Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor

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Two cases of myopathy associated with ezetimibe are reported. In the first case, a woman on ezetimibe monotherapy presented with muscle pain and an elevated concentration of creatine kinase (CK) on two occasions, with ezetimibe 10 mg and with ezetimibe 5 mg after a washout period. The recurrence of muscle pain after washout and the CK increase both supported the hypothesis that ezetimibe alone can be linked to myalgia. In the second case, a man had been treated with atorvastatin, and ezetimibe 10 mg was added to improve his lipid profile. Two months later, the patient complained of muscle pain and a CK increase was noted. The appearance of symptoms when adding ezetimibe to atorvastatin supports a potential pharmacokinetic and/or a pharmacodynamic interaction between these two drugs. These cases suggest that ezetimibe monotherapy as well as ezetimibe associated with the use of a statin may induce myalgia. The mechanism by which ezetimibe could cause muscle pain is not known.

Key Words: Ezetimibe; Monotherapy; Myalgia; Myopathy; Statins

A clear relationship has been established between plasma cholesterol concentration and the risk of coronary artery disease (CAD). Even though a large arsenal of drugs exists to treat elevated cholesterol, many dyslipidemic patients are not reaching treatment goals according to guidelines (1). In the management of hypertension, it is reasonable for physicians to combine many drugs with different modes of action to achieve the recommended lipid concentration (2). Some studies have investigated a new cholesterol absorption inhibitor (ezetimibe) in combination with statins (3-6). Ezetimibe is the first member in a class of selective cholesterol absorption inhibitors that works by impairing the intestinal reabsorption of hepatically excreted biliary cholesterol and dietary cholesterol (7,8). Due to the potential risk of myopathy with statins alone (9), or when used in combination with fibrates (10) or possibly niacin (11,12), ezetimibe becomes an attractive choice to use alone or with a statin to achieve lipid targets. Recently, Fux et al (13) described two cases of myopathy associated with a statin-ezetimibe association. In previous papers evaluating this specific association (3-6), the investigators did not provide sufficient information about adverse muscular events. In these studies, only patients receiving statins in combination with ezetimibe complained of muscle pain and/or had creatine

Une myopathie associée à l'ézetimibe dans le cas d'une monothérapie et en association avec un inhibiteur de la 3-hydroxy-3-méthylglutaryl coenzyme A-réductase

Nous rapportons deux cas de myopathies associées à l'ézetimibe. Une femme se présente avec des douleurs musculaires et une élévation de la créatine kinase (CK) sous ézetimibe en monothérapie et ce en deux occasions : 1) avec ézetimibe 10 mg et, 2) avec ézetimibe 5 mg après une période sans traitement. La réapparition des douleurs musculaires après la période sans traitement et l'augmentation des CK appuient l'hypothèse selon laquelle l'ézetimibe seul pourrait causer des myalgies. Afin d'améliorer le profil lipidique d'un homme traité avec de l'atorvastatine, un traitement d'ézetimibe 10 mg fut ajouté. Deux mois plus tard, le sujet présente des douleurs musculaires associées à une augmentation des CK. L'apparition des symptômes à l'ajout de l'ézetimibe au traitement à l'aide d'atorvastatine soutient une interaction pharmacocinétique ou pharmacodynamique potentielle entre ces deux médicaments. Nos résultats indiquent que l'ézetimibe en monothérapie autant qu'en association avec des statines pourrait induire de la myalgie. Le mécanisme par lequel l'ézetimibe pourrait causer des douleurs musculaires n'est pas connu.

kinase (CK) elevations 10 or more times the upper limit of normal (3-6).

Two cases of myopathy are reported here, one patient with muscle pain and CK elevation during treatment with ezetimibe monotherapy, and another patient with muscle pain and CK elevation after combining ezetimibe with atorvastatin therapy. To our knowledge, no case of myalgia with CK elevation associated with ezetimibe in monotherapy has been previously reported.

CASE PRESENTATIONS

Patient 1

A 42-year-old woman was referred to Hôpital Laval (Sainte-Foy, Québec) for management of dyslipidemia. She also suffered from Raynaud's phenomenon, which worsened during menses. Her history was positive for migraine headaches and she experienced thoracic pain while using pizotifen malate. A coronary angiogram was performed with the use of ergonovine maleate to unmask vasospastic angina, and the test was negative. She also had a strong positive family history of CAD. She had two brothers who died from CAD at 39 and 47 years of age. Her father suffered myocardial infarctions at 39 and 40 years of age but was still alive at age 73. Her mother underwent a

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TABLE 1
Patient 1 clinical data

Date	Drug(s)	CK (U/L)*	Symptoms	Lipid profile (mmol/L)			Other parameters
				LDL	HDL	TG	
February 19, 2003	Simvastatin 10 mg HS	234	Muscle pain	4.03	2.14	0.56	–
June 4, 2003	Ezetimibe 10 mg OD	280	Muscle pain	2.36	1.73	0.31	Electrophoresis of CK: CK-MM 100%, no atypical CK. Apo A-1 1.84 g/L, homocysteine 5.0 µmol/L (normal 4 µmol/L to 14 µmol/L), LP (a) 691 mg/L (normal <300 mg/L)
October 1, 2003	Washout (baseline)	132	None	4.51	2.01	0.36	AST† 25 U/L, ALT‡ 22 U/L
November 4, 2003	Ezetimibe 5 mg OD	236	Muscle pain	3.28	1.80	0.41	AST 29 U/L, ALT 23 U/L
December 9, 2003	Washout (baseline)	416	Muscle pain	4.05	1.48	0.51	AST 25 U/L, ALT 22 U/L
February 23, 2004	Washout	111	None	4.78	1.73	0.50	Apo B 1.00 g/L, AST 20 U/L, ALT 15 U/L
May 3, 2004	Gemfibrozil 300 mg BID	183	Muscle pain	4.32	1.77	0.46	Apo B 0.64 g/L, AST 23 U/L, ALT 18 U/L

*Normal 24 U/L to 170 U/L; †Aspartate aminotransferase (AST) normal <40 U/L; ‡Alanine aminotransferase (ALT) normal 0 U/L to 40 U/L. Apo A-1 Apolipoprotein A-1; Apo B Apolipoprotein B; BID Two times daily; CK Creatine kinase; HDL High density lipoprotein; HS At bedtime; LDL Low density lipoprotein; LP (a) Lipoprotein (a); MM Muscle muscle; OD Once daily; TG Triglyceride

TABLE 2
Patient 2 clinical data

Date	Drug(s)	CK (U/L)*	Symptoms	Lipid profile (mmol/L)			Other parameters
				LDL	HDL	TG	
October 3, 2000	Atorvastatin 20 mg HS	93	None	2.49	1.04	2.31	Homocysteine 10.2 µmol/L
July 10, 2001	Atorvastatin 40 mg HS	–	None	2.81	1.09	2.96	AST† 30 U/L, ALT‡ 40 U/L
September 24, 2003	Atorvastatin 40 mg HS	112	None	2.78	1.22	2.22	LP (a) 1410 mg/L, (normal <300 mg/L), AST 24 U/L, ALT 18 U/L
November 5, 2003	Atorvastatin 40 mg HS Ezetimibe 10 mg HS	606	Muscle pain	2.56	1.34	1.91	Apo B 1.04 g/L AST 40 U/L, ALT 29 U/L
December 10, 2003	Medication stopped	509	Muscle pain	3.51	1.39	2.17	AST 34 U/L, ALT 27 U/L
February 4, 2004	Rosuvastatin 40 mg OD	67	–	2.77	1.40	2.06	AST 42 U/L, ALT 29 U/L

*Normal 24 U/L to 170 U/L; †Aspartate aminotransferase (AST) normal <40 U/L; ‡Alanine aminotransferase (ALT) normal 0 U/L to 40 U/L. Apo B Apolipoprotein B; CK Creatine kinase; HDL High density lipoprotein; HS At bedtime; LDL Low density lipoprotein; LP (a) Lipoprotein (a); OD Once daily; TG Triglyceride

coronary artery bypass graft surgery and vascular surgery for peripheral artery disease. The patient also suffered from syncope in the past and investigations, including an endocavitary electrophysiological study, tilt table test and monitoring with a 9525 Reveal monitor (Medtronic, USA) were negative. The patient was a nonsmoker and numerous treatments with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor for dyslipidemia were unsuccessful. She presented with muscle pain after using multiple statins (rosuvastatin, atorvastatin, etc), including a treatment with simvastatin during which CK values were measured (Table 1). She also presented with pan-corporal urticaria following a three-week treatment with fenofibrate (160 mg daily). Lipid profiles at baseline and during treatment are shown in Table 1. Her medication consisted of acetylsalicylic acid 80 mg once daily (OD).

In light of the numerous, unsuccessful attempts to lower her low density lipoprotein (LDL) concentration with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, ezetimibe 10 mg OD was prescribed on May 22, 2003, without any concomitant medications but acetylsalicylic acid 80 mg. Her LDL and high density lipoprotein (HDL) concentrations decreased by 41% and 19%, respectively, but she presented with fatigue and muscle pain on June 4, 2003 (Table 1). Then, a 16-week washout period was completed and ezetimibe 5 mg daily was prescribed on October 9, 2003. Compared with her baseline values, her LDL and HDL values decreased by 27% and 10%, respectively. Again, on November 4, 2003, she presented with

muscle pain with CK elevation. Ezetimibe was withdrawn and gemfibrozil 300 mg two times daily was introduced, which eventually was also withdrawn because of myalgia despite acceptable results in terms of her lipid profile (Table 1).

Patient 2

A 52-year-old man was referred for risk factor management and follow-up at Hôpital Laval. He had suffered from myocardial infarctions in 1994 and 1999. In 1999, an angioplasty with stenting of the circumflex artery was performed and, following an acute coronary syndrome three months later, angioplasty with a stent deployed to the right coronary artery was performed. The patient is an exsmoker and had been treated with atenolol 50 mg, acetylsalicylic acid 80 mg, clopidogrel 75 mg and ramipril 5 mg, all OD, as well as atorvastatin 20 mg OD since December 2000. Lipid profiles are shown in Table 2. One year later, atorvastatin was increased to 40 mg daily as LDL cholesterol concentration deteriorated slightly (LDL 3.21 mmol/L, HDL 1.05 mmol/L and triglyceride 1.94 mmol/L). The patient did not complain of any side effects following the increment of atorvastatin (Table 2). On September 24, 2003, ezetimibe 10 mg OD was added. Two months later, the LDL concentration had decreased by 8% and the HDL concentration had increased by 10%, but the patient had muscle pain. Laboratory testing showed an increased CK concentration (Table 2). Thus, all hypolipemic agents were withdrawn in November. Unfortunately, the patient was admitted for an acute coronary

syndrome in late December 2003 (Table 2). He underwent an angiogram that showed diffuse atherosclerosis without significant stenosis. He was discharged from the hospital on rosuvastatin 40 mg OD. A lipid profile was obtained four weeks later and is shown in Table 2. No muscle pain was noted by the patient.

DISCUSSION

So far, there has been no strong clinical evidence that ezetimibe's use is related to an increased risk of myotoxicity with CK elevation. Nonetheless, these patient reports suggest that ezetimibe in monotherapy as well as in association with statins may induce myalgia.

A study (3) of 48 healthy men investigated the potential for pharmacodynamic and/or pharmacokinetic interactions between ezetimibe and lovastatin. One patient receiving lovastatin 40 mg plus ezetimibe 10 mg withdrew from the study on day 8 due to an adverse event characterized by moderately severe myalgia, without CK elevation. Another patient (lovastatin 20 mg plus ezetimibe 20 mg) reported moderate muscle pain on day 13. He continued treatment, and myalgia decreased on day 15 and resolved by day 17. No CK value was reported for this patient. Another study (4) included 710 patients with LDL concentration of 3.37 mmol/L or greater and assessed whether the coadministration of ezetimibe and simvastatin would be more effective than simvastatin alone in achieving optimal LDL concentrations. In this cohort, more patients in the ezetimibe plus simvastatin than in the simvastatin monotherapy group experienced adverse events that were considered to be related to the study treatment. There was no case of rhabdomyolysis during the study. One patient in the ezetimibe plus simvastatin group experienced elevation of CK, defined as 10 or more times the upper normal limit, which was associated with muscle symptoms that were considered to be possibly related to the treatment (4). In another study of 788 patients comparing the efficacy and safety of coadministered ezetimibe plus simvastatin with atorvastatin monotherapy (5), there were two cases of CK elevation without muscle symptoms in the ezetimibe plus simvastatin group and one case of CK elevation with muscle symptoms in ezetimibe plus simvastatin group compared with none in the atorvastatin group (5). No further information is available because these studies did not assess the incidence of myopathy. Recently, Fux et al (13) reported two cases of patients whose CK concentration increased after ezetimibe was added to the statin therapy. One of the patients also developed myalgia and tendinopathy. They concluded that because the symptoms appeared when ezetimibe was added to statin monotherapy, diminished after withdrawal of ezetimibe, and normal CK concentration persisted following the reintroduction of statin monotherapy, this supported a potential interaction between ezetimibe and statins (13).

Our first patient presented with muscle pain and elevated CK concentration on ezetimibe monotherapy on two occasions, with ezetimibe 10 mg and with ezetimibe 5 mg after a washout period. To our knowledge, there is no previous report of myopathy with ezetimibe alone with elevated CK concentrations. The washout period between ezetimibe 10 mg and ezetimibe 5 mg and the recurrence of muscle pain supports the hypothesis that ezetimibe alone can cause myopathy. Although CK elevation was not spectacular, the patient presented with clinically relevant muscle pain that was not experienced in the absence of the drug. The patient had no muscle

pain or elevated CK concentration while off the medication. She exercised three to four times a week without limitation or signs of muscular problem. Thus, any other causes of myositis or muscle pain were not investigated, and since being off of the medication the patient has had no complaints. The sole investigation was the protein electrophoresis and the results are shown in Table 1.

Phillips et al (14) reported patients who developed muscle symptoms but had a normal CK concentration while receiving statin therapy. These patients had demonstrable weakness measured by standard techniques of functional capacity and muscle strength. Interestingly, muscle biopsies showed evidence of mitochondrial dysfunction, including increased lipid stores, fibres that did not stain for cytochrome oxidase activity and ragged red fibres. These pathological and biochemical findings in patients with statin myotoxicity suggest impaired fatty acid oxidation (14). These findings reversed when the patients were no longer receiving statin therapy. Thus, serum CK concentration may not be truly predictive of statin-associated myopathy (14). The same group reported that 18 patients over 30 years of age had myopathic symptoms on ezetimibe alone within two weeks of beginning therapy (15). Unfortunately, there were no CK values reported. These patients had intolerance of multiple lipid-lowering therapies before the use of ezetimibe, an elevated fasting respiratory exchange ratio while not taking a lipid-lowering therapy and often had hypertriglyceridemia (15). The fasting respiratory exchange ratio has been useful in detecting impaired fatty acid oxidation in patients (16). They concluded that because this reaction occurred with ezetimibe monotherapy and was accompanied with other signs of impaired fatty acid oxidation, the toxicity may not be related to a pharmacokinetic interaction but to impaired fatty acids oxidation. Indeed, the concept of lipotoxicity is of importance and is evolving in the literature (17).

In another study (18) the same group demonstrated that several patients with statin myotoxicity had elevated triglyceride concentrations. The incidence of hypertriglyceridemia in patients with statin-induced muscle toxicity is higher than would be expected if it were unrelated to the muscle toxicity. It is likely that some patients with mitochondrial dysfunction have elevated triglycerides due to impaired beta oxidation. Such patients would be expected to have an elevated fasting respiratory exchange ratio reflecting the inability to properly oxidize fatty acids even before exposure to lipid-lowering therapy. Lipid-lowering therapy may exacerbate this mitochondrial dysfunction by reducing fatty acid substrate and potentially impairing fatty acid transfer or by acting directly as a mitochondrial toxin (18). However, in the case reported here, the patient had a normal triglyceride concentration at the beginning of and during the treatment. However, it cannot be ruled out that she did not have fatty acid oxidation abnormalities.

In the present study, patient 2 presented with myopathy and muscle pain while on the combined treatment of atorvastatin plus ezetimibe. Evidence supporting a potential pharmacokinetic and/or pharmacodynamic interaction between ezetimibe and atorvastatin includes appearance of symptoms when adding ezetimibe to atorvastatin. Moreover, CK concentration returned to normal after using another statin in monotherapy. The mechanism underlying a potential pharmacokinetic interaction is not well understood. Competitive inhibition of the glucuronidation processes between the two drugs is a possible explanation (19,20). Both

drugs are glucuronidated by the uridine diphosphate glycosyltransferase 1 family, polypeptide A1 enzyme (21,22). The clinical relevance of inhibition of glucuronidation remains to be established and this possibility does not explain the appearance of muscle toxicity in the patient on ezetimibe alone. Further investigations will be required to test the pharmacokinetics interaction hypothesis. Of course a pharmacodynamic interaction is also of consideration. As mentioned earlier, there is a potential risk of myopathy with statins alone (9), statin-fibrate association (10) and possibly with statin-niacin combination (11,12). It is therefore reasonable to assume that a drug with a new mechanism of action could potentially increase the risk of myopathy due to its cholesterol reducing action per se.

CONCLUSION

The present report suggests that ezetimibe in monotherapy may induce myalgia in patients who are intolerant of statins due to statin-induced myalgia or myopathy. Moreover, this phenomenon may also appear in association with a statin, as suggested by our second patient. Thus, ezetimibe or a drug's metabolite may need to be absorbed by the gastrointestinal tract to interact with muscles to induce myalgia or myopathy. Accordingly, a potential pharmacokinetic and/or pharmacodynamic interaction could be important to elucidate, as ezetimibe is usually prescribed with a statin. Additional research will probably elucidate the mechanism of this important adverse drug outcome. There is also a possibility that the lipid-lowering therapy alone should not incriminate per se but instead an underlying disorder of muscle fat metabolism in some vulnerable patients that predisposes them to myotoxicity on such therapies.

Moreover, these cases emphasize the need to develop new diagnostic tools to identify lipid-lowering drug-associated myalgia or myopathy more accurately.

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