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Prescribing...

Statins and Coenzyme Q10

- June's bulletin looks at the role, if any, of Coenzyme Q 10 in patients on statins who develop muscle-related problems.
- While statistically uncommon, they can have a profound effect on a patient's quality of life and hence adherence to therapy.
- The risk is greater in older people, ladies and in people with significant comorbidities.

What is Coenzyme Q10 ?

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is involved in the production of mevalonic acid in the cholesterol biosynthesis pathway. This pathway also results in the production of other bioactive molecules including coenzyme Q10, which is also known as ubiquinone or ubidecarenone. Coenzyme Q10 is a naturally-occurring coenzyme with antioxidant effects that is involved in electron transport in mitochondria and is thought to play a role in energy transfer in skeletal muscle. Muscle-related problems are a frequently reported adverse effect of statins and it has been hypothesised that a reduced endogenous coenzyme Q10 concentration is a cause of statin-induced myopathy. Coenzyme Q10 supplementation has therefore been proposed to reduce the adverse muscular effects sometimes seen with statins. This bulletin considers whether coenzyme Q10 has a place in the management of statin-induced myopathy.

What is statin-induced myopathy ?

The symptoms of statin myopathy range from muscle weakness, cramps and myalgia, to myositis and life-threatening rhabdomyolysis. An increase in creatine kinase often, but not always, accompanies the symptoms. Myopathy is a dose-dependent effect of all statins, although the likelihood of the effect is higher with some statins than others: the high incidence with cerivastatin led to its withdrawal worldwide in 2001. Lipophilic statins such as simvastatin and atorvastatin are more concentrated in non-hepatic cells and are thought to be more likely to affect skeletal muscle than hydrophilic statins such as pravastatin.

The risk of myopathy is also increased with older age, female sex, genetic profile and comorbidities such as hypothyroidism, hepatic or renal impairment and diabetes.

Lipophilic drugs are known to be much more susceptible to oxidative metabolism by the cytochrome P450 (CYP450) system. It is thought that statins metabolised by this system are more likely to produce muscle toxicity because of the risk of interactions with drugs that inhibit CYP450, and in particular the CYP3A4 isoform. Simvastatin and to a lesser extent atorvastatin are metabolised by CYP3A4, and drugs that inhibit this isoenzyme can increase exposure to these statins.
Concurrent use of some medicines increases the risk of myopathy with statins. Such medicines include amiodarone, amlodipine, azole antifungals, ciclosporin, diltiazem, gemfibrozil and macrolide antibiotics; grapefruit juice also interacts with some statins.

What is the incidence of myopathy and how does it happen ?

According to the UK Medicines and Healthcare products Regulatory Agency, muscle-related problems are the most frequently reported adverse effect of statins. Data from randomised trials, cohort studies, published case reports and spontaneous reports have been used to estimate the incidence of statin-related adverse effects as follows:

- Mild muscle pain: 190 cases per 100,000 patient years
- Myopathy: 5 cases per 100,000 patient years
- Rhabdomyolysis: 1.6 cases per 100,000 patient years.

The mechanism underlying statin-induced muscle damage is unclear. Proposed mechanisms include decreased cholesterol in skeletal muscle membrane or depletion of isoprenoids including coenzyme Q10 through inhibition of the mevalonate pathway leading to impaired mitochondrial function, vitamin D deficiency, induction of apoptosis, and disturbed calcium metabolism.

Muscle symptoms affect adherence to statin therapy and may have a considerable impact on the lives and wellbeing of affected patients.

What is the advice of the Medicines and Healthcare products Regulatory Agency advice ?
Patients should be advised to seek prompt medical attention if they experience muscle problems while taking statins. Myopathy may not be clinically serious to start with, but can rarely progress to potentially fatal rhabdomyolysis. Review statin treatment if muscle problems occur. For some patients, stopping statin treatment may be appropriate. If statin treatment must be continued despite muscle problems, consider using a lower statin dose or switching to a different statin.

Is there a role for Coenzyme Q10 ?
Coenzyme Q10 is widely available as a supplement from healthfood shops and pharmacies. In the UK and hence Guernsey, it is not available as a licensed medicinal product. Some studies have shown that treatment with statins reduces endogenous coenzyme Q10 concentration, while others have shown no effect. Furthermore, the theory that myopathy is due to the effects of statins on coenzyme Q10 synthesis has limitations: despite statins lowering serum coenzyme Q10 concentrations, a consistent decrease in myocyte coenzyme Q10 levels has not been shown. Coenzyme Q10 supplements help increase plasma concentrations of the substance, but the effect of supplementation on statin-induced myopathy is less clear.

Is there any clinical evidence to support its use ?
Some studies have shown a beneficial effect on statin-induced myopathy with coenzyme Q10 supplementation. However, others have shown no significant effect.

Two small controlled studies reported that coenzyme Q10 improved myopathy symptoms in patients taking statins. In one 3-month double-blind placebo-controlled trial in 60 patients with mild to moderate myopathy associated with statin therapy (atorvastatin [mean dose 17–18mg/day], fluvastatin [mean dose 80mg/day], rosuvastatin [mean dose 10–12mg/day] or simvastatin [mean dose 25–27mg/day]), coenzyme Q10 200mg daily was given alone or with selenium. Myopathy (assessed with a visual pain scale scoring from 0 [no pain] to 10 [worst pain ever]) improved in the group taking coenzyme Q10 compared with placebo: there were reductions in the intensity of muscle pain (absolute decrease -3.5 vs. -0.1 with placebo, $p<0.001$), frequency of muscle cramps and statin-associated fatigue after 3 months' treatment with coenzyme Q10. The addition of selenium did not have any effect. Similarly, a double-blind randomised trial in 32 patients showed a reduction in muscle pain associated with statin therapy (atorvastatin [10–20mg], lovastatin [40mg], pravastatin [40mg] or simvastatin [10–80mg]). Muscle pain, as assessed using a brief pain inventory questionnaire, was reduced after 1 month's treatment with coenzyme Q10 100mg daily compared with vitamin E supplementation (change in pain severity score -2.03 vs. +0.34, $p<0.001$). However other controlled studies have not shown any beneficial effect of coenzyme Q10 supplementation.

Three studies reported no benefit. Differences in study design, including the use of various statin regimens and the use of vitamin E rather than a placebo in one study, might go some way to explaining conflicting results. The three studies that reported no beneficial effect of coenzyme Q10 supplementation were the only ones that included a power calculation to ensure an appropriate sample size.

Are there significant adverse effects of coenzyme Q10
Coenzyme Q10 is generally well tolerated with negligible adverse effects reported in clinical trials. Mild gastrointestinal discomfort has been reported in less than 1% of patients in clinical trials. One author has suggested that because coenzyme Q10 may have hypoglycaemic and hypotensive effects, its use should be monitored in patients taking medicines for diabetes or hypertension. Case studies have reported a potential interaction between coenzyme Q10 and warfarin leading to a decreased international normalised ratio (INR).

What do UK guidelines say ?
Guidelines from NICE do not recommend coenzyme Q10 supplementation to increase adherence to statins.

Conclusion
Coenzyme Q10 is involved in electron transport in mitochondria and is thought to play a role in energy transfer in skeletal muscle. It is a product of the same cholesterol-producing pathway that statins affect through their inhibitory action on 3-hydroxy-3-methylglutaryl coenzyme A reductase. There is not enough evidence to recommend Coenzyme Q10 supplementation to reduce the adverse muscular effects sometimes seen with statins. Clinicians managing patients who experience muscle problems when taking a statin should investigate possible causes, consider stopping and rechallenging with the statin, switching to a different statin or lowering the dose if the symptoms prove to be related to the treatment.

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