

Local guidelines for primary care dental teams regarding the risks to patients of bisphosphonate related osteonecrosis of the jaws.

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Introduction

The association between osteonecrosis of the jaws and intravenous (IV) bisphosphonates was first noted in the literature in 2003 (Marx, 2003), since then there have been worldwide reports of the association with both IV and oral bisphosphonates. In the UK (as worldwide) the majority of cases reported were associated with IV bisphosphonates with 77 reported cases in comparison with 9 cases associated with oral bisphosphonates (May 2006).

Bisphosphonate related osteonecrosis of the jaws has become a serious oral complication of the use of bisphosphonates with a significant impact on an individual's quality of life. However this must be considered alongside the great treatment benefits from their use.

At present guidelines such as these are based upon the existing literature and expert clinical opinion they will need to be continually updated and amended in light of the emerging evidence in this field.

Benefits of bisphosphonate therapy

IV Bisphosphonates are primarily used in the treatment and management of cancer related conditions. These include hypercalcaemia of malignancy, skeletal related events associated with bone metastases from solid tumours e.g. breast, prostate and lung cancer and myeloma (American Association of Oral Maxillo Facial Surgeons (AAOMS), 2006). They are effective in preventing and reducing hypercalcaemia (stabilising bony pathology and preventing skeletal fractures). Although they have not been shown to increase survival rates they significantly improve quality of life for patients with advanced cancer affecting the skeletal system.

Oral bisphosphonates are used mainly for the treatment and prevention of osteoporosis however they are also used for the treatment of Paget's disease and osteogenesis imperfecta in childhood.

Risks of bisphosphonate therapy

Since the first reports of cases by oral maxillo facial surgeons of non healing bone in the maxillo facial region in patients first treated by IV bisphosphonates there have been several case reports, reviews and letters published in the literature. The condition has generally presented as exposed bone with other signs including; pain, swelling, infection, loosening of teeth and numbness or feeling of heaviness in the jaws

To distinguish bisphosphonate related osteonecrosis (BRON) from other conditions involving delayed healing the AAOMS adopted the following working definition.

Patients may be considered to have BRON if **all** of the following three characteristics are present:

1. Current or previous treatment with a bisphosphonate;
2. Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaw

The exact mechanism of bisphosphonate related osteonecrosis is not known, but there is evidence that bisphosphonates inhibit the function of osteoclasts:

- Inhibiting osteoclast development from precursor cells
- Stimulating osteoclast inhibitory factor
- Increasing osteoclast apoptosis (cell death)
- Reducing osteoclast activity
- And the down-regulation of matrix metalloproteases

In the bloodstream bisphosphonates bind avidly to the bone and with slow bone turnover it is thought that the half life in bone of IV preparations may be as long as ten years.

Incidence of BRON

With regard to IV bisphosphonates current best estimates of the cumulative incidence are approximately 0.8-12%.

With oral bisphosphonates the risk is considerably lower than for the IV bisphosphonates. Based on data from the manufacturer of alendronate the incidence was calculated as 0.7/100,000 person years of exposure. This was estimated from the number of reported cases divided by the number of pills prescribed since the drug gained approval and converted to patient years.

Risks are therefore much greater for those receiving IV treatment. However with over 190 million oral bisphosphonate prescriptions world wide and 41,000 in Bradford it is likely that practitioners will treat patients taking bisphosphonates and indeed a case of BRON.

Prescribing data for Bradford

Prescribing data can give an estimate of the numbers of patients involved although this may be an overestimate as patients are often re-prescribed such drugs within the time period analysis. Currently in Bradford within a six month period 87 patients are taking IV bisphosphonates. The majority are prescribed by Haematology and Oncology Consultants. Within haematology about 20 new patients per year with Myeloma are prescribed IV bisphosphonates.

Approximately 41,000 prescriptions for oral bisphosphonates are dispensed annually in primary care in Bradford and Airedale (based on 2006 data). This equates to approximately 4,300 patients, with prescriptions mainly for osteoporosis.

Risk factors

Drug related

- IV administered bisphosphonates have a higher risk than oral.
- Potency of IV and oral drugs increases risk (see appendix 1)
- Duration of therapy, with increased duration increasing risk. E.g. the most potent IV bisphosphonate Zometa may produce exposed bone in 6-12 months, in comparison with the oral bisphosphonate Fosamax when taken as recommended which may take 3 years or more to produce bone exposure (Marx, 2007).

Local Factors

- **Dento-alveolar surgery - Patients undergoing IV Bisphosphonate therapy are 7-times more likely to develop osteonecrosis if they have dentoalveolar surgery. Of IV BRON cases approximately 75% are precipitated by some type of invasive dental procedure.**
- **Local anatomy - Cases are more common in mandible than maxilla and where the mucosa is thin overlying bony prominences e.g. tori, bony exostoses and the mylohyoid ridge.**
- **Concomitant oral disease - Patients with a history of dental/periodontal abscesses have a seven-fold risk of developing osteonecrosis.**

Demographic Factors

- Age - in multiple myeloma patients treated with IV Bisphosphonates 9% increased risk with each decade

Systemic Factors

- Cancer diagnosis - Risk is greater for patients with multiple myeloma than for patients with breast cancer. Those with breast cancer have a greater risk than those with other cancers.

Other Factors

- The following are also thought to be risk factors;
Corticosteroid therapy, diabetes, smoking, alcohol, poor oral hygiene and chemotherapeutic drugs.

Patient management

Consultants in haematology and oncology will ensure that all patients about to commence treatment with IV bisphosphonates are alerted to the need to have a dental assessment and care. Those who have a General Dental Practitioner will be advised to make an appointment and be given an information letter (see appendix 2) to give to their dentist. Those who have no dentist will be referred to the appropriate salaried dental service for assessment and care

(see appendix 3 - referral form). This service will be piloted for an initial 1 year period to establish the level of need for such care, the level of referrals will inform the need for an additional commissioned service.

Prior to treatment with IV bisphosphonates:

- Patients should have a thorough oral examination, all invasive treatment completed and optimal periodontal health achieved. Delaying the onset of IV bisphosphonate treatment should be discussed with medical oncologists if thought necessary. Close collaboration between the dentist and the oncologist/haematologist is essential.
- Rehabilitation of the dentition including endodontic therapy.
- Preventive advice, caries control, oral hygiene instruction and use of chlorhexidine.
- Ensuring proper fit of dentures, to avoid mucosal or periodontal damage, using soft linings where appropriate.
- Removal of large or multilobulated tori with thin overlying mucosa
- Advice and support can be obtained from the Consultant in Restorative dentistry.

Patients already receiving IV bisphosphonates:

- Maintain good oral hygiene and dental care to avoid dentoalveolar surgery.
- Existing periodontal disease should be treated non-surgically with supragingival scaling, chlorhexidine and doxycycline as appropriate.
- Un-restorable teeth should be treated endodontically with coronal amputation rather than by removal.
- Great care should be taken if using rubber dam clamps to avoid mucosal damage.
- Review the fit of dentures regularly to prevent mucosal trauma and consider soft linings for dentures if appropriate.
- Restorative advice and support should be obtained from the consultant in restorative dentistry as necessary
- If the patient presents with periodontal or periapical infection seek the advice of local maxillo facial department regarding the correct antibiotic regime.
- If extraction or dento alveolar surgery is essential refer to local maxillo facial surgeons.
- These patients effectively have a lifetime special care need.

Patients already receiving oral bisphosphonates:

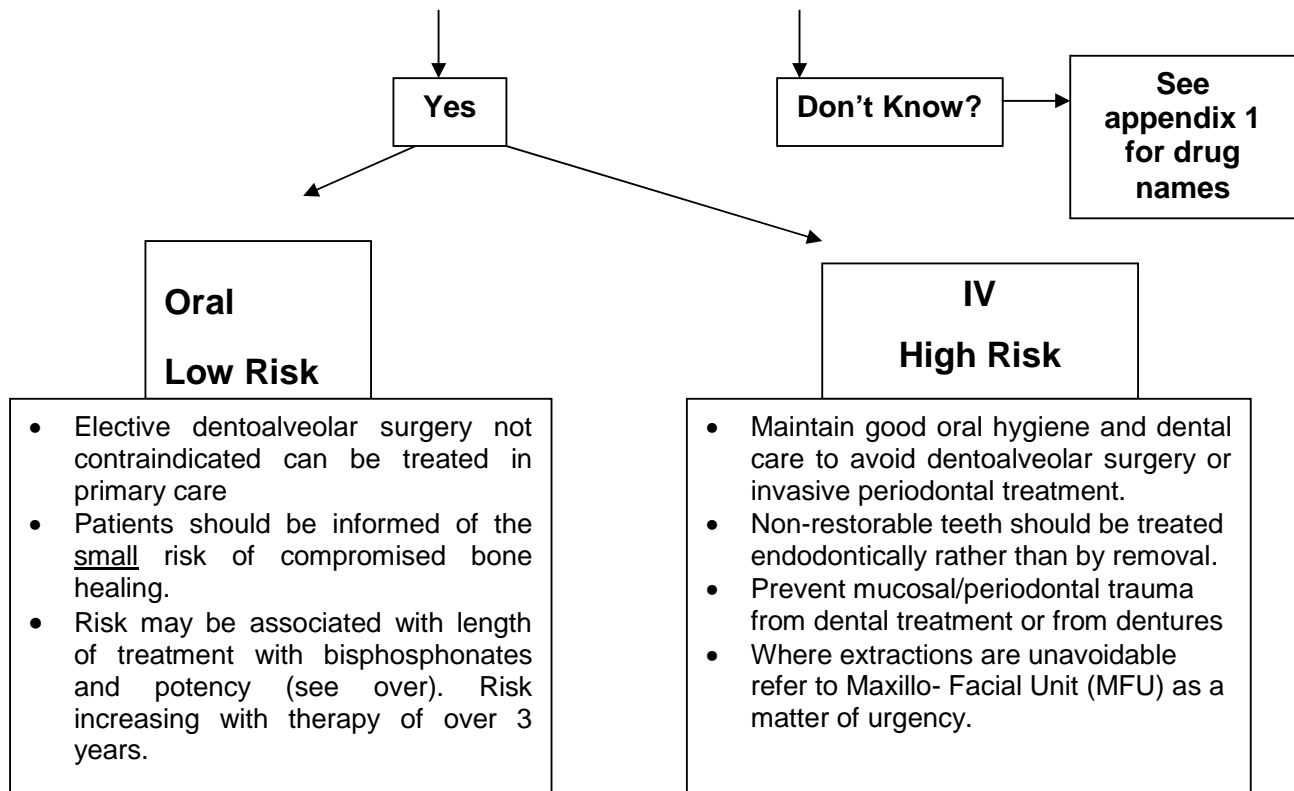
- Elective dent alveolar surgery is not contraindicated the risk of osteonecrosis is low.
- However patients should be informed of the small risk of compromised bone healing.
- Atraumatic extractions where possible with the avoidance of raising mucoperiosteal flaps, and careful follow up of healing.

- Practice preventive measures, caries control, oral hygiene instruction.
- Risk may be associated with length of treatment with bisphosphonates and potency (see appendix 1). Risk increasing with therapy of over 3 years. This area does however require further analysis and research.

Patients with an established diagnosis of BRON:

- All such patients oral / dental care should be provided in consultation with their maxillo-facial surgeon.

Is your patient receiving Bisphosphonates?



Is your patient about to be treated with IV Bisphosphonates?

- Prior to treatment with IV bisphosphonates;
- Patient should be treated urgently as priority cases, as they will probably have bone metastases.
 - Delaying onset of IV care should be discussed with appropriate consultant e.g. oncologist, haematologist, rheumatologist.
 - Patient should have a thorough oral examination, all invasive treatment completed and optimal periodontal health achieved.
 - Patient must achieve good oral hygiene and dental care
 - Potentially compromised teeth should be extracted, to avoid extractions after the IV treatment has started.
 - For complex cases requiring urgent advice on establishing a treatment plan referral to consultant in restorative dentistry.

References

American Association of Oral and Maxillofacial Surgeons. (2006) Position paper on bisphosphonate - related osteonecrosis of the jaws.

Barker K and Rogers S (2006) Bisphosphonate- Associated Osteonecrosis of the Jaws: A guide for the General Dental Practitioner. *Dental Update* 33; 270-275.

Hellstein JW. Marek CL. (2006) Bisphosphonate Induced Osteochemonecrosis of the Jaws: An ounce of prevention may be worth a pound of cure. *Spec Care Dentist* **26**(1): 8-12

Marx RE. (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic [Letter]. *J Oral Maxillofac Surg*; **61**:1115-8

Marx RE . Oral and intravenous bisphosphonate- induced osteonecrosis of the jaws: history, etiology, prevention and treatment. Illinois, Quintessence Publishing Co, 2007.

Appendix 1**Bisphosphonate Preparation Currently Available in UK**

| | Primary Indication | Nitrogen containing | Dose | Route | Relative potency* |
|-------------------------------------|---|---------------------|---|-------|-------------------|
| Disodium Etidronate (Didronel®) | Paget's Disease | No | 5 mg/kg as a single daily dose for up to 6 months; doses above 10 mg/kg daily for up to 3 months may be used with caution but doses above 20 mg/kg daily are not recommended; after interval of not less than 3 months may be repeated where evidence of reactivation—including biochemical indices (avoid premature retreatment) | Oral | 1 |
| Disodium Etidronate (Didronel PMO®) | Treatment of osteoporosis, prevention of bone loss in postmenopausal women (particularly if hormone replacement therapy inappropriate), and prevention and treatment of corticosteroid-induced osteoporosis | No | given in 90-day cycles, 1 <i>DidroneI</i> ® tablet daily for 14 days, then 1 <i>Cacit</i> ® tablet daily for 76 days | Oral | |

| | | | | | |
|--|--|-----|--|------|-------|
| Tiludronic Acid (Skelid®) | Paget's Disease | No | 400 mg daily as a single dose for 12 weeks; may be repeated if necessary after 6 months | Oral | 50 |
| Alendronic Acid (Fosamax® /Fosamax Once Weekly®) | Treatment of postmenopausal osteoporosis and osteoporosis in men | Yes | 10 mg daily Or 70 mg once weekly (in postmenopausal osteoporosis) | Oral | 1,000 |
| | Prevention of postmenopausal osteoporosis | | 5 mg daily | | |
| | Prevention and treatment of corticosteroid-induced osteoporosis, | | 5 mg daily 10 mg daily (postmenopausal women not receiving hormone replacement therapy) | | |
| Alendronic Acid with colecalciferol (Fosavance®) | Treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency | | 1 tablet once weekly | Oral | |
| Risedronate Sodium (Actonel®/Actonel Once a Week®) | Paget's Disease | Yes | 30 mg daily for 2 months; may be repeated if necessary after at least 2 months | Oral | 1,000 |
| | Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures | | 5 mg daily or 35 mg once weekly | | |
| | Prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women | | 5 mg daily | | |

| | | | | | |
|--|---|--|---|---|-------|
| Ibandronic Acid (Bonviva®/Bondronat®) | Reduction of bone damage in bone metastases in breast cancer | Yes | 50 mg daily | Oral | 1,000 |
| | Treatment of postmenopausal osteoporosis | | 150 mg once a month | Oral | |
| Ibandronic Acid (Bondronat®) | Reduction of bone damage in bone metastases in breast cancer | | 6 mg every 3–4 weeks | IV infusion | |
| | Hypercalcaemia of malignancy | | according to serum calcium concentration, 2–4 mg in single infusion | IV infusion | |
| | Treatment of postmenopausal osteoporosis | | over 15–30 seconds, 3 mg every 3 months | IV injection | |
| Disodium Pamidronate (generic concentrate/Aredia® dry powder) | Hypercalcaemia of malignancy | | Yes | according to serum calcium concentration 15–60 mg in single infusion or in divided doses over 2–4 days; max. 90 mg per treatment course | |
| | Osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma | 90 mg every 4 weeks (or every 3 weeks to coincide with chemotherapy in breast cancer) | | | |
| | Paget's disease | 30 mg once a week for 6 weeks (total dose 180 mg) or 30 mg in first week then 60 mg every other week (total dose 210 mg); max. total 360 mg (in divided doses of 60 mg) per treatment course; may be repeated every 6 months | | | |
| Zoledronic Acid (Aclasta®) | Paget's Disease | | 5 mg as a single dose over at least 15 minutes | IV infusion | |

| | | | | | |
|---|--|-----|--|------|---------|
| Zoledronic Acid (Zometa®) | Reduction of bone damage in advanced malignancies involving bone | Yes | 4 mg every 3–4 weeks (with calcium and vitamin D supplement) | | 10,000+ |
| | Hypercalcaemia of malignancy | | 4 mg as a single dose | | |
| Sodium Clodronate (Bonefos®, Loron®) | Osteolytic lesions, hypercalcaemia & bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma | | 1.6g daily in single or 2 divided doses, increased if necessary to max. 3.2g daily | Oral | |
| | Hypercalcaemia of malignancy | | 300mg daily for max. 7-10 days, or 1.5g single dose | i/v | |

*potency relative to etidronate

Appendix 2

Dear Dental Colleague

Re: ***place sticker with patient name/hospital no. on.***

This patient is about to start a course of treatment involving IV bisphosphonates. You will be aware that there is an increased risk of impaired wound healing in the mouth, leading to bisphosphonate related osteonecrosis (BRON). It is important that patient is dentally fit before his/her bisphosphonate treatment is started. Could you please see him/her as a matter of urgency (within 1-2 weeks) to confirm that he/she is dentally fit. If he/she does need dental treatment to make them dental fit could you please prioritise this, as any delay will prevent him/her receiving necessary urgent medical treatment.

For advice on the bisphosphonates protocols please contact Mr V K Joshi, Restorative Consultant on 01274 365942.

For advice on the patient's medical condition please contact **details of referring consultant to be inserted**

To discuss the medical care of this patient please ring:

Thank you for your co-operation.

Yours sincerely

HAEMATOLOGY/ RHEUMATOLOGY CONSULTANT

Appendix 3.



Bradford Salaried Dental Service

Referral Form for patients commencing treatment with IV Bisphosphonates

| | |
|--|--|
| Name of referring Consultant: _____ Title _____ Postcode: _____ Tel No: _____ | Name of GMP: _____ Address: _____ Postcode: _____ Tel No. _____ |
|--|--|

Patient Surname: _____ Other Names: _____

D.O.B. _____ Hospital No. _____ Tel No/ Mobile No. _____

Home / Mailing Address _____

_____ Postcode: _____

Reason for referral: _____

Medical history _____

Current medication _____

Does the patient need an interpreter? Yes/No.

If yes, what language is spoken: _____

Signature: _____ Date: _____

Please return to: Clinical Director, Bradford Salaried Dental Service, The Dental Office,
Leeds Road Hospital, Maudsley Street, Bradford BD3 9LH
Tel: 01274 363650 Fax: 01274 363474