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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

VOLUME 23, NUMBER 1, FEBRUARY 2004

- ☆ Risk factors for myopathy and rhabdomyolysis with the statins
- ☆ High dose cyproterone and hepatotoxicity
- ☆ Serotonin syndrome

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

Apomorphine (Uprima)
Aripiprazole (Abilify)
Ezetimibe (Ezetrol)
Fondaparinux (Arixtra)
Galantamine (Reminyl)
Lercanidipine (Zanidip)
Levetiracetam (Keppra)
Meloxicam (Mobic)
Pioglitazone (Actos)
Pramipexol (Sifrol)
Reboxetine (Edronax)
Rosiglitazone (Avandia)
Sibutramine (Reductil)
Tadalafil (Cialis)
Tegaserod (Zelmac)

1. RISK FACTORS FOR MYOPATHY AND RHABDOMYOLYSIS WITH THE STATINS

Four statins (HMG CoA inhibitors) are available in Australia for the treatment of hypercholesterolaemia: simvastatin, atorvastatin, pravastatin and fluvastatin. Each of the statins may cause myalgia or rhabdomyolysis. Cerivastatin was removed from the market worldwide because of an unacceptably high rate of rhabdomyolysis, including fatal cases, particularly when used with gemfibrozil.[1]

The rates of muscle disorders observed in clinical trials of statins have not been significantly different from those with placebo,[2] but wider clinical use involves individuals having multiple disease states or taking potentially interacting medication. Recent reviews indicate that factors which increase the plasma concentrations of statins are associated with an increase in the risk of myalgia, myopathy and, particularly, rhabdomyolysis.[3,4] For simvastatin and atorvastatin which are metabolised by the liver enzyme CYP3A4 these factors are presented in Table 1.

Table 1: Factors increasing the risk of muscle disorders with simvastatin and atorvastatin

Substances inhibiting metabolism by CYP3A4	cyclosporin, diltiazem, verapamil, macrolide antibiotics, azole antifungals, protease inhibitors, grapefruit juice
Medicine inhibiting metabolism by other means	gemfibrozil
Disease states	diabetes, hypothyroidism, renal and hepatic disease
Advanced age	≥ 70 years
High statin dose	≥ 40 mg/day

ADRAC has received 91 reports of rhabdomyolysis with simvastatin and 26 with atorvastatin, as well as many reports of myalgia, myopathy or creatine kinase (CK) increase. Table 2 (top section) shows the percentage of cases with identified risk factors, as defined in Table 1. For simvastatin the factors listed most commonly in reports describing rhabdomyolysis were age ≥ 70 years (40 reports) dose ≥ 40 mg (33), cyclosporin (19), gemfibrozil (21), diltiazem (20) and diabetes (15). Over half of the simvastatin cases with rhabdomyolysis had more than one identified risk factor. Individuals with several risk factors may be at risk of developing rhabdomyolysis, rather than a less serious muscle disorder.

A feature of the cases of rhabdomyolysis is that long term statin therapy was well tolerated until after a change in medication (e.g. increase in the dose of statin, or addition of clarithromycin or diltiazem).

Table 2: Frequency of risk factors in ADRAC reports of muscle disorders with the statins

Statin	Myalgia/ myopathy/ CK increase	% with risk factors	Rhabdo-myolysis	% with risk factors
Simvastatin Total reports 2493	518	37%	91	94%
Atorvastatin Total reports 1055	237	45%	26	73%
Pravastatin Total reports 442	99	41%	5	80%
Fluvastatin Total reports 248	68	54%	2	100%

Pravastatin and fluvastatin are not metabolised by CYP3A4 and are less subject to increases in plasma concentration by interaction with other drugs. ADRAC reports of muscle disorders with these statins are shown in Table 2 (bottom section). The dominant risk factors for pravastatin and fluvastatin were advanced age and high dose. The lower number of cases of rhabdomyolysis with these statins is probably associated with the lesser likelihood of drug interaction, but is also related to the lower usage in Australia (From 1992 to November 2003, 85% of statin prescriptions have been for simvastatin or atorvastatin).

High doses of statins should be used with caution in the elderly, in patients with renal or hepatic insufficiency, hypothyroidism or diabetes. Particular caution should be observed in patients taking simvastatin or atorvastatin with these conditions, if gemfibrozil, cyclosporin or diltiazem are being taken concomitantly. Consideration should be given to temporary discontinuation of simvastatin or atorvastatin, if short-term macrolide antibiotic or azole antifungal therapy is required. Patients should be advised to report to their doctor if muscle aches, pains or weakness develop.

References
1. *Aust Adv Drug Reactions Bull* 2001;20(1):3.
2. Gotto AM. *Arch Intern Med* 2003;163:657-9.
3. Thompson PD, Clarkson P, Karas RH. *JAMA* 2003;289: 681-90.
4. Ballantyne CM, Corsini A, Davidson MH et al. *Arch Intern Med* 2003;163:553-64.

2. HIGH DOSE CYPROTERONE AND HEPATOTOXICITY

High dose cyproterone (50mg, 100mg; Androcur, Androcur-100) is used predominantly for advanced prostate carcinoma. For the year ending June 2003, 59,000 prescriptions were dispensed for the 50mg or 100mg tablets and 97% of patients prescribed these tablets were male.

Over the years, ADRAC has received 105 reports implicating high-dose cyproterone. The most common adverse reactions are related to the liver with 32 reports. Other more commonly reported reactions include fatigue, dyspnoea, asthenia, confusion, depression and deep vein thrombosis.

All except one of the hepatic reactions involved male patients being treated for prostate cancer, whose ages ranged from 56 to 92 (median: 77) years. Time to onset of liver dysfunction ranged from 4 days to 4 years (median: 4-5 months); only 4 cases had a time to onset under a month.

Where liver function test results were available, the majority indicated the presence of cholestatic hepatitis, but some showed marked elevation of hepatocellular enzymes (AST, ALT). Most patients were jaundiced. Ten patients died, nine due to hepatic failure. One patient with early stage prostate carcinoma received a liver transplant. Eleven patients had recovered at the time of reporting.

While cyproterone-induced hepatotoxicity is rare, it can be fatal or life-threatening. Severe hepatic reactions have not been reported to ADRAC with the use of low dose cyproterone (1-2mg) in combination with ethinyloestradiol (Brenda, Diane, Juliet) or oestradiol (Climen).

Although the value of monitoring is not clear, it would be reasonable to monitor liver function tests intermittently in patients taking long-term high-dose cyproterone.

3. SEROTONIN SYNDROME

Serotonin syndrome is caused by excessive central nervous system and peripheral serotonergic activity. It most commonly occurs with a combination of serotonergic agents, but may also occur with a single agent. A combination of agents increasing serotonin by different mechanisms, such as by inhibition of serotonin uptake and serotonin metabolism, is associated with a high risk of the syndrome.[1] Table 1 lists agents which have been associated with serotonin syndrome.

Serotonin syndrome is a clinical triad of cognitive-behavioural changes, autonomic dysfunction and neuromuscular dysfunction. At least three of the features listed in Table 2 must be present.[1,2] There is no laboratory test to aid diagnosis. The syndrome often occurs within a day of a change in treatment (increase in dose or addition of another serotonergic agent) and the evolution of symptoms is rapid. It should not be confused with neuroleptic malignant syndrome which is clinically similar, but is an idiosyncratic response to neuroleptic agents, usually occurs after longer periods of treatment and develops over a period of days or weeks.[1]

ADRAC has received 161 reports of serotonin syndrome. The majority describe the syndrome in association with the concomitant use of 2 or more serotonergic agents, in particular SSRIs (68), tramadol (29), moclobemide (23), venlafaxine (18), tricyclic antidepressants (18) and St John's wort (8). In 61 reports, the serotonin syndrome developed in association with a single agent: SSRIs (40), moclobemide (5), venlafaxine (5) and tramadol (5). Serotonin syndrome with tramadol was the subject of an earlier Bulletin article.[3]

Table 1: Agents causing serotonin syndrome

Antidepressants	SSRIs, monoamine oxidase inhibitors (including moclobemide), tricyclics, mirtazapine, venlafaxine
Antiparkinsonians	Amantadine, bromocriptine, levodopa, selegiline, carbergoline, pergolide
Illicit drugs	Cocaine, hallucinogenic amphetamines such as MDMA (ecstasy), LSD, etc.
Migraine therapy	Dihydroergotamine, naratriptan, sumatriptan, zolmitriptan
Other agents	Tramadol, carbamazepine, lithium, reserpine, sibutramine, St. John's wort, bupropion, pethidine, morphine

Table 2: Clinical features of serotonin syndrome

Cognitive-behavioural changes	agitation mental status changes (confusion, hypomania)
Autonomic dysfunction	sweating diarrhoea fever shivering hypertension
Neuromuscular dysfunction	hyperreflexia incoordination myoclonus tremor

Serotonin syndrome is potentially serious. Reports to ADRAC have described confusion (31), convulsions (23), hypertension (22), hallucinations (12) and delirium (7). In the majority of reports, the signs and symptoms developed within 24 hours of the addition of another serotonergic agent or an increase in dose of an agent. Patients responded to withdrawal of the serotonergic agent(s) and appropriate treatment. Recovery was documented in 85% of the cases where the outcome was known and the remainder of patients had not recovered at the time of reporting.

Health professionals should note the drugs that may cause serotonin syndrome, alone or in combination with other serotonergic agents, and be alert to the features of serotonin syndrome. Patients should be informed of the risk and symptoms of serotonin syndrome when serotonergic agents are prescribed.

References
1. Langford N.J. *Adv Drug Reaction Bull* Dec 2002, No. 217
2. Sternbach H. *Am J Psychiatry* 1991;148:705-13.
3. *Aust Adv Drug Reactions Bull* 1991;21:14

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

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from at the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", or from the Adverse Drug Reactions Unit ☎ 02-62328386, 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 "adverse drug reaction reporting" on the right.

Further information can be obtained from the ADRAC Secretariat:

☎ 1800 044 114 Fax: 02-62328392 Email: adrac@health.gov.au

(Problems with therapeutic devices should be reported on 1800-809361)

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The Bulletin is also available on the Internet at: http://www.tga.gov.au/adr/aadrb.htm (with full references).
All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606