Bisphosphonates and osteomyelitis of the jaw

By Dr Luke Bereznicki and Professor Gregory Peterson

Learning objectives:
After reading this article, the reader should be able to:
• Discuss the characteristics and pathogenesis of bisphosphonate-associated osteomyelitis of the jaw (BAOMJ)
• Discuss the incidence of BAOMJ
• Describe the role of pharmacists in the prevention of BAOMJ.

Introduction
Bisphosphonates are routinely used in the management of osteoporosis, Paget's disease and malignancies associated with hypercalcaemia (e.g. metastatic bone disease and multiple myeloma). Bisphosphonates are associated with a significantly reduced risk of fracture and other skeletal complications in patients with Paget's disease and osteoporosis. In patients with malignancy, the risks associated with bisphosphonate treatment need to be balanced against the benefits of therapy on the underlying malignancy. Approximately three million prescriptions were dispensed for alendronate and risedronate in the 2006–2007 financial year in Australia, predominantly as once-weekly preparations for osteoporosis. While bisphosphonates are well tolerated, in 2003 a number of cases of bisphosphonate-associated osteomyelitis of the jaw (BAOMJ) were first reported. In this article we will review the incidence, pathogenesis and prevention of BAOMJ.

Adverse effects of bisphosphonates
The most common adverse effects of oral bisphosphonates are gastrointestinal. Based on a recent pooled analysis, mild upper gastrointestinal events (e.g. reflux, oesophageal irritation, nausea, vomiting and heartburn) occur more commonly with etidronate than with other oral bisphosphonates; in the same analysis there was no difference between alendronate, risedronate and placebo. The rate of upper gastrointestinal complications in patients taking oral bisphosphonates in practice may be as high at 30%, most of which are assumed to be caused by the drug. It is worth noting that a similar incidence was found in placebo-controlled trials, in both the bisphosphonate and the placebo groups, reflecting a high background incidence of upper gastrointestinal events in people with osteoporosis. For example, in the Fracture Intervention Trial, 57.5% of those receiving alendronate and 46.2% of those receiving placebo reported ≥1 episode of upper gastrointestinal symptoms. Upper gastrointestinal adverse effects occur very commonly, and may result in poor adherence and/or poor persistence with therapy. For those who discontinue oral bisphosphonates because of mild gastrointestinal symptoms, a rechallenge of a bisphosphonate may be tolerated in between 50% and 85% of cases.

Cytokine storm (fever, body aches and an influenza-like syndrome) is a common adverse effect of first-time intravenous bisphosphonate therapy. It may affect up to 25% of patients and usually lasts two to three days. Symptoms can be minimised by co-administration of paracetamol.

In 2003 a more serious adverse effect was linked to bisphosphonate therapy — osteonecrosis of the jaw (ONJ). Bisphosphonates are not the only known cause of ONJ; it may be associated with radiation therapy or be induced by steroid therapy. Several names are used to describe the condition, the most common being bisphosphonate-associated osteonecrosis of the jaw and bisphosphonate-associated osteomyelitis of the jaw (BAOMJ). The initial published cases of BAOMJ were associated with treatment of bone malignancy, and followed dental extraction. ONJ is a serious condition associated with painful areas of exposed bone which fail to heal. The characteristics of the currently available bisphosphonates in Australia are shown in Table 1.
Bisphosphonates and ONJ

History
The US Food and Drug Administration first issued a warning to health professionals in 2004 concerning the discovery of an association between bisphosphonates and ONJ. Initial reports arose from patients who received intravenous bisphosphonates for the management of bone malignancy. Similar cases were subsequently reported in Australia. Australian regulatory committees followed suit and released adverse drug reaction reports concerning ONJ in 2005 and 2006. Precautionary statements regarding ONJ were added to the product information for bisphosphonate products in early 2005.

As of December 2007, 209 Australian reports of ONJ associated with bisphosphonates had been received. Australian reports have so far involved alendronate, pamidronate, ibandronate, risedronate, clodronate and zoledronic acid but not disodium etidronate. Most cases of BAOMJ have occurred two to three years into therapy with intravenous bisphosphonates and after five years with oral therapy. The median duration of therapy prior to diagnosis is between 20 and 40 months.

Characteristics of ONJ
ONJ generally appears as an intra-oral lesion with exposed yellow-white hard bone. The exposed bone has smooth or ragged borders, and lasts for >3 weeks. Painful ulcers may be present in the surrounding soft tissue and may cause jaw pain. Symptoms range from painless exposed bone to severe jaw pain. In the majority of reports (approximately 60%), BAOMJ is preceded by dental extraction, but less commonly it can occur in the absence of dental surgery and may follow simple trauma (e.g. denture trauma). Only 5% of cases worldwide have been reported in patients with Paget's disease or osteoporosis. Approximately 87% of cases of BAOMJ occur with intravenous bisphosphonates. A recent review of 368 published case-reports of BAOMJ found that 94% involved patients with multiple myeloma or bony metastases who were receiving intravenous bisphosphonates.

Pathogenesis of BAOMJ
The exact cause of BAOMJ is not known, and it is not clear why some patients develop the condition or are affected more severely than other patients. Prolonged use of bisphosphonates may reduce the rate of bone turnover and result in the accumulation of microcracks, resulting in reduced mechanical competence. Normally, these regions of microdamaged bone would be removed by the bone remodelling process. Bone remodelling involves osteoclasts resorbing old damaged bone and osteoblasts replacing this with new bone. Bisphosphonates reduce the rate of bone remodelling, and may therefore impair the removal of microdamaged regions of bone. It is not known whether this repair process is more important in the jaw or why the effect of bisphosphonates on the jaw bones are so different to their effects on other bones.

Although not weight-bearing, jaws are subject to significant pressure during chewing, swallowing and talking. Additionally, following tooth extraction, jaws are exposed to microorganisms, which may also affect the remodelling process and demand for repair. The mandible has a uniquely restricted blood supply, which may be further impaired by local trauma. Accumulating evidence points to an impaired immune response and the development of local bone infections as a trigger for BAOMJ. Some evidence suggests that the immunocompromised are at risk of BAOMJ, and that some cases respond to antibiotic treatment. Under normal circumstances, healing occurs rapidly following dental extraction. Normal extraction site healing involves osteoclastic activity to remodel the tooth socket and form new bone. The presence of bisphosphonate-affected bone,
in combination with bacteria found abundantly in saliva, may result in the inability to respond to the challenge of healing.¹⁰

In summary, there are thought to be five main mechanisms of BAOMJ:

a) Impaired healing;

b) Angiogenesis;

c) Local toxicity;

d) Immunomodulation; and

e) Infections.⁶

It is likely that a combination of these factors leads to the development of BAOMJ. These mechanisms may prevent jaw bones healing from infections and microdamage. Additional medication, particularly chemotherapy and corticosteroids, may also contribute to the condition, due to synergistic antiangiogenic effects.¹⁰ Some potential causative factors of BAOMJ are shown in Table 2.

**Incidence of BAOMJ**

The true incidence of BAOMJ is not known. Adverse event reporting to manufacturers of bisphosphonates indicates a reporting rate of approximately one event per 100,000 person-years of exposure for oral bisphosphonates.²⁴ However, not all reports are adjudicated, and much of the information required to classify the reports properly is not available. Almost 45 million patients have been treated with bisphosphonates for osteoporosis worldwide, with only around 300 cases of BAOMJ reported in non-cancer patients.²⁶ Based on recently released case-reports of BAOMJ from Australia and Israel, the incidence may be higher than previously estimated for oral bisphosphonates.²¹,²² In the majority of these case-reports, alendronate was implicated as the causative agent. Based on sales of oral bisphosphonates during the time period of the Australian reports, the frequency of BAOMJ could be as high as one event per 2,260 to 8,470 patients (0.01% to 0.04%) treated, or around one event per 20,000 patient-years of exposure to oral bisphosphonates. If extractions were carried out, the calculated frequency was one in 296 to 1,130 cases (0.09% to 0.34%). However, in clinical trials of bisphosphonates for osteoporosis, no cases on BAOMJ were reported. These trials involved over 60,000 patient-years of exposure, involving follow-up periods of three to 10 years.⁶,²⁶ There are a number of reasons for this wide range of estimates; the type of study (retrospective versus prospective), inconsistent definition of BAOMJ and a possible lack of adjudication may all play a role.

The majority of cases of BAOMJ have been in patients with malignancies, particularly multiple myelomas,²⁴,²⁵ advanced breast cancer and prostate cancer.⁶ Cancer patients receive 10 to 15 times higher doses of bisphosphonates at an increased frequency per year than osteoporosis patients. The majority of potential BAOMJ case reports (so far numbering around 3,000) were cancer patients who received zoledronic acid or pamidronate, the most commonly used intravenous bisphosphonates.⁶ The incidence was reported as one in 100 at the end of the first year of treatment, and 11% to 21% after four years, depending on the bisphosphonate used.¹⁶ Increased duration of bisphosphonate treatment, larger doses and increased frequency of administration all appear to be risk factors for the development of BAOMJ.²⁶ Based on Australian case reports, the frequency of BAOMJ in bone malignancy cases, treated with mainly intravenous zoledronate or pamidronate, was one in 87 to 114 (0.88% to 1.15%).²¹ If extractions were carried out, the calculated frequency of ONJ was one in 11 to 15 (6.67% to 9.1%).²¹

In summary, the actual incidence of BAOMJ is not clear in cancer or non-cancer patients. In the Australian study by Mavrokokki et al., the reported incidence of BAOMJ in patients taking oral bisphosphonates for osteoporosis was 0.01% to 0.04%.²¹ This study used un adjudicated cases reported via a postal survey. A German study with adjudication of reported cases reported a BAOMJ incidence of 1 case per 263,158 patients treated with oral bisphosphonates (0.0004%).²⁷

**Implications of BAOMJ**

Table 3 lists a summary of recommendations for health care professionals regarding BAOMJ. Medical practitioners prescribing bisphosphonates are encouraged to consider dental referral of the patient before starting treatment, despite the lack of data regarding BAOMJ. This is especially important for the elderly, who are at increased risk. All health professionals can reinforce the importance of good

### Table 2. Common risk factors that may predispose to ONJ. (Taken from Wimalawansa, 2008.⁹)

<table>
<thead>
<tr>
<th><strong>Local causes</strong></th>
<th><strong>General causes</strong></th>
</tr>
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<tr>
<td>Invasive oral therapy (e.g. dental surgery, extraction)</td>
<td>Age &gt; 70 years and diabetes mellitus</td>
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<tr>
<td>Intra-oral trauma exposing jaw bones to oral microflora; osteomyelitis</td>
<td>High doses of frequently administered bisphosphonates and long duration of treatment</td>
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<tr>
<td>Poor oral or dental hygiene, periostitis and other jaw cavity infections</td>
<td>Concomitant use of glucocorticoids and/or chemotherapy</td>
</tr>
<tr>
<td>Local jaw ischaemia (e.g. infections, injection of vasoconstrictive agents)</td>
<td>Immunocompromised status</td>
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<tr>
<td>Viral infections*</td>
<td>Chronic use of tobacco or intravenous drug use</td>
</tr>
<tr>
<td>Removable dentures (risk of trauma and infection risk)</td>
<td>Osteolytic cancers and metastatic bone disease</td>
</tr>
<tr>
<td>Head and neck radiotherapy*</td>
<td>*Patients with these risk factors should not be categorised as BAOMJ</td>
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</tbody>
</table>

⁶ Patients with these risk factors should not be categorised as BAOMJ.
oral hygiene, given that the risk of BAOMJ is thought to be higher in people with pre-existing poor dental hygiene. Patients who take bisphosphonates should be aware of the symptoms of ONJ that may occur during or after treatment with bisphosphonates. These include toothache, pain, swelling or numbness of an area of the jaw or a discharge around a dental implant. Pharmacists should provide and discuss consumer medicines information with their patients. Information regarding the dental problems associated with bisphosphonates is now part of this information, and pharmacists can put this information into context for their patients. Patients should also inform their dentists that they are taking or have been taking a bisphosphonate, as this may influence their dental management.

**Conclusion**

The small risk of BAOMJ needs to be considered in the context of the substantial benefits of bisphosphonates. There are many uncertainties regarding the association of bisphosphonates with ONJ. BAOMJ appears to be a class effect of bisphosphonates. The bulk of cases of BAOMJ occur in cancer patients who are treated with intravenous bisphosphonates. Dental procedures and pre-existing poor dental hygiene greatly increase the risk of BAOMJ. The prevalence of BAOMJ in patients treated with oral bisphosphonates for osteoporosis varies between 0.7 and 3.8 cases per 100,000 patient-years. In cancer patients treated with intravenous bisphosphonates, the estimated prevalence ranges from 0.5 to 10 cases per 100 treated patients. Pharmacists should be aware of this potential complication of bisphosphonate therapy, and counsel and monitor their patients accordingly.

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**References**


**CPO questions on pages 932.**

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**Before bisphosphonate prescription**

*The medical practitioner should discuss with the patient*

- Benefits of bisphosphonate treatment
- Risk of adverse effects including ONJ
- Risk/benefit of other treatment options
- Dental referral if in doubt

**The dental practitioner should**

- Make the patient dentally fit with a low chance of future extractions

**The pharmacist can**

- Discuss ONJ with their patients, using the consumer medicines information

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**Patients on bisphosphonates**

*The medical practitioner should*  
- Promptly refer to an appropriate dental specialist for investigation, if there is suspicion of ONJ

*The dental practitioner should*  
- Be aware of bisphosphonate dosage and other risk factors
- Avoid extractions or other jaw bone surgery
- Obtain informed consent if surgery is unavoidable
- Perform extractions under antibiotic prophylaxis, minimal trauma and suture socket

*The pharmacist can*  
- Be aware of the presenting clinical features of ONJ
- Refer for expert management if ONJ is suspected