Elevation of CKP induced by ezetimibe in monotherapy

Report on two cases

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SUMMARY
Few cases of myopathy have been reported in patients treated with ezetimibe as monotherapy or in association with a statin. We report on two cases of elevation of CKP that occurred upon monotherapy with ezetimibe, which were reversible after discontinuation of the drug. In both cases, patients previously experienced intolerance with other lipid-lowering agents. The pathogenesis of muscle toxicity associated with ezetimibe is not known yet. An interaction with statin or a toxicity mechanism common to several lipid-lowering drugs have been suggested. A potential role of induction of glucuronidation by numerous associated drugs can also be involved. Although association of ezetimibe with myopathy seems to be uncommon, special attention should be given to patients treated with ezetimibe who had a previous intolerance to other lipid-lowering drugs and who received several drugs.

Key-words: Ezetimibe · Myopathy · Side effects · Statin.

Meas T, Cimadevilla C, Timsit J, Mouly S, Guillausseau PJ. Elevation of CKP induced by ezetimibe in monotherapy: report on two cases
Diabetes Metab 2006;32:364-366

RÉSUMÉ
Élévation de la créatine phospho-kinase (CPK) induite par l’ézetimibe en monothérapie : à propos de 2 cas.

De rares cas de myopathie sous ézetimibe en monothérapie ou en association avec une statine ont été publiés. Nous rapportons deux cas d’élévation de la créatine phospho-kinase (CPK) associés à une monothérapie par ézetimibe, et régressifs après arrêt de celle-ci. Dans les deux cas, les patients avaient eu antérieurement une intolérance à un autre traitement hypolipémiant. La physiopathologie des effets secondaires musculaires de l’ézetimibe reste inconnue. Une interaction avec les statines ou un mécanisme de toxicité musculaire commun à différentes classes d’hypolipémiants ont été évoqués. Dans ces deux observations les patients recevaient de nombreux médicaments qui impliquent la voie métabolique de la glucuronidation. Une interaction médicamenteuse impliquant ce mécanisme peut aussi être évoquée. Bien que ces observations soient rares, elles incitent à porter une attention particulière aux patients traités par ézetimibe qui avaient présenté auparavant une intolérance à un autre hypolipémiant et qui sont polymédiqués.

Mots-clés : Ezétimibe · Myopathie · Effets secondaires · Statines.

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Received: April 24th, 2006; accepted: May 16th, 2006.
Ezetimibe is the first member of a new class of selective cholesterol absorption inhibitors. The drug and its active glucuronide metabolite impair intestinal reabsorption of both dietary and biliary excreted cholesterol through inhibition of a membrane transporter [1]. Treatment with ezetimibe is indicated in patients with hypercholesterolemia, either as an alternative to 3-hydroxy-3- methylglutaryl-CoA reductase (HMG CoA-reductase) inhibitors when statins are not well tolerated, or in combination therapy when cholesterol level targets are not achieved with statins alone. In clinical trials involving more than 2,000 patients treated with ezetimibe alone, a significant increase in creatine kinase protein (CKP), a marker for muscular cell destruction, has been unusually reported (excess of 10-fold upper normal value in less than 1% of the population) [2]. However, some case reports have been published recently, indicating that treatment with ezetimibe may be associated with muscle toxicity [3-6].

We herein report on two patients with significant CKP elevation following ezetimibe treatment.

Case 1

A 48-year-old man had type 2 diabetes and arterial hypertension. He had moderate diabetic retinopathy and nephropathy with mild renal failure (creatinine clearance 60 ml/min). He was treated with benazepril, irbesartan, hydrochlorothiazide, diltiazem, aspirin and insulin. Hypertension and diabetes were well controlled (HbA1c 6-7%). Cholesterol and triglyceride plasma levels were increased and fenofibrate 200 mg/d was started. CKP plasma levels had been repeatedly normal before treatment. After several years, the patient complained of mild muscle pain of the lower limbs, and CKP levels were found increased to 1.7 and 2.4 fold the upper normal range (N). Fenofibrate was stopped and muscular pain disappeared. Since LDL cholesterol (LDLc) remained high in this patient with multiple risk factors, simvastatin 20 mg/d was given but due to general discomfort treatment was stopped after 10 days. CKP levels were within normal limits (0.5 N). As LDLc remained elevated, fenofibrate was started. After 4 days the patient developed a skin rash, and the treatment was stopped. Two months later, ezetimibe treatment 10 mg/d was started. Twenty-five days later, blood examination revealed CKP being 43 times above the upper normal range while the patient did not complain of any muscle pain. Ezetimibe was stopped and CKP rapidly returned to normal, and remained normal after a 3-month follow-up.

Discussion

We report an isolated elevation of CKP, under ezetimibe therapy, with no clinical signs. However, this elevation raised up to 43 times above the normal range and can be considered as a biological myopathy. Few cases with elevated CKP levels or myopathy after treatment with ezetimibe alone or in association with statin have been reported. Interestingly, these cases share similar features [3-6]. Almost all these patients have experimented previous myopathy or elevation in the CKP when treated with other classes of lipid-lowering drugs, before being treated with ezetimibe. It has been suggested that a common mechanism, i.e. impaired fatty acid oxidation, could be responsible for muscle toxicity [3]. A recent meta-analysis that compared muscle safety profiles of ezetimibe/simvastatin and simvastatin monotherapy did not show any difference in the incidence of myopathy between the two groups [7]. However, Phillips reported that among 30 patients with intolerance to lipid-lowering therapies, myopathic symptoms occurred in 18 with ezetimibe monotherapy [8]. Alternatively, a potential interaction between ezetimibe and statins has been raised [6]. Indeed, in two patients symptoms appeared after addition of ezetimibe to statin monotherapy, and diminished after withdrawal of ezetimibe, and CKP levels were persistently normal at continuation or reintroduction of statin monotherapy.

In our two cases, patients received angiotensin 2 receptor antagonists. N-glucuronidation represents a major biotransformation route for this drug [9]. After ingestion, ezetimibe is rapidly glucuronidated into its active metabolite [10]. Inhibition of drug metabolism by a co administered drug may result in decreased metabolic clearance and/or increased bioavailability of the parent compound. Whether or not angiotensin 2 receptor antagonists may alter the excretion and metabolite profiles of ezetimibe and increased the likelihood of drug-induced toxicity is unknown and deserves further investigation.
Conclusion

This as well as previous reports suggests that, until the pathophysiology of this myopathy has been elucidated, physicians should be warned that muscle toxicity or even myopathy may occur in patients having a history of muscular side effects with other lipid-lowering therapies, in whom they switch for ezetimibe and/or in those receiving another drug undergoing intestinal and/or liver glucuronidation, due to the risk of drug-drug interaction.

References