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

Jenny New, Kathie Le, Kimberly A. Wong, Shelley J. Choi, Charles L. Danh, Joseph D. Hall, and Elena Kret-Sudjian

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

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: Acute Coronary Syndrome; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; CKD: Chronic Kidney Disease; GFR: Glomerular 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
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

Figure 1. The thienopyridines, 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].
ticagrelor along with an ARB presented an important potential multiple comorbidities and a convoluted medication regimen, being treated with ARBs [10]. In our complex patient with years old, with moderate or severe renal impairment, and those month after initiation of ticagrelor especially in patients ≥ 75 ticagrelor notes that renal function should be monitored one Medicines Agency Summary of Product Characteristics for rates of renal adverse events [7]. In contrast, the European related serious adverse events. However, it does not address that overall treatment groups in PLATO did not differ for renal- Medicines Agency Summary of Product Characteristics for 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 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.

Ticagrelor is becoming a widely used medication in the population of patients affected by acute coronary syndrome. Ticagrelor on its own, and more importantly in 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


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].

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ticagrelor with ARB (N=511)</th>
<th>Clopidogrel with ARB (N=508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Increase &gt; 50%</td>
<td>57 (11.2%)</td>
<td>36 (7.1%)</td>
</tr>
<tr>
<td>Renal-related AE</td>
<td>73 (8.4%)</td>
<td>48 (4.3%)</td>
</tr>
<tr>
<td>Renal-function AE</td>
<td>51 (4.5%)</td>
<td>31 (2.8%)</td>
</tr>
</tbody>
</table>

Abbreviations: AE: adverse events