

An Out of the Ordinary Case Report of Ticagrelor Furthering Rhabdomyolysis Induced by Atorvastatin

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Abstract: *Rhabdomyolysis is an evidential aftermath of statin therapy and contemporaneous use of medications like ticagrelor that inhibit cytochrome P450-3A4 enzyme increases its risk by causing muscle necrosis and release of myoglobin into circulation. We hereby report a case of a 63 year old male patient who was commenced on ticagrelor, post transluminal coronary angioplasty on a background of atorvastatin therapy resulting in rhabdomyolysis with acute kidney injury and hyperkalemia. This case highlights the need for awareness of drug interactions with atorvastatin and lastly, importance of early diagnosis and management of rhabdomyolysis so as to prevent the development of further complications.*

Keywords: Rhabdomyolysis, atorvastatin, ticagrelor

1. Introduction

Cholesterol is one of the final product of mevalonate pathway in which, HMG-CoA (B-hydroxy B-methylglutaryl-CoA) reductase located in the endoplasmic reticulum converts HMG-CoA to mevalonate and this constitutes to the rate limiting step.¹ This enzyme is inhibited by group of drugs called statins which are redistributed in the liver and are structural analogue of HMG-CoA, thereby putting a stop to synthesis of mevalonate.²

Dual antiplatelet therapy with Aspirin and Ticagrelor is recommended after acute coronary syndrome (ACS) as per the guidelines of European Society of Cardiology and American Heart Association and furthermore, statins are advocated in patients with ACS as an intensive lipid lowering therapy and thereby reducing the cardiovascular risk.³ Ticagrelor metabolised by cytochrome P450-3A4 enzyme, increases the potency of statins which are also metabolised by the same group of enzymes and hence associated with increased risk of rhabdomyolysis.^{4,5}

We report an exquisite case of Ticagrelor precipitating rhabdomyolysis induced by statin and complicated by acute kidney injury (AKI) and hyperkalemia.

2. Case Report

A 63 year old male presented to our emergency department with complaints of backache, pain in both the lower limbs, nausea and decreased appetite since one week. There was no history of fever, breathlessness, oliguria and seizures.

He was a known hypertensive since 20 years, but on regular treatment with tablet amlodipine 5mg and atorvastatin 40mg once daily in view of dyslipidemia. He was also a known case of ischemic heart disease (IHD), was hospitalised 3 months back in view of anterior wall myocardial infarction and had undergone percutaneous transluminal coronary angioplasty with a single drug eluting stent in left anterior descending artery. He was also a known case of acute kidney injury (AKI) on chronic kidney disease (CKD), non-oliguric and never required dialysis for the same. His current medications on presentation included tablet pantoprazole 40mg, aspirin 75mg, amlodipine 5mg, atorvastatin 40mg, once daily and ticagrelor 90 mg twice daily.

On arrival to intensive care unit (ICU) & on examination, he was conscious, obeying commands, hemodynamically stable and was maintaining a mean arterial pressure of 70 mmHg without any vasopressor support. He was afebrile, maintaining a room air saturation of 98% with a respiratory rate of 15 cycles/minute. Power in both upper and lower limbs was 5/5 as per medical research council (MRC) grading with no sensory and motor deficits. ABG done was suggestive compensated metabolic acidosis with hyperkalemia (potassium of 7.7 meq/L). Chest X-ray appeared to be normal and ECG was suggestive of old anterior wall MI changes. Ultrasound screening of thorax showed minimal left pleural effusion and screening 2D-ECHO was suggestive of concentric LVH, no RA/RV dilation, no pericardial effusion, EF of 45%. USG abdomen revealed bilateral renal parenchymal disease and small kidneys. Urine on appearance was dark coloured (figure 1).

His blood test revealed normal hemogram, sodium of 124meq/L (normal value= 135-145 meq/L), potassium of 7.5

meq/L (normal value= 3.5-5.5 meq/L), urea of 173 mg/dl (normal range= 10-45 mg/dl), creatinine of 9.3 mg/dl (normal range= 0.6-1.2 mg/dl), CPK-NAC (N-acetyl cysteine activated creatinine phosphokinase) was 47,210 (normal range= 25-125 U/L), CPK-MB was in normal limits, AST (aspartate transaminase) was 1060 IU/L (normal value=5-35 IU/L), ALT (alanine transaminase) was 970 IU/L (normal value=5-40 IU/L), urine routine and microscopy was positive for red blood cells(RBC), protein and myoglobin. Serum myoglobin was hence sent, which turned out to be >30,000 ng/ml (normal value= 28-72 ng/ml). CRP was 8.4 mg/L (normal value= 2.8-5 mg/L).

Nephrology consultation was hence taken, and he was advised hemodialysis and hence a triple lumen hemodialysis catheter was inserted in the right internal jugular vein under USG guidance. Post dialysis his labs were repeated. Table 1 shows the results of the blood test.

As mentioned earlier, the patient was on oral anti-hypertensives and statins for a long time. It has been only since last 3 months, when ticagrelor got added to his previous medications. Due to his clinical presentation of severe myalgia with markedly elevated CPK-NAC levels and serum myoglobin with the presence of urine myoglobin, made us provisionally diagnose this as a case of ticagrelor leading to statin induced rhabdomyolysis. Differential diagnosis of inflammatory myositis was also considered and ruled out eventually by history and laboratory findings. Atorvastatin was withheld after the confirmation of diagnosis and ticagrelor was changed to clopidogrel. The patient responded dramatically in the form of improvement of symptoms and reduction in serial CPK-NAC levels. The patient was dialysed totally 4 times during the course of stay in the hospital before he got discharged in a stable condition.



Figure 1: Showing dark coloured urine suggestive of myoglobinuria

Table 1: Results of blood tests

Investigations	Day 1 (on admission)	Day 2	Day 5
Serum Sodium (meq/L)	124	130	140
Serum potassium (meq/L)	7.5	5.1	4.5
Blood urea (mg/dl)	173	119	76
Serum creatinine (mg/dl)	9.3	6.93	4.06
CPK- NAC (mcg/L)	47,210	-	11,538
Serum myoglobin (ng/ml)	>30,000	-	-

(CPK-NAC: N-acetyl cysteine activated creatinine phosphokinase)

3. Discussion

The risk of rhabdomyolysis which is characterised by skeletal muscle breakdown leading to release of sarcoplasmic proteins namely, AST & ALT, creatinine kinase (CK) and electrolytes and thereby causing life endangering complications like AKI, hyperkalemia and cardiac arrhythmias is higher when statins are given concurrently with other drugs causing inhibition of cytochrome P450-3A4 enzyme.⁶

In our literature search, we found 2 such similar cases of rhabdomyolysis due to interaction of statin with ticagrelor. In the first case report, patient was on higher dose of atorvastatin, 80 mg once daily, and had acute renal failure and higher CK and myoglobin levels.⁷ In the other case, the patient was on rosuvastatin, 40 mg once daily. After consuming ticagrelor for a week, patient had landed up with acute renal failure and elevated CK levels though this drug doesn't require cytochrome P450-3A4 enzyme for its metabolism.⁸

The gamut of statin induced myopathy varies from myalgia, myositis and rhabdomyolysis to high up CK levels which might remain asymptomatic, with mean duration of statin therapy prior to onset of symptoms ranges from 1-60 days.⁹

Lipophilic statins (for example; atorvastatin, lovastatin and simvastatin) have aloft potential for myotoxic out-turn than the hydrophilic statins (for example; rosuvastatin, pravastatin and fluvastatin) in patients with already existing muscle disease.¹⁰

Hospitalisation and intravenous hydration in order to prevent renal damage remains the main stay of treatment for patients with clinically notable rhabdomyolysis and once muscle symptoms have resolved, the use of lower dose of same statin or replacing other statin in place of the prior one or using other class of lipid lowering drugs such as bile acid binding resins and ezetimibe is used for managing dyslipidemia.¹¹

The superiority of ticagrelor over clopidogrel is that, it elevates the serum concentration of statin and hence, provides shielding effect in patients with coronary artery disease.³ In this epoch of polypharmacy, it is very important to understand the importance of drug interaction which are frequently over passed and can result in morbidities.

4. Conclusion

Rhabdomyolysis is an exotic but an intimidating complication that can transpire as a result of statin use alone or when used in conjunction with other drugs, that increase the potency of statin and hence we need to be watchful about the same and adjust the dosage of drugs to avoid the pharmacological interactions.

Highlights

An intensivist should be aware of the fact that newer anti-platelet drugs like ticagrelor can trigger statin induced rhabdomyolysis.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that his name and initials will not be published and due efforts will be made to conceal his identity.

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Conflicts of interest

There are no conflicts of interest.

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