Medicine in the Elderly

Lovastatin-induced acute rhabdomyolysis

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Summary: Severe rhabdomyolysis complicated by respiratory and renal failure developed three weeks after initiation of low dose lovastatin therapy in a 79 year old, non-immunocompromised patient. The concomitant use of gemfibrozil may increase the risk of this complication.

Introduction

Lovastatin, a 3 HMG-CoA reductase inhibitor, is a new cholesterol-lowering drug that has been reported to cause a transient rise in creatine kinase (CK) in rare cases. Severe rhabdomyolysis has also recently been reported in cardiac transplant patients receiving multiple drugs including cyclosporin and lovastatin.^{1,2}

We report a case of lovastatin-induced acute rhabdomyolysis after only 3 weeks of therapy in a patient not receiving concomitant immunosuppressive therapy.

Case report

The patient was a 79 year old female with diffuse atherosclerosis involving her coronary, iliac and femoral arteries. In addition, chronic, stable angina pectoris, severe intermittent claudication, systolic hypertension, mild chronic renal insufficiency, hypercholesterolaemia, and hypertriglyceridaemia were present. Her medical regimen included digoxin, nadolol, enalapril, disopyramide, frusemide, nitroglycerine, and gemfibrozil. Four weeks prior to admission she was started on lovastatin, 20 mg daily. Three weeks later she noted the onset of progressive generalized weakness without myalgias and within 5 days she was admitted to the hospital unable to raise herself to a standing position. There was no history of trauma, seizure, fever, or any antecedent viral infection.

On admission, generalized muscle weakness was evident, while no neurological abnormalities were found. She was not in respiratory distress at this time. Her admission creatine kinase (CK) was 16,000 IU/l with an MB fraction of 41.5 IU/l. By

the fifth hospital day the CK peaked at 148,000 IU/l. The serum aldolase and aspartate transaminase (AST) were elevated. The free thyroxine, serum protein electrophoresis, electrolytes, and complement were normal. The rheumatoid factor and antinuclear antibody tests were negative. Technetium pyrophosphate and gallium scans were negative for myocardial uptake of either agent. An electromyogram revealed myopathic changes in the proximal muscles.

Lovastatin and gemfibrozil were discontinued upon admission. Over the initial week of hospitalization, skeletal muscle strength diminished and her pulmonary vital capacity declined steadily. By the twelfth hospital day endotracheal intubation and mechanical ventilation became necessary. With supportive therapy her muscle strength improved and she was weaned from mechanical ventilatory support. The CK returned to normal by the sixteenth hospital day. A deltoid muscle biopsy (Figure 1) revealed muscle fibre necrosis with histiocytic cell infiltrates. Immunofluorescent stains for IgA, IgG, IgM, C₃, fibrinogen, and albumen were all negative.

Discussion

Drug-induced rhabdomyolysis is extremely rare but has been reported with pentamidine,³ doxylamine, phenylpropanolamine,⁴ diphenhydramine,⁵ theophylline,⁶ halothane,⁷ and cytarabine.⁸ Tobert⁹ reported 17 cases (0.04%) of lovastatin-associated rhabdomyolysis out of approximately 4000 patients participating in several clinical trials with this drug. Five of these patients were concomitantly receiving cyclosporin, 6 received gemfibrozil (2 received both cyclosporin and gemfibrozil), 2 received niacin, and 6 received none of these other drugs. Using these numbers, the relative risk for

Figure 1 Deltoid muscle biopsy specimen: (a) showing necrosis of individual muscle fibres in the absence of inflammatory infiltrate; (b) degeneration of isolated muscle fibres with accumulation of sarcoplasmic nuclei and macrophage activity. (Haematoxylin and eosin; original magnification, $\times 280$.)

developing rhabdomyolysis from lovastatin was calculated at 0.15% for patients receiving no concomitant therapy, 5% for patients receiving gemfibrozil with lovastatin (as in our patient), and 2% for patients also receiving niacin. If cyclosporin, gemfibrozil, and lovastatin were used together, the relative risk jumped to 28%. The nature of the presumed interaction between gemfibrozil and lovastatin is unknown. Plasma levels of lovastatin metabolites were not elevated by the concomitant use of gemfibrozil, leading Tobert⁹ to theorize the interaction to be 'pharmacodynamic' rather than 'pharmacokinetic.'

The cause of lovastatin-induced rhabdomyolysis remains unknown. Serum drug levels were markedly elevated in two patients^{1,2} and were not reported in the other patients. Decreased hepatic

clearance of the drug has been hypothesized as a cause of this phenomenon.¹⁰ In a case strikingly similar to ours, Goldman¹¹ hypothesized that inhibition by lovastatin of 3-hydroxy-3-methylglutaryl coenzyme A reductase, by reducing the synthesis of mevalonic acid and its derivatives – ubiquinones, dolichols, and isopentyladenine – interrupted normal muscle membrane glycoprotein synthesis.

The effect of advanced age on lovastatin metabolism or the development of lovastatin-associated rhabdomyolysis is unknown. None of Tobert's 17 reported patients was more than 70 years old. Three of his patients had various biliary disorders which could have reduced lovastatin biliary clearance and it is clear that the incidence of biliary tract disease increases with age.^{12,13} The

onset of muscle involvement has been reported from 6 weeks to 16 months after the initiation of therapy. Our patient, who had no evidence of hepatic dysfunction, developed symptoms after 3 weeks of taking lovastatin 20 mg daily.

While the use of pharmacological agents to reduce serum lipids in older patients may seem controversial, ample evidence exists which suggests that the treatment of coronary heart disease (CHD) risk factors is as important in the elderly as it is in the young.¹⁴ Cholesterol elevation, and in particular LDL-cholesterol elevation, is associated with significant increases in CHD incidence for both sexes at all ages.^{15,16} Evidence of a reduction in mortality in a large group of older post-myocardial infarction patients who experienced a drug-induced decrease in serum cholesterol was reported by Canner.¹⁷ Results of the Lipid Research Clinics

Coronary Primary Prevention Trial also suggests this favourable effect.¹⁸ Symptomatic femoral atherosclerosis has also been shown to improve after drug therapy of hyperlipidaemia.¹⁹ Our patient had angina pectoris, was a survivor of a previous myocardial infarction, had severe intermittent claudication, and had significant elevations in both total and LDL-cholesterol levels. Which drugs provide the safest means of pharmacological control of cholesterol elevation in the elderly remains to be determined.

Whether advanced age may increase the risk of rhabdomyolysis from lovastatin is unknown. In the absence of a proven benefit to the use of systemic cholesterol lowering agents in the elderly, their administration should be viewed with extreme caution.

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