CLINICAL PRACTICE

Clinical Vignettes

Rhabdomyolysis and AKI with Atorvastatin and Sitagliptin Use in the Setting of Low 25-Hydroxyvitamin D Levels

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We report a case of an 86-year-old woman admitted to the hospital with rhabdomyolysis and acute kidney injury 3 weeks after starting sitagliptin while on long-term atorvastatin therapy. She also had low levels of 25-hydroxyvitamin D and mild chronic kidney disease, which may have contributed to the development of rhabdomyolysis. A review of the literature reveals four previous reports of this drug interaction in elderly patients, some with underlying kidney disease.

KEY WORDS: sitagliptin; statins; vitamin D; rhabdomyolysis; drug interaction; acute kidney injury.
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CASE

An 86-year-old Hispanic woman presented to the emergency department with a chief complaint of generalized weakness and muscle pains for 2 weeks. She also complained of nausea, vomiting, diarrhea, yellow skin, dark-colored urine, and light stools. The patient reported that her generalized weakness and other symptoms developed 1 week after starting sitagliptin and progressively worsened. Her past medical history included type 2 diabetes mellitus (DM), hypertension, hyperlipidemia, and stage 3 chronic kidney disease (CKD). Her medications on admission included aspirin 81 mg daily, atorvastatin 20 mg daily, sitagliptin 100 mg daily, glipizide 10 mg daily, and metformin 500 mg twice daily (BID). The sitagliptin was started 3 weeks prior to presentation.

Her vital signs were remarkable for a temperature of 99.2 °F (37 °C) and blood pressure of 154/65 mmHg. Otherwise, vitals were in the normal ranges. Her examination was notable for tenderness in the arms and legs, jaundice, and scleral icterus. She did not have any abdominal tenderness or hepatosplenomegaly. Her lab values at the time of admission are shown in Table 1 and are notable for elevated creatinine (4.44 mg/dL), creatine phosphokinase (CPK) 13,636 U/L, alkaline phosphatase (859 U/L) and bilirubin (8.3 mg/dL). Her 25-hydroxyvitamin D (25(OH)D) was low at 13.7 ng/mL (normal range: 30–100 ng/mL). She was admitted to the hospital, and her oral antidiabetic agents and atorvastatin were stopped. She was started on intravenous isotonic sodium bicarbonate along with insulin for glycemic control.

The patient underwent several diagnostic procedures for evaluation of her muscle weakness and abnormal laboratory findings. Hepatic imaging showed no relevant findings on right-upper-quadrant ultrasound and magnetic resonance cholangiopancreatography (MRCP). Hepatitis A, B, and C serology test results were negative. Her acetaminophen levels were within normal range. She underwent a workup for possible causes of rhabdomyolysis including an autoimmune panel that was negative for antinuclear and anti-smooth muscle antibodies. Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) tests were negative. Thyroid-stimulating hormone (TSH) and free T4 test results were normal.

She was continued on intravenous hydration and monitored. The CPK continued to rise, peaking at 49,875 U/L before trending down to 609 U/L at the time of discharge on hospital day 16. The patient reported a significant improvement in her symptoms of muscle weakness and pain. Although her kidney function continued to improve over time, it never returned to baseline. She was discharged to a rehabilitation center, with Levemir for glycemic control along with sodium bicarbonate 650 mg BID and aspirin 81 mg once daily. She was not discharged on oral antidiabetic agents, vitamin D, or statins. One week later her creatinine was 1.73 mg/dL, which trended down to 1.30 mg/dL 5 months later and finally to 1.10 mg/dL. The level of 25 (OH)D measured 2 months after discharge was 27.1 ng/mL. She was restarted on atorvastatin 20 mg with no recurrence. Sitagliptin is now listed as an allergy in the medical record.

DISCUSSION

Here we report the case of an 86-year-old woman with stage 3 CKD who developed severe rhabdomyolysis and acute kidney injury (AKI) in the setting of a recent addition of sitagliptin to her chronic atorvastatin use. We believe that the interaction between these two medications caused the rhabdomyolysis. Possible contributors to the rhabdomyolysis were her CKD and low 25(OH)D levels. A literature review showed four previously reported cases of rhabdomyolysis in the setting of the use of sitagliptin and a statin (Table 2). All of the cases were

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Table 1 Lab Values at Admission and Discharge

Lab test	Admission	Discharge
Sodium (meq/L)	139	138
Potassium (meq/L)	3.6	3.2
Chloride (meq/L)	101	97
Bicarbonate (meq/L)	17	18
Creatinine (mg/dL)	4.44	2.03
BUN (mg/dL)	65	22
CPK (U/L)	13,636	609
Alkaline phosphatase (U/L)	859	574
Bilirubin (mg/dL)	8.3	3.7
SGOT (U/L)	721	182
SGPT (U/L)	261	262
Magnesium (mg/dL)	1.9	1.9
Calcium (mg/dL)	8.9	8.7
Phosphorus (mg/dL)	3.6	3.7
Amylase (U/L)	180	188
Lipase (U/L)	289	132
INR	1.8	1.1
PT (s)	18.2	
PTT (s)	38.7	
25(OH)D (ng/mL)	13.7	27.1 (2 months after discharge)

BUN blood urea nitrogen, CPK Creatine Phosphokinase, SGOT serum glutamicoxaloacetic transaminase, SGPT serum glutamic-pyruvic transaminase, INR international normalized ratio, PT prothrombin time, s seconds, PTT partial thromboplastin time, 25(OH)D 25-hydroxyvitamin D

in patients 75 years of age or older, some with underlying CKD. All had recently been started (6 months or less) on sitagliptin.

Sitagliptin, an oral antihyperglycemic agent approved by the U.S. Food and Drug Administration (FDA) in 2006, is used for controlling blood sugars in patients with type 2 DM. It belongs to a class of drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors, which act by inhibiting the inactivation of GLP-1 and GIP by the DPP-4 enzyme. Increased levels of GLP-1 and GIP stimulate the glucose-dependent release of insulin and suppress glucagon secretion. This leads to lower glucose levels without the risk of inducing hypoglycemia and weight change, making it a safer alternative to sulfonylureas.[5] Side effects commonly seen with sitagliptin include runny nose, sore throat, headache, back pain, joint or muscle pain, nausea, abdominal pain, diarrhea, constipation, and pancreatitis. Sitagliptin, like most DPP-4 inhibitors, is excreted by the kidney, requiring appropriate dose adjustments in patients with reduced kidney function.[6] Low 25-hydroxyvitamin D [25(OH)D] levels have been independently associated with varying degrees of muscle-related adverse events such as myopathy and myalgias. There have also been case reports and cross-sectional studies linking an increased risk of statin-induced myopathy with low 25(OH)D.[7, 8]

Sitagliptin is mostly (80%) excreted via the kidneys, and dose adjustments are recommended for patients with CKD.[9] Statins, on the other hand, are mainly metabolized by hepatic cytochrome CYP450 enzymes, although they are also excreted by the kidney. Various mechanisms have been proposed for the interaction between the two medications, ranging from the effects of sitagliptin on renal excretion of statins to interaction at the level of hepatic metabolism.[1–4]

One case report of simvastatin-induced rhabdomyolysis in the presence of sitagliptin proposed that the nephrotoxicity of sitagliptin led to reduced renal excretion of simvastatin.[2] This was based on a study showing that sitagliptin caused renal tubular necrosis and loss of renal parenchyma in rats.[10] The case report noted that the serum concentration and terminal half-life of sitagliptin can be increased in kidney disease, possibly leading to increased serum concentration of the statin, and subsequently to dose-related muscle breakdown in the patient.

However, a clinical trial studying the effects of sitagliptin on the pharmacokinetics of simvastatin in 12 healthy human subjects 18–45 years of age, both men and women, showed no effect on the metabolism of simvastatin.[11] The authors recommended no dose adjustment when simvastatin was co-administered with sitagliptin. Similarly, another study in 10 patients found no effects of simvastatin use on the pharmacokinetics of sitagliptin, and no dose adjustment was recommended for either drug.[12]

In one case report of rhabdomyolysis induced by lovastatin and sitagliptin, the authors suggested an interaction between the statin and sitagliptin at the level of CYP3A4 as the cause. They posited that because both are metabolized by CYP3A4,

Table 2 Case Reports of Rhabdomyolysis from Combining Sitagliptin and Statin Therapies

Case report	Medications	Duration of statin use	Duration of sitagliptin use	Patient baseline characteristics	Medical history	Peak CPK levels	Baseline kidney function
Bhome and Penn 2012[1]	Atorvastatin + sitagliptin	5 years	6 months	75, male, white	Type 2 DM, HTN, dyslipidemia,	10,9710	Normal
Kao et al. 2008[2]	Simvastatin 80 mg + sitagliptin 100 mg	4 months	3 weeks	76, male	Type 2 DM, dyslipidemia, CAD, AFib	22,000	Baseline CKD with baseline creatinine 2.3 mg/dL
DiGregorio and Pasikhova 2009[3]	Lovastatin 40 mg + sitagliptin 100 mg	12 years	19 days	75, female, white	Type 2 DM, HTN, dyslipidemia	N/A	N/A
Campos-Davila et al. 2014[4]	Atorvastatin 80 mg + sitagliptin	N/A	N/A	80, male	Type 2 DM, HTN, dyslipidemia, MI, recent stroke	1253	N/A
Current case report	Atorvastatin 20 mg, sitagliptin 100 mg	1 year	3 weeks	86, female, Hispanic	Type 2 DM, HTN, osteoporosis, hypomagnesaemia, dyslipidemia	49,875	Baseline CKD stage 3 (eGFR 50–60)

HTN hypertension, CAD coronary artery disease, AFib atrial fibrillation, DM diabetes mellitus, MI myocardial infarction, CKD chronic kidney disease, CPK creatine phosphokinase, N/A not available

when co-administered, they may compete for the same enzyme, resulting in increased serum concentration of the statin, leading to statin-induced rhabdomyolysis.[3] Two other case reports of rhabdomyolysis with atorvastatin and sitagliptin had similar suggestions, indicating that sitagliptin leads to increased serum concentration of atorvastatin through its effects on hepatic metabolism by CYP3A4 rather than on renal excretion.[1, 2, 4] A comprehensive review of the literature suggests that atorvastatin and sitagliptin are not prone to pharmacokinetic drug–drug interactions, either separately or in a fixed-drug combination.[13]

Statins reported thus far to induce rhabdomyolysis in interaction with sitagliptin are lovastatin, atorvastatin, and simvastatin. These are all metabolized by hepatic CYP3A4. The link to cytochrome metabolism is further supported by the lack of any reported rhabdomyolysis[14] caused by interaction of sitagliptin with statins that are not significantly metabolized by CYP3A4, such as pravastatin, rosuvastatin, pitavastatin, and fluvastatin.[14]

The other factor considered to contribute to the patient's rhabdomyolysis was her low level of 25(OH)D. This was not fully investigated in previous case reports of sitagliptin and statins (Table 2). The 25(OH)D levels, which were likely chronically low, were probably a contributing factor to the rhabdomyolysis, but the sitagliptin was the direct precipitating factor.

Low levels of 25(OH)D have been associated with varying degrees of myopathy independently as well as with an increased risk of statin-induced myopathy.[15] Various possible mechanisms have been proposed for this interaction between 25(OH)D and statins, as 25(OH)D affects the muscle at both genomic and non-genomic levels. It plays an important role in muscle cell differentiation and proliferation through modulation of transcription factors, and is essential for maintaining contractility and myogenesis via the transport of calcium into the sarcoplasmic reticulum.[16–18] This suggests a possible mechanism via increased predisposition to statin-induced myopathy because of decreased transcription of proteins required to maintain the structure and functioning of myocytes and sarcolemma.

The binding of the 1,25-dihydroxyvitamin D to the vitamin D receptors (VDRs) found in the small intestinal mucosa, kidney, and certain specialized cells in the liver (including Kupffer, stellate, and endothelial cells) has been suggested as a pathway for enhancing the transcription of CYP3A4.[19] This introduces the idea that the catabolism of 25(OH)D can lead to increased levels of the CYP3A4 enzyme. Vitamin D and its hydroxylated compounds are also known to induce CYP450, CYP2C9, and CYP2B6.[20] This could explain statin-induced myopathy in patients with reduced vitamin D levels, where insufficient CYP activity may lead to decreased metabolism of the statin and increased toxicity.[21] These findings may be further corroborated by studies evaluating statin reintroduction after 25(OH)D supplementation in patients with low 25(OH)D levels who were statin-intolerant because of muscle-related adverse events. A study showed that of 146 patients with statin intolerance due to myopathy or myonecrosis, 131 (88%) patients showed reversal of the intolerance with supplementation of vitamin D.[8] A proposed marker of vitamin D levels <20 ng/mL has been introduced as a predictor of muscular adverse events during statin treatment.[7] As discussed previously, most of the reported cases of statin-induced rhabdomyolysis have been associated with statins metabolized by CYP enzymes, substantiating the role of cytochrome metabolism.

CONCLUSION

The co-prescription of statins and sitagliptin is becoming common in patients with type 2 DM and hyperlipidemia. Our patient had been taking atorvastatin for a year, and her symptoms began 1 week after starting sitagliptin. This is the fifth report of rhabdomyolysis caused by the interaction of a statin with sitagliptin. Previous case reports, however, did not look at the role of vitamin D within the statin–sitagliptin interaction. We suggest that clinicians remain vigilant when using these medications in combination, especially in older patients with underlying CKD. Further studies are needed to confirm the associations between sitagliptin, statins, low 25(OH)D levels, and rhabdomyolysis.

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