BISPHOSPHONATE OSTEONECROSIS OF THE JAWS (BONJ)

PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
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As the use of bisphosphonate drugs has increased, so has awareness of one complication; osteonecrosis of the mandible or maxilla (BONJ). This causes the jaw bone to become exposed to the mouth, either following an extraction or through spontaneous ulceration of the oral mucosa overlying the avascular bone. Although BONJ has been recognised for many years in cancer patients receiving intravenous bisphosphonate therapy as supportive treatment, it is also a possible adverse effect of high potency oral bisphosphonates for the prevention or management of osteoporosis. Dr Alexander Crighton, Consultant in Oral Medicine and Honorary Clinical Senior Lecturer in Medicine in Relation to Dentistry at the Glasgow Dental Hospital & School, provides an update. A more detailed article is on our website.

Background

BONJ seems to affect less than 1% of bisphosphonate treated patients, but with increasing use of these drugs the number of patients affected is also rising. Why this condition is a problem only in the jaws is unclear, but may relate to more extensive osteoclast suppression in the highly vascular alveolar bone of the jaws. This can lead to normal bone turnover being completely suppressed rather than simply reduced. It is not a permanent change; when bisphosphonate treatment stops, the bone remodelling gradually returns and BONJ lesions heal. This can take time so BONJ can be a clinical problem several years after discontinuing the drug.

Identifying patients at risk of developing BONJ

It is possible for a necrotic area of bone to be covered with healthy mucosa and not identified until a tooth is extracted and the socket fails to heal. In the absence of a definitive investigation or laboratory test, clinical factors are used to judge the osteonecrosis risk for an individual patient. The following factors are among those that increase risk:

- Increasing age
- Use of higher potency drugs, eg zoledronate
- Intravenous administration
- Treatment of more than two years
- Co-morbidities, eg cancer, diabetes, steroid use

From this, it can be seen that an otherwise healthy individual who has been on alendronic acid for six months to prevent future osteoporosis is at a lower risk of developing BONJ than an older patient receiving IV zoledronate for two years to reduce the skeletal effects of myeloma.

Dental care and BONJ

There is little evidence that dental treatment stimulates osteonecrosis but it may uncover existing lesions when teeth are extracted. Mucosal trauma from poorly fitting dentures is another trigger for bone exposure. Optimal dental care should be available for patients as soon as they start taking these drugs, as the lag between starting a bisphosphonate and potential development of BONJ gives time for good oral health to be established within a preventative regime.

In this issue . . .

Website
http://www.ggcformulary.scot.nhs.uk

What should the prescriber do before starting a bisphosphonate?

- Ensure the patient is aware of BONJ and the low risk this poses in the context of the need for medical treatment.
- Advise the patient to report any oral symptoms such as dental mobility, pain or swelling.
- Strongly advise patients to attend their dentist for an oral health check.
- Consider using an alternative drug if the patient is at a higher risk of BONJ.

What should a dentist do for patients on, or starting, a bisphosphonate?

- Ensure patients know about BONJ and its risk relative to their oral care.
- Start or continue a maximal preventative regime.
- Carry out routine dental care ensuring any caries and periodontal diseases are brought under control.
- Ensure prostheses are well fitting and causing no mucosal trauma.
- Extract teeth of poor prognosis before therapy established.
- Seek specialist advice for extractions required in patients on bisphosphonates for more than two years and for those seeking elective surgical procedures, such as implant placement.

Any suspected BONJ lesions should be referred to a dental specialist experienced in treating this condition. Advice on prevention or management of BONJ can be obtained from the Oral Medicine or Oral Surgery Departments of Glasgow Dental Hospital on 0141 211 9643.

Postscript Extra – clopidogrel and PPIs

Postscript Extra No 16 has been superseded by *Postscript Extra* No 17. This bulletin provides an update on the prescribing advice in relation to patients prescribed both clopidogrel and a proton pump inhibitor. This follows advice from the European Medicines Agency that the concerns on concomitant use of clopidogrel and PPI related specifically to omeprazole and esomeprazole.

See **www.ggcformulary.scot.nhs.uk/PS%20Extra/PS%20Extra.htm**

Alphabetical list of most recent ADTC decisions
For full details of SMC advice, visit **www.scottishmedicines.org**

Drug	Indication under consideration (There may be other licensed indications)	NHSGGC decision	
Azacitidine (Vidaza®)	Treatment of adult patients not eligible for haematopoietic stem cell transplantation with intermediate-2 and high-risk myelodysplastic syndrome, chronic myelomonocytic leukaemia or acute myeloid leukaemia.	Non-*Formulary*	x
Cladribine (LITAK®)	Treatment of hairy cell leukaemia.	(S) *Formulary* (Total *Formulary*) Acknowledge new formulation. Restricted to use in accordance with regional protocol.	✓R
Dornase Alfa (Pulmozyme®)	To improve pulmonary function of cystic fibrosis patients with a forced vital capacity of greater than 40% of predicted. (*Formulary* appeal).	(S) *Formulary* (Total *Formulary*) Responsibility for monitoring rests with specialist service.	✓R
Everolimus (Afinitor®)	Treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor targeted therapy.	Non-*Formulary*	x
Extended released epidural morphine (Depodur®)	Relief of post-operative pain following major orthopaedic, abdominal or pelvic surgery.	Non-*Formulary*	x
Ezetimibe (Ezetrol®)	Primary hypercholesterolaemia (Guideline review)	Non-*Formulary* Following consultation with the Heart MCN and based on a lack of clinical outcome data, ezetimibe had been removed from the NHSGGC Lipid Guidelines and a request by the MCN to have it removed from the GGC *Formulary* was upheld.	x
Ketoprofen/omeprazole (Axorid®)	Symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis in patients with a previous history or who are at risk of developing NSAID associated gastric ulcers, duodenal ulcers and gastroduodenal erosions in whom continued treatment with ketoprofen is essential.	Non-*Formulary*	x
Metformin powder for oral solution (Glucophage®)	Type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control: • In adults, metformin may be used as monotherapy or in combination with other oral anti-diabetic agents or insulin; • In children, from 10 years of age and adolescents, metformin may be used as monotherapy or in combination with insulin.	*Formulary* (Preferred List) Acknowledge new formulation. Restricted to patients who are unable to swallow the solid dosage formulation	✓R
Metformin prolonged release tablets (Glucophage SR®)	Type 2 diabetes mellitus (as above)	Non-*Formulary* This formulation is not added to the *Formulary* due to limited clinical benefit and additional cost over standard tablets.	x
Omalizumab (Xolair®)	Add-on therapy to improve asthma control in children (6 to <12 years of age) with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. Omalizumab treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma.	(S) *Formulary* (Total *Formulary*) Acknowledge new indication. Restricted to patients who are prescribed chronic systemic steroids and in whom all other treatments have failed. The response to omalizumab treatment should be assessed in all patients at 16 weeks and treatment should be discontinued in patients who have not shown a marked improvement in overall asthma control.	✓R

For NICE advice, visit **www.nice.org.uk** For previous ADTC decisions, visit **www.ggcformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	NHSGGC decision	
Rupatadine (Rupafin®)	Symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria in adults and adolescents (over 12 years of age).	Non-*Formulary*	x
Saxagliptin (Onglyza®)	As add-on combination therapy for adult patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control.	(S) *Formulary* (Total *Formulary*) Restricted to use, only in combination with metformin when a sulphonylurea is contraindicated or not tolerated. In primary care, it is expected that initiation would follow interaction between the GP/Diabetic Specialist Nurse and the consultant contact within the acute sector.	✓R
Tacrolimus 0.1% ointment (Protopic®)	Maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in adult patients (≥16 years) experiencing a high frequency of disease exacerbations (ie occurring 4 or more times a year) who have had an initial response to a maximum of 6 weeks' treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).	(S) *Formulary* (Total *Formulary*) Acknowledge new indication. Use is restricted to initiation by dermatologists in secondary care who have experience in treating atopic dermatitis using immunomodulatory therapy.	✓R
Tacrolimus 0.03% ointment (Protopic®)	Maintenance treatment of moderate to severe atopic dermatitis in children (aged 2 to 15 years) for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (ie occurring 4 or more times a year) who have had an initial response to a maximum of 6 weeks' treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).	(S) *Formulary* (Total *Formulary*) Acknowledge new indication. Use is restricted to initiation by dermatologists in secondary care who have experience in treating atopic dermatitis using immunomodulatory therapy.	✓R
Temsirolimus (Torisel®)	Treatment of adult patients with relapsed and/or refractory mantle cell lymphoma.	Non-*Formulary*	x

✓ =*Formulary* ✓R =*Formulary* (restricted) x =non-*Formulary* ? = awaiting final decision (S) =specialist initiation only (S) =specialist use only

"If I could change one thing…"

This is the first of our new series (see page 4) and is based on a real event.

Hypos and diet Irn Bru - inappropriate management of hypoglycaemia

Why do diabetes and its treatment seem so poorly understood? Diabetes leads to elevated blood sugar and diabetes treatments lower the blood sugar; some can cause hypoglycaemia (insulin and sulphonylureas).

A clammy, pale, confused patient was witnessed being fed an orange fizzy drink by a staff nurse who had correctly diagnosed hypoglycaemia. When the patient failed to respond to the treatment it was realised that the drink was diet Irn Bru. A patient whose blood sugar is less than 3.5 needs immediate rapid acting glucose by mouth as long as they are alert. Suitable examples and quantities include

- Lucozade 100-130mls
- Full calorie Coke, lemonade, Irn Bru etc 150mls
- Fresh orange, apple, pineapple juice 150mls
- 5 full size, full calorie Jelly Babies
- 5 Dextrosol or Lucozade tablets

Unconscious patients, patients who are fasting, or patients who are unable to swallow, must be given either intravenous glucose (250mls of 10% or 125mls of 20%); or 1mg IM glucagon (GlucaGen Hypokit)

If glucagon has been given within the last 24 hours, it will be unlikely to work a second time because it is a hormone that releases stored glucose from the liver; the stores will have been exhausted after the first use.

Patients taking treatment that can cause hypoglycaemia should be warned and instructed to carry suitable quantities of rapid acting carbohydrate, especially when driving or exercising.

If I could change one thing, ward staff would be regularly updated on emergency management of hypoglycaemia and there would be a secure supply of appropriate hypo treatments that are regularly checked and replenished.

Antipsychotic use in dementia

The use of antipsychotic drugs in patients with dementia has gained significant media interest over the past few years in terms of safety and appropriateness of therapy. In this article, Dr Fiona McGibbon from Old Age Psychiatry describes some of the issues.

According to a 2009 Department of Health-commissioned report, only 20% of the 180,000 antipsychotic prescriptions dispensed annually in England to patients with dementia actually provide any benefit. It also claimed that antipsychotic use results in an extra 1,620 cerebrovascular events and 1,800 deaths a year. The problem is that the behavioural and psychiatric symptoms of dementia (BPSD), eg aggression, psychosis, depression, sleep disturbance, agitation and wandering are common and require treatment. Although they may remit spontaneously, the symptoms can be persistent and severe, significantly impairing quality of life. They are a common precipitant to admission to a care home.

Antipsychotic drugs have long been used to treat BPSD, despite poor evidence of efficacy. There is some trial evidence supporting the use of olanzapine and risperidone to treat psychosis, and for risperidone in the treatment of aggression . However, the studies demonstrating efficacy also revealed an increased risk of cerebrovascular events. In 2004, the CSM reported a trebling of the annual risk of stroke in patients with dementia from 1.1% to 3.3%. A recommendation was made not to use olanzapine and risperidone in patients with dementia. This led to prescribing of alternative antipsychotics which were unlicensed and had even less evidence of efficacy. In 2008, a European assessment of published observation data concluded that a similar risk could not be excluded for the typical antipsychotics.

Clearly, antipsychotic use needs to be reviewed in a measured fashion. In response to the CSM report, the Faculty for the Psychiatry of Old Age of the Royal College of Psychiatrists issued a joint guidance note with the British Geriatrics Society, the Royal College of General Practitioners and the Alzheimer's Society which was updated in 2005. This recognises the over-use of antipsychotics but outlines situations where cautious use is appropriate.

Antipsychotic medication should be considered when:
• the problem symptom is severe and treatment is required quickly, eg dangerous or distressing to the patient or others;
• there is no clear situational trigger;
• the problem behaviour occurs in a setting where carers cannot cope with serious behaviour problems.

Where the decision is taken to initiate an antipsychotic, the '3T' approach is recommended:
• Drug treatments should have a specific **Target**.
• The starting dose should be low and then be **Titrated** upwards.
• Drug treatments should be **Time** limited.

There is evidence that antipsychotics can be withdrawn successfully in people who have been relatively free from symptoms for three months .

Vitally, any decision about the treatment of BPSD with antipsychotics should only be taken after as full an assessment as possible. Clinicians need to carefully weigh up the risks and benefits, preferably in consultation with the multidisciplinary team and the patient's family. Those over the age of 80 are at a higher risk of a cerebrovascular event from antipsychotic medications and it would seem logical that people with other risk factors for cerebrovascular disease, eg diabetes, hypertension, known cerebrovascular disease, smoking, cardiac arrhythmias, would be the same, though there is no trial evidence to support this.

In milder cases, BPSD may be appropriately managed with environmental manipulation or behavioural treatments. However, no single non-pharmacological intervention, eg multi-sensory stimulation, bright light therapy, aromatherapy etc, has an evidence base that would justify its use as a direct alternative to antipsychotic drug treatment.

The assessment and decision should be clearly documented and prescribing should be regularly reviewed. It may be necessary to take account of the Adults with Incapacity (Scotland) Act 2000. This sets out the system for protecting adults who are unable to make decisions and allows other people to make decisions on their behalf about medical treatment.

Small change: big results

We are introducing a new column to *PostScript,* "If I could change one thing . . .", featuring views from our readers about something we could, or should, change in practice to improve the quality of healthcare. We are not looking for anything too complex or lengthy and the editorial team can help you prepare it for publication.

Do you see an obvious way to
• reduce risk to patients?
• improve clinical care?
• improve prescribing?
• improve communication?
• reduce waste?
• reduce costs?

We can acknowledge the author or publish anonymously. Make it a "rant of the day" if it is something that gets you really wound up! Please send all thoughts and contributions to audrey.thompson@ggc.scot.nhs.uk For our first article, see page 3.

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