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Ticagrelor Leads to Statin-Induced Rhabdomyolysis: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 72
Final Diagnosis: Rhabdomyolysis
Symptoms: Muscle pain
Medication: Ticagrelor
Clinical Procedure: —
Specialty: Cardiology

Objective: Unusual clinical course

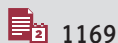
Background: Following acute coronary intervention in cardiology patients, the combined medical therapy with the platelet inhibitory drug ticagrelor and a statin medication (e.g., simvastatin) is recommended according to international guidelines. Yet combined therapeutic regimens have the potential of pharmacological interaction with both ticagrelor and simvastatin being metabolized by CYP3A4. Rhabdomyolysis is a known side-effect of statin therapy and combined therapy increases the susceptibility to this complication.

Case Report: A 72-year-old patient presented to our Emergency Department with typical signs of rhabdomyolysis consisting of muscular cramps and pain in both legs and a significant elevation of creatinine kinase (CK). Five months prior to this presentation, he had been hospitalized due to acute coronary syndrome followed by a coronary intervention of a high-grade left anterior descending artery stenosis. His long-term medication included simvastatin 20 mg daily, which he had taken for several years, and ticagrelor, which had been added to his medication following coronary intervention. The patient showed fast recovery of symptoms and rapid normalization of CK levels upon treatment change from ticagrelor to clopidogrel with a paused statin administration.

Conclusions: The combined use of ticagrelor with low dose simvastatin poses a risk for rhabdomyolysis even in patients with normal kidney function. Patients treated with ticagrelor might require changes in statin therapy and dose adjustments in order to avoid pharmacological interactions and higher risk for adverse effects.

MeSH Keywords: Acute Coronary Syndrome • Angiostatins • Rhabdomyolysis

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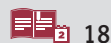
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Background

After acute coronary syndrome (ACS), dual antiplatelet therapy with aspirin and ticagrelor (or prasugrel) is recommended according to the guidelines of the American Heart Association [1,2] and the European Society of Cardiology [3,4]. A significantly reduced rate of death from vascular causes, myocardial infarction, or stroke was shown in patients who had ACS, with or without ST-segment elevation, who had treatment with ticagrelor compared to clopidogrel [5].

Furthermore, an intensive lipid lowering therapy with statin is recommended in patients with ACS [6,7]. To evaluate the need for drug treatment of hypercholesterolemia, elevation of total cholesterol and low-density lipoprotein-cholesterol (LDL-C) are relevant. Intervention strategies are dependent of the total cardiovascular risk and LDL-C level [8].

A relevant side effect of statin-therapy is myopathies. From 1997 to 2000 more than 600 reported cases of rhabdomyolysis were documented from the Adverse Event Reporting System Database of the Food and Drug Administration [9,10].

Ticagrelor is metabolized through the enzymes cytochrome P450 (CYP) 3A4/3A5 and is also a weak inhibitor of CYP3A [11]. Thus, ticagrelor may increase the potency of statins, which require CYP3A4 for their metabolism. Therefore, a concomitant use of ticagrelor with doses of simvastatin or lovastatin greater than 40 mg is not recommended [12,13]. Another frequently used combination with statin therapy is the application of cyclosporine A in renal transplant recipients and post-transplant hyperlipidemia. It has been suggested that a similar problem with an increased rate of rhabdomyolysis occurs due to metabolism by CYP3A4. Therefore, a change from simvastatin to fluvastatin, which is metabolized by P450 CYP2C9, is suggested [14].

Case Report

A 72-year-old patient presented to our emergency department (ED) with muscle pain in both legs and cramps in his calves. Five months prior to this presentation, he had been hospitalized due to ACS followed by a coronary intervention of a high-grade left anterior descending artery stenosis with percutaneous transluminal coronary angioplasty and drug-eluting stent implantation. His further diagnoses included a coronary three-vessel disease with previous interventions of the right coronary artery, intermediate and first diagonal branch, a few years ago. Echocardiography showed an ejection fraction of 50% with a diastolic dysfunction grade II. Brain natriuretic peptide (BNP) levels were normal (8.5 pg/mL). Furthermore, a mitral valve regurgitation grade I was noted. Additional risk

factors were arterial hypertension and chronic obstructive pulmonary disease GOLD grade II. His medication upon his current presentation consisted of acetylsalicylic acid 100 mg 1-0-0, ticagrelor 90 mg 1-0-1, ramipril 2.5 mg 1-0-1, pantoprazole 20 mg 1-0-0, simvastatin 20 mg 0-0-1, tiotropium bromide inhalation 1-0-1, and beclomethasone plus formoterol 100/6 µg inhalation 1-0-1.

His blood results showed an elevated creatinine kinase (CK) of initially 4,117 U/L (normal 38–174 U/L). Measurement of CK was performed according to the International Federation of Clinical Chemistry modified by Szasz [15]. Myoglobin was also elevated with 426 µg/L (normal <110 µg/L). The muscle-brain type CK was within normal range (42 U/L) with a percentage of 1%.

Due to his clinical presentation, in combination with the observed increased CK blood levels, we diagnosed rhabdomyolysis. His long-term medication included simvastatin in a low dose (20 mg/day), with ticagrelor added to the daily medication five month prior to presentation at our ED. The treatment consisted of an intravenous substitution of liquids. We paused the administration of simvastatin on day one and changed the antiplatelet therapy with ticagrelor to clopidogrel. The patient showed fast recovery of symptoms and normalization of CK levels. Table 1 shows the results of the blood tests. Kidney function was normal at all times represented by CK and urea values. The change of CK levels at different time points are graphically depicted in Figure 1. We released the patient from the hospital on day 3. The patient presented to our outpatient clinic seven days later (day 10) for follow-up, and was free of symptoms with normal blood test results.

Discussion

Here we report the first published case of rhabdomyolysis in a patient with normal kidney function and low-dose simvastatin therapy, most likely due to co-medication with ticagrelor.

Two case reports of rhabdomyolysis due to interactions of ticagrelor with statins were found in our literature search. In the first case report, the patient, in addition to elevated CK and myoglobin values, had acute renal failure and was treated with high-dose atorvastatin (80 mg daily) [9]. In the other case report, statin therapy consisted of 40 mg rosuvastatin, a drug that is not metabolized by CYP3A4. One week after taking ticagrelor, the patient showed an acute renal failure with elevated serum CK resulting in accumulation of rosuvastatin and presumably resulted in rhabdomyolysis [16]. In addition, it has been reported that unrecognized hypothyroidism can be a risk factor for rhabdomyolysis in combination with low dose statin and should be screened before starting statin therapy [17].

Table 1. Blood test results.

	Standard value	Day 1 (11 a.m.)	Day 1 (8 p.m.)	Day 2	Day 3	Day 10
Creatinine (mg/dl)	0.9–1.3	1.09	1.1	1.14	1.1	1.11
Urea (mg/dl)	6–19.8	–	17	12	10	14
Creatinine kinase (U/l)	38–174	4117	4451	2439	1867	135
Muscle-brain type CK (U/l)	<25	42	52	31	31	0
Myoglobin (µg/l)	<110	426	442	277	476	–
Lactate dehydrogenase (U/l)	100–247	336	–	–	260	–

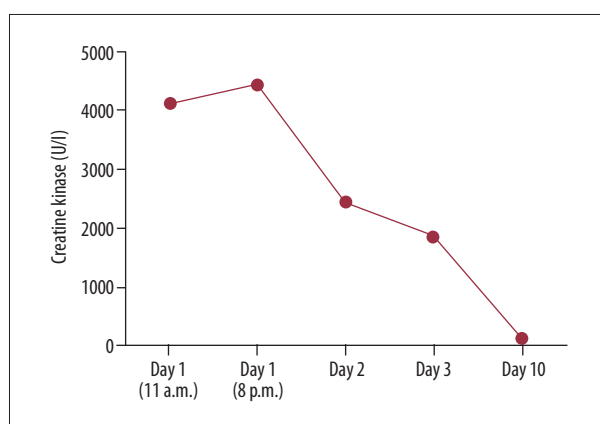


Figure 1. Changes of creatinine kinase (CK) levels in U/L at different time points. Treatment: day 1: paused administration of simvastatin, substitution of liquids; day 2: conduction and change of antiplatelet therapy from ticagrelor to clopidogrel; day 10: follow up, patient presented without remaining symptoms.

In our patient, TSH (thyroid stimulating hormone) was within normal range (0.86 mU/L [0.3–3.0 mU/L]) indicating an euthyroid metabolic state.

Pharmacological interaction due to metabolism of simvastatin and ticagrelor through CYP3A4 has been proven [11]. In a recent randomized controlled study co-administration of ticagrelor or placebo with simvastatin showed an increase of maximum plasma concentration by 81% and increase of area under the plasma concentration-time curve from zero to infinity by 56%. Results for atorvastatin showed a lower effect [18].

Product information for ticagrelor recommends co-administration with simvastatin at a maximal dose of 40 mg [12,13]. Our case report, together with the aforementioned report of increase of simvastatin-plasma-concentrations when combined with ticagrelor, demands a re-evaluation of this recommendation. Our patient only received 20 mg simvastatin per

day and showed no muscular symptoms in the years before starting the medication with ticagrelor.

In every patient who receives the addition of ticagrelor as a medication, its combination with a CYP3A4-metabolized statin should be avoided. As aforementioned, simvastatin showed a higher increase of plasma levels compared to atorvastatin. This indicates that at least a dose adjustment of simvastatin should be performed; however, the therapy could thus become less effective. A change to other statins, for example rosuvastatin or fluvastatin, which are not metabolized by CYP3A4, should therefore be considered. Further randomized controlled trials are needed to assess safety and interactions in more detail.

Moreover, it is suspected that the benefit of treatment with ticagrelor compared to clopidogrel might also be due to increased statin serum concentrations that have a positive and protective effect in patients with coronary artery disease [12].

Conclusions

The combination of ticagrelor with simvastatin poses a risk for rhabdomyolysis even with low-dose simvastatin, as shown in this case report. This, individual re-evaluation of statin therapy and doses should be performed when co-prescribed with ticagrelor in order to avoid adverse effects. While our findings are the first to describe rhabdomyolysis due to an interaction of simvastatin with ticagrelor in a patient with normal kidney function, future research is needed to determine dosage and risk profiles in this patient population. Until then, the findings of this study should be taken into account when it comes to guideline-based therapy in patients with acute coronary syndrome.

Conflicts of interest

None.

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