EDITORIAL

# Statins and muscle damage

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Muscle damage is an uncommon, but important, adverse reaction to HMG CoA reductase inhibitors ('statins').[1] Patients may experience a range of musculoskeletal symptoms varying from mild aching to severe pain, usually in proximal muscle groups. Muscle stiffness and weakness also occur to a varying degree. The concentration of creatine kinase (CK) in the blood is usually increased.

Mild symptoms, (myalgia) are usually associated with minimal elevation of CK concentrations (3–10 times upper limit of normal). Myalgia occurs in 2–7% of patients treated with statins in randomised clinical trials, but the incidence is similar in placebo-treated patients.

In myopathy, CK concentrations are more than 10 times the upper limit of normal, with or without symptoms. Myopathy occurs in 0.1–0.2% of clinical trials, at a slightly greater rate than in placebo-treated patients.[1]

The most serious type of muscle damage, rhabdomyolysis, occurs only rarely but is important to recognise as it may be fatal.[1] Rhabdomyolysis is associated with CK concentrations more than 40 times the upper limit of normal. The patient often has severe muscle pain, stiffness and weakness, with constitutional symptoms of fever and malaise. Their urine may be dark and of small volume, because of myoglobinuria and impaired renal function.

Stopping the drug is the only specific treatment for muscle damage. The symptoms usually resolve rapidly (within a few days to weeks) after withdrawal of statin therapy.

The mechanism of muscle damage is unknown at this stage. Risk factors include high blood concentrations of statins, increasing age, multisystem disease, hypothyroidism, acute illness, major surgery, low body weight and female gender. Drugs that affect the cytochrome P450 system can increase the concentrations of statins that are metabolised by this enzyme system (all statins but pravastatin).[2] Combination therapy with nicotinic acid and gemfibrozil can also result in muscle damage.

The combination of gemfibrozil and cerivastatin was largely responsible for about 100 deaths from complications of rhabdomyolysis. This led to the withdrawal of cerivastatin from world markets in 2001, and increased the attention given to statin-associated muscle damage.[3] Gemfibrozil inhibits a recently reported pathway of hepatic glucuronidation, which appears to be involved in the metabolism of most statins, particularly cerivastatin.[4]

Recently, histologically-confirmed muscle damage has been found in four patients with normal CK concentrations.[5] Muscle damage was suspected because of weakness and/or severe myalgia, which responded to statin withdrawal and recurred on statin rechallenge. The histochemical changes observed on muscle biopsy suggested a defect in mitochondrial respiratory chain function. These histological changes resolved three months after statin withdrawal in the three patients who had repeat biopsies. As none of the four patients had high concentrations of statins in their blood, they may have had some kind of increased susceptibility to muscle damage with statin therapy. This finding extends previous observations made in Australia.[6]

The prevalence of muscle damage in patients with normal CK concentrations is unknown. The disorder must be seriously considered in any patient taking a statin who complains of muscle aches and pains and/or weakness in spite of normal CK concentrations. A trial of statin withdrawal should be considered.

A plan to manage myopathy in patients on statin therapy has been outlined in the USA.[3] Baseline renal, thyroid and hepatic function tests and CK concentrations are recommended before starting statin therapy. Muscle symptoms should be assessed

## In this issue ...

The recent proposal that everyone over 55 years old should take a cocktail of drugs, including a statin, would expose many people to adverse effects. Ian Hamilton-Craig alerts us to the finding that a statin can be causing muscle damage even when a patient's concentrations of creatine kinase are normal.

Damage to cardiac muscle releases troponins into the circulation. Peter Hickman and Julia Potter explain how these troponins can help in the diagnosis of myocardial infarction.

Early diagnosis of childhood deafness is important and several States have introduced screening tests for newborn babies. Harvey Coates and Kim Gifkins discuss the types of screening and some of their limitations.

An accurate diagnosis is essential before subjecting patients to immunotherapy. Richard O'Brien reminds us of some of the safety issues.

after 6–12 weeks and at each follow-up visit. If muscle symptoms occur the CK should be measured. This advice was published before the finding that muscle damage can occur with a normal CK concentration, so the recommendations regarding statin withdrawal may be too conservative.

Controlled trials have shown that statins improve overall mortality and the incidence of all forms of cardiovascular disease in patients at increased risk of these diseases. Muscle damage must be placed in the context of the recognised benefits of statin therapy. Clinicians should be aware of the need for vigilance in the monitoring of symptoms. Patients should be advised to report any symptoms at the earliest stage in order to prevent the rare, but more serious, muscle complications of statin therapy.

In many cases (perhaps the majority), muscle symptoms will prove to be unrelated to statin therapy. In others, elevated CK concentrations may be the result of exercise or minor muscle damage from trauma. Statin withdrawal and rechallenge may also be subject to a pronounced placebo effect. There is also the potential to further reduce compliance if patients were to believe that any muscle ache or pain they experience may be related to statin therapy. These considerations suggest that the management of statin muscle damage will not be straightforward until there is a specific diagnostic test available.

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*Conflict of interest: none declared*

# Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

## Preparing tranexamic acid 4.8% mouthwash

Editor, – The beneficial haemostatic effect of tranexamic acid 4.8% mouthwash has been demonstrated in oral anticoagulant treated patients undergoing minor oral surgery.[1,2] However there is no proprietary product readily available to dental practitioners in private practice (Aust Prescr 2002;25:105–6). A practical solution to this problem is the use of Cyclokapron tablets dispersed in water. A crude mouthwash can be prepared by placing a tranexamic acid 500 mg tablet into 10–15 mL of water in a metric measure. The tablet will disperse in approximately 3–5 minutes on standing and quicker with intermittent swirling. Tranexamic acid is readily soluble in water[3], however inactive tablet excipients will still be present after adequate mixing. The resulting slurry has little or no taste. Patients should be instructed to swirl the total preparation including the undissolved residue around the mouth for two minutes and then to expel. This is repeated four times a day for up to seven days.[1,2] Although this method has not been formally validated, sufficient tranexamic acid should be present in the saliva to reduce fibrinolysis.[4]

Unfortunately the Pharmaceutical Benefits Scheme does not subsidise tranexamic acid 500 mg tablets when prescribed by a dental practitioner. However, they are available as a private dental prescription at a cost of around $31 for a broken pack quantity of 20 tablets. For dental practitioners with no access or assistance from a public teaching hospital this approach partly addresses the issue of having ready access to the mouthwash, although it will not be suitable for all patients.

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## Asthma delivery devices

Editor, – Thank you for the review of asthma therapy delivery devices (Aust Prescr 2003;26:5–7). This article covered important common sense issues in asthma treatment delivery. As suggested by the author, practical issues of use and patient acceptability dominate the decision between a number of otherwise acceptable drug delivery methods. An additional practical issue, in the experience of many Top End practitioners, is that dry powder devices often do not