Bisphosphonates, oral implants and osteonecrosis of the jaw: a review and guidelines

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Abstract

Bisphosphonate drug groups are widely used in the treatment of bone disorders. They may be taken orally or intravenously. One complication of their use is a relatively new clinical condition known as osteonecrosis of the jaw (ONJ). This condition is reported to exclusively affect the mandible and maxilla to different degrees. Dental professionals will increasingly manage patients who are at risk of developing ONJ as the use of these drug groups is rising. Furthermore, knowledge among many healthcare professionals about bisphosphonates and their side effects is limited. Therefore, ONJ presents a challenge to the professional and requires a good understanding of how to manage the clinical situation. The purpose of this paper is to review the bisphosphonate drug groups, their effects on bone activity and how they may affect treatment outcome with oral implants. Guidelines for management of patients who are at risk of developing ONJ are also addressed.

Key words: Osteonecrosis of the jaw, bisphosphonates, oral implant, guidelines

Introduction and background

Bisphosphonates are a group of synthetic analogues of pyrophosphate which is a normal by-product of metabolism (Rodan and Fleisch, 1996; Martin and Grill, 2000; Flint et al., 2006; McLeod et al., 2007). They have physicochemical effects similar to pyrophosphates; however, unlike pyrophosphates, they are able to suppress osteoclast bone resorption (Odvina et al., 2005; Otomo-Corgel, 2007). Additionally, they have anti-tumour effects that help in stopping and preventing bone metastasis (Fournier et al., 2002; Melo and Obeid, 2005; Peng et al., 2007).

Bisphosphonates are used extensively and effectively in the treatment of bone disorders such as osteoporosis, Paget’s disease, cancer-associated hypercalcaemia and bone metastases (Rodan and Fleisch, 1996; Flint et al., 2006; McLeod et al., 2007). It has been reported that bisphosphonates have a strong affinity to bone minerals (Rodan and Fleisch, 1996; Marx, 2003; Migliorati et al., 2005; Flint et al., 2006) and have a half-life of up to 10 years (Lin et al., 1999; Flit et al., 2006) depending on their type and the duration of the treatment (Rodan and Fleisch, 1996; Migliorati et al., 2005; Ott, 2005). Bisphosphonates are stored in bone and then released and reincorporated into newly formed bone (Martin and Grill, 2000). Thus, the effect of bisphosphonates on bone activity may continue even after the treatment has ceased (McLeod et al., 2003; McLeod et al., 2009). For example, alendronate was found to be eliminated from bone at 200 days in rats, 3 years in dogs and 12 years in humans (Lin et al., 1999).

The differences in mineral binding and potency of bisphosphonates are attributed to the differences in the chemical structure of each bisphosphonate (Wang et al., 2003; Graham and Russell, 2007; Mínguez-Serra et al., 2008; McLeod et al., 2009). The basic molecular structure of bisphosphonates consists of two phosphate (PO3) groups bound to a central carbon atom and two side chains (R1 and R2) that are attached to the carbon atom (Figure 1). While the ability of each bisphosphonate to bind to bone minerals is determined by its R1 group, its mode of action and strength are determined by the R2 group (Mínguez-Serra et al., 2008; McLeod et al., 2009). As a result, potency, binding affinity, distribution, accumulation and release differ between the types of bisphosphonates (Otomo-Corgel, 2007).

Mode of action

Bisphosphonates are categorised into two classes: nitrogen-and non-nitrogen-containing groups. The two groups appear to have different mechanisms of action by which they target osteoclasts and consequently will negatively affect their ability to resorb bone (Reszka and Rodan, 2003; Wang et al.,
The use of bisphosphonates was found to be associated with a recently recognised pathologic condition more likely to affect the jaws and has been known as osteo-chemo-necrosis, bisphosphonate-associated osteo-necrosis (BON) or osteonecrosis of the jaw (ONJ) (Rodan and Fleisch, 1996; Martin and Grill, 2000; Fournier et al., 2002; Marx, 2003; Melo and Obeid, 2005; Licata, 2005; Marx et al., 2005; Odvina et al., 2005; Flint et al., 2006; McLeod et al., 2007, Peng et al., 2007; Masson et al., 2009).

ONJ is defined as an area of exposed bone in the maxillofacial region that does not heal within eight weeks after its identification in a patient who has not received radiotherapy to the craniofacial region, but is on or has previously been receiving bisphosphonate (Khosla et al., 2007). Clinical presentation of ONJ is similar to that of osteoradionecrosis and is often progressive, leading to painful areas of alveolar bone exposure in the mandible and less frequently in the maxilla. It is associated with tooth mobility, parasthesia and intra- and extra-oral fistula (Marx, 2003; Marx, 2005; Migliorati et al., 2005; Flint et al., 2006). In the early stages of ONJ, affected bone appears to be normal radiographically (Minguez-Serra et al., 2008). However, an increase in alveolar bone sclerosis, widening of the periodontal ligament and thickening of the lamina dura around teeth can be seen in patients receiving bisphosphonates (McLeod et al., 2009). ONJ has been reported to occur after minor surgical procedures such as tooth extraction and also spontaneously, without trauma or surgery (Marx 2003; Ruggiero et al., 2004; Assael, 2004; Ficarra et al., 2005; Melo and Obeid, 2005; Flint et al., 2006; Woo et al., 2006; Mavrokokki et al., 2007; McLeod et al., 2009). When ONJ occurs after extraction, it leads to delay in socket healing (Melo and Obeid, 2005; McLeod et al., 2009) with oedema and erythyma of the surrounding tissues (Ott, 2005).

ONJ was first reported to be associated with intravenous forms of bisphosphonates i.e. pamidronate and zoledronic acid (Ruggiero et al., 2004; Ruggiero and Mehrotra, 2009); however, ONJ is now reported to be associated with oral bisphosphonate use as well (Flint et al., 2006, Grant et al., 2008; Etminan et al., 2008). The majority of reported cases of ONJ have, however, occurred in patients taking intravenous bisphosphonates for cancer treatment (Woo et al., 2006; Etminan et al., 2008; Edwards et al., 2008). Conversely, it has been reported that short-term oral use of bisphosphonates could lead to ONJ after certain dental procedures are performed (Sedghizadeh et al., 2009). Marx and colleagues (2007) found a direct exponential relationship between the size of the exposed bone and the duration of oral bisphosphonate use. Furthermore, a clinical study by Thumbigrere-Math and co-workers (2009) reported that the mean interval for the development of ONJ was longer in patients with osteoporosis receiving oral bisphosphonates, than in cancer patients receiving intravenous bisphospho-
Figure 2. Mode of action of bisphosphonate preparations on osteoclasts

![Diagram of mode of action of bisphosphonate preparations on osteoclasts]

Table 1. Bisphosphonate compounds, trade names, methods of administration and nitrogen content (Ott, 2005; Graham and Russell, 2007)

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Trade name</th>
<th>Administration</th>
<th>Nitrogen-containing</th>
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<tbody>
<tr>
<td>Etidronate</td>
<td>Difosfen®, Osteum®</td>
<td>Oral</td>
<td>No</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>Skelid®</td>
<td>Oral</td>
<td>No</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Acrel®, Actonel®</td>
<td>Oral</td>
<td>Yes</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Adrovance®, Alendrocare®, Bifoal®, Fosamax®, Fosavance®</td>
<td>Oral</td>
<td>Yes</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Bondenza®, Bondronat®, Bonviva®</td>
<td>Oral / Intravenous</td>
<td>Yes</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Bonefos®</td>
<td>Oral / Intravenous</td>
<td>No</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Aredia®, Linoten®, Pamifos®</td>
<td>Intravenous</td>
<td>Yes</td>
</tr>
<tr>
<td>Zolendronate</td>
<td>Aclasta®, Zometa®</td>
<td>Intravenous</td>
<td>Yes</td>
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</tbody>
</table>

It has been estimated that ONJ occurs in about 20% of patients taking intravenous bisphosphonates; however, the percentage decreased to less than 0.05% in patients taking oral bisphosphonates (between zero and 0.04%). The percentage slightly increased if extractions were carried out (Mavrokokki et al., 2007; Edwards et al., 2008). In the UK in 2006, 77 cases of ONJ were reported to be associated with intravenous bisphosphonates compared with 9 cases associated with oral bisphosphonates (Bradford and Airedale NHS, 2007). The Irish Medicines Board (2008) received 16 individual case reports of ONJ suspected to be associated with the use of bisphosphonates (Irish Medicines Board, 2010). The vast majority of ONJ occurred with intravenous zolendronic acid used for the treatment of malignant conditions. However, the total number of cases treated orally/intravenously was not specified. According to the risk of developing ONJ, bisphosphonate dependant patients can be categorised into two groups: high and low risk patients. High risk patients include those receiving intravenous bisphosphonates in conjunction with chemo-, radiotherapy or corticosteroid treatment, primarily patients with an underlying malignant disease and bone metastases. Low risk patients include those who take only oral bisphosphonates and patients with non-corticoid-induced osteoporosis (Marx et al., 2005; Piesold et al., 2006). Table 2 displays risk factors associated with ONJ.

Why are the jaws affected?
The osteoclasts are responsible for bone resorption which is a vital step in the bone turnover process (Lee et al., 1998; O’Brien et al., 2002; Scully et al., 2006). Bone turnover is needed in order to repair micro-damages that may occur in bone tissues (Lee et al., 1998; O’Brien et al., 2002; Scully et al., 2006, Warreth et al., 2009). The bisphosphonate drug groups were found to accumulate in areas of high bone turn
over. The presence of teeth and periodontal ligaments in the alveolar bone and the chronic low grade trauma associated with mastication renders the jaw a very active area for bone turnover (Flint et al., 2006). Therefore, the jaw bone develops a relatively high concentration of bisphosphonates. When the physiological need for repair increases in inflammation or with surgical insult, the bone tissue does not respond in an effective way to restore the damage and ONJ occurs (McLeod et al., 2009). Furthermore, ONJ arises more commonly in the mandible as a result of the thin mucosa covering bony prominences e.g. the mylohyoid ridge (Marx, 2003; Marx et al., 2005) which makes the underlying mucosa and alveolar bone vulnerable to injury. It was speculated that in ONJ, bone homeostasis is considerably compromised to a degree in which even minor trauma could delay healing (Melo and Obeid, 2005).

### Oral implants and ONJ

The association between bisphosphonate therapy and ONJ raises the question of safety when placing oral implants into the jaws of patients who are taking bisphosphonates or who are at risk of developing bone disorder and will subsequently need treatment with bisphosphonates. A definitive answer has not been found in the literature. Stark and Epker (1995) reported failure of osseointegrated implants approximately six months after treatment with oral bisphosphonate (Etidronate) was commenced. However, in this study additional factors such as the development of a para-functional habit may have contributed to the implant failure. Grant and colleagues (2008) reported that implant success rates for patients who received oral bisphosphonate therapy were comparable with those who did not receive this therapy. This study included 115 patients; 33 patients were on oral bisphosphonate for more than three years prior to implant surgery, 56 patients were on bisphosphonate treatment for less than three years prior to the surgery, while the remaining 26 patients started bisphosphonate therapy after implant surgery. The authors recommended that an alternative treatment should be considered in patients who have been taking oral bisphosphonates for a period greater than three years or those receiving concomitant treatment with prednisone. Another study by Jeffcoat (2006) reported a high implant success rate in a group of patients who had received oral bisphosphonates and for those who had not (100% and 99.2% respectively). This single-masked controlled study included 25 patients who had taken oral bisphosphonates for one to four years prior to inclusion in the study, and who were seen for follow up for at least three years. The study also included 25 age-matched controls. There is general agreement however, that placement of oral implants in patients who are receiving intravenous bisphosphonates is absolutely contraindicated (Hwang and Wang, 2006; Minguéz-Serra et al., 2008). In a recent systematic review and analysis of one prospective and three retrospective studies (217 patients) Madrid and Sanz (2009) concluded that the placement of an implant may be considered a safe procedure in patients taking oral bisphosphonates for a period less than five years, with regard to the occurrence of ONJ.

Implant placement requires an osteotomy preparation which has been found to generate microdamage in peri-implant bone (Hoshaw et al., 1994; Huja et al., 1999; Warreth et al., 2009). This type of microdamage was also reported to occur around osseo-integrated implants due to the imposed occlusal forces (Hoshaw et al., 1994; Huja et al., 1999). Bone microdamages are defined as discontinuities in the calcium-rich bone matrix and represent fissures or breaks in the hydroxyapatite crystals (Lee et al., 2003). These microdamages may act as a bone remodelling stimulus (Burr et al., 1985; Mori and Burr, 1993; Bentolila et al., 1998; Lee et al., 2002; O’Brien et al., 2003) that leads to bone repair and prevents their accumulation (Carter and Hayes, 1977; Burr et al., 1985; Frost, 1991, 1994; Mori and Burr, 1993). Following the generation of micro-damages, osteoclasts come into direct contact with the damaged bone and resorption begins. Osteoblasts (bone forming cells) are then attracted to the site and new bone is produced. In this way, the damaged area is repaired with new bone (Taylor et al., 2007).

A series of animal studies (Mashiba et al., 2000, Mashiba et al., 2001a; Mashiba et al., 2001b) have shown suppression in bone resorption (cortical and trabecular bone of beagle dogs), an increase in micro-damage accumulation and a deterioration in the mechanical properties after administration of bisphosphonates for one year. Thus, if the major therapeutic action of bisphosphonate is to suppress osteoclast activity affecting bone resorption which is one of the main steps of bone turnover (remodelling), then it is logical to suggest that the microdamage will accumulate and bone repair would be inhibited (Mashiba et al., 2000, Mashiba et al., 2001a; Mashiba et al., 2001b), leading eventually to implant failure. Bisphosphonates are rapidly cleared from plasma and 20%-80% are deposited in bone primarily, because of their high affinity to bone minerals.

### Table 2. Risk factors associated with ONJ (Modified from Migliorati et al., 2005)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Systemic</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous use of bisphosphonates</td>
<td>Tooth extractions</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>Surgical bone manipulation</td>
</tr>
<tr>
<td></td>
<td>Cancer metastatic to bone such as breast, lung and prostate</td>
<td>Trauma from denture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of oral infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor oral health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>History of radiotherapy</td>
</tr>
</tbody>
</table>

Table 2. Risk factors associated with ONJ (Modified from Migliorati et al., 2005)
The remainder is excreted via the kidney (Fleisch, 1997; Howland and Mycek, 2006). This affinity may cause the peri-implant bone to be saturated with bisphosphonates. The ability of bone to repair the damages through the remodelling processes will be compromised with a risk of implant failure (Mínguez-Serra et al., 2008). This applies when using intravenous bisphosphonates or as a result of the prolonged use of the oral route since this use may expose the bone to a high level of the drug, whose clearance may take over ten years (Lin et al., 1999; Howland and Mycek, 2006). Scully and colleagues (2006) concluded that the prolonged use of bisphosphonate can suppress bone remodelling capacity to the point where bone repair, in response to damage is negatively affected.

It is understood that continuous bone remodelling in peri-implant bone is required for successful osseointegration. This continuous remodelling makes the areas highly active. Thus, if bisphosphonate drugs accumulate in these areas and if microdamages are generated, their removal mechanism will be negatively affected. These may compromise the osseointegration process and lead to implant failure.

In conclusion, placement of oral implants in patients taking intravenous bisphosphonates is absolutely contraindicated (Hwang and Wang, 2006; Mínguez-Serra et al., 2008) and more conservative and less invasive approaches should be considered whenever possible (Bradford and Airedale NHS, 2007; The Irish Medicines Board, 2008; McLeod et al., 2009). In patients taking oral bisphosphonates, the matter is debatable and further studies are required to reach a definitive conclusion (Fugazzotto et al., 2007). As of this time, there is little evidence to suggest that oral bisphosphonate therapy could negatively affect the outcome of implant placement when taken for a period of less than three years (Grant et al., 2008). However, extra caution should be taken when dental services are delivered to these patients (Wang et al., 2003; Jeffcoat, 2006).

**Dental care and oral bisphosphonate treatment**

Suitable dental care and oral hygiene are vital for all patients who are receiving bisphosphonate therapy, irrespective of the type of bisphosphonate taken, in order to eliminate or reduce risk of developing ONJ. Care of patients may be divided into two stages (despite them being interrelated): before initiation of bisphosphonate treatment and during treatment. However, all available guidelines for management of patients on bisphosphonate are based on expert opinions and are not based on scientific evidence (Edwards et al., 2008; Khan et al., 2008; Stassen, 2008, Masson et al., 2009, Rogers et al., 2010).

**Before initiation of bisphosphonate treatment**

All patients who will be prescribed a bisphosphonate should receive a routine oral examination in order to exclude any source of infection and/or potential sources such as deep caries lesions or periodontal disease that may flare up during the course of the treatment in which a radical invasive treatment would need to be carried out, that would increase the possibility of ONJ development. The patient should be informed about the risk of developing ONJ and the importance of good oral hygiene and regular oral examinations should be highlighted.

Unrestorable teeth should be extracted and root canal treatment may be considered in cases of those teeth which are restorable. Radiography, such an orthopantomograph is needed in order to exclude any clinically undetected pathology before the commencement of bisphosphonate treatment. Any invasive dental procedures should be completed before the initiation of such treatment to allow bone recovery (Khan et al., 2008). Good communication between the dentist and the patient’s physician, who will be prescribing the bisphosphonate, is also important.

**During bisphosphonate treatment**

All patients should be informed of the possibility of developing ONJ simultaneously, or as a result of dental treatment such as extractions. Regular checkups should continue and their importance should be emphasised. Any caries lesions should be treated and periodontal conditions should be assessed and dealt with accordingly. Since invasive surgical procedures may place the patient at risk of developing ONJ, the patient should be informed of this risk and alternative treatment options such as endodontic treatment, instead of extraction should be considered and performed when possible. Any tooth extractions should be carried out asatraumatically as possible. Follow up periods should be arranged until the sockets are completely closed and healed. In order to minimise the incidence of infection, antibiotics should be prescribed. A preoperative prescription of 3g of amoxicillin and 500mg three times daily for 5 days has been recommended (Stassen, 2008, Rogers et al., 2010). If the patient is allergic to penicillin, an alternative antibiotic such as a combination of erythromycin and metronidazole has been suggested. This antibiotic cover is based on the risk of infection and not on the patient’s bisphosphonate therapy, as there is no evidence to suggest that the occurrence of ONJ can be inhibited by the use of antibiotics (Khan et al., 2008). The patient should also be instructed to rinse with 0.2% chlorhexidine mouth wash daily, before and after any surgical procedures involving bone, until the surgical site has healed.

It is recommended to use a local anaesthetic agent with no vasoconstrictor as bisphosphonates may have anti-angiogenic effects which cause hypo-vascularisation and reduction in blood flow in the jaw bone (Woo et al., 2006; Stassen, 2008, Rogers, 2010). Generally, primary soft-tissue closure of the surgical area is of paramount
importance and should be considered where possible in order to minimise the risk of infection and speed up the healing process. The sutures should not be tight to the degree that they may interfere with the blood supply of the area, which may delay healing (Stassen, 2008; Rogers et al., 2010).

All regular restorative procedures may be conducted in patients receiving oral bisphosphonate therapy. Prosthodontic appliances such as complete or partial dentures should be adjusted for a perfect fit. Defective dentures should be dealt with quickly to prevent trauma to the underlying soft tissue and possible ulceration and bone exposure. Causes that make the denture unstable, such as unsatisfactory occlusion should be corrected to avoid any further complications. The denture should be examined for over extensions, and once found, they should be corrected. Additionally, the use of soft liners on dentures has been recommended (Melo and Obeid, 2005).

Routine endodontic procedures can be used and root canal instrumentation should be confined to the root canal space. In order to avoid extraction, unrestorable teeth may be endodontically treated. The crown may be removed and a proper coronal seal provided. This may allow for their gradual exfoliation. Endodontic surgical procedures should follow the same recommendations used for any oral and maxillofacial surgical procedure. Scaling and root debridement should be carried out with caution. Patients should be advised to report any oral symptoms, such as pain or swelling to their general practitioner (Irish Medicines Board, 2010) and treatment should be sought.

Stopping of oral bisphosphonates before and after treatment has been suggested in order to allow bone remodelling recovery and facilitate healing (Stassen, 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008). However, the removal of bisphosphonates from bone may take several years (Lin 2008).

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Conclusions

The risk of developing ONJ in patients receiving bisphosphonate therapy represents a clinical challenge. ONJ associated with intravenous bisphosphonates is more frequent, more severe and less responsive to treatment than ONJ associated with oral bisphosphonates (Thumbigrere-Math et al., 2009).

In general, the treatment of patients receiving oral or intravenous bisphosphonate therapy should principally be preventive in nature (Migliorati et al., 2005; Irish Medicines Board, 2010). Any alteration in the patient’s bisphosphonate treatment should only be considered after consultation with their physician.

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