Rhabdomyolysis Induced by Simvastatin-diltiazem Interaction in Unrecognized Hypothyriodism: Case Report and Literature Review

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Abstract

Simvastatin, the 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. Our patient suffered from unrecognized hypothyroidism for a long time and had been stable for more than one year on low-dose simvastatin therapy of hypercholesteremia. However, rhabdomyolysis occurred with the addition of diltiazem. This is one of scanty reports of rhabdomyolysis induced by simvastatin-diltiazem drug interaction, but the first report in hypothyroid patient. This patient 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. Meanwhile, rhabdomyolysis induced by simvastatin-diltiazem drug interaction and its clinical significance is reviewed. (**JPBS 2010;Volume 23 No.1:8-10**)

Key Words: *Simvastatin, Diltiazem, Drug-interaction, Rhabdomyolysis, Hypothyriodism*

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 can reduce cardiovascular mortality and morbidity by lowing serum cholesterol. Now that statins have been the first-line drugs for hypercholesteremia, their efficacy and safety on the other hand have emerged as a major concern [1]. Generally, statins are well tolerated; adverse effects include reversible elevation in transaminases, myositis and rhabdomyolysis[2], which are characterized by myoglobinuria, myalgia and a rise in creatine kinase (CK), are unusual.[3] 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]

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Hypothyroidism is the most common secondary cause of hypercholesteremia, and cholesterol-lowing medication with statins has been reported to be linked to rhabdomyolysis in hypothyroid patients.[5] In addition, hypothyroidism itself is the common cause of rhabdomyolysis.[6] Until now, only several cases have been reported on simvastatin-diltiazem drug interaction related to 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 the first case report 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/m^2) sought medical help at the Institute of Geriatric Cardiology of Chinese People's Liberation Army 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 hypercholesteremia, bronchial asthma, allergic rhinitis, oesophageal ulcer, fatty liver and coronary atherosclerotic heart disease (CHD). Prior to the admission, the patient has been taking simvastatin (20mg p.o.q.n.) for more than one year when diagnosed as hypercholesteremia and CHD. One month before admission, he developed angina pectoris and daily dose of diltiazem (30mg p.o.b.i.d.) was started.

On physical examination, the patient's vital signs were temperature, 36.5° C; pulse, 80 beats per minute and paced; blood pressure, 110/60; and respirations, 18 breaths per minute. Physical examination also showed palpebral edema, but was otherwise largely unremarkable. Laboratory evaluation at admission revealed serum CK of 5885.4 U/L (normal up to 200); serum creatinine of 140.5 μmol/L (normal up to 110); cholesterol of 6.29 mmol/L (normal up to 5.70); aspartate aminotransferase (ALT) of 45.9 U/L (normal up to 40); aspartate amino transferase (AST) of 141.1 U/L; MM isoenzymes of CK of 99.5 U/L (normal up to 16); lactic acid dehydrogenase (LDH) of 316.3 U/L (normal up to 250).

The patient was diagnosed as rhabdomyolysis. Simvastatin and diltiazem were discontinued immediately after the admission. Intravenous fluids were immediately started. He was given forced alkaline diuresis (intravenous normal saline with bicarbonate). The level of CK peaked at 6884.0 U/L on the 3rd day. Although there were not any obviously remarkable symptoms in this patient, it was highly suspectable that he might suffer from asymptomatic hypothyroidism. Thyroid function tests confirmed the diagnosis of severe hypothyroidism: TT3, 0.84 nmol/L; TT4, 16.92 nmol/L; FT3, 2.57 pmol/L; FT4, 6.48 pmol/L; TSH, >150mU/L. The diagnosis was further supported by ultrasonograpy, which revealed diffuse atrophy of thyroid gland. Levothyroxine (50 μg p.o.q.d. Merck KGaA, Germany), as replace therapy, was prescribed to the patient at once. Two weeks later, another 25 μg was added. The levels of serum cholesterol, ALT, AST, CK, and CK-MM were monitored regularly during the hospitalization. At discharge, laboratory test results showed CK level of 159.3 U/L and cholesterol level of 5.59 mmol/L while diltiazem (30mg p.o.b.i.d.) was restarted. The patient complained some mild residual weakness until 1 month after hospitalization, but has otherwise made a full recovery. Palpebral edema disappeared and levels of creatinine and transaminase were also normalized.

The latest follow-up was carried out on September 2009; Thyroid function was completely rectified. The biochemical test values were as follows: TC 5.46 mmol/L, LDL-C 2.64 mmol/L, HDL-C 1.54 mmol/L, ALT 18.5 U/L, AST 16.5 U/L, CK 188.9U/L and CK-MM 7.2 U/L. The complete clinical recovery and normalization of his laboratory data suggested that he was completely recovered from the attack and now, receives the following medication: levothyroxine 100μg p.o.q.d., diltiazem 60 mg p.o.b.i.d.

Discussion

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 with an increase in serum CK of 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.[7] Currently, statins and hypothyroidism have been accepted as the underlying causes of rhabdomyolysis [6-8], in which drug interactions with statins are common. In the present case, rhabdomyolysis happened following the co-administration of simvastatin and diltiazem in the setting of undiagnosed hypothyroidism.

Statins, like 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 inhibitors of CYP3A4 (potent CYP3A4 inhibitors such as macrolide antibiotics, azole antifungals, protease inhibitors and nefazodone; moderate CYP3A4 inhibitors such as amiodarone, cyclosporine, danazol, diltiazem and verapamil) are co-administrated with such statins. In clinical practice, it is common that patients who take statins to prevent or treat CHD often concurrently take some other drugs for cardiovascular disorders, in particular, calcium channel blockers such as verapamil and diltiazem which can inhibit the activity of CYP3A4. A naturalistic study by Molden et al [9] showed that diltiazem (35.10 %), verapamil (29.39 %), erythromycin (19.59 %) and clarithromycin (11.84 %) were the most commonly co-prescribed CYP3A4 inhibitors. Co-administration with inhibitors of CYP3A4 (e.g. diltiazem) may increase the plasma concentrations of statins that are metabolized by the isoenzyme. The effects of diltiaem 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-fold, the area under the serum concentration-time curve (AUC) of simvastatin by 5-fold and the elimination half-life by 2.3-fold.[4] Therefore, even if a low dose of simvastatin is prescribed, this drug interaction would result in the side effects of high dose of simvastatin. Diltiazem as a CYP3A4 inhibitor is a potential risk factor of myopathy if co-administered with simvastatin [10]; however, only very scanty cases have been reported in the past years. Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis has been sporadically reported in cardiac transplant recipient [11], renal transplant patient [12, 13], liver transplant patients [14] and the other patients.[15, 16] The underlying cause of the seemingly higher incidence of simvastatin-diltiazem drug interaction in transplant patients may be that the patients are at higher risk of developing hyperlipidemia, which contributes to CHD and cardiovascular events. In addition, the occurrence of statin-related rhabdomyolysis is usually associated with increased plasma concentration of statins.[17] Furthermore, Masica and coauthors' work [18] suggested that the interaction of lovastatin with diltiazem does not occur systemically and is primarily a first-pass effect. Also, That is, such kind of drug interaction usually happens in oral dosing but not in intravenous dosing. For the similar pharmacokinetic characteristics of

lovastatin and simvastatin, the above phenomenon can be anticipated in simvastatin. However, diltiazem as a weak or moderate CYP3A4 inhibitor can be used cautiously with small doses of CYP3A4-dependent statins [19], but patients who take both simvastatin and diltiazem may need lower doses of simvastatin to achieve the recommended reduction in cholesterol [20].

In the present case, it is not difficult for us to speculate that the patient had suffered from unrecognized hypothyroidism for a long time and simvastatin was prescribed to correct hypercholesteremia and improve CHD. However, the physician did not realize that hypercholesteremia in this patient might be secondary to hypothyroidism. It is much more perishing that diltiazem was thereafter prescribed to improve angina pectoris. In fact, the patient had taken simvastatin for more than one year but rhabdomyolysis did not occur until the addition of diltiazem.

Three predisposing factors co-existing in one patient is uncommon, and whenever we prescribe statins, we should rule out the secondary causes of hypercholesteremia. The knowledge of the pharmacokinetic and pharmacodynamic properties of statins and the mechanisms of drug interaction with other drugs helps to avoid these adverse effects. Patients taking atorvastatin, lovastatin, simvastatin, the substrates of CYP3A4, should avoid concurrent use of CYP3A4 inhibitors (e.g. diltiazem), especially when predisposing factors of rhabdomyolysis (e.g. hypothyroidism) co-exist. If one cannot avoid, fluvastatin, pravastatin and rosuvastatin which do not interact with inhibitors of CYP3A4 should be considered. All patients taking statins should be taught to be alert to elevated hepatic transaminases, and any unexplained myalgia or weakness. Therapy should be discontinued once serum CK is dramatically elevated or myopathy is highly suspected or diagnosed.

Conflict Of Interest

No conflict of interest was declared.

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