Abstract

Osteonecrosis of the jaws, or the threat of it, because of the use of bisphosphonates, is an increasing problem facing all dentists and oral surgeons. The link is somewhat circumstantial but compelling and there are emerging risk factors that increase a patient’s susceptibility to developing osteonecrosis including the use of intravenous bisphosphonates, length of time taking the drug, smoking and possibly a genetic predisposition. There is a lack of randomised trial evidence regarding the best strategies for prevention and treatment of the condition. This article discusses current evidence, largely from observational studies on the development, prevention and management of bisphosphonate-related osteonecrosis.

Key words: bone, complication, dento-alveolar, mandible, maxilla, wound healing

Introduction

The bisphosphonate group of drugs are used widely for a variety of indications related to diseases of, or affecting, bone (Table 1). An unfortunate complication in the use of these drugs is osteonecrosis of the jaw bones, usually following dental extractions or oral surgery but sometimes spontaneously. For dentists and oral surgeons, the two problems essentially related to bisphosphonates are firstly, the prevention of osteonecrosis when tooth removal is required; and secondly, the management of osteonecrosis when it occurs.

Mode of action

The drugs are readily bound to the mineral crystals of the bone and progressively accumulate within it. The drugs inhibit osteoclasts and cause them to undergo apoptosis. Long-term absence of osteoclastic activity causes the bone to become hypermineralised, somewhat akin to the process which occurs in osteopetrosis.

Bisphosphonates have a high affinity with sites of active turnover in bone which may be one of the reasons why the jaw bones are adversely affected. Intravenous bisphosphonates are accumulated more quickly than oral bisphosphonates, with oral formulations estimated to take approximately 5 years to reach levels equivalent with intravenous drugs. There is a range of potency with etidronate being the least potent and zoledronic acid the most potent. Bisphosphonates containing nitrogen are the most potent and are almost exclusively the only forms that have been associated with osteonecrosis. There is one case report of osteonecrosis occurring following a dental extraction in a patient using the non-nitrogen containing sodium clondronate.

Recently, American researchers have demonstrated in vitro that pretreatment of murine keratinocytes with pamidronate inhibited cell proliferation and suggested that this inhibition of oral mucosal cells may have a role in the development of osteonecrosis of the jaws.

Osteonecrosis

The American Association of Oral and Maxillofacial Surgeons (AAOMS) published a position paper on bisphosphonate-related osteonecrosis of the jaws in 2006 and have recently published an update on the original. For clarity of diagnosis and to distinguish from other related conditions, they have defined a condition as osteonecrosis if each of these three criteria...
are met: 1) current or previous bisphosphonate use; 2) exposed bone in the maxillofacial region that has persisted for more than 8 weeks; and 3) no history of radiation therapy to the jaws\(^7\).

Marx was first to describe the association of bisphosphonate use with osteonecrosis of the jaws in 2003\(^8\). Since that time, there have been a vast number of reported cases and most oral surgeons are accumulating many of their own such cases\(^9–43\). Whilst the majority of cases occur following tooth extraction (Figs 1 & 2) or oral surgical procedures, osteonecrosis can occur spontaneously and is often lingually or over tori or exostoses where the mucosa is generally thin and nonkeratinised\(^30,44\). Tongue ulceration has also been reported because of the trauma of rubbing against exposed bone in the mandible\(^45\).

Figure 3 illustrates an interesting case of the author’s involving an elderly lady with end-stage Paget’s disease of bone. Her upper left second premolar and first molar teeth were extracted in March 1999. The wound never healed and the necrosis has progressed slowly since then. It emerged subsequently that she received pamidronate and zolendronate as part of a clinical trial in 1999 so this was the author’s first case of osteonecrosis. This case has recently been reported elsewhere\(^46\).

The original reports and the majority of subsequent reports have related largely to intravenous bisphosphonates that have been used to treat and manage bone metastases. However, an increasing number report osteonecrosis related to the use of the nitrogen-containing oral bisphosphonates most usually taken for osteoporosis or osteopenia\(^42,44,47,48\). The incidence of osteonecrosis in patients undergoing oral surgical procedures has been estimated to be less than 0.09%\(^49\) and up to 5% of those receiving intravenous forms\(^10,47,50,51\). A recent survey reported the mean incidence of osteonecrosis in a series of patients taking oral bisphosphonates to be 0.1%; this ranged from 0.04% in those taking the drugs for less than 1 year to 0.21% with over 4 years of use\(^52\).

**Table 1** Bisphosphonates available in UK (from BNF 58, September 2009)

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Proprietary name</th>
<th>Route</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronic acid (N)</td>
<td>Fosamax Fosavance(^1)</td>
<td>Oral</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Disodium etidronate</td>
<td>Didronel</td>
<td>Oral</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Disodium pamidronate (N)</td>
<td>Aredia</td>
<td>IV</td>
<td>Hypercalcaemia of malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paget’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bone metastases of breast cancer/myeloma</td>
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<tr>
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<td></td>
<td>Paget’s disease</td>
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<tr>
<td>Ibandronic acid (N)</td>
<td>Bondronat Bonviva</td>
<td>IV</td>
<td>Bone metastases of breast cancer</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hypercalcaemia of malignancy</td>
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<td>Osteoporosis</td>
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<td></td>
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<td></td>
<td>Paget’s disease</td>
</tr>
<tr>
<td>Risedronate sodium (N)</td>
<td>Actonel</td>
<td>Oral</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Sodium clodronate</td>
<td>Bonefos</td>
<td>Oral &amp; IV</td>
<td>Hypercalcaemia of malignancy</td>
</tr>
<tr>
<td>Tiludronic acid</td>
<td>Skelid</td>
<td>Oral</td>
<td>Bone metastases of breast cancer</td>
</tr>
<tr>
<td>Zoledronic acid (N)</td>
<td>Aclasta</td>
<td>Oral</td>
<td>Paget’s disease</td>
</tr>
<tr>
<td></td>
<td>Zometa</td>
<td>IV</td>
<td>Paget’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malignancy involving bone</td>
</tr>
</tbody>
</table>

\(^1\) With colecalciferol.  
N, nitrogen-containing; IV, intravenous.
Unlike osteoradionecrosis and osteomyelitis, which is much more commonly encountered in the mandible, osteonecrosis because of bisphosphonate therapy occurs almost as frequently in the maxilla as in the mandible in some reported series.

It is interesting to note that bisphosphonates are also used for the management of osteogenesis imperfecta in children and adolescents. A recent case series from Sweden of 64 young patients using intravenous pamidronate, many of whom had had dental extractions, did not demonstrate one single case of osteonecrosis.

Risk factors

In addition to the local risk factors cited above related to the teeth and oral mucosa, there are a number of other reported comorbidities encountered in patients who develop osteonecrosis which could be interpreted as risk factors. Given that osteonecrosis occurs more frequently in those receiving the intravenous form and that such patients are usually being treated for malignant conditions, it is not surprising that chemotherapeutic drugs including corticosteroids are commonly recorded.

Smoking is a well recognised factor that affects wound healing and general homeostasis in the oral cavity. It is not surprising then that it is also reported to be associated with osteonecrosis development.

Marx et al. have described the use of a bone biochemical marker, C-terminal telopeptide (CTX), to assess the risk of osteonecrosis in patients taking oral bisphosphonates. This measures a cross-linked peptide found in type I collagen in bone which correlates with bone turnover; it is therefore reduced in patients using bisphosphonates. Marx reported that a rising CTX during a ‘drug holiday’, when patients ceased taking their drugs for a period, reduced the risk of osteonecrosis development.

A recent German study reported that osteonecrosis of the jaw was more prevalent in patients who had received more cycles of zoledronic acid, and suggested that the length of exposure and cumulative dose are important risk factors.

The role of genetics was studied in a case-controlled study of a series of multiple myeloma patients with...
osteonecrosis of the jaws (22 cases) and without osteonecrosis (65 matched controls). These Spanish workers demonstrated differences in the distribution of polymorphisms within the cytochrome P450 CYP2C8 gene between the cases and controls; this appears to be one of the first indications of a possible method of predicting which patients will develop osteonecrosis of the jaws.

**History repeating**

Whilst necrosis of the jaw bones because of the use of bisphosphonate drugs is a 21st century phenomenon, over 100 years ago, the same disease was commonly observed in those working with phosphorus. Miners of the mineral and those working in match factories were reported to experience non-healing bone in their jaws and this was known as ‘Phossy jaw’.

**Prevention of osteonecrosis**

As with all patients who are about to commence an intervention, which results in an increased potential for dental complications (radiotherapy, immunosuppression, etc.), a thorough oral and dental examination should precede the commencement of bisphosphonates, especially intravenous forms. Teeth of doubtful prognosis should be removed, periodontal health should be achieved and oral hygiene should be optimised and then maintained once the patient is receiving the bisphosphonate. Because not all osteonecrosis occurs following dental extractions or oral surgical procedures, consideration should also be given to the removal of prominent, particularly multilobular tori and ensuring dentures are atraumatic to the underlying oral mucosa.

For patients already using bisphosphonates who present with carious teeth, root canal treatment should take priority over extraction. For teeth with unrestorable crowns, consideration should be given to decoronation and root treatment of the roots. To avoid conventional extraction, a novel method of orthodontic extrusion has been suggested which culminates in eventual exfoliation of the tooth.

When patients absolutely require a dental extraction, there is, as yet, no randomised, or even controlled trial evidence of best practice. Case series, individual case reports and more recently guidance and position statements have been published. Certainly, there is an emerging view that those receiving intravenous drugs (usually for malignant disease) should be managed differently to those receiving oral drugs (usually for osteoporosis).

The AAOMS and the Canadian guidelines recommend, where possible, a drug holiday of 3 to 6 months prior to an elective oral surgical intervention.

Prophylactic antibiotics given before and following the procedure have been recommended especially in patients being treated for cancer. Regardless of bisphosphonate use, such patients may be considered for surgical antibiotic prophylaxis in any case because of their higher than average risk for infection. Penicillins are recommended and Marx recommends penicillin V 500 mg four times a day for 5 days after the procedure. For many in the UK, the obvious alternative to penicillin for those allergic would be clindamycin, but this is not recommended as it lacks activity against some of the organisms known to colonise osteonecrotic jaws namely *Eikenella* and *Moraxella* species. However, we do not want to be blindly prescribing antibiotics with dubious efficacy for such patients with the potential consequences of adverse reactions and resistance ending up in a similar situation to endocarditis prophylaxis.

**Treatment of bisphosphonate osteonecrosis**

Because of the relatively recent description of this condition, there are no controlled or randomised trials in existence yet. The best evidence to date comes from observational studies of case series. In the ever-increasing number of published treated cases, however, there is a large variation in protocols and variable success rates. The AAOMS position paper has produced a useful staging of the osteonecrosis and suggested treatment strategies for each of the four stages. Some of the larger published series are discussed below.

It is an almost reflex reaction for a surgeon when faced with necrotic tissue to undertake some form of debridement or curettage. Ruggiero et al. were the first to describe a large series of 63 cases of osteonecrosis, the majority of whom had received intravenous bisphosphonates for malignant disease. In this series, patients underwent a variety of surgical procedures ranging from sequestrectomies to total maxillectomies. The results were disappointing with recurrence or progression of the osteonecrosis in almost all cases. Two cases also received hyperbaric oxygen and many patients had their bisphosphonate therapy stopped, but neither of these appeared to affect the outcome. There are two interesting observations that can be made from this report. Firstly, with the exception of the seven patients who had osteoporosis, the remainder were on chemotherapy during the duration of the observation period. Secondly, cases that were asymptomatic with
necrotic and exposed bone were managed successfully with local measures and irrigation. Hyperbaric oxygen alone has been reported to result in remission or resolution many patients in one small trial. Marx et al. reported the outcomes of 97 patients who were managed using a long-term antibiotic protocol of oral phenoxymethylpenicillin (penicillin V) (500 mg tds) and 0.12% chlorhexidine mouth rinse adding oral metronidazole (500 mg tds) with more severe or refractory cases. For those cases developing severe cellulitis, they received co-amoxiclav (1000 mg/500 mg) IV. He reported that 90% of these patients functioned pain free during the observation period following this protocol.

A recent retrospective multi-centre study reported on 78 patients with clinical resolution in 43 (55%) of these. The treatments undertaken were non-surgical in 11 cases (local antisepsis and systemic antibiotics) and various degrees of surgery in the remaining. In this series, radical surgery comprising segmental resection or marginal resection achieved the highest level of clinical resolution. However, no follow-up periods were stated for this cohort. Interestingly, they also reported that half of the patients receiving non-surgical management achieved resolution of their osteonecrosis.

Another treatment modality, which is combined with a surgical debridement and/or reconstruction, is the use of platelet rich plasma (PrP). PrP is derived from the patient’s own blood and is a concentrated solution of the patient’s platelets. As a result, it is rich in the growth factors normally contained in platelets such as the platelet derived growth factors, transforming growth factors (TGFβ1 and TGFβ2), vascular endothelial growth factor and epithelial growth factor. A small number of observational studies have reported its use in the treatment of osteonecrosis of the jaws with favourable outcomes.

### Bisphosphonates and dental implants

The orthopaedic literature has randomised trial evidence that in patients given systemic bisphosphonates, a higher torque was required to remove bone fixation devices. Animal studies of bisphosphonate-coated steel screws have demonstrated better fixation. A similar finding has been reported in relation to bisphosphonate-coated dental implants in both animal and human studies.

In relation to the placement of dental implants in patients receiving dental implants, evidence is scarce. Jeffcoat reported a controlled trial (nonrandomised) in which dental implants were placed in 25 patients who had been taking oral alendronate or risendronate for a mean of 3 years. An age-matched control group who were not receiving bisphosphonates also received a comparable number of implants. A 100% success rate was observed after 3 years follow-up in the treatment group with no significant difference to the control group.

A large observational report of 115 patients who had taken oral bisphosphonates and received 468 dental implants reported just two implant failures (failure to integrate) in two patients and no cases of osteonecrosis.

### Summary and conclusions

Osteonecrosis of the jaws following the use of bisphosphonates is a growing problem facing all dentists and oral surgeons. From the observational data available, it is currently more likely to develop in those patients receiving the intravenous form, but can also occur with the use of any nitrogen containing bisphosphonate. It should be remembered that only a minority of the patients taking the drug develop osteonecrosis of the jaws.

Currently, there is no reliable trial evidence to guide clinicians on how to either prevent osteonecrosis or treat it when it occurs. It seems likely that molecular and/or genetic investigations will in the future be the key to predicting which patients using bisphosphonates are likely to develop osteonecrosis of the jaw bones.

### References


