Treatment injury case study

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Sharing information to enhance patient safety *October 2008*

EVENT: Erythromycin and simvastatin interaction INJURY: Rhabdomyolysis

Case study

Ted, a 55-year-old accountant, was referred acutely to hospital by his GP following a three-week period of increasing general weakness.

At first Ted had difficulty getting dressed because of numbness in his hands, and later found he was unable to walk further than the next room. He had also fallen as a result of his increasing unsteadiness.

Ted had been taking a variety of medications on a long-term basis (five years or more), including:

- cilazapril 5mg, bendrofluazide 5mg and aspirin 100mg, for hypertension
- simvastatin 40mg daily, for hyperlipidaemia
- serotide and ventolin, for chronic asthma.

Four weeks earlier, he had also been prescribed erythromycin for a chest infection.

Ted was admitted to the medical ward and was seen by the registrar. A physical examination confirmed the increased weakness and numbness, with no specific muscle tenderness.

Blood tests showed a creatine kinase (CK) of 22,188; an elevated myoglobin; aspartate transferase (AST) 750; and alanine transferase (ALT) 449. Renal function, however, was normal.

The registrar made a provisional diagnosis of myopathy, after which a chest X-ray was arranged, intravenous fluids begun and simvastatin and erythromycin stopped.

Overnight, Ted remained weak and complained of pain in his legs. He was seen by the medical team next morning, and repeat blood tests showed his CK had increased to 24,437; AST to 782; and ALT to 459.

A diagnosis of drug-induced myopathy was made, and it was arranged to monitor Ted's blood results daily. Over the next few days Ted's CK continued to climb, peaking at 30,134. He remained weak but was able to mobilise with more ease.

Eventually, Ted was discharged from hospital with a diagnosis of rhabdomyolysis. He was still weak and required a walking frame. At the time of discharge, Ted's CK was 24,543; ALT 912; and AST 892.

Key points

- Adverse effects can result from the interaction of other drugs with simvastatin
- The effects of mixing statins and liver enzyme inhibitors will be apparent within days
- Adverse effects are dose dependent, and more likely if the other agents involved are myotoxic or elevate statin plasma levels
- Low doses of statins are advised for patients already on known liver enzyme inhibitors
- Patients taking certain drugs should not be prescribed some types of statin – see expert commentary
- Patients should be made aware of the symptoms of adverse reactions, and told to stop taking the statin if symptoms arise.

Case study

Expert commentary

Carl Burgess MD, FRACP, FRCP

This case illustrates a major adverse effect that may occur following a drug interaction with simvastatin.

On their own, the hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) are remarkably safe, with clinical trials demonstrating myopathy in 0.1-0.2% of patients, and rhabdomyolysis occurring on exceptionally rare occasions. These adverse effects are dose dependent, and occur more frequently if the statins are co-prescribed with agents that are themselves myotoxic, or that elevate statin plasma levels.

Drug interactions with statins can cause inhibition of transport proteins in the gastrointestinal tract and liver, resulting in higher plasma levels and myotoxic effects. More importantly for the development of myotoxicity, however, is the inhibition of liver enzymes (cytochrome P450 3A4) responsible for the metabolism of simvastatin and atorvastatin.

Four statins are registered for use in New Zealand: simvastatin, atorvastatin, pravastatin and rosuvastatin (see table). They differ in their pharmacokinetics and metabolism, with simvastatin and atorvastatin much more likely to be affected by enzyme inhibitors than pravastatin or rosuvastatin.

Liver enzyme inhibitors include:

- potent inhibitors such as protease inhibitors and the azole antifungal agents, ketoconazole and fluconazole
- mild inhibitors (which primarily affect simvastatin) such as the macrolide antibiotics, erythromycin and clarithromycin
- weak to moderate inhibitors such as the calcium antagonists, verapamil and diltiazem.

The transport and enzyme inhibitor cyclosporine has also been shown to increase the plasma levels of all four statins, while other agents such as amiodarone, niacin and fibrates (except fenofibrate) require a reduction in the dose of simvastatin or atorvastatin. Grapefruit juice in excess of 1 litre per day will also increase plasma concentrations of simvastatin and atorvastatin.

When inhibitors are added to statins, the effects are seen within days.

In conclusion, low doses of statins (particularly simvastatin and atorvastatin) should be commenced for patients who are already on known inhibitors.

Atorvastatin and simvastatin should not be prescribed to patients who require or are using protease inhibitors – for these patients, pravastatin is preferred (see Special Authority).

Where an azole antifungal must be prescribed, avoid simvastatin and reduce the dose of atorvastatin.

Lastly, inform patients of the classic symptoms of pain and weakness (mainly involving the proximal muscles) and tell them to stop taking the statin if such symptoms arise.

Some properties of statins available in New Zealand

	Simvastatin	Atorvastatin[1]	Pravastatin[1]	Rosuvastatin[2]
Absorption (%)	60-85	30	35	50
Bioavailability (%)	5	12	18	20
Gut wall/liver metabolism, P450 enzyme	+++ (3A4;2C8)	+++ (3A4)	+ -	+ (2C9)[3]
Transport protein substrate	Yes	Yes	Yes	Yes

1 Subsidised by Special Authority only (see NZ Pharmaceutical Schedule)

2 Not subsidised in New Zealand

3 Minimal metabolism, excreted via bile and kidney

References/Websites

1. Neuvonen P, Niemi M & Backman J. (2006). Drug interactions with lipid-lowering drugs: Mechanisms and clinical relevance. Clin Pharmacol Ther 80:565-81
2. Herman R. (1999). Drug interactions and the statins. CMAJ 161:1281-6.
3. Bellosta S, Paoletti R & Corsinin A. (2004). Safety of statins: Focus on clinical pharmacokinetics and drug interactions. Circulation. 109 (supplement III): 50-57
4. Hansten P. (2003). Possible risks to patients receiving statins combined with other medications. J Am.Coll.Cardiol. 41:519-20.
5. http://.depts.washington.edu/hivaids/drug/case5/discussion.html.

Claims information

Between July 2005 and September 2008, ACC received 19 treatment injury claims relating to simvastatin. Of these, 13 claims were accepted and seven of the accepted claims related to myopathy and rhabdomyolysis. Medications that were prescribed with simvastatin included amiodarone and erythromycin (trio), erythromycin, itraconazole, bezafibrate and venlafaxine.

How ACC can help your patients following treatment injury

Many patients may not require assistance following their treatment injury. However, for those who need help and have an accepted ACC claim for treatment injury, a range of help is available.

This help will depend on the specific nature of the injury and the applicant's personal circumstances, but may include things like:

- a contribution towards treatment costs
- weekly compensation for lost income (if there's an inability to work because of the injury)
- help at home, with things like housekeeping and childcare
- a contribution to the cost of travel to and from treatment
- changes to the home, such as the installation of rails and wheelchair ramps
- personal aids, such as crutches and wheelchairs.

No help can be given until a claim is accepted, but it's a good idea to keep receipts for any injury-related costs, as ACC may be able to reimburse these.

It's important to make a claim for a treatment injury as soon as possible after the injury. This will ensure ACC is able to investigate, make a decision and, if covered, help your patient with their recovery.

About this case study

This case study is based on information amalgamated from a number of different accepted claims. The name given to the patient is therefore not a real one.

The case study has been produced by ACC's Treatment Injury Centre, to provide health professionals with:

- an overview of the factors leading to treatment injury
- expert commentary on how similar injuries can be avoided in the future.

Send your feedback: AdminTeamTI&PS@acc.co.nz

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