SciMedCentral

JSM Internal Medicine

Case Report

A Case of Acute Renal Failure and Rhabdomyolysis associated with the Concomitant Use of Ticagrelor, Rosuvastatin, and Losartan

Jenny New[1], Kathie Le[2], Kimberly A. Wong[3], Shelley J. Choi[3], Charles L. Danh[3], Joseph D. Hall[4], and Elena Kret-Sudjian[3]

[1]*Department of Pharmacy, University of California San Francisco, USA*
[2]*Department of Pharmacy, University of California Davis, USA*
[3]*Department of Internal Medicine, University of California Davis, USA*
[4]*Department of Psychiatry, University of California Davis, USA*

***Corresponding author**
Kimberly Wong, Department of Internal Medicine, University of California Davis, 4150 V Street Suite 1100 Sacramento, CA 95817, CA, USA, Tel:1-916-734-7058; Fax: 1-916-734-7074; E-mail: kiawong@ucdavis.edu

Submitted: 30 October 2016

Accepted: 27 January 2017

Published: 31 January 2017

Keywords

- Ticagrelor
- Rhabdomyolysis
- Rosuvastatin
- ARB
- Acute kidney failure

Abstract

Adverse effects from prescription drugs remain a major cause of morbidity and death in the US. Ticagrelor is a P2Y12 receptor antagonist approved for the reduction of stent thrombosis in patients with acute coronary syndrome (ACS). Current American Heart Association/American College of Cardiology (AHA/ACC) treatment guidelines for ACS recommend antiplatelet therapy, high-intensity statins, and angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) especially for patients with hypertension or chronic kidney disease (CKD). In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was associated with fewer deaths from vascular causes, myocardial infarction, and stroke in patients with CKD. However, it also was associated with significant increases in serum creatinine compared to the clopidogrel group.There are no anticipated pharmacokinetic interactions between ticagrelor, statins, and ACEI/ARBs, and there have been few reported cases of rhabdomyolysis associated with the use of statins in combination with ticagrelor. Herein, we report a case of acute renal failure and rhabdomyolysis associated with the concomitant use of ticagrelor, rosuvastatin, and losartan. Clinicians should be aware of this potential interaction in patients with both ACS and CKD.

ABBREVIATIONS

ACS: **A**cute Coronary Syndrome; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; CKD**:** **C**hronic Kidney Disease; GFR**:** **G**lomerular Filtration Rate; PLATO: Platelet Inhibition and Patient Outcomes trial; FDA**:** Federal Drug Administration

INTRODUCTION

Side effects of prescription drugs remain a major cause of morbidity and death in the United States. Systematic reviews of hospital charts found that even properly prescribed drugs cause about 1.9 million hospitalizations a year [1-3]. However, it is also well-known that certain medications have clear mortality benefits in patients with cardiovascular disease. Current AHA/ACC guidelines for treatment of ACS recommend antiplatelet therapy, a high-intensity statin, and an ACEI/ARB, especially for patients with hypertension, diabetes mellitus, CKD, or heart failure [1]. Ticagrelor is an oral P2Y12 receptor antagonist approved in 2011 to help reduce the rate of cardiovascular thrombotic events and stent thrombosis in patients with ACS (Figure 1). Unlike the thienopyridine antiplatelet agents, ticagrelor is a direct drug that binds the ADP receptor reversibly and has the off-target effect of inhibition of adenosine reuptake. Note that high-intensity statins such as rosuvastatin and atorvastatin are recommended in patients with ACS regardless of low-density lipoprotein (LDL) levels to reduce the rate of recurrent myocardial infarction, cardiac mortality, and stroke. Furthermore, ACEI/ARBs are recommended for patients with ACS to reduce mortality and offer additional renal benefit in patients with CKD.

Most prescription drug interactions result from a change in absorption, metabolism, or elimination of medications. The

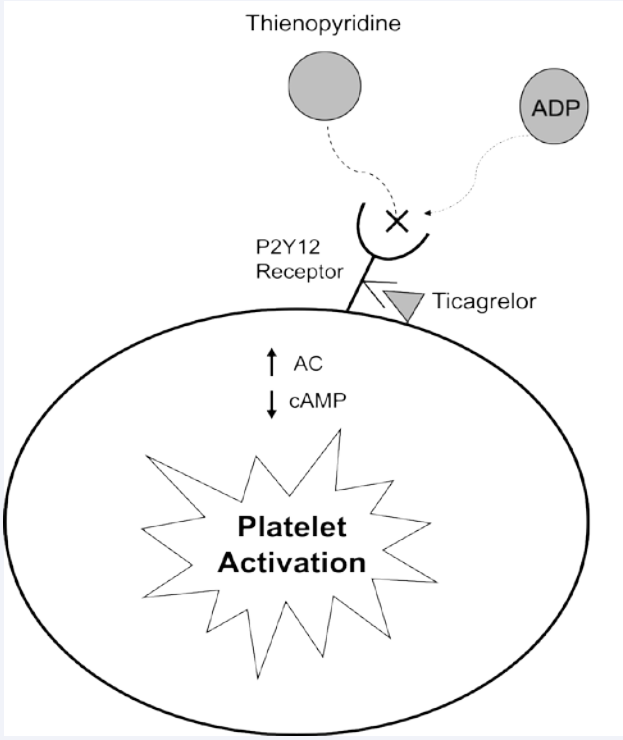

Figure 1 The theinopyridines, clopidogrel and prasugrel, are prodrugs that are metabolized to their active compounds and antagonize the P2Y12 receptor through irreversible binding at the ADP binding active site. Ticagrelor inhibits platelet activation through reversible binding at a non-competitive site [11].

combination of ticagrelor, statins, and ACEI/ARBs is widely prescribed for ACS patients, and there are no anticipated pharmacokinetic interactions between these drugs. To date there have been very few reported cases of rhabdomyolysis associated with the use of statins in combination with ticagrelor. van Vuren et al. first reported on a case involving ticagrelor-induced renal failure leading to rosuvastatin-related rhabdomyolysis [4]. Kido et al., also described a case of rhabdomyolysis precipitated by suspected CYP450 interaction between ticagrelor and high-dose atorvastatin [5]. Herein, we report a case of acute renal failure and rhabdomyolysis associated with the concomitant use of ticagrelor, rosuvastatin, and losartan.

CASE PRESENTATION

A 66-year-old Caucasian woman was admitted with progressive bilateral leg weakness and fatigue. Ten days before admission, she developed proximal muscle weakness. Previously ambulatory, the patient became wheelchair bound. Review of systems was positive for nausea without vomiting, decreased urine output, and myalgias. Six weeks prior, she had been hospitalized for chest pain and unstable angina. Coronary angiography revealed that an old coronary artery bypass site graft had an 80% in-stent restenosis, and two drug eluting stents were placed. Her coronary disease was concerning for failure of dual antiplatelet therapy with aspirin and clopidogrel, and clopidogrel was subsequently replaced by ticagrelor. Other medications on discharge included rosuvastatin, losartan, and metoprolol succinate. Serum creatinine on discharge was 1.1 mg/dL.

The patient's medical history included severe coronary artery disease with prior five-vessel coronary artery bypass surgery 15 months prior and a percutaneous coronary intervention 13 months prior, stage 3 CKD secondary to type 2 diabetes mellitus with small vessel disease and a baseline creatinine of 1.3-1.4 mg/dL, as well as peripheral artery disease. There was a family history of coronary artery disease but no history of CKD. She did not smoke, drink alcohol, or use intravenous drugs.

On admission her serum creatinine was 10.4 mg/dL. Other labs include a creatine kinase of 28167 U/L, potassium of 5 mmol/L, phosphorus of 13.2 mmol/L, bicarbonate of 17 mmol/L, and pH of 7.29. Urine microscopy revealed sheets of leukocytes, granular casts, and granular debris. Physical exam was significant for limited ability to maintain hip flexion against resistance, which lasted only seconds. Medication reconciliation showed that the patient was incorrectly taking aspirin together with both clopidogrel and ticagrelor. Her rosuvastatin was discontinued along with losartan. The decision was then made to change ticagrelor to prasugrel. Over the following week of hospitalization, she received intense intravenous fluid resuscitation and phosphorus binders. Her creatinine fell from 10.4 mg/dL to 4.09 mg/dL, and her BUN from 141 mg/dL to 33 mg/dL. Despite these measures, she developed worsening nausea, dysgeusia, orthopnea, lethargy, and a downtrending urine output from 1300 mL/day on presentation to 900 mL/day. On day 7 of her hospital stay, hemodialysis was initiated and continued daily thereafter. By day 9, she symptomatically felt much improved. She was discharged on hospital day 22 to a skilled nursing facility on hemodialysis three times a week.

DISCUSSION

Myopathy and rhabdomyolysis are well known adverse effects of HMG-CoA reductase inhibitors, especially in patients who are 65 years of age or older, female, have uncontrolled hypothyroidism, or renal dysfunction. However, the incidence is rare [6]. Rosuvastatin is a commonly prescribed high-intensity statin that is renally dose-adjusted for CrCl < 30 mL/min to a maximum dose of 10 mg daily [7].The use of ticagrelor with rosuvastatin is not expected to produce a significant pharmacokinetic drug interaction as the CYP450 metabolism of rosuvastatin is minimal.

In PLATO, ticagrelor was associated with significantly fewer deaths from vascular causes, myocardial infarction, and stroke compared to clopidogrel (17.3% vs. 22%) in patients with CKD (defined as creatinine clearance <60 ml/min). Ticagrelor also produced a greater absolute risk reduction in this population compared to patients with normal renal function (7.9% vs. 8.9%) [8]. These results were also reflected in the PEGASUS-TIMI 54 trial. The data suggests that patients with CKD may have better outcomes on ticagrelor over clopidogrel. However, it must be noted that in PLATO sub-analysis, ticagrelor was associated with significant increases in serum creatinine at 12 months of therapy compared with the clopidogrel group: 7.4% of the ticagrelor group experienced increases in serum creatinine of more than 50% from baseline compared to 5.9% of those receiving clopidogrel [6].

The mechanism by which ticagrelor increases serum

creatinine is unknown. It is hypothesized that inhibition of adenosine reuptake by ticagrelor reduces glomerular filtration rate (GFR) through vasoconstriction of the afferent renal arteriole. This theory is further supported by data derived from PLATO wherein patients concomitantly taking ticagrelor and ARBs (but curiously not ACEI) had greater rates of creatinine increases of more than 50%, renal-related adverse events, and renal function adverse events compared to patients taking both clopidogrel and an ARB (Table 1) [4]. Patients with reduced baseline renal function may rely on hemodynamic compensatory mechanisms within the kidney to maintain GFR. The modulation of this intrinsic balancing act by ticagrelor could contribute to a decline in renal function [8,9]. It is then conceivable that in our patient with CKD on rosuvastatin 40 mg daily, a deterioration of renal function attributed to the combination of ticagrelor and losartan could have led to significant accumulation of rosuvastatin and rhabdomyolysis. As the newest addition to her medication regimen, ticagrelor likely precipitated this cascade of adverse events, which could have potentially been avoided had her renal function been monitored after its initiation.

A search using common drug reference databases including Micromedex and Lexicomp shows no documented interactions between ticagrelor, rosuvastatin and losartan. The Federal Drug Administration (FDA) package insert for ticagrelor states that serum creatinine increases were observed in PLATO but that overall treatment groups in PLATO did not differ for renal-related serious adverse events. However, it does not address the combination of ticagrelor and ARBs in producing higher rates of renal adverse events [7]. In contrast, the European Medicines Agency Summary of Product Characteristics for ticagrelor notes that renal function should be monitored one month after initiation of ticagrelor especially in patients ≥ 75 years old, with moderate or severe renal impairment, and those being treated with ARBs [10]. In our complex patient with multiple comorbidities and a convoluted medication regimen, ticagrelor along with an ARB presented an important potential interaction that precipitated acute worsening of kidney disease and the unfortunate development of rhabdomyolysis due to the accumulation of rosuvastatin.

Table 1: Renal adverse events in patients taking ARBs in addition to ticagrelor vs clopidogrel from PLATO (2009). Adapted from Table (1) of DiNicolantonio et al: Angiotensin Receptor Blockers Worsen Renal Function and Dyspnea on Ticagrelor [9].

Adverse Event	Ticagrelor with ARB (N= 511)	Clopidogrel with ARB (N =508)
Creatinine Increase > 50%	57 (11.2%)	36 (7.1%)
Renal-related AE	73 (8.4%)	48 (4.3%)
Renal-function AE	51 (4.5%)	31 (2.8%)
Abbreviations: AE: adverse events		

Ticagrelor is becoming a widely used medication in the population of patients affected by acute coronary syndrome. Ticagrelor on its own, and more importantlyin patients concomitantly taking ARBs, can cause a worsening of renal function. Clinicians should pay close attention to the possible development of renal impairment and rhabdomyolysis when prescribing a drug regimen that includes the combination of ticagrelor, ARBs, and a statin –especially in elderly patients and those with pre-existing kidney disease. Consideration should be made for close monitoring of renal function after initiation of ticagrelor in these high risk scenarios.

REFERENCES

1. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with Non–ST-Elevation acute coronary Syndromes. J Am Coll Cardiol. 2014; 64: e139–e228.
2. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, et al. Ticagrelor versus Clopidogrel in acute coronary syndromes in relation to renal function: Results from the Platelet inhibition and patient outcomes (PLATO) trial. Circulation. 2010; 122:1056–1067.
3. Light, Donald W. and Lexchin, Joel and Darrow, Jonathan J. Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs (June 1, 2013). JLME. 2013; 3: 590-610.
4. van Vuren AJ, de Jong B, Bootsma HPR, Van der Veen MJ, Feith GW. Ticagrelor-induced renal failure leading to statin-induced rhabdomyolysis. Neth J Med. 2015; 73:136–138.
5. Kido K, Wheeler MB, Seratnahaei A, Bailey A, Bain JA. Rhabdomyolysis precipitated by possible interaction of ticagrelor with high-dose atorvastatin. J Am Pharma Assoc. 2015; 55: 320–323.
6. Shannon J, John S, Ferrara J, Best S, Allen SN. Statin-Associated Myopathy. US Pharma. 2012; 37: 55–59.
7. Brillinta [package insert]. Wilmington, DE: AstraZeneca: 2011, 2013, 2015.
8. DiNicolantonio JJ, Serebruany VL. Angiotensin receptor Blockers worsen renal function and Dyspnea on Ticagrelor: A potential Ticagrelor-Angiotensin receptor blocker interaction? Clin Cardiol. 2012; 35: 647–648.
9. Federal Drug Administration. Ticagrelor Drug Approval Package: Complete Response Review.
10. Brilique Summary of Drug Characteristics. European Medicines Agency.
11. Wallentin L. P2Y12 inhibitors: Differences in properties and mechanisms of action and potential consequences for clinical use. Euro Heart J. 2009; 30:1964–1977.

Cite this article

New J, Le K, Wong KA, Choi SJ, Danh CL, et al. (2017) A Case of Acute Renal Failure and Rhabdomyolysis associated with the Concomitant Use of Ticagrelor, Rosuvastatin, and Losartan. JSM Intern Med 2(1): 1004.