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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Osteonecrosis of the jaw with bisphosphonates
- ☆ Dose reduction of LMWH (enoxaparin) in chronic kidney disease
- ☆ Life threatening blood dyscrasias with oral terbinafine

Please report **all** suspected reactions to these **Drugs of Current Interest**

Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Ezetimibe/Simvastatin (Vytorin)
Fenofibrate (Lipidil)
Pimecrolimus (Elidel)
Pregabalin (Lyrica)
Teriparatide (Fortéo)
Iron sucrose (Venofer)

1. Osteonecrosis of the jaw (ONJ) with bisphosphonates

ADRAC has previously drawn attention to the problem of osteonecrosis of the jaw (maxilla or mandible) occurring in the context of treatment with bisphosphonates.[1] Further Australian cases have been published.[2,3] Up to June 2006 ADRAC has received 106 reports of this type, as shown below:

Zoledronate (IV)	69
Pamidronate (IV)	33
Alendronate (oral)	19
Risedronate (oral)	2
Clodronate (IV and oral)	1
Ibandronate (IV)	1

A recent review of 368 published case reports of ONJ found that 94% involved patients with multiple myeloma or bony metastases who were receiving intravenous bisphosphonates.[4] A small proportion, however, involved patients receiving oral bisphosphonates for treatment of osteoporosis. This review also found that 60% of cases were preceded by a dental surgical procedure, usually dental extraction. The mechanism of ONJ is unknown. Bisphosphonates may impair bone vascularity or immune mechanisms which may be of particular importance in the jaw because of the bacterial flora of the mouth and repeated bacterial exposure with chewing. Bisphosphonate-induced reduction of bone turnover may cause adynamic bone and impair healing of the socket after tooth extraction.[4]

Prevention is of the utmost importance.[4] Accordingly, any patient being considered for bisphosphonate treatment should be informed of the symptoms of ONJ and, if they occur, to bring these to the attention of their dental practitioner. Therapy should only be initiated if individual risk versus benefit assessment is thought to be favourable. Dental assessment and treatment should be completed before commencing bisphosphonate treatment. Patients receiving bisphosphonates should be strongly advised to tell their dentist that they are taking these medicines before any dental procedure is carried out.

Recognition: Health professionals should be aware of the presenting clinical features of this condition, which include altered local sensation (hyperaesthesia or numbness), maxillofacial pain, "toothache", denture sore spots, loose teeth, exposed bone in the oral cavity, impaired healing, recurrent or persistent soft tissue infection in the oral cavity, and marked oral odour. The onset can be from months to years after commencing bisphosphonate therapy.

Management: The risk of osteonecrosis is significantly increased after dental extraction.[4] Any patient in whom the diagnosis of osteonecrosis of the jaw is suspected or confirmed should be referred for expert management. Antibiotics, antiseptic mouth rinses, withdrawal of bisphosphonates and removal of loose sequestra have been reported to be beneficial in some cases.[4] Extensive surgical excision/debridement of the necrotic tissue has so far proven to be ineffective and may worsen the condition.

References:
1. ADRAC. Bisphosphonates and osteonecrosis of the jaw. *Aust Adv Drug React Bull* 2005;24:3
2. Purcell PM, Boyd IW. Bisphosphonates and osteonecrosis of the jaw. *Med J Aust* 2005;182:417-418.
3. Carter G, Goss AN, Doecke C. Bisphosphonates and avascular necrosis of the jaw – a possible association. *Med J Aust* 2005;182:413- 415.
4. Woo S, Hellstein JW, Kalmar JR. Systematic Review: bisphosphonates and osteonecrosis of the jaws. *Ann Int Med* 2006;144:753-761.

2. Dose reduction of LMWH (enoxaparin) in chronic kidney disease

Although Low Molecular Weight Heparins (LMWH) are a convenient and effective alternative to unfractionated heparins, it is important to remember that LMWH such as enoxaparin also have associated risks. LMWH have a longer half life than unfractionated heparins, their anticoagulant effect is not routinely monitored, and their effects are harder to reverse in cases of bleeding. The clearance of enoxaparin is decreased in chronic kidney disease, hence the dose of enoxaparin should be reduced in this situation.[1]

In 2005-2006, ADRAC received 10 reports of death associated with haemorrhage after the use of enoxaparin, bringing the total to 46 since 1997.

In 3 of the reports received in 2005, patients with chronic kidney disease received inappropriate doses. Two of the reports also implicated an incorrect dose for the weight of the patient. Other risk factors include use of other anticoagulants, age (neonates, children, and the elderly), pregnancy and the extremes of body weight (< 40 kg or > 100 kg).[2,3]

Before commencement of LMWH therapy, the patient's renal function should be assessed. In patients with severe chronic kidney disease (GFR < 30 mL/min), requiring therapeutic anticoagulant doses, the dose of enoxaparin should be reduced from 1 mg/kg twice daily or 1.5 mg/kg once daily to 1 mg/kg once daily.[1] An alternative is to use unfractionated heparin with dose monitoring by aPTT. Similarly, in patients with unstable or deteriorating renal function, unfractionated heparin is preferred. Where there is a high bleeding risk, such as in the post-operative period, unfractionated heparin is preferred, since rapid and complete reversal of anticoagulation can be achieved. If there is a high probability of proceeding to surgery in the next 5 days (including for coronary angioplasty), unfractionated heparin with the usual aPTT monitoring is advised.

References:
1. Clexane Product Information June 2005. Aventis Pharma Pty Limited. MIMS On-line.
2. Eikelboom JW, Hankey J. Low molecular weight heparins and heparinoids. *Med J Aust* 2002;177:379-383.
3. Heparin contraindicated in severe renal impairment. *WHO Drug Information* 2005;19:24-25.

3. Life threatening blood dyscrasias with oral terbinafine

Oral terbinafine (Lamisil) is indicated for severe ringworm unresponsive to topical treatment and onychomycosis in adults. Prescribers should be aware that there are three serious, *albeit* rare, reactions associated with oral terbinafine – white blood cell disorders, severe skin reactions and severe hepatotoxicity. These reactions have not been reported with topical forms of terbinafine (Lamisil cream or gel).

ADRAC reminded health professionals of the association between oral terbinafine and blood dyscrasias in October 2004.[1] ADRAC has now received 16 reports of white blood cell dyscrasias with oral terbinafine, including agranulocytosis (7), neutropenia (7) and pancytopenia (2) from a total of 663 reports.

A recent report demonstrates some of the important features of this reaction. A healthy 60 year old female had been taking terbinafine for a month for onychomycosis of the big toe. She developed mouth ulcers, fever and myalgia and presented to hospital with a white blood cell count of 1.3 x 10^9/L and a neutrophil count of zero. She recovered after treatment with IV antibiotics and granulocyte colony stimulating factor (GCSF). In this case, the time to onset of around 4 weeks is consistent with 11 other reports to ADRAC, which specified a time to onset of 4-6 weeks. As occurred in the most recent report, the majority of patients develop signs of infection. Recovery is usually rapid following withdrawal of terbinafine and appropriate treatment. Recovery was documented in 11 of the 16 reports, although in one case a 79 year old female developed agranulocytosis about 2 months after initiation of terbinafine, and died from septic shock despite treatment with GCSF and antibiotics. Another characteristic of these reports is the severity of the neutropenia. In the 12 cases where values were reported, they ranged from 0.0-0.9 x 10^9/L.

Patients taking terbinafine for longer than a month should be advised to be alert for any symptoms of possible infection/neutropenia, such as fever, sore throat or mouth ulcers. Total white blood cell count and neutrophil count should be checked if symptoms develop since a delay in diagnosis is likely to be associated with an increase in morbidity and mortality.

Reference:
1. ADRAC. Terbinafine and blood dyscrasias. *Aust Adv Drug React Bull* 2004;23:19.

Update and clarification:

Medic Alert Devices. *Aust Adv Drug React Bull* 2006;25:6:
The website address for the SOS Talisman locket is http://www.sostalisman.com

Problems with colloids in fluid resuscitation: *Aust Adv Drug React Bull* 2006;25:10:
The sentence *'Given that saline and albumin have been shown to be of equivalent efficacy'* is intended to convey findings from the SAFE* study showing similar clinical outcomes at day 28 after fluid resuscitation. The SAFE study does not provide a rigorous comparison of efficacy between saline and albumin.
*The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *NEJM* 2004;350: 2247-2256.

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAC encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

*ALL suspected reactions to **new drugs** (see **drugs of current interest,** front page**)**
*ALL suspected drug interactions
*Suspected reactions causing
- •Death
- •Admission to hospital or prolongation of hospitalisation
- •Increased investigations or treatment
- •Birth defects

For blue cards
Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", from the Adverse Drug Reactions Unit ☎ 02-6232-8386, or from the website: http://www.tga.gov.au/adr/bluecard.pdf

Reports can also be submitted electronically, by going to the TGA web site (http://www.tga.gov.au) and clicking on "report problems" on the left.

For further information from the ADRAC Secretariat:
☎ 1800 044 114 Fax: 02-6232-8392 Email: adrac@health.gov.au

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The Bulletin is also available on the Internet at: **http://www.tga.gov.au/adr/aadrb.htm**

All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606