Case Report

Rhabdomyolysis induced by simvastatin-diltiazem interaction in unrecognized hypothyroidism

Ran Zhang¹, Hai-Hong Ran², Cai-Yi Lu¹, Wei Gao¹, Ya Huang¹, Yu-Ling Gao¹, Qiong-Xiang Yang¹

¹Institute of Geriatric Cardiology; ²Department of Geriatric Hematology, Chinese PLA General Hospital, Beijing 100853, China.

Abstract Simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, is widely prescribed to patients with hypercholesteremia and its muscular toxicity has been widely reported. The metabolism of simvastatin depends on the enzymic activity of cytochrome P450 3A4 (CYP3A4) and inhibitors of CYP3A4 can result in clinical events by interacting with simvastatin. Diltiazem is a moderate inhibitor of CYP3A4, which is known to increase the serum concentration of simvastatin. Here we report a patient with unrecognized hypothyroidism who had been stable for more than one year on low-dose simvastatin therapy of hypercholesteremia and rhabdomyolysis occurred with the addition of diltiazem. This is one of scanty reports of rhabdomyolysis induced by simvastatin-diltiazem drug interaction, especially in hypothyroid patient. This case reminds the clinicians that although diltiazem as a moderate CYP3A4 inhibitor can be used cautiously with small doses of CYP3A4-dependent statins (e.g., simvastatin), these two commonly used drugs should be avoided in hypothyroid patient (J Geriatr Cardiol 2010; 7:126-128).

Key Words Simvastatin; diltiazem; drug-interaction; rhabdomyolysis; hypothyroidism

Introduction

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have significant health benefits in patients with high risk for cardiovascular diseases and reduce cardiovascular mortality and morbidity by lowering serum cholesterol. Generally, statins are well tolerated and adverse effects include reversible elevation in transaminases, myositis and rhabdomyolysis.¹,² Rhabdomyolysis is characterized by myoglobinuria, myalgia and a rise in serum level of creatine kinase (CK).³ A case-crossover study on 93, 831 patients found that an annual incidence of statin-induced myopathy or myalgia was around 689 per million per year.² Statins toxicity appears to be drug-dose- and plasma-concentration-related. The metabolism of simvastatin is primarily cytochrome P450 3A4 (CYP3A4)-dependent and therefore, when CYP3A4 inhibitors are co-administered, plasma-concentration of simvastatin may increase dramatically. Among CYP3A4 inhibitors, diltiazem is a moderate one, which can cause increased plasma-concentration of simvastatin and high levels of HMG-CoA reductase inhibitory activity in plasma and is associated with an increased risk of musculoskeletal toxicity.⁴ Hypothyroidism as one of the most commonly secondary causes of hypercholesteremia, accounts for the incidence of 10-15% in hypercholesteremia and it has been reported that about 11.7% of patients with undiagnosed hypothyroidism accidentally received statins.⁵ Cholesterol-lowering medication with statins has been reported to be linked to rhabdomyolysis in hypothyroid patients.⁶ In addition, hypothyroidism itself is a common cause of rhabdomyolysis.⁷ Until now, only several cases have been reported on simvastatin-diltiazem drug interaction related rhabdomyolysis. Herein, we reported a case of hypercholesterolemia secondary to asymptomatic hypothyroidism and rhabdomyolysis triggered by simvastatin-diltiazem drug interaction. To our knowledge, this is one of few case reports that potential simvastatin-diltiazem drug interaction resulted in rhabdomyolysis in unrecognized hypothyroidism. Meanwhile, we reviewed the literatures published in the past years relating to simvastatin-diltiazem drug interaction and discussed its clinical significance in hypothyroidism.

Case report

A 59-year-old man (weight, 74 kg; height, 172 cm; body mass index, 25.01 kg/m²) sought medical help at the Institute of Geriatric Cardiology of Chinese PLA General Hospital with complaint of myalgia for 25 days in September 2008. He denied vigorous physical exercise and alcohol use before the suffering. His medical history included hypere-
Rhabdomyolysis has been recognized as a potentially life-threatening clinical syndrome derived from striated muscle dissolution or disintegration, with the clinical symptoms of myalgia, weakness and muscle cramps, and main laboratory finding of increase in serum CK greater than 10 times the upper limits of normal. The most common predisposing factors accounting for rhabdomyolysis are crush injury, muscle overexertion, alcohol abuse and certain medicines and toxic substances. Statins use and hypothyroidism are both underlying causes of rhabdomyolysis. In the present case, rhabdomyolysis happened following the co-administration of simvastatin and diltiazem in the setting of undiagnosed hypothyroidism.

Statins, such as simvastatin, lovastatin, and atorvastatin, are the substrates of CYP3A4 and their metabolism depends on the enzymic activity of CYP 3A4; therefore, drug toxicity is common when potent CYP3A4 inhibitors such as macrolide antibiotics, azole antifungals, protease inhibitors and nefazodone, or moderate CYP3A4 inhibitors such as amiodarone, ciclosporineA, danazol, diltiazem and verapamil are co-administered with such statins. In clinical practice, it is common that patients who take statins to prevent or treat CHD concurrently take some other drugs for cardiovascular disorders, in particular, calcium channel blockers such as verapamil and diltiazem that can inhibit the activity of CYP3A4. A naturalistic study by Molden et al showed that in 245 co-prescriptions of CYP3A4 inhibitors with simvastatin, diltiazem (35.10%), verapamil (29.39%), clarithromycin (19.59 %) and clarithromycin (11.84 %) were the most commonly co-prescribed CYP3A4 inhibitors. Co-administration with inhibitors of CYP3A4 may increase the plasma concentrations of statins that are metabolized by the isoenzyme. The effects of diltiazem on the pharmacokinetics of simvastatin have been investigated in several studies. Diltiazem significantly increased the mean peak serum concentration of simvastatin by 3.6-fold, simvastatin acid by 3.7, the area under the serum concentration-time curve (AUC) of simvastatin by 5 and the elimination half-life by 2.3-fold. Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis has been sporadically reported in cardiac transplant recipient, renal transplant patient, liver transplant patients and other patients. The underlying cause of the seemingly higher incidence of simvastatin-diltiazem drug interaction in transplant patients may be that transplant patients are at higher risk of developing hyperlipidemia, which contributes to CHD and cardiovascular events. The occurrence of statin-related rhabdomyolysis is usually associated with increased plasma concentration of statins. Furthermore, Masica and coauthors’ work suggested that the interaction of lovastatin with diltiazem do not occur systemically and be primarily a first-pass effect, because such kind of drug interaction usually happens in oral dosing but not in intravenous dosing. Diltiazem as a weak or moderate CYP3A4 inhibitor can be used cautiously with small doses of CYP3A4-dependent
statins, but patients who take both simvastatin and diltiazem may need lower doses of simvastatin to achieve the recommended reduction in cholesterol.

In the present case, the patient had suffered unrecognized hypothyroidism for an uncertain but probably a long time and simvastatin was prescribed for hypercholesteremia and CHD. Rhabdomyolysis did not occur until the addition of diltiazem. Knowledge of the pharmacokinetic and pharmacodynamic properties of statins and the mechanisms of drug interaction with other drugs may help to avoid these adverse effects. Patients taking atorvastatin, lovastatin, and simvastatin, the substrates of CYP3A4, should avoid concurrent use of CYP3A4 inhibitors, especially when predisposing factors of rhabdomyolysis (eg, hypothyroidism) coexist. If the use of CYP3A4 inhibitors is necessary, fluvastatin, pravastatin and rosuvastatin that do not interact with inhibitors of CYP3A4 should be considered. All patients taking statins should be educated to be alert to elevated hepatic transaminases, any unexplained myalgia or weakness.

References