Yazdana Arrain

Tahir Masud

Recent Recommendations on Bisphosphonate-Associated Osteonecrosis of the Jaw

Abstract: There is increasing awareness of the importance of osteonecrosis of the jaw developing in patients taking bisphosphonates. A recent working party of the American Society for Bone and Mineral Research has developed recommendations on the prevention and treatment of this condition which dentists will find useful.

Clinical Relevance: As bisphosphonates are now being used widely in the treatment of several conditions including osteoporosis, Paget's disease and metastatic malignancy, dentists should be able to recognize osteonecrosis of the jaw and how it is managed.

Dent Update 2008; 35: 238-242

In the last few years there has been increasing awareness of the link between bisphosphonates and osteonecrosis of the jaw (ONJ). As more data emerge, it is important to share current knowledge and new guidelines.

As some dental practitioners may not be familiar with this family of drugs, it is important to discuss the growing range of bisphosphonates and their uses so that patients who are at risk of developing ONJ are identified.

Bisphosphonates are pyrophosphate analogues that inhibit osteoclastic function and thereby decrease bone resorption. Medically, they are useful drugs in the treatment of osteoporosis, Paget's disease, hypercalcaemia and in patients with cancer. In this respect, in cancers that metastasize to the bone, bisphosphonates reduce risks of complications, such as spinal cord compression, fractures and bone pain. However, the vast majority of oral bisphosphonate prescriptions are for patients with osteoporosis. It is important for dentists to realize that osteoporosis is a serious condition which leads to significant health problems and expense to health and social services, costing the country £1.8 billion every year.[1] It leads to 180,000 fragility fractures in the UK annually, including 70,000 hip fractures, which are associated with morbidity and mortality.[2] Patients with cancer, especially those receiving anti-cancer drugs, are often also given bisphosphonates, usually in intravenous formulations and in higher doses than used for osteoporosis and other non-cancer conditions.

Yazdana Arrain, BDS, DRDP, GDP and Clinical Lecturer in Restorative Dentistry, University of Birmingham School of Dentistry, St Chad's Queensway, Birmingham B4 6NN and **Tahir Masud,** MA (Oxon), MBBS (Lond), MSc (Nott), FRCP, Professor of Musculoskeletal Gerontology, University of Derby and Consultant Physician, Nottingham University Hospitals NHS Trust, Hucknell Road, Nottingham, NG5 1PB, UK.

Currently used bisphosphonates

Currently available bisphosphonates in the UK include etidronate, clodronate, alendronate, risedronate, tiludronate, ibandronate, pamidronate and zoledronate. The latter two are available only in intravenous form and ibandronate can be used orally or intravenously.

Owing to the rising concern over bisphosphonate associated ONJ, a working party of 24 members from US National Institutes of Health and Canadian Institutes of Health Research was appointed by the American Society for Bone and Mineral Research (ASBMR). These experts covered a range of disciplines, including histology, epidemiology, oromaxillofacial, rheumatology, oncology and other essential medical fields. The important messages from the working party report[3] are summarized below.

Definitions

A confirmed case of bisphosphonate-associated ONJ

This was defined as 'an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a healthcare worker, in a patient who was receiving, or had been exposed to, a bisphosphonate and had not had radiation therapy to the craniofacial region'.

	Patients with osteoporosis or other non-malignant disease taking bisphosphonates >3yrs	Patients with malignancy, starting or already receiving bisphosphonates
Dental regime	Regular dental visits, oral health maintenance.	Regular dental visits, oral health maintenance – 6 to 12 monthly dental exams or as clinical/dental status demands.
Dental exam pre-bisphosphonate therapy	No – as risk of ONJ is low no additional dental examination is needed or change to routine dental care.	Yes – before starting IV bisphosphonates for bone metastasis. Invasive procedures, if needed, should be carried out and healing completed before starting bisphosphonates IF THE PATIENT'S CLINICAL TREATMENT ALLOWS, LIAISE WITH PHYSICIANS/ONCOLOGISTS. If not possible, need careful follow up of surgical sites.
Extractions	Extractions are not contra-indicated as risk of ONJ low. Root treatment preferable, if coronally unrestorable can amputate to root level after root treatment and seal.[5] If extract, best to carry out atraumatic extractions and careful socket follow up – refer if chronic exposed bone.	Avoid extractions wherever possible as increased risk of ONJ – root treatment preferable and if coronally unrestorable can amputate to root level after root treatment and seal.[5] For periodontally affected teeth – only extract if excessive mobility and aspiration risk. Symptomatic teeth in an area of exposed bone that is already exposed and necrotic can be extracted as established necrotic process will not be exacerbated by this. If unsavable, eg vertical root fracture and extraction needed, very careful follow up of surgical site important.
Periodontal disease	Perio surgery is appropriate if it reduces or eliminates disease. Can carry out modest bone contouring.	Perio surgery is not recommended. Non-surgical perio treatment only.
Dentures	Need good fitting dentures.[5]	Good fitting dentures possibly with soft lining to prevent trauma.[5]
Endodontics	Avoid apical surgery. Conventional orthograde endodontics recommended rather than extraction where possible. Good coronal seal maintenance important.	Avoid apical surgery. Conventional orthograde endodontics recommended rather than extraction where possible. Good coronal seal maintenance important.
Implants	Currently not contra-indicated if taking bisphosphonates but prudent to gain informed consent which should be documented (risk assessment).	Not recommended and avoid elective surgery such as tori removal.

Table 1. Current dental recommendations for bisphosphonate patients (ASBMR Working Party Report[3]).

A suspected case of bisphosphonate-associated ONJ

This was defined as 'an area of exposed bone in the maxillofacial region that had been identified by a healthcare provider and had been present for < 8 weeks in a patient who was receiving, or had been exposed to, a bisphosphonate and had not had radiation therapy to the craniofacial region'.

Suspected cases of bisphosphonate-associated ONJ should be followed up and referred to a specialist. Differential diagnosis includes:

- Periapical pathology caused by a carious infection;
- Tumours;
- Mucositis;
- Infectious osteomyelitis;
- Neuralgia-inducing cavitational osteonecrosis (NICO).

Similarly, other mucosal oral conditions, such as periodontal disease, may show exposure of bone as above but, without a history of bisphosphonate use, they cannot fall into the category of bisphosphonate-associated ONJ.

Incidence of bisphosphonate associated ONJ

Both published and unpublished data on ONJ were reviewed by the working party. Current knowledge on incidence suggests that:

- The incidence of ONJ in oral bisphosphonate therapy for osteoporosis is low (between 1 in 10,000 to 1 in 100,000), but it was recognized that this figure could turn out to be higher as more data are collected.
- Cancer patients on high dose intravenous bisphosphonates were more at risk (ranging from 1 in 10 to 1 in a 100 patients), depending upon the duration of the bisphosphonate treatment.

Clinical features of ONJ

Symptoms and signs of ONJ may include:

- Pain;
- Swelling;
- Pus formation;
- Parasthesia;
- Ulceration of soft tissue;
- Sinus tracts (intra-oral or extra-oral);
- Loosening teeth; and
- Exposed bone.

Pain	Must be dealt with first appropriately.
Infection	1. Oral rinses such as 0.12% Chlorhexidene. 2. If there is infection systemic antibiotics are given. 3. Maintain an infection-free oral environment (especially in multiple myeloma patients being considered for stem cell transplantation).
Surgical treatment	1. This should be delayed or be conservative. 2. Sharp edges removed to stop soft tissue trauma. 3. Loose bony sequestra removed without exposure of uninvolved bone. 4. Segmental jaw resection may be needed for symptomatic patients with large segments of necrotic bone or pathological fracture.
Altering bisphosphonate therapy regime	Some experts suggest stopping bisphosphonate therapy in cancer patients with established ONJ if the patient's clinical situation allows. No published data yet to suggest this helps. The half life of bisphosphonates in the skeleton is high. Recommendation is to look at clinical situation, eg for aggressive skeletal metastatic disease one may continue bisphosphonates. For mild skeletal disease or for therapy for prevention of metastases can consider discontinuation. Discussion with patient's physician/oncologist is important.
Other considerations	1. In advanced ONJ in patients with limited ability to eat additional nutritional supplements important, eg tube feeding. 2. Hyperbaric Oxygen: effectiveness of this procedure has not been established.

Table 2. Management of established ONJ (ASBMR Working Party Report[3]).

Risk factors for ONJ

Risk factors include:

- Bisphosphonates (particularly intravenous);
- Length of bisphosphonate therapy exposure;
- Cancer and anti-cancer treatments;
- Dental extractions;
- Oral bone surgery;
- Intra-oral trauma;
- Poorly fitted dental appliances;
- Glucocorticoid use;
- Smoking;
- Alcohol abuse; and
- Periodontal/dental disease.

Diagnosis of ONJ

It is essential to refer ONJ suspected/diagnosed patients, together with a panoramic radiograph (if available), to a specialist. In general dental practice

the working party recommends taking a panoramic radiograph as a good baseline record. Conventional radiographs have limitations. When there are radio-opaque sequestra, then radiographically metastatic lesions can be differentiated sufficiently from osteonecrosis. However, if the lesion is osteolytic, radiographs are not useful. Early lesions may also be missed.

The suggested further specialist investigative procedures may include:

Bone imaging techniques

- CT for differential diagnosis;
- Cone beam CT gives detail on thickness of cortex, integrity and marrow involvement, cancellous bone mineral density (BMD) and irregularities after tooth extraction.

Soft tissue and bone marrow imaging techniques

MRI recognizes ischaemic areas with the use of contrasting agents but it may give false positives.

Functional/physiological tests

- Technetium-99 radioisotope scintigraphy – in patients with metastatic bone disease, where clinically indicated;
- Positron emission tomography – not very useful as poor resolution with high radiation dose;
- Bone resorption markers such as the collagen telopeptide (CTX) may be of some value in assessing the risk of bisphosphonate-induced osteonecrosis by indicating oversuppression of bone turnover.[4]

Biopsy

In most cases, biopsy is not necessary and may even be detrimental to bone healing. However, when there is a history of parenteral bisphosphonate therapy for metastatic cancer, then the possibility of metastases to the jaw should be seriously considered and, if no biopsy is taken, the reason should be recorded in the patient's notes.

However, there is a need for more research to develop diagnostic procedures further.

Prevention of ONJ

All patients with osteoporosis or other non-malignant disease will need good oral hygiene and regular routine dental examinations and hygiene. For those patients taking bisphosphonates for more than 3 years, recommended actions are shown in Table 1. There are also important differences in approach to patients taking bisphosphonates for osteoporosis and non-malignant disease compared to patients with malignancy who are starting or already taking bisphosphonates.

Management of bisphosphonate-associated ONJ

Once ONJ has developed, managing the condition can be challenging. After diagnosis, the important aspects of treatment are shown in Table 2.

General recommendations of the working party

It is important to have good communication between physicians and dentists. Patients should be encouraged by their physicians to inform their dentist if they are taking a bisphosphonate. All patients should be informed of benefits and potential risks of bisphosphonates, including ONJ, the signs and symptoms of ONJ, as well as risk factors. Patients should be advised to maintain good oral hygiene and have regular routine dental visits. In areas where there is limited access to dental care, patients and physicians should be educated about ONJ. In this situation, it is even more important to maintain good oral homecare, as dental disease prevention is essential.

Conclusions

As further data are published, we will learn more about the true extent of ONJ. It is important to recognize that ONJ is not common in patients who are given bisphosphonates for osteoporosis, but the incidence is much higher in cancer patients and those receiving bisphosphonates as part of their anti-cancer drug regime. More studies are essential on the prevalence, risk factors, morbidity and cost implications of ONJ. Management of ONJ is difficult and expensive. Prevention, wherever possible, is therefore the key. This will have to start at primary care levels. Education and regular updated guidelines for general practitioners are important to try and limit the impact of ONJ.

References

1. Burge R, Worley D, Johansen A, Bhattacharyya S, Bose U. The cost of osteoporotic fractures in the UK. Projections for 2000-2020. *J Drug Assess* 2001; **4**: 91–107.
2. NICE. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fractures in postmenopausal women. Technology appraisal guidance 87. London: National Institute for Health and Clinical Excellence, 2005.
3. Khosla S, Burr D, Cauley J, Dempster D, Ebeling P, Felsenberg D *et al*. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007; **22**: 1479–1491.
4. Marx RE. *Oral and Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws. History, Etiology, Prevention and Treatment.* Chicago: Quintessence Publishing Co Inc, 2007: p.86.
5. Barker K, Rogers S. Bisphosphonate-associated osteonecrosis of the jaws: a guide for the general dental practitioner. *Dent Update* 2006; **33**: 270–275.

CPD ANSWERS

April 2008

1. A, B, D	6. A, B, D
2. A, B, D	7. A, C
3. A, C,	8. A, B, D
4. A, B, D	9. B, D
5. B, C, D	10. B, C

Erratum

EACD GDP Guidelines – *Dent Update* 2008; **35**: 210–211.

Stephen Davies wishes to replace the fourth sentence in his article with:
'The paramount recommendation is that reversible therapeutic measures should be considered before irreversible measures'.