Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC). Members of ADRAC are Associate Professor Duncan Topliss (Chair), Dr Vicki Kotsirilos, Professor David Isaacs, Dr Cecilie Lander, Professor John McNeil, Associate Professor Peter Pillans, Dr Simone Strasser, Dr Dana Wainwright

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Statins and peripheral neuropathy
- ☆ Avascular necrosis with interferon alfa-2b in CML
- ☆ Angioedema – still a problem with ACE inhibitors
- ☆ Evidence-based medicine: pitfalls of overlooking safety

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

Aripiprazole (Abilify)
Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Fenofibrate (Lipidil)
Iron sucrose (Venofer)
Levetiracetam (Keppra)
Pimecrolimus (Elidel)
Reboxetine (Edronax)
Sibutramine (Reductil)
Teriparatide (Fortéo)

1. STATINS AND PERIPHERAL NEUROPATHY

ADRAC has received 281 reports of peripheral neuropathy or symptoms consistent with this diagnosis attributed to statins (see Table), and first highlighted this association in 1993.[1] Thirteen of the 281 cases were confirmed by nerve conduction studies. Both sensory and mixed sensorimotor peripheral neuropathies were reported. The time to onset ranged from one dose to 4.5 years.

Table: ADRAC **c**ases of peripheral neuropathy with the statins

Drug	Total cases	Sole suspected drug (%)	Recovered (%)
Simvastatin (Zocor, Lipex)	136	64 (47%)	59 (43%)
Atorvastatin (Lipitor)	108	70 (65%)	60 (56%)
Pravastatin (Pravachol)	26	14 (54%)	17 (65%)
Fluvastatin (Lescol, Vastin)	11	6 (54%)	9 (82%)
Total	281	155 (54%)	145 (52%)

Many patients requiring statin therapy have conditions which predispose them to peripheral neuropathy, particularly diabetes mellitus and chronic renal failure.[2] Thus the observation of an association is not necessarily indicative of causation. However, recovery on withdrawal of the statin was noted in approximately half of the ADRAC cases (see Table), including cases where the patient also had diabetes, and some reports describe positive rechallenge. In two cases, symptoms developed after an increase in dose.

Statin-associated peripheral neuropathy may persist for months or years after withdrawal of the statin.[2,3] In two ADRAC cases of persistent peripheral neuropathy, motor and sensory conduction tests showed minimal recovery 4 and 12 months, respectively, after discontinuation of simvastatin, despite clinical improvement.[3] A further 21 cases had not recovered at the time of reporting, between one and eight months after discontinuation of the statin. In two other reports, the problem was persisting after 3 and 5 years, respectively.

The incidence of statin-induced peripheral neuropathy appears to be low. A study, which excluded patients with predisposing disease, attributed 4.5 cases per 10,000 person-years to statin use.[4]

Consideration should be given to drug withdrawal if patients taking a statin develop sensory or motor disturbances.

References
1. Paraesthesia and neuropathy with hypolipidaemic agents. *Aust Adv Drug Reactions Bull* 1993; 12:2.
2. Chong PH, et al. *Pharmacotherapy* 2004;24:1194-1203
3. Phan T, et al. *J Neurol Neurosurg Psychiatry* 1995;58: 625-8.
4. Gaist D, et al. *Neurology* 2002;58:1333-7.

2. AVASCULAR NECROSIS WITH INTERFERON ALFA-2B IN CML

Out of a total of 426 reports involving interferon alfa-2b (Intron A), ADRAC has received 6 reports of avascular necrosis, aseptic necrosis or osteonecrosis in association with the treatment of chronic myelogenous leukaemia (CML). The site was the femoral or humoral head as identified by a bone scan or MRI. Daily doses varied from 3 to 10 million units, and the time to onset was 3-8 weeks.

Kozuch et al described three cases of avascular necrosis of the femoral head in CML patients treated with interferon alfa.[1] All had thrombocytosis and loss of response (not described in the ADRAC reports). Avascular necrosis has occurred without interferon treatment in CML, but it has been exacerbated by interferon alfa treatment.[1]

Since there appear to be no literature reports of avascular necrosis for interferon alfa in other indications, Kozuch et al concluded that the avascular necrosis may be the result of an interaction between CML and interferon alpha therapy. Interferon alfa can inhibit angiogenesis, which may cause avascular necrosis, and the stress of weight bearing may make the femoral head particularly vulnerable.[2]

The possibility of avascular necrosis should be considered if bone or joint pain develops in patients with CML given interferon alfa.

References
1. Kozuch P, et al. *Cancer* 2000 Oct 1; 89 (7):1482-9.
2. Smith DWE. *Medical Hypotheses* 1997;49:497-500.

3. ANGIOEDEMA – STILL A PROBLEM WITH ACE INHIBITORS

Of the over 7,000 reports of angioedema received by ADRAC since 1970, ACE inhibitors account for 916 (12.6%). Angioedema may present with acute onset of soft-tissue swelling of part or all of the face (periorbital, peri-oral, lips), tongue, pharynx and neck. Oedema of the gastrointestinal tract resulting in attacks of abdominal pain, vomiting and diarrhoea has also been rarely reported with ACE inhibitors.[1] Angioedema can be life-threatening, and may require prompt parenteral administration of adrenaline if the airway is compromised. The cause may not always be obvious as the first occurrence may be after months or even years of ACE inhibitor therapy. Angioedema may also occur episodically with long symptom-free intervals.

In a case recently reported to ADRAC, an elderly female who had been taking ramipril for a year without adverse effect experienced several episodes of unilateral swelling of the face, lips, jaw line and cheek each lasting 2-3 days over a 4-month period. She made a complete recovery after withdrawal of ramipril. In another case, the patient had 20 episodes of angioedema in 12 months before an association was made with perindopril.

ADRAC first advised of the risk of angioedema with ACE inhibitors in 1993[2] and noted its occurrence with angiotensin II antagonists in 1999.[3] ADRAC now has 119 reports with angiotensin II antagonists. With ACE inhibitors the reaction is thought to be associated with potentiation of bradykinin, causing increased vascular permeability and vasodilation.[4] The mechanism with the angiotensin II antagonists is unclear but it has also been postulated to be by bradykinin activation.[4,5] Individuals with a history of angioedema with ACE inhibitors may occasionally develop it with an angiotensin II antagonist as well.[4,5]

References
1. Chase MP, et al.. *J Clin Gastroenterology* 2000;31:254-7.
2. Angioedema. *Aust Adv Drug Reactions Bull* 1993;12:3.
3. Angiotensin II receptor antagonists. *Aust Adv Drug Reactions Bull* 1999;18:2.
4. Howes LG, Tran D. *Drug Safety* 2002;25:73-6.
5. Abdi R, et al. *Pharmacotherapy* 2002;22:1173-5.

4. EVIDENCE-BASED MEDICINE: PITFALLS OF OVERLOOKING SAFETY

The results of large-scale long-term clinical trials can carry enormous weight, especially when the disease treated is common and warrants long-term intervention, and the results show significant benefit without serious adverse effects. However, the trial design needs to be studied with care, because many patients encountered in the clinical setting would not have met the inclusion criteria and the protocol would have included careful monitoring for serious adverse effects. A recent Canadian study of the impact of the Randomized Aldactone Evaluation Study (RALES)[1] highlights the possible adverse consequences of uncritically applying the results of a large scale clinical trial.[2]

In the RALES study, patients with severe heart failure (NYHA class III or IV) were randomised to spironolactone or placebo.[1] An ACE inhibitor was being used by 95% of the patients. After 24 months the death rate with spironolactone was 30% less than that with placebo. The difference was attributed to a lower risk of death from progression of heart failure and sudden death from cardiac causes with spironolactone. Patients with elevated serum creatinine or potassium were excluded and regular checks of serum potassium were conducted throughout the duration of the study.

The Canadian study of the impact of RALES[2] tracked a five-fold increase ($p < 0.001$) in spirono-lactone prescriptions among patients older than 65 years who had recently been hospitalised for heart failure and were taking an ACE inhibitor. Over the same period, there was a three-fold increase in hospitalisation for hyperkalaemia in the same patient population (to 11/1000 patients; $p < 0.001$). The death rate in hospital from hyperkalaemia also increased by a factor of three (to 2/1000; $p < 0.001$). There was no significant concurrent decline in hospitalisation for heart failure.

The authors of the Canadian study proposed the following possible explanations for the overall adverse outcome of application of the RALES study in the clinical setting:

- serum potassium not carefully monitored;
- baseline characteristics and conditions developing during therapy that predispose to hyperkalaemia overlooked;
- excessive doses of spironolactone used; and
- dietary intake of potassium increased.

Two other studies[3,4] have delivered cautionary messages for the application of RALES with one finding that 21% of attempts to treat heart failure with spironolactone were halted because of raised serum potassium or creatinine.[3] It is noteworthy that of the 27 ADRAC reports of hyperkalaemia associated with the use of spironolactone in combination with an ACE inhibitor or an angiotensin II receptor antagonist, 19 were received since the publication of RALES.

Large scale clinical drug trials have become fundamental to the advancement of knowledge and improvement in clinical practice in medicine, but application to the individual patient requires consideration of the potential for serious adverse effects and assessment of the risk for that patient. Where there are risk factors for adverse reactions, initial use of the drug at low doses with monitoring for changes in key symptoms and laboratory parameters may allow benefit without a serious adverse event.

References
1. Pitt B, et al. *New Engl J Med* 1999;341:709-17.
2. Juurlink DN, et al. *New Engl J Med* 2004;251:543-51.
3. Witham MD, et al. *Brit J Clin Pharmacology* 2004;58:554-7.
4. Tamirisa KP, et al. *Amer Heart J* 2004;148:971-8.

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 (with complete references).

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