Rosuvastatin-Induced Rhabdomyolysis as a Result of Drug Interaction With Sitagliptin: A Case Report

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ABSTRACT: Rhabdomyolysis was not reported in clinical trials with Sitagliptin alone. However, several reports in the literature on rhabdomyolysis resulted from the interaction between statins and Sitagliptin. In patients with type 2 diabetes and hyperlipidemia, it is expected to co-prescribe statins and Sitagliptin. Herein, we report the case of a 64-year-old woman with rhabdomyolysis should be caused by a drug-drug interaction between Rosuvastatin and Sitagliptin. The patient denied any history of weakness or myalgia during past medical assessments.

KEYWORDS: Rosuvastatin, sitagliptin, myopathy, rhabdomyolysis

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Introduction

Sitagliptin is a novel oral glucose-lowering drug that works through the incretin hormone system. Pharyngitis and headaches are the most frequent side effects, although a few major adverse events were observed in clinical studies. Because there is limited long-term safety experience, dose modification is recommended for renal insufficiency.[1] Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are often used to treat hyperlipidemia. Skeletal muscle complaints, such as clinically significant myositis and rhabdomyolysis, small increases in blood creatine kinase (CK), myalgia with or without raised CK, muscular weakness, cramping, and chronic myalgia are the most frequent adverse effects. Factors including impaired hepatic and renal function, diabetes, hypothyroidism, and concomitant medicines can all increase the risk of rhabdomyolysis and other statin side effects.[2] Skeletal muscle tissue is injured and rapidly degrades in rhabdomyolysis, a dangerous medical illness that can be fatal if not treated promptly. Rhabdomyolysis in adults can should be caused by a variety of factors, including infections, medication interactions, hormonal or metabolic issues, extended immobility, severe activity, and crush injuries.[3] The European Medicines Agency (EMA) recently issued a pharmacovigilance safety warning regarding the potential development of myopathy and rhabdomyolysis when using dipeptidyl peptidase 4 (DPP-4) inhibitors.[4,5] The warning was issued due to several instances of co-administration of statins and DPP-4 inhibitors, which raised concerns about potential drug-drug interactions.[6] It is crucial to study this potentially significant danger and the underlying drug-drug interaction theory since statin usage is likely shared among individuals with diabetes.[7] We aim to raise awareness about one of the frequently prescribed drug combinations, Sitagliptin and Rosuvastatin, which cause rhabdomyolysis of the skeletal muscle in a patient. Despite being an isolated case, we recommend and support conducting more clinical studies in this area.

Case Presentation

A 64-year-old woman (height: 156 cm, weight: 65 kg) arrived at the emergency department complaining of muscle weakness and vomiting. On arrival, she stated that she had been experiencing nausea and vomiting for the past 10 days, with her muscle weakness and fatigue worsening over the past 3 days. Additionally, she expressed feeling lethargic and having reduced frequency and volume of urine in the past 3 days. Before admission, she had 3 instances of watery diarrhea daily. Her past medical history indicated diabetes and hypertension, dating back 30 years, as well as ischemic heart disease, which was diagnosed 3 years ago.

Her medications included Zipmet® (Metformin 500 mg/Sitagliptin 50 mg) twice a day, Synoripa® (Empagliflozin 5 mg/metformin 500 mg) daily, tab Nitroglycerine 6.4 mg twice a day, Aspirin 80 mg daily, Valzomix® (Amlodipine 5 mg/Valsartan 160 mg) daily, Rosuvastatin 40 mg daily, Gabapentin 100 mg daily, Clopidogrel 75 mg daily, Indapamide 2.5 mg daily, Hydrochlorothiazide 25 mg daily, Escitalopram 10 mg daily, Pantoprazole 40 mg daily, and Insulin Lantus 30 unit daily.

Her vital signs were as follows: blood pressure (BP): 133/67 mmHg, pulse rate (PR): 97/min, respiratory rate (RR): 20/min, temperature (T): 37°C, saturation of oxygen (O_2 SAT): 96%. Her examination of the head and neck region showed no abnormalities. The pupils were equal and reactive to light. Both oral and nasal mucosa were dry. While lying face down, no neck veins were visible. Lung sounds were normal, and heart sounds S1 and S2 were audible with no murmurs. The abdomen was soft and not tender, with normal bowel sounds.

Table 1. Subsequent laboratory findings.

PARAMETER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 12	DAY 19 (FOLLOW-UP)
P (mg/dL)	7.6	6.09	5.4	5.3	5.62	6.33	6.92	4.8
Ca (mg/dL)	8.6	7.97	7.9	8	8.94	9.70	9.80	9.7
K (mEq/L)	8	5.3	5.1	5.9	5.5	4.8	4.7	4.1
Na (mEq/L)	131	130	124.9	133.2	141.5	144	139.5	143
Mg (mg/dL)	2.4	2	1.9	1.81	2.42	2.6	2.51	–
LDH	1464	1900	1494	1076	968	949	801	–
CPK (U/L)	22000	12000	5530	2830	–	–	–	–
Alb (g/dL)	3.3	2.6	2.5	2.6	2.4	2.6	2.8	–
BUN (mg/dL)	132	131	141	149	145	143	116	149
Cr (mg/dL)	9.97	10.24	10.1	11.1	10.93	10.64	8.74	5.01
Hb	11.1	9.5	8.7	8.3	8.5	8.1	7.9	–
WBC	11.8	6.7	6.9	6.6	6.9	7.6		
PLT	309	263	271	263	287	335		
Uric acid (mg/dL)	9.7	9	9.3	10.3	9.6	10		

Abbreviations: P, phosphorus; Ca, calcium; Na, sodium; K, potassium; Mg, magnesium; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; Alb, albumin; BUN, blood urea nitrogen; Cr, serum creatinine; Hb, hemoglobin; PLT, platelet count; WBCs, white blood cells.

Peripheral pulses were equal in strength and amplitude. The patient had +3 pitting edema in the lower extremities. No other significant findings were observed during the examination. Her laboratory values at the time of admission are shown in Table 1.

Her ECG also demonstrated hyperkalemia with T wave peaking, prolonged QRS, and shortening QT and PR interval.

Upon sonography examination, it was found that both kidneys were normal in size, both kidneys were normal in size, with normal echogenicity and corticomedullary differentiation on both sides, and the thickness of the parenchyma is also normal. There was no evidence of stone in the pelvicalyceal system, and no hydronephrosis was observed on the left side. However, fullness was noted in the right kidney. Additionally, the bladder was empty and adequately distended with a Foley balloon. The urine sediment was examined and reported as evidence of acute kidney injury such as brown casts by a nephrologist. The urine sediment examination was not repeated because the patient had diabetic nephropathy that was being treated with valsartan and rosuvastatin.

The patient was diagnosed with acute kidney injury (AKI) in the setting of severe rhabdomyolysis accompanied with characteristic biochemical abnormalities of hyperkalemia, hyperphosphatemia, hyperuricemia, and elevated creatine phosphokinase levels.

Upon admission to the emergency room, the patient underwent received initial treatment which included a sonographic evaluation of the kidneys and urinary tract and an electrocardiogram (ECG), Considering the potassium level greater than 8 mEq/L, the administration of Indapamide 1.5 and Hydrochlorothiazide 20 was suspended. To manage hyperkalemia, the patient received calcium gluconate injections. Additionally, the patient received 50 cc of 10% dextrose serum and 2 vials of sodium bicarbonate. Moreover, the patient was subjected to subcutaneous and intravenous (IV) routes to receive 10 units of regular insulin.

For therapeutic interventions, Rosuvastatin 40 and Citalopram were discontinued. Water intake was limited to manage the patient's hyponatremia. The patient received IV sodium bicarbonate, and insulin therapy was initiated. Oral hypoglycemic agents were stopped, and supportive care was provided.

The effectiveness of therapeutic interventions was assessed daily to determine the need for emergency dialysis. Investigations comprised tests for daily checks of sodium (Na), potassium (K), uric acid, CPK, calcium (Ca), phosphorous (P), lactate dehydrogenase (LDH), and complete blood count (CBC). The patient's fluid intake and output were closely monitored, and daily examinations were carried out. After 3 successive days of reduced creatinine levels and clinical improvement, the patient was discharged on the 12th day of hospitalization after receiving dialysis. Creatine phosphokinase (CPK) value decreased and was recorded at 1220 U/L on discharge time. Follow-up tests were conducted 7 days post-discharge, which were as follows: fasting blood sugar (FBS): 161 mg/dL, urea: 149 mg/dL, serum creatinine (Cr): 5.01 mg/dL, Ca: 9.7 mg/dL, P: 4.8 mg/dL, Na: 143 mEq/L, and K: 4.1 mEq/L (Table 1).

Discussion

Rhabdomyolysis is a severe syndrome caused by destroying muscle fibers and releasing their contents, including myoglobin, CPK, LDH, potassium, phosphates, and aldolase, into the bloodstream. Typical metabolic alterations include hyperkalemia, metabolic acidosis, hypocalcemia, hypercalcemia, hyperuricemia, hyponatremia, and hyperphosphatemia. This condition, caused by direct or indirect muscle damage, can lead to complications such as myalgia, weakness, and swelling, usually associated with myoglobinuria and AKI in 13% to 50% of all cases.[8]

Extreme physical activity, trauma, toxins and infections, malignant hyperthermia, endocrine disorders, and sometimes drug influence are the causes of this clinical syndrome.[9] Here, we reported the case of a 64-year-old woman who developed rhabdomyolysis within a few days after Sitagliptin was added to Rosuvastatin. The patient denied any history of weakness or myalgia during past medical assessments. She did not have any other known etiologies for developing rhabdomyolysis, such as a history of recent trauma, crush injury, prolonged immobilization, recent surgery, seizures, drug abuse, or alcoholism. The worsening of her renal function suggests that the initiation of Sitagliptin therapy precipitated this event.

Sitagliptin is a DPP-4 inhibitor that improves blood sugar control in adults with type 2 diabetes mellitus. The excretion of this drug is mainly unchanged through renal tubular secretion in the urine. Therefore, the maximum serum concentration and the terminal half-life of Sitagliptin are increased in renal failure.[10] Rosuvastatin belongs to the family of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. The ortho and para-hydroxylated forms are the active metabolites of this drug, which are responsible for most of the reactions. Statins block the cholesterol synthesis pathway by converting HMG-CoA to mevalonate.[11] Rhabdomyolysis is a well-documented side effect of statins.

Rhabdomyolysis was not reported in clinical trials with Sitagliptin alone. However, several reports in the literature of rhabdomyolysis have been caused by interaction between statins and Sitagliptin.[1,6,12,13] It has been suggested that the interaction between Sitagliptin and statins may be due to its effects on the renal excretion of statins and interference in the level of liver metabolism.[1,6,12,13] A study concluded that the nephrotoxicity of Sitagliptin leads to a decrease in the renal excretion of Simvastatin.[6] Also, a competitive interaction between statin and Sitagliptin at the level of CYP3A4 was suggested as the cause of this interaction, which leads to an increase in the serum concentration of statin, causing rhabdomyolysis.[1,6,12,13] However, several clinical trials showed that Sitagliptin does not affect the pharmacokinetics of Simvastatin.[14,15] Therefore, no dose adjustment is recommended when co-administering Simvastatin with Sitagliptin. Finally, a review found that the incidence of this interaction varies among all statins. This interaction depends on how much hepatic CYP3A4 metabolizes that statin. Therefore, we expect to see fewer drug interactions with drugs that are not significantly metabolized by CYP3A4, such as Pravastatin, Rosuvastatin, Pitavastatin, and Fluvastatin.[16]

About 16% of Sitagliptin is metabolized by CYP3A4, CYP2C8, and P-glycoprotein, and 80% is excreted unchanged in the urine. Both Rosuvastatin and Sitagliptin are substrates for CYP3A4 and P-glycoprotein.[3,17] Organic anion transporter protein OATP-C from the bloodstream is a major elimination pathway of Rosuvastatin.[17] This elimination, in turn, leads to significant drug interactions with other CYP3A4 inhibitors, which may lead to complications such as myopathy.[3] This response is thought to be dose-dependent, and factors such as worsening renal function that increases statin serum levels may increase the risk of myopathy.[3]

Treatment depends on the severity. For less severe cases, treatment includes drinking fluids, getting out of the heat, and resting. Moderate to severe cases may need IV fluids and hospital admission. IV fluids help flush out the muscle proteins and electrolytes and can prevent dangerous heart rhythms and loss of kidney function.[18] The first step involves treating the underlying disease, followed by massive hydration and conservative management.[19]

This patient developed rhabdomyolysis within a few days of adding Sitagliptin to her continuing medical therapy, which included Rosuvastatin. The drug-drug interaction between Rosuvastatin and Sitagliptin caused toxicity and rhabdomyolysis. In contrast, previous studies reported a reaction when Sitagliptin is co-administered with the other statins, mainly metabolized by cytochrome CYP3A4.[20]

We should consider the types of concomitant medications which may also affect kidney function and serum statin levels. In this particular case, the dosage of these drugs had been consistent for a long time before the onset of symptoms or worsening of renal function, and this issue indicates the onset of complications with the start of Sitagliptin treatment.

Conclusion

If Sitagliptin and Statins are prescribed together, it is crucial to be cautious of potential drug-drug interactions and elevated risks, especially in high doses, to elderly patients and individuals with underlying renal insufficiency.

Author Contributions

AA: Conceptualization; investigation; project administration; MM: investigation; writing – original draft; writing – review and editing; MP: investigation; writing – original draft; writing – review and editing; SB: Conceptualization; investigation; Validation.

Informed Consent

Written informed consent was obtained from the patient to publish this report following the journal's patient consent policy.

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