Ticagrelor-induced acute kidney injury can increase serum concentration of statin and lead to concurrence of rhabdomyolysis

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Introduction

The 2016 American Heart Association/American College of Cardiology guidelines advise the use of dual antiplatelet agents for patients with acute coronary syndrome (ACS) (1). Ticagrelor is a reversible oral antagonist of the ADP receptor P2Y12. It is rapidly absorbed and metabolized by cytochrome P450 (CYP) 3A4. Therefore, ticagrelor suggests a potential for drug interactions with other CYP3A4 substrates (2).

Statins are recommended for preventing cardiovascular disease after ACS (3). These statins are associated with myalgia; elevation of creatine phosphokinase (CK) concentrations; and rarely, rhabdomyolysis. Rhabdomyolysis caused by statins is susceptible to occur when the renal function is impaired (4). Here we describe a patient in whom ticagrelor-induced acute kidney injury (AKI) increased the serum concentration of statin and then, eventually, led to concurrence of rhabdomyolysis.

Case Report

An 80-year-old woman was suffering from nausea and vomiting for 2 months. She had no history of trauma, infection, severe exercise, seizures, uncontrolled blood glucose, and use of herbal medication. She had type 2 diabetes mellitus and hypertension. She had taken some medicines, including aspirin, 100 mg; amlopidine, 5 mg; and valsartan, 80 mg once daily and vildagliptin, 50 mg and metformin, 850 mg twice daily.

Two months prior, she underwent percutaneous coronary intervention for unstable angina. She received a secondary prevention regimen including ticagrelor 180 mg and rosuvastatin 20 mg once daily. At that time, her serum creatinine (Cr) concentration was 0.91 (reference, 0.9-1.2 mg/dL).

Initial laboratory workup showed a serum Cr concentration of 3.99 mg/dL and CK concentration of 25165 U/L. No other cause of AKI was found. She was diagnosed as having an AKI Stage 3 because of rhabdomyolysis. All medicines, except aspirin and ticagrelor, were discontinued, and intravenous fluid infusion was started; normal saline was administered at a rate of 120 cc/h.

Her clinical presentation remained unchanged over the next 6 days. Serum Cr concentration further increased to 6.48 mg/dL and CK concentration increased to 5,227 U/L. Hemodialysis was initiated. After four sessions of hemodialysis, her CK concentration improved to 432 U/L. However, ecchymosis was found at the insertion site of the temporary dual-lumen hemodialysis catheter. The prothrombin time was 18.2 s, activated partial thromboplastin time was 62.4 s, fibrinogen concentration was 178 mg/dL, and D-dimer concentration was >20 µg/mL, which indicated disseminated intravascular coagulation (DIC).

The patient was transferred to the intensive care unit for mechanical ventilation and continuous renal replacement therapy (CRRT). She was given 5 packs of packed RBC, 1 pack of fresh frozen plasma, and 10 packs of cryoprecipitate. Owing to the possibility of ticagrelor playing a role in AKI and DIC, ticagrelor was changed to clopidogrel 75 mg once daily. Five days after discontinuation of ticagrelor, the patient’s clinical presentation remained unchanged, and CRRT was discontinued. Her Cr concentration was maintained at 1.1-1.3 mg/dL, and rhabdomyolysis did not recur.

Discussion

The incidence of statin-induced rhabdomyolysis varies from one drug to another, according to that reported by FDA, where simvastatin accounts for 18.3%, atorvastatin accounts for 11.5% and pravastatin accounts for 7.3% cases (4). Rosuvastatin showed a tendency of inducing rhabdomyolysis to a greater extent than simvastatin (5). Even with a low dose of statin, rhabdomyolysis can be induced by drug–drug interactions (6).

Ticagrelor is mainly metabolized by CYP3A4, which increases the effect of statin metabolized by the same CYP3A4 (2). Ticagrelor co-treatment can provoke development of rhabdomyolysis induced by statins. However, this patient had rhabdomyolysis because of the combination of ticagrelor and rosuvastatin, which is independent of the CYP3A4 metabolism (7).

Rhabdomyolysis due to rosuvastatin may be an independent event of ticagrelor-induced AKI. However, the interaction between ticagrelor and rosuvastatin cannot be ignored. The first is the case of itraconazole, which increases serum concentration of rosuvastatin independent of the CYP3A4 metabolism (8) and the second is the past case of rhabdomyolysis caused by a combination of ticagrelor and rosuvastatin (9). Further research is needed on the exact reason for this interaction.

Conclusion

Ticagrelor can induce renal dysfunction and therefore, requires meticulous precautions on drug–drug interaction when used with statins. Unlike simvastatin or atorvastatin, rosuvastatin tends to be overlooked in the concern about reaction when in combination with ticagrelor. Therefore, when using ticagrelor with rosuvastatin, the risk of hyperactivity of rosuvastatin due to ticagrelor-rosuvastatin interaction should be recognized.
References


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Worth listening to the kidney: An uncommon cause of congestive heart failure

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Introduction

Renal arteriovenous fistulas (AVFs) are rare communications between the arterial and venous systems. Increased blood flow can cause high preload and congestive heart failure. We aimed to highlight the great importance of physical examination by which a proper diagnosis of AVF and successful treatment can be achieved, thus leading to full recovery.

Case Report

A 64-year-old female patient was admitted to our clinic with dyspnea. She had a 4-year history of dyspnea and visited medical centers with no satisfaction. Her past history included right nephrectomy due to renal calculi 33 years ago.

On admission, she presented with tachypnea, normal blood pressure, and no fever. Her low oxygen saturation increased to 95% with oxygen supply. She had sinus rhythm with 90 bpm and no pathologic signs. Jugular distention was noticed. Fine rales were heard in the basal area of the lungs. Ascites and hepatomegaly with a lower board 2 cm below the costa were noted. Lower extremities showed edema. Interestingly, a murmur was