Acute effects of low-dose statins on serum cholesterol and creatinine kinase activity

YOHAN P SAMARASINGHE, GRAHAM BALL, MICHAEL D FEHER

Abstract

One of the potential side effects of the HMG CoA reductase inhibitors (statins) is a rise in creatinine kinase (CK) activity. This is sometimes accompanied by myalgia and rarely by rhabdomyolysis. Statins are increasingly being started earlier in the presentation of acute coronary syndromes but the rise in CK activity that they may cause could be a potential confounding factor in the diagnosis of myocardial infarction (MI) in this population.

In this open-labelled, prospective study, 12 hypercholesterolaemic, Caucasian subjects, with a significant cardiovascular risk, were commenced on low-dose statin therapy. Blood samples were taken prior to commencing the statin then on day three and seven for lipid profile and CK activity. Patients maintained their normal lifestyles and usual medication. Interviews were conducted at each visit.

A consistent fall in total and low density lipoprotein (LDL) cholesterol levels was shown over the study period of one week. Apart from one participant, who had a CK rise on day three with accompanying myalgia, there was no consistent change in CK activity within the group. High density lipoprotein (HDL) cholesterol levels also did not show any significant change over the week.

We conclude that the rapid and consistent fall in both total and LDL cholesterol levels with low-dose statin was not paralleled by any consistent change in CK activity. The lack of change in CK activity over one week, following acute initiation of statin therapy, is unlikely to cause difficulty in the diagnosis of MI. If the beneficial effects of statin therapy are due to cholesterol reduction, then acute initiation in coronary syndromes would be favourable.

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Introduction

An increase in the activity of the muscle enzyme, creatinine kinase (CK) has been previously documented as a potential side effect of HMG CoA reductase (statin) therapy. This alteration in CK activity is occasionally associated with clinical myalgia and, rarely, with the more serious complication of rhabdomyolysis. An elevation in CK activity has traditionally been the first biochemical marker of MI. As there is increasing evidence from clinical trials to introduce statin therapy early in the clinical management of patients with acute coronary syndromes,[1-5] this alteration of CK activity may be a diagnostic confounder in the diagnosis of MI in such patients. To-date, there is little information on the acute effects following initiation of statin therapy on muscle enzyme (CK) activity and serum cholesterol lowering.

Aims

The aims of the study were to investigate the acute effects over seven days of low-dose statin therapy on both muscle enzyme activity (CK) and the lipid profile (including total, LDL and HDL cholesterol) in patients who require statin therapy.

Methods

This study was a short-term, open-label intervention study. Subjects who required statin therapy for the management of their hypercholesterolaemia were recruited from the Lipid Clinic at the Chelsea and Westminster Hospital. The inclusion criteria were a CK within the laboratory reference range, a total cholesterol of $\geq$ 5 mmol/L in conjunction with a confirmed history of previous cardiovascular disease or a calculated (Framingham equation) 10-year CHD risk score of > 15%. The exclusion criteria included alcohol excess (> 21 units per week), untreated hypothyroidism, a history of recent trauma or recent myocardial infarction.

Serial biochemistry was performed on each patient on the day before initiation of statin therapy and on three and seven days after commencement of drug therapy. Both CK activity and lipid profile were assayed by standard laboratory techniques. LDL was calculated with the Friedwald equation. There was no strict recommendation for the subjects to fast as the primary end point of the study was muscle enzyme activity and total cholesterol, both of which are not altered by the fed state. No specific statin drug was chosen, but prescribing was left to the discretion of the physician looking after the patient. Only a low dose was used over the seven-day study period. All subjects were instructed not

Figure 1. Change in total cholesterol following acute administration of low-dose statin in 12 hypercholesterolaemic subjects over one week

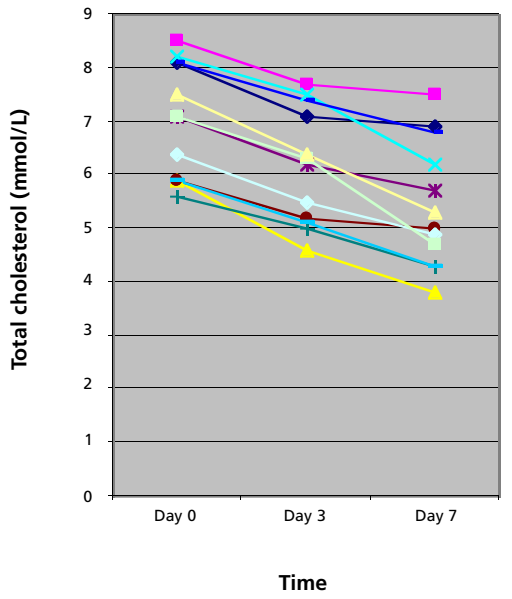
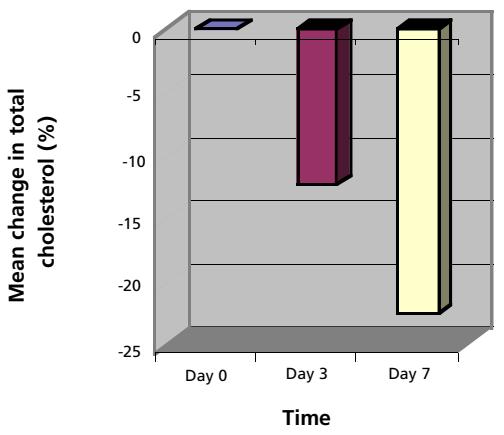
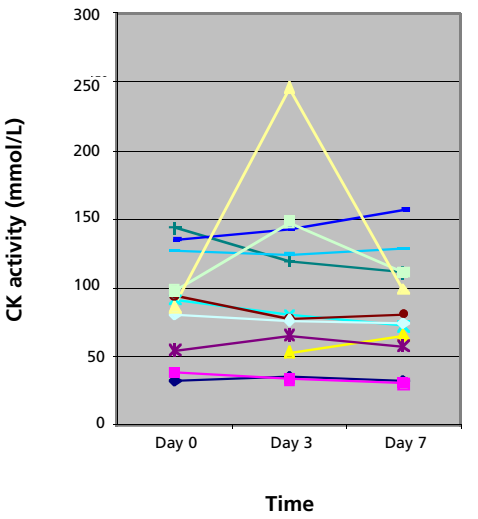


Figure 2. Mean change (%) in total cholesterol following administration of a low-dose statin therapy in 12 hypercholesterolaemic subjects over one week



to alter their diet or change any other treatment over the study period. All subjects had also previously been given appropriate lipid-lowering dietary instruction. Subjects gave signed and informed consent and the study had the ethical approval from the local Ethics Committee.

Figure 3. Creatinine kinase (CK) activity following acute administration of low-dose statin therapy in 12 hypercholesterolaemic subjects over one week



Results

Twelve Caucasian patients (five men, seven women) with a mean age of 67.7 (SD±10.8) years with confirmed hypercholesterolaemia (mean cholesterol 7.0 mmol/L; SD±1.1) were studied. The doses of statin drugs were: atorvastatin 10 mg (n=4), cerivastatin 100 µg (n=1), cerivastatin 200 µg (n=1), pravastatin 10 mg (n=1), pravastatin 20 mg (n=1), simvastatin 10 mg (n=2), and simvastatin 20 mg (n=2). The total cholesterol and LDL cholesterol for subjects showed a consistent fall at three days, which was consistently greatest by the seventh day (figure 1). The percentage reduction in total cholesterol and LDL cholesterol at day three was 12.3% and 15%, respectively and was further reduced by day seven to 22% and 27%, respectively (figure 2). The HDL change was minimal compared to baseline for each subject. There was a marginal reduction in HDL at day three, but by day seven there was no significant change from baseline. There was a consistent reduction in serum triglycerides by 3% on day three and 24% at day seven. As the samples were not from a fasting state, this was not analysed any further.

By contrast to the cholesterol-lowering effect, there was no significant alteration in CK activity (figure 3). All subjects, except one, tolerated the statins without adverse effect. This one subject complained of generalised myalgic symptoms on day three and day seven – their CK activity had increased by three times the baseline level on day three but this increase was reversed by day seven. Myalgic symptoms ceased with the withdrawal of the statin therapy after day seven. There were only minor variations in CK activity for each subject. This finding has been previously observed in young male volunteers who had their CK activity measured on a daily basis over a week (Samarasinghe YP *et al*. unpublished data).

Key messages

- Rises in CK activity caused by early initiation of statin therapy in acute coronary syndromes may confound the diagnosis of myocardial infarction in the absence of more specific tests for myocardial damage
- This small study on 12 hypercholesterolaemic patients showed a rapid and consistent fall in both total and LDL cholesterol levels after low-dose statin therapy after one week
- This was not paralleled by any consistent change in CK activity
- There was no change in HDL cholesterol
- It is unlikely that acute initiation of statin therapy will cause difficulty in the diagnosis of myocardial infarction. Further, larger studies are needed

Discussion

An uncommon but important side effect of statin therapy is the associated rise in CK activity that may occur in the presence or absence of clinical myalgia. The importance of CK elevation is not only as a biochemical marker of myositis or, rarely, rhabdomyolysis, but as a traditional diagnostic marker of myocardial necrosis. Early administration of statin therapy in the management of acute coronary syndromes may have clear advantages with regard to a rapid lipid lowering as well as other pleiotrophic effects, but it may produce a potential confounder in the diagnosis of an acute coronary event if the CK rise is secondary to the statin administration. Other causes of raised CK activity include trauma, alcohol excess, untreated hypothyroidism and other causes of myositis. These may be additional confounders to the diagnosis of myocardial necrosis, but are often excluded from both history and clinical examination.

The addition of statin therapy is now increasingly recommended in the early management of patients post-MI. Currently, there are very little data establishing safety with regards to CK activity. Traditional clinical practice incorporates total CK activity as a diagnostic marker of MI. The more specific MB fraction of CK activity and, more recently, troponin I and T are even more specific, but not widely available in clinical practice. Findings from the current study may have important implications for the role of statin therapy in the management of acute coronary syndromes.

In the present study, the most notable finding was the lack of association between the lipid response (cholesterol lowering) and the CK effect over a seven-day period following the initiation of low-dose statin therapy. The strength of the observation can be seen from the rapid reduction in total and LDL cholesterol concentrations that were consistently seen with a variety of statin compounds. In the one patient who developed myalgic symptoms, the CK increase reflected the clinical state but was not associated with any different reduction in cholesterol lowering.

It was of interest to note that most of the lipid-lowering effects due to statin therapy usually occur within the first week, with additional and smaller effects continuing for four to six weeks thereafter. Any direct link with the cholesterol-lowering effects of statin and muscle enzyme response should have been manifested within this time.

This current study used only low-dose statin therapy. By contrast, higher doses have been used in the major primary[6,7] and secondary prevention trials[8,9] where only sporadic cases of raised CK were reported. It therefore appears that the dose of statin may not be an important factor in relation to any CK alteration. In the previously reported intervention trials, statin therapy was initiated several months after the clinical event. It is of additional interest that in one individual in our present study, the rise in CK paralleled the clinical myalgia and myositis. Despite this, there was still the typical cholesterol-lowering effect. Myopathy is an uncommon finding associated with a statin therapy and has been reported to have a prevalence of ~1 in 1,000[10] and may occur without significant CK change.

There are several potential theoretical benefits for the commencement of statin therapy following acute MI. These include potential plaque stabilisation, beneficial effects on endothelial function, and other positive pleiotropic effects via the nitric oxide pathway and by decreasing the inflammatory process.[11,12] To date, there are few studies specifically assessing the acute effects of statin administration during the peri-infarct period. The FLORIDA study, using high dose fluvastatin (40 mg b.d.) within eight days of presentation of myocardial infarction, did not show any significant clinical benefit in 265 patients after six weeks.[13] The full details of biochemical safety data have not been reported. In the MIRACL study, high-dose atorvastatin (80 mg) was prescribed to 1,538 patients with unstable angina or MI.[1] The reduction in the composite end point after 16 weeks treatment was mainly accounted for by the significant difference in symptomatic myocardial ischaemia requiring hospitalisation. This study reported no cases of confirmed myositis, which was classified as a CK elevation of > 10 times the upper limit of normal. No further details regarding CK alterations were presented in the publication. It is, therefore, uncertain whether there were some individuals with elevations of CK to a lesser extent, with or without myalgic symptoms.

This present study has shown that over a short time-scale of seven days, there is a consistent and rapid reduction in serum cholesterol, with no change in HDL cholesterol, with low-dose statin therapy. These lipid effects were paralleled by no consistent change in CK activity. It would appear that any potential confounding in the diagnosis of MI by a measurement of CK activity is unlikely to be due to statin therapy. To formally assess the safety of early statin therapy with regards to CK activity, larger numbers of patients are required with further biochemical parameters.

Editors' note

The authors declare no conflict of interests in this study. (An accompanying editorial on 'Statins: myalgia and myositis' can be found on pages 193–4 of this issue.)

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