A case to remember…

Simvastatin-induced myositis occurring in a patient with viral hepatitis A

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Keywords
Simvastatin, myositis, hepatitis

Teaching Point

1. Statin therapy should be discontinued in patients presenting to hospital with significant acute liver disease of any cause.

Case Report

A 60 year old female was admitted with jaundice, malaise & loss of appetite. Two weeks before admission she had complained of diarrhoea with abdominal pain. There was no previous history of jaundice, blood transfusion or foreign travel. She denied pruritus, and stools were of normal colour, although her urine was dark. She was non-smoker & did not drink alcohol regularly. She was known to have ischaemic heart disease & hypercholestolaemia and had been taking ramipril 5mg , clopidogrel 75mg, simvastatin 20mg & omeprazole 20mg daily for the previous two years.

On examination she was jaundiced without organomegaly or other stigmata of chronic liver disease. Clinical examination was otherwise normal. Initial liver function tests (LFT) showed raised bilirubin 119 (normal <15), alanine transaminase (ALT) 4560 (normal <45), alkaline phosphatase (ALP) 182 (normal <190), Albumin 25 (normal range 35-50). Urea, creatinine and other electrolytes were within normal range. Serum amylase was 125 (normal <300). Full Blood count and clotting screen were normal. Hepatitis serology screening revealed raised IgM antibodies to Hepatitis A Virus. Hepatitis C antibody & Hepatitis B surface antigens were not detected. Abdominal ultrasound was normal. A diagnosis of acute hepatitis A was made and she was discharged home after 48 hours, her LFT's showing improvement with ALT 2940, ALP 147 and albumin 24.

Two weeks later she was readmitted with symptoms of myalgia, causing difficulty in climbing up stairs and rising unaided from a sitting position. On examination she remained jaundiced but chest, cardiovascular & abdominal examination was normal. There was bilateral tenderness over the quadriceps muscles with significantly reduced power of hip flexion and extension (grade 4). Tendon reflexes were all present and symmetrical, and there was no sensory loss.

Repeat liver function tests showed serum bilirubin 139, ALT 374, ALP 316 and Albumin 23. Full Blood Count and electrolytes were normal. However creatinine kinase (CK) level was markedly raised at 10490 (normal range <190). Thyroid function was normal.

A presumptive diagnosis of acute myositis was made, proposing that the most likely cause was the continuous use of simvastatin in the presence of acute hepatitis. On this basis the simvastatin was stopped and she was observed in hospital. Within 48 hours of discontinuation of the drug her muscle pain and weakness had significantly improved, enabling her to get out of the bed and walk unaided. Seven days after discontinuing simvastatin her CK levels had returned to normal & her liver function tests showed significant improvement with bilirubin 44, ALT 88 ALP 232 & albumin 31. Five weeks later her liver function test returned to normal. She was recommenced on simvastatin three weeks after normalisation of her LFT and four months later her follow up LFT & CK have remained normal.

Discussion

Simvastatin is a lipid-lowering agent, derived from a fermentation product of *Aspergillus terreus.* After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding b-hydroxyacid form which is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.[1] Evidence of the reduction in mortality from ischaemic heart disease and cerebrovascular disease has led to the widespread use of simvastatin and other drugs in this class ('statins') in primary and secondary prevention.[2]

Although highly effective in reducing cholesterol levels, one serious and potentially fatal complication of statin usage the development of acute muscle damage. Myositis and rhabdomyolysis are well-

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recognised, albeit rare side-effects.[1] Such symptoms are dose-related and usually occur shortly after commencing the drug or following increases in the dosage. The mechanisms by which statins produce their effects on muscle are not well understood and are likely to be complex.[1,3] A number of theories have been proposed, including:

- Destabilisation of cell membranes;[3]
- Reduction in production of small regulatory proteins important for myocyte maintenance, resulting in increased cytotoxicity.[3]
- A shift towards anaerobic metabolism causing mitochondrial dysfunction.[4]

In Randomised controlled trials the frequency and severity of myositis did not differ between treated and placebo groups.[1,2] It has therefore been postulated that other factors may increase the likelihood of muscular damage.[1,5,6] One such factor is liver cell damage. Since statins are metabolised by the cytochrome P-450 enzymes in the liver, any disruption of hepatocyte function may lead to an increase in the plasma level of the drug.[5]

The rapid resolution of our patient's symptoms following discontinuation of the drug would support our assertion that simvastatin was the most likely cause of her myositis. Given that she had been taking the drug at this dose for 2 years without any problems it appears likely that this was caused by a sudden rise in the plasma level of the drug as a result of the acute hepatocyte damage.

Following our experience with this case we would suggest that statin therapy should be temporarily discontinued in any patient with significant acute liver cell damage, irrespective of its aetiology.

References

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