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Leading article

Bisphosphonate osteonecrosis of the jaw—a literature review of UK policies versus international policies on bisphosphonates, risk factors and prevention

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Abstract

There has been an exponential rise in the literature of osteonecrosis and its complications in patients taking bisphosphonate drugs. Despite this increase, there is little evidence-based publications on how best to manage this complication. In this article (the first of two on bisphosphonate related jaw complications), we compare the guidelines produced by national specialist medical associations and expert panels on the prevention of bisphosphonate osteonecrosis of the jaws and review the evidence behind these guidelines.

Keywords: Bisphosphonate; Osteonecrosis; Jaw bone; Risk factors; Prevention

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BONJ) was first reported in 2003, and since then a large number of case series have been published, but few reports on the management of the condition or its prevention in patients who are prescribed bisphosphonates are based on evidence.[1]

While a number of national professional associations have set up expert panels to review the evidence and construct guidelines (Table 1), much published material represents the view of single groups and is based only on their individual experience, or is a review of published guidelines, which does not constitute strong evidence on which to base clinical decisions.[2–16]

This article concentrates on the prevention of BONJ, and the next will focus on its management. Both compare the recommendations made by different expert groups, and review some of the evidence behind them.

Bisphosphonates

Background

Bisphosphonates are pyrophosphate analogues that share a common phosphorous–carbon–phosphorous chemical core, and inhibit the resorption of bone.[17] Their potency is partly related to the existence of a nitrogen side chain. Parenteral and oral preparations are available with differing bio-availabilities.

Risks of bisphosphonates

Treatment with bisphosphonate drugs is associated with several complications including renal and gastrointestinal side effects, particularly oesophageal ulceration, but the most serious is that of osteonecrosis of the jaw.[18] The identification

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Table 1
Published guidelines on the prevention of bisphosphonate-associated osteonecrosis of the jaws.

Reference number	Referred to within text	Expert panel representation or endorsement	Year published
2,3	Australian	Australian and New Zealand Bone and Mineral Society Osteoporosis Australia Medical Oncology Group of Australia Australian Dental Association	2006, 2007
4,5	AAOMS	American Association of Oral and Maxillofacial Surgeons	2006, 2009 (updated)
6,7	CAOMS	Canadian Association of Oral and Maxillofacial Surgeons Canadian Society of Endocrinology and Metabolism Ontario Society of Oral and Maxillofacial Surgeons Canadian Academy of Oral and Maxillofacial Pathology and Oral Medicine American Association of Clinical Endocrinologists International Bone and Mineral Society International Society of Clinical Densitometry	2008, 2009
8,9	ADA	American Dental Association	2006, 2008 (updated)
10	Spanish	Spanish Expert Panel Oncology, Haematology, Urology and Stomatology	2007
11,12	AAE	American Association of Endodontists	2006, 2007
13	AAOM	American Academy of Oral Medicine	2005
14	French	French Expert Panel	2009
15	ASBMR	American Society for Bone and Mineral Research	2007
16	BDA	British Dental Association	2008

of this disease process has been widely publicised through multiple case reports since 2003 and has led to changes in the advice given on drug leaflets.[1,19]

Incidence

Establishing the incidence of BONJ remains difficult partly because different definitions are used for the condition, and partly because some mild, self-resolving cases are not identified.[20] Published incidences range from 0.7/100,000 prescribed patient years to 0.34% in population studies, and up to 10% in specific groups such as patients with myeloma who are prescribed bisphosphonates intravenously.[2,21,22]

Risk factors

Osteonecrosis of bone is an uncommon disease with several recognised risk factors, all of which are increased in the presence of bisphosphonates (Table 2).[4,5,7,15,21,23–30]

BONJ seems to be associated with patients who have been taking the drug for an extended period of time.[30] Current evidence suggests that those at serious risk of BONJ are likely to have been given bisphosphonates parenterally for at least 12 months, or orally for at least 36 months, although a small number of cases report patients who have taken them for much shorter durations.[5,31,32]

Prevention

Prevention of BONJ requires a number of different measures to be considered.

Appropriate use of bisphosphonate drugs

The first step in the prevention of BONJ concerns the appropriate prescribing of bisphosphonates, but as this is beyond the scope of this article, the reader is referred to appropriate publications on the management of conditions for which these drugs are recommended.[33–35]

Preparation of patients

When bisphosphonates are recommended it is important that the prescribing physician informs patients of the risks and benefits of the drug chosen. This must include information on the risk of BONJ and advice to attend a dental professional for a full oral assessment.[2–6,15]

Almost all published guidelines note the need for patients to be dentally fit before commencing bisphosphonate treatment, and some evidence is emerging that careful dental preparation before treatment can reduce the risk of BONJ.[2,6–10,13–15,36–39]

In their advice on the requirements before treatment, guidelines from the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the American Academy of Oral Medicine (AAOM) have distinguished between bisphosphonates given orally and those given intravenously, but there is no evidence to support this approach.[5,13] While the incidence of BONJ is higher in the parenteral group, the complication of assessing individual risk on the basis of duration of treatment and existing conditions make it more logical, and simpler, to adopt a generic approach which states that all patients should, where possible, be dentally fit before beginning treatment.

Guidelines from the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS), the American Dental

Table 2
Risk factors associated with osteonecrosis.

	First author and reference
Systemic factors	
Age	McLeod[17]
Systemic disease (renal failure, anaemia, obesity, diabetes)	Hohnecker[19]
	Cheng[20]
	Bamias[21]
	Krauth[22]
Smoking	McLeod[17]
	Bamias[21]
	Khamaisi[23]
Concurrent medication	
Immunosuppressants	Hohnecker[19]
	Khamaisi[23]
Chemotherapy agents	Hohnecker[19]
	Khamaisi[23]
Bisphosphonate-related risk factors	Australian Dental Association[3]
	Hohnecker[19]
	Khamaisi[23]
Bisphosphonate potency	
Duration of treatment	
Local risk factors	
Dentoalveolar surgery	Australian Dental Association[3]
	Migliorati[13]
	Wessel[24]
	Arrain[26]
Oral infection (periodontal and dental abscesses)	Australian Dental Association[3]
	Migliorati[13]
	Hohnecker[19]
	Khamaisi[23]
Poor oral hygiene	American Association of Endodontists[11]
	Jadu[25]
	Arrain[26]
Intraoral trauma	Hohnecker[19]
	Khamaisi[23]

Association (ADA), the American Society for Bone and Mineral Research (ASBMR), and the British Dental Association (BDA) suggest that patients who have practiced appropriate dental care and report no acute dental problems require only routine dental follow-up, but what constitutes appropriate dental care is difficult to assess objectively, and again we suggest that patients should be dentally fit and should attend a dental practitioner for a full assessment if they have not done so in the last 6 months .[6–9,15,16] If dental problems are identified every effort should be made to have them treated before beginning bisphosphonate treatment (Mehrotra B, et al. Outcomes of bisphosphonate-related osteonecrosis of the jaw. Importance of staging and management: a large single institution update. Paper published in conjunction with the American Society of Clinical Oncology meeting, Chicago, 2008: 20526),[4,38–42] and if extractions are indicated, this should be delayed until the extraction site has healed fully (14–21 days).[5] If a medical condition makes delay difficult or inadvisable it is likely that most dental problems could be treated after drug treatment has begun, with the most invasive procedures done first, as the risk of BONJ is associated with long-term use rather than single dosage.[13–15,42]

When a patient presents to a dental care professional before commencing treatment it is helpful if the prescribing physician has communicated the indication for the bisphosphonate, the likely preparation to be used and the potential duration of treatment, factors which provide some insight into the risk of BONJ, and the patient's prognosis.[28,36] Existing conditions and other risk factors for osteonecrosis should be carefully assessed (Table 2).[5,20] Dental hard and soft tissues should be examined for disease, and any dental prosthesis examined carefully.[2–10,18] Teeth currently in an acceptable condition but unlikely to be retained in the long-term need careful consideration after reflecting on the patient's dental and general health. As future exodontia is a risk factor for BONJ, it may be sensible to consider such treatment now, particularly where long-term bisphosphonate treatment is likely.[10]

It is important to review existing dental prostheses and carefully design any that are planned, as mucosal breakdown associated with prostheses is the second most commonly identified risk factor in the development of BONJ lesions.[43]

Part of the dental review should include instruction in oral hygiene to minimise the risk of future dental disease,[38,39] and patients should also be instructed about the clinical signs and symptoms of BONJ, and advised to seek professional advice early if they are concerned.[5,15]

During and after the prescription of bisphosphonate drugs

Although evidence suggests that the duration of and preparation for bisphosphonate treatment are important indicators of the risk of developing BON, many guidelines continue to categorise risk according to the route by which the drug is given. Although guidelines by AAOMS, ADA, and CAOMS group patients according to the route of administration, duration of administration, and symptoms in an attempt to account for individual clinical risk, it may confuse the issue unnecessarily.[5,6,8]

What is patient-specific risk?

Currently there are no reliable or widely available tests for the risk of BONJ. Marx et al. suggested the use of CTX, a surrogate marker of bone turnover to assess patients taking bisphosphonates orally.[44] While he suggested a CTX concentration associated with a low risk, the study included only a relatively small number of patients and must still be considered experimental. A study by Kunchur et al. similarly showed a possible association between low CTX concentrations and BONJ in patients having extractions (where CTX

values were available before treatment), but again numbers were too low considering the generally low prevalence of BONJ to make strong conclusions.[45] They did not find an association between the presence of BONJ and current CTX concentrations, as some patients had already stopped bisphosphonate treatment. Other authors have decried the use of CTX and similar markers of bone turnover to assess the risk of BONJ with dental extractions, and there is no strong evidence for their routine use at this time.[46,47]

Although dental panoramic radiographs and other methods of imaging such as computed tomography and single positron emission computed tomography may be useful in establishing a diagnosis of BONJ, and in delineating the extent of the problem, they have no predictive value in its prevention.[48–52]

Continuous drug dosing

Guidelines from AAOMS and CAOMS suggest a drug holiday in patients taking bisphosphonates intravenously who require invasive dental treatment, particularly extractions.[5,7] Although ADA, AAOM, and Spanish guidelines state that there is no evidence to support the use of drug holidays, evidence is emerging that such a drug-free period might be useful.[9,10,13,53]

The need for continuous dosing will depend largely on the indication for the drug. While such treatment may be necessary for malignant disease including bone metastasis, there is no evidence to suggest that a brief drug-free period would be a problem for some malignant conditions such as hypercalcemia and for benign disease where the indication for the drug is generally associated with reducing long-term risk.[15] Any decision on drug holidays must be made in careful consultation with the prescribing physician because of the risk of adverse events if treatment is stopped.[54]

The duration of such a drug-free period remains controversial because of the lack of a clinical correlation between bone turnover (assessed biochemically) and the risk of BONJ with invasive dental procedures.[44,45,55]

When urgent dental treatment is required CAOMS recommend that bisphosphonates are stopped after treatment until the tissues have healed completely. They also recommend a drug-free period of three to six months before treatment for non-urgent cases.[6] AAOMS guidelines recommend a drug holiday before treatment in patients taking bisphosphonates orally only if there are coexisting risk factors such as use of steroids, in which case they recommend a three-month drug holiday before treatment, to continue until healing is complete.[5]

Based on the duration of time taken for CTX concentrations to rise, a drug-free period of three to six months before treatment (longer with more potent bisphosphonates, and where treatment has been instituted for longer), and until the treatment site has healed completely is the best available evidence to date.[44,45]

Awareness of bisphosphonate prescription

Patients should be made aware of the risk of BONJ when first prescribed bisphosphonates, and should be advised to inform the dental care professionals they come in to contact with. The study by McLeod et al. showed a lack of awareness by dentists of patients taking bisphosphonates.[17] Dental care professionals need to take specific measures to identify both new and returning patients who are taking these drugs because of the potentially serious risk of BONJ to quality of life.[3,6,20]

Appropriate dental treatment—least invasive option

BONJ is most commonly associated with procedures that stimulate the bone around the teeth, and is therefore particularly associated with exodontia, periapical surgery, implantology, and periodontal surgery, although non-interventional causes of bone stimulation such as periapical or periodontal infection may have the same effect.[9,43] Other common associations are with recurrent oral mucosal trauma such as that caused by ill fitting dentures, or the presence of bony prominences of the oral cavity such as mandibular or palatal tori.[9,43]

Generally it is recommended that high-risk procedures should be avoided, and there should be a reliance on restorative treatment including root canal treatment and non-invasive periodontal surgery.[2,5,15,16] In teeth that cannot be restored, removal of the crown and endodontic treatment of the remaining roots should be considered.[8,11,16]

Guidelines from AAOMS and ADA state that elective dentoalveolar surgery does not seem to be contraindicated in patients taking bisphosphonates orally unlike those taking them intravenously, although they recommend that patients should be advised of the small risk of compromised bony healing after operation.[5,6] The ADA recommend the staging of non-urgent dental treatment, allowing two months between sextants to assess for the development of BONJ before the next one is treated.[9] The risk of BONJ in those taking bisphosphonates orally may remain lower than that given intravenously, but increasing numbers of reports of BONJ in patients taking the drugs orally suggest that dentoalveolar surgery is a specific risk factor.[56,57]

The use of osseointegrated dental implants is controversial. Although some have reported good success rates for implants in patients taking bisphosphonates, the nature and duration of the prescription generally are not clearly defined, and it would be expected that the risk of complication is low in patients on low potency drugs for short periods.[5,9,10,58] The specific risks to patients should therefore be considered when contemplating implant treatment, and appropriate consent obtained.[15,16,56]

It is unrealistic to suggest that dentoalveolar surgery must be avoided in high-risk patients as it is dictated by the dental clinical need, but less invasive procedures should be consid-

Table 3
Adjunctive measures for the prevention of BONJ where invasive dental treatment is required.

Preoperatively	Mouth rinse with 0.12% or 0.2% chlorhexidene
	Prophylactic antibiotics: amoxicillin 3 g orally 1 h preoperatively or clindamycin 600 mg orally 1 h preoperatively, if allergic to penicillin
Perioperatively	Conservative surgical technique
	Primary closure of soft tissue where possible
Postoperatively	Chlorhexidene mouth rinse for 2 weeks, or until mucosal healing
	Postoperative antibiotics for 5 days: penicillin V 250 mg four times a day doxycycline 100 mg every day, or metronidazole 200 mg three times a day, if allergic to penicillin

ered, and appropriate warnings given where such procedures are required.

Appropriate precautions

Use of perioperative antibiotics and a chlorhexidene mouthwash have been suggested to reduce the risk of postoperative BONJ where invasive dental treatment is necessary (Table 3). Australian and Spanish guidelines recommend the use of perioperative antibiotics whereas ADA and BDA guidelines state that there is no evidence of benefit in their use.[3,9,10,16] This is a contentious area in general dental publications although there is evidence that perioperative antibiotics do significantly reduce the risk of postoperative infections and alveolar osteitis after dentoalveolar surgery.[59] It is equally recognised that BON is not linked directly to infection, so the clinical relevance is difficult to establish, but at least one study has reported a reduced incidence of BONJ in patients who were given prophylactic antibiotics.[60] Mcleod et al. suggested that while the absolute risk reduction is small, the effects of developing BONJ are potentially catastrophic, so any measures which may be beneficial should be considered.[61] Ingress of micro-organisms into healing sockets or oral wounds will increase local inflammation and produce a greater reaction in local tissue than in a healthy wound. As current theories on the pathophysiology of BONJ suggest that healing of soft tissue and bone is impaired by bisphosphonates, and any additional interference with healing pathways may explain the development of BON lesions, measures to reduce such interference are recomended.[62]

There are different recommendations about which antibiotics to use.[3,10,13,60,61,63] Malden et al.[63] suggested that the most common pathogens, based on culture and sensitivity tests, are *Actinomyces, Eikenella* and *Moraxella* species, so penicillin V (phenoxymethylpenicillin) 500 mg four times a day is a suitable antibacterial regimen. In patients allergic to penicillin doxycycline 100 mg once daily is advised. Metronidazole 200 mg three times a day has been effective in patients refractory to the above antibiotics. Considering the target pathogens, it should be noted that amoxicillin and clindamycin are not first line drugs for prophylaxis in this condition. This contrasts with the Spanish guidelines which suggest giving amoxicillin and clavulanic acid 875/125 mg three times a day orally, or clindamycin 300 mg three to four times a day for two days before, and for ten days after the extraction. Australian guidelines recommend amoxicillin 2 g before operation, and Mcleod et al. suggested amoxicillin 3 g before operation, or clindamycin 600 mg in patients allergic to penicillin, then amoxicillin 250 mg three times a day, or clarithromycin 250 mg twice a day, or metronidazole 200 mg three times a day.[2,61] Antibiotics, if used, should be continued until there is an adequate oral mucosal seal over the wound, which should be within five days, but for no longer than is necessary.[64]

Use of chlorhexidene mouth rinse has also been advocated in ADA and Spanish guidelines.[9,10] Rinsing with a chlorhexidene solution before operation has been shown to reduce the risk of alveolar osteitis after dentoalveolar surgery, and is recommended for the prevention of BONJ by many authors.[61,63,65,66] Spanish guidelines recommend rinsing with 0.12% chlorhexidine twice daily for 15 days after extraction, followed by review by the operating surgeon to ensure satisfactory healing, whereas ADA guidelines recommend continued use of the mouthwash for 2 months depending on healing.[9,10,66] This simple and relatively inexpensive procedure, while not mentioned in other series, seems to have no serious contraindications.[65]

Appropriate technique

Teeth should be extracted using the least traumatic technique, preferably one tooth at a time, or by a sextant-by-sextant approach. If obvious sharp margins of the socket wall or interradicular bone are seen after the procedure, they should be reduced selectively without lifting the periosteum from the bone.[9,10,13] Large soft tissue flaps should be avoided, and wounds closed primarily where possible.[2] Techniques to reduce the trauma of dental extractions have been proposed, such as the use of orthodontic elastics, but have not gained widespread acceptance.[67]

Oral wounds should be closed primarily where possible to reduce the gap that the healing mucosa must bridge to form a seal, and to reduce the time for ingress of oral micro-organisms.[2,5,60]

BONJ is already seen as a difficult disease to treat and manage so the emphasis must remain on its prevention from the beginning. Risk factors likely to cause or exacerbate it should be identified and, ideally, eliminated or reduced as much as possible. Clinicians should be aware of risks factors and methods of prevention, and convey them to the patient. Unfortunately there are still more suggestions than evidence regarding best practice on how to manage risk and prevent the occurrence of BONJ in patients taking bisphosphonate drugs.

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