Bisphosphonates and osteonecrosis of the jaw

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Recently an association between bisphosphonate use and a rare dental condition termed 'osteonecrosis of the jaw' (ONJ) has been reported. Patients with osteoporosis and Paget disease who take bisphosphonates have a significantly reduced risk of fracture and other skeletal complications. This represents significant health benefits, against which the small risk of ONJ needs to be considered. In patients with bone malignancy, the risk of ONJ needs to be balanced against the benefit of therapy on the underlying malignancy. There are still many uncertainties about this condition. This position paper seeks to summarise what is currently known about ONJ to provide information to medical practitioners and dental practitioners.

Bisphosphonates are widely used in the management of osteoporosis, Paget disease and metastatic bone disease, multiple myeloma and other malignancies associated with hypercalcaemia. In Australia there were 2.3 million bisphosphonate prescriptions in 2003. This equals the number of amoxycillin prescriptions in the same year.[1] In 2004 this had increased to 2.5 million bisphosphonate prescriptions, predominantly as a once weekly oral therapy.[1] Generally, the side effects of bisphosphonates are minimal, however, in 2003 there were sporadic cases reported in the *Journal of Oral and Maxillofacial Surgery* of necrosis of the jaw following dental extractions.[2–4] These patients were all receiving bisphosphonates, mainly intravenous pamidronate and zoledronate for the management of bone malignancy. Similar cases were also reported in Australia.[5,6] Osteonecrosis of the jaw (ONJ) is a significant complication with painful areas of exposed bone in the mouth which fail to heal.

The discovery of a possible association between bisphosphonates and ONJ prompted both the United States Food and Drug Administration (FDA) and Novartis, the manufacturer of two intravenous bisphosphonates used in cancer chemotherapy, to issue a warning to health care professionals in September 2004. The warning contained information about bisphosphonates and the risk of ONJ.[7] These actions had been paralleled in Australia with adverse drug reaction reports in the medical literature[8,9] and the publication by Novartis of guidelines for health professionals[10] and patients.[11] Detailed reports of cases occurring in South Australia have also been independently reported.[12,13]

What is osteonecrosis of the jaw?

A clear definition is lacking. A working definition of ONJ is 'an area of exposed bone that persists for more than 6 weeks'. Clinically it should be suspected in individuals who develop exposed bone in the maxillofacial area following dental surgery. The symptoms vary from painless exposed bone to severe jaw pain. Pain is particularly a problem when there is associated tissue infection. Less commonly, it can also arise in the absence of dental surgery and is thought to follow simple trauma such as denture trauma. The presence of active bone malignancy or radiotherapy effects to the site, as well as viral and bacterial infections, need to be excluded by an appropriate specialist.

Why does osteonecrosis of the jaw occur?

The cause(s) of ONJ are not known. Nor is it clear why some patients develop the condition or suffer it more severely than others. Bone remodelling involves osteoclasts resorbing old damaged bone and osteoblasts replacing this with new bone. Bisphosphonates reduce the rate of bone remodelling and so removal of microdamaged regions of bone may be impaired. Whether this repair process is more important in the region of the jaw, and particularly when there is an extraction socket exposed to bacteria, is not known.

Why the effect of the bisphosphonates on jawbones would be different to other bones is unclear, but there are known differences in their development, consequent

bone structure and vascularity. The jawbones are subjected to constant high stresses from masticatory activity such as chewing, swallowing and talking. The teeth, which are retained in the jaw by the periodontal ligaments, protrude through the mucosa into the mouth and are bathed in saliva. Saliva has a high bacterial load. In healthy individuals there are many physical and immunological mechanisms that cope with these forces and the presence of high bacterial levels.[14] Under normal circumstances healing rapidly occurs following tooth extraction. Even though 5% of extractions result in a nonhealing osteitis (dry socket) this spontaneously resolves within 2–3 weeks.

Normal extraction site healing involves osteoclastic activity to remodel the tooth socket and create new bone. It may be that the bisphosphonate affected bone, in combination with the bacterially infested saliva in the socket, results in the inability to respond to this healing and infection challenge.

How common is the problem?

The incidence of ONJ is not known. Estimates range from one in 2000–10 000 patients, but the incidence has not been defined precisely for malignant conditions or in the setting of treatment of osteoporosis and Paget disease. The majority of published case reports involve patients with malignancy receiving intravenous bisphosphonates, but a small proportion of patients were receiving oral bisphosphonates for treatment of osteoporosis.[9]

Osteoporosis

In regard to individuals with osteoporosis treated with oral alendronate, no cases were observed during the preclinical studies in which alendronate was used in far higher doses than that currently approved for osteoporosis. Similarly no cases were seen in controlled clinical trials involving more than 17 000 patients.[15] Alendronate has been on the market for 10 years, during which time the total exposure to the drug is estimated at around 20 million patient years. However, as at mid 2006, Merck Sharp and Dohme had received 170 reports of potential jaw osteonecrosis associated with alendronate. This represents 0.7 reports per 100 000 person years of exposure. In Australia, it is estimated 400 000 patients have been treated with alendronate. In the South Australian series of 15 cases, five had been on oral alendronate alone and one had been on the combination of intravenous pamidronate and oral alendronate.[13] In an Australia wide survey of oral and maxillofacial surgeons, 30 of a reported 149 cases were receiving alendronate and a further three cases were on combinations with alendronate and other bisphosphonates.[16] Using the Australian survey data, it was estimated that the risk of ONJ for an osteoporotic patient following an extraction was of the order of one in 1000.[16] A recent German study estimated the incidence of ONJ in the nononcology setting at less than one in 100 000,[17] which is also considerably lower than the Australian survey.

Malignancy

The risk is greater for patients with bone malignancy who are likely to have received intravenous bisphosphonates such as pamidronate and zoledronate. In the retrospective case review at the MD Anderson Hospital, a study of 4000 cancer patients revealed 33 cases of ONJ, of these 16 of 1340 (1.2%) were patients with breast cancer, 15 of 550 (2.8%) were cases of myeloma, and there were two other cases giving an overall incidence of 0.83%.[17] In the Australian survey, there were 82 of 149 cases of osteonecrosis receiving zoledronate, pamidronate or combinations.[16] The risk appeared greatest for patients over the age of 55 years who were otherwise medically compromised, for example with diabetes or on corticosteroids as well as their underlying malignancy. If however patients receiving bisphosphonates for bone malignancy had dental extractions, then the risk of ONJ was increased. The Australian survey estimated that the risk of ONJ following an extraction in the setting of malignancy was of the order of 10%.[16]

It should be noted that these Australian data are from a retrospective postal survey with no validated or adjudicated diagnosis, and therefore from an epidemiological view, should be viewed with caution.

Implications for medical practitioners

Physicians who prescribe bisphosphonates must be aware of this rare but potential side effect in the nononcology setting and should discuss it with their patients (*Table 1*). Despite the lack of data, it appears to be prudent to recommend assessment of dental health before commencing treatment with bisphosphonates. The treating physician should inquire about the state of the patient's dental health and if in doubt, refer the patient to see a dentist to be made dentally fit before or shortly after commencing a course of bisphosphonate therapy, as long as the patient's skeletal condition permits a delay in initiation of therapy. The imperative for this is much greater in patients with malignancy.

Patients receiving bisphosphonate treatment should be informed of the need to maintain adequate levels of dental health. It is not known whether there is any benefit in temporarily withdrawing bisphosphonate therapy before extractions.

Implications for dental practitioners

Before commencing dental treatment a recent medical history is essential (*Table 1*). The dental profession in Australia has recently been advised to include questions relating to bone disease and the bisphosphonates.[13] They have also been advised of the risk of dental extractions and other treatment involving bone surgery for patients on bisphosphonates. If a patient is referred for oral assessment before commencement of bisphosphonates, the prime aim should be to minimise the risk that the patient may subsequently require extractions. Dentures also need to be well fitting.[18–20]

For patients receiving bisphosphonates, a risk assessment needs to be made. If they are in a high risk category then avoiding extractions if at all possible is best. This may require endodontic (root filling) treatment rather than an extraction. In patients where there is no choice but to extract the tooth, this should be performed with the minimum of soft tissue flap raising and trauma to the bone. A single pre-extraction antibiotic dose of 2 g amoxicillin for those who are not allergic is recommended. Similarly, the socket is best opposed and sutured. It should be noted however, that there is not a strong evidence basis for these proposals. Dental implants are relatively contraindicated in patients on bisphosphonates.[9] There are reported cases of patients who have undergone loss of osseo-integration of previously successful implants. Normal bone turnover is essential

Table 1. Recommendations for medical practitioners and dental practitioners

Before bisphosphonate prescription

- The medical practitioner should discuss with the patient
  - benefits of bisphosphonate treatment
  - risk of adverse events including ONJ
  - risk/benefit of other treatment options
  - consider dental referral if in doubt
- The dental practitioner should
  - make the patient dentally fit with a low chance of future extractions

Patients on bisphosphonates

- The medical practitioner should
  - if suspicion of ONJ, then prompt referral to appropriate dental specialist for investigation
- The dental practitioner should
  - be aware of bisphosphonate dosage and other risk factors
  - avoid extractions or other jaw bone surgery
  - if surgery unavoidable then obtain informed consent
  - perform extractions under antibiotic prophylaxis, minimal trauma and suture socket

for ongoing osseo-integration. In the event of nonhealing exposed jaw bone, detailed specialist investigations need to be made to confirm the diagnosis. There should be close communication between the prescribing physician and the treating dentist or specialist.

Future directions

There are many unknowns regarding the process of bisphosphonate associated ONJ. There is lack of a generally agreed upon case definition. The precise pathophysiology is unknown. There appear to be different risks between the different types of bone diseases and medication regimens. Therefore, there is a need for ongoing animal and clinical research about these issues.[21]

Conclusion

Patients with osteoporosis and Paget disease who take bisphosphonates have a significantly reduced risk of fracture and other skeletal complications. This represents significant health benefits against which the small risk of ONJ needs to be considered. One approach is to ensure appropriate oral health and dental treatment before prescription. Prevention by ensuring adequate oral health before treatment is indicated, particularly if high doses or intravenous routes are employed.

Resources

Australian New Zealand Bone Mineral Society www.anzbms.org.au
Osteoporosis Australia www.osteoporosis.org.au
Medical Oncology Group of Australia www.moga.org.au
Australian Dental Association www.ada.org.au

Conflict of interest: Professor Sambrook is a member of the Merck Sharp and Dohme Osteoporosis Advisory Group and Novartis Advisory Board. Professor Olver has no conflict of interest. Professor Goss has advised Novartis and Merck Sharp and Dohme on ONJ and bisphosphonates.

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