate (5 mg/daily) in conjunction with conventional treatment on alveolar bone height and density, using intra-oral radiographs and cone beam computed tomography.[28] They concluded that bisphosphonate had a significantly positive effect on these outcome measures in their cohort of postmenopausal women with moderate to severe chronic periodontitis, however, no control group was used.

Important caveats when interpreting these findings relate to the small sample sizes and limited study durations. Overall, these papers challenge the concept that bisphosphonates have a negative effect in periodontal disease and may in fact show benefit in mild and moderate cases.

Orthodontics

Within orthodontics, potential benefits of bisphosphonates have been considered in the context of root resorption and anchorage maintenance. Root resorption is a common but undesirable side-effect of orthodontic treatment, and a small number of animal studies have demonstrated a potential role for bisphosphonates in its prevention. A split-mouth study in mice found that local injection of bisphosphonate solutions (unspecified) during fixed appliance therapy resulted in significantly less root resorption at treated sites compared with control sites.[33] This effect was thought to result from bisphosphonate-induced apoptosis of odontoclasts. A similar study by Liu *et al.* demonstrated that local subperiosteal injection of clodronate, a non-nitrogeneous bisphosphonate, elicited significantly reduced root resorption at treated sites compared with control sites in rats.[34] However, in addition to the small sample sizes used in these studies, it is notable that prevention of root resorption was observed in the context of reduced overall tooth movement, which in itself may be considered an unfavourable outcome during orthodontic treatment.[33,34]

Reduced tooth movement during orthodontic treatment can however be advantageous, specifically in relation to anchorage, which is defined as 'the resistance to unwanted tooth movement'.[35] Current methods for anchorage maintenance are suboptimal, with reliance on patient compliance (for example, headgear, elastics) or use of invasive procedures (for example, mini-screw implant placement).[36] Studies have suggested beneficial effects of bisphosphonates on anchorage. Liu *et al.*'s study, mentioned previously, found that the subperiosteal injection of clodronate caused significant and dose-dependent reduction in tooth movement. Another small case-control animal study (N = 30) showed local irrigation of zoledronate into extraction sites reduced orthodontic tooth movement of adjacent teeth.[36] Bisphosphonates may also facilitate anchorage indirectly, as local injection of zoledronate into implant osteotomy sites has shown to significantly improve mini-screw implant stability by promoting greater volumes of trabecular bone formation surrounding the implants.[37] These small-scale animal studies have highlighted some potential effects of bisphosphonates in reducing root resorption and tooth movement, which could be beneficial in protection of the dentition during orthodontic treatment and support for anchorage when locally applied. This research is at an early stage, therefore the potential relevance of this research to humans must be viewed with caution.

Osteomyelitis

Diffuse sclerosing osteomyelitis (DSO) is a form of osteomyelitis characterised by chronic non-suppurative inflammation, most commonly affecting the posterior body or ascending ramus of the mandible. Radiographic features include sclerosis, and occasionally osteolysis,[38] whilst clinical features include pain, trismus and swelling.[39] DSO is thought to be a manifestation of SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome, a rare condition for which treatment can be challenging. Treatment options typically include non-steroidal anti-inflammatory drugs, antibiotics or systemic immuno-suppressants, whilst bisphosphonates have primarily been harnessed for patients with DSO resistant to other treatment modalities. There are now multiple case reports describing individual patients experiencing benefit from a single intravenous bisphosphonate infusion, in some instances after symptomatic DSO of more than ten years' duration.[40] The largest report to-date followed seven patients for two to four years and demonstrated that regular infusions of

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pamidronate (maximum four infusions per year) resulted in improvements in subjective and objective measures of disease activity.[38] Two of the seven patients became entirely asymptomatic after treatment, whilst the other patients all reported subjective improvements in pain. DSO disease activity can also be measured objectively using Technetium-scans (Tc-scans), as these scans show increased uptake of Technetium in the region of the DSO lesion. The study by Kujpers *et al.* demonstrated reduced Technetium uptake in affected regions after bisphosphonate therapy, implying that the reported reductions in pain were the result of reduced overall disease activity, rather than merely a placebo effect. Nevertheless, although these reports suggest that bisphosphonate therapy may be effective for DSO recalcitrant to other therapeutic options, there remains a lack of consensus on ideal dosage regimens and the most appropriate type of bisphosphonate, although the majority of reports to date cite use of pamidronate.[40,41] Moreover, the precise mechanism of action of bisphosphonates within DSO remains to be deciphered.

Conclusion

This review highlights recent literature supporting potential benefits of the application of bisphosphonates in various fields of dentistry. Ambiguity remains on the type of bisphosphonate to be used and the optimum dose and route of application. There is growing evidence to suggest that topical application does not cause osteonecrosis of the jaws despite the association between high doses of systemic bisphosphonate and this undesirable condition. Whilst the results of these studies are promising, there are not enough long-term studies in humans and therefore should be interpreted with caution. Further research on this aspect of bisphosphonates is warranted.

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