Severe skin reactions and venous thromboembolism with strontium ranelate (Protos)

Statins and muscle disorders – be careful with the dose

Hepatic toxicity with nitrofurantoin

Please report all suspected reactions to these Drugs of Current Interest

Atomoxetine (Strattera)  Ranibizumab (Lucentis)
Ezetimibe and simvastatin (Vytorin)  Rosuvastatin (Crestor or Viacor)
Moxonidine (Physiotens)  Strontium ranelate (Protos)
Paliperidone (Invega)  Varenicline (Champix)
Pregabalin (Lyrica)  Ziprasidone (Zeldox)
1. **Severe skin reactions and venous thromboembolism with strontium ranelate (Protos)**

Strontium ranelate (Protos) has been available in Australia since April 2006 for the treatment of postmenopausal osteoporosis, to reduce the risk of fracture. It was listed on the PBS in April 2007 as an Authority-required item for the treatment of osteoporosis in women aged 70 years or older with a bone mineral density T-score of -3.0 or less, or for the treatment of established postmenopausal osteoporosis in patients with fracture due to minimal trauma. The use of strontium ranelate under the PBS has been steadily increasing since its initial listing, and is now over 8,000 prescriptions per month.

The most common adverse reactions to strontium ranelate are nausea and diarrhoea, however prescribers should also be aware of the possibilities of severe skin reactions, and venous thromboembolism (VTE).

In November 2007, the European Medicines Agency (EMEA) issued an alert concerning the incidence of severe skin reactions, particularly “drug rash with eosinophilia and systemic symptoms” (DRESS), and also Stevens Johnson syndrome. Both of these are potentially life-threatening conditions. In Europe, there were 16 reports of DRESS, two of which were fatal. The reaction started within 3-6 weeks of commencing strontium ranelate, and was initially manifest as rash accompanied by fever.

To date in Australia, there have been 47 reports of suspected adverse reactions to strontium ranelate, including 16 reports of rash, one of which was accompanied by fever, and one by eosinophilia. There have been no reports of fatalities.

We have received a single report of severe cholestatic hepatitis (peak bilirubin 570, ALP 2300) with eosinophilia, rash, and itch, in a 62 year old woman who had been taking strontium ranelate 2 g daily for 2 months. A liver biopsy was consistent with drug-induced hepatitis. Hepatic adverse reactions were not observed during clinical trials of this medicine.

In clinical trials, the incidence of VTE was greater in the patients taking strontium ranelate than in the placebo group (annual incidence 0.9% versus 0.6%). There have been three Australian reports of deep venous thrombosis and one report of superficial vein thrombosis, occurring after 1-4 months of treatment with strontium ranelate. Two of the patients had risk factors for VTE (one had a past history of VTE, and the other had recent orthopaedic surgery).

Patients should be advised to stop treatment, and seek medical advice, at the first appearance of a rash. Treatment may include the use of steroids, and recovery may be prolonged. Once stopped, the drug should not be recommenced. Strontium ranelate should be used with caution in patients with risk factors for VTE.

Reference:

2. **Statins and muscle disorders – be careful with the dose**

Muscle disorders are well known to be associated with the statins, with risk factors including age > 70 years, various disease states (diabetes, hypothyroidism, renal and hepatic disease), concurrent use of CYP3A4 inhibitors and, importantly, the dose of the statin. ADRAc continues to receive reports describing myositis/rhabdomyolysis occurring in situations where statin therapy has been initiated at an inappropriately high dose. The following vignette is a case in point.

A 65 year old woman with a history of hypothyroidism (treated with replacement therapy), asthma, Meniere’s disease and gastro-oesophageal reflux was commenced on simvastatin 80 mg daily for treatment of hypercholesterolaemia. After four months she noticed the onset of severe pain and weakness in her lower limbs, which required admission to hospital. She had myoglobinuria and grossly elevated serum creatine kinase (14,450 IU/L), establishing the diagnosis of rhabdomyolysis.
High dose simvastatin is a major risk factor and hypothyroidism, if under-treated, is also a risk factor for rhabdomyolysis.

By late 2007, the TGA had received 5,846 adverse reaction reports implicating a statin. Of these, almost one third described muscle disorders such as myalgia, myopathy, myositis, or rhabdomyolysis (which, when severe were associated with myoglobinuria and, in extreme cases, renal failure).

Prescribers are reminded that statin treatment should commence with the lowest possible dose which may then be titrated if necessary according to lipid levels, while monitoring for adverse reactions, especially any symptoms of muscle disorders.

References:

3. **Hepatic toxicity with nitrofurantoin**

The antibiotic nitrofurantoin has been available in Australia for over 30 years and is widely used for the treatment and prophylaxis of urinary tract infection (UTI). About 120,000 prescriptions per year for nitrofurantoin are dispensed under the PBS. Up to April 2008, TGA has received 637 reports of adverse reactions in association with nitrofurantoin, including 17 reports of death.

ADRAC has previously highlighted the many toxicities associated with nitrofurantoin, including pulmonary fibrosis, interstitial pneumonitis, and peripheral neuropathy. Hepatic reactions are also associated rarely with nitrofurantoin, but these may be less well-recognised. Two recent reports to ADRAC of submassive hepatic necrosis in association with nitrofurantoin in women in their mid-50s prompted a review of reports of hepatic adverse events with this drug.

Of the 637 reports received for nitrofurantoin, 119 (19%) describe hepatobiliary reactions, including 32 considered serious. A fatal outcome due to hepatic toxicity was documented in 7 cases; other reports documented hepatic failure (2), hepatitis (13) or jaundice (4). Nitrofurantoin was the sole suspected drug in 17 of the serious cases and the majority of the 32 reports involved women aged over 50 years taking nitrofurantoin 50 to 200 mg/day for the treatment of acute UTI (11 cases), recurrent UTI (11 cases) or prophylactically (10 cases). Reaction onset time (available in 23 of the 32 reports) was variable, ranging from 2-10 days in 10 cases, 1-4 months in 4 cases, and over a year in 9 cases.

Product Information documents for nitrofurantoin include precautionary warnings about the possibility of hepatic reactions.

Patients should be alerted to the symptoms of nitrofurantoin toxicity and advised to stop the drug if there are concerns; LFTs should be monitored if clinically indicated. Prescribers should remain mindful of the potential for multiple, severe but rare toxicities associated with this medicine and consider whether the risks are justified.

References
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 website: <http://www.tga.gov.au/adr/bluecard.pdf> or from the Adverse Drug Reactions Unit ☏ 02-6232-8744.

Reports can also be submitted electronically, by going to the TGA website <http://www.tga.gov.au> and clicking on “report problems” on the left.

ISSN 0812-3837 © Commonwealth of Australia 2008

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