

> THE PATIENT
76-year-old woman

> SIGNS & SYMPTOMS

- Weakness and pain in arms and legs
- Dark urine
- History of vertebral osteomyelitis

Antonios Charokopos, MD, MS; Tariq Muhammad, MD; Sidana Surbhi, MD; Andrei Brateanu, MD
Yale-New Haven Hospital, Department of Internal Medicine, Conn (Dr. Charokopos); Department of Internal Medicine, Cleveland Clinic, Ohio (Drs. Muhammad, Surbhi, and Brateanu)

antonios.charokopos@yale.edu

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> THE CASE

A 76-year-old Caucasian woman presented to the emergency department with a 7-day history of weakness and pain in her arms and legs. She had a history of *Candida albicans* vertebral osteomyelitis that had been treated for 3 months with fluconazole; non-Hodgkin lymphoma that had been in remission for 6 months; diabetes mellitus; hyperlipidemia; and hypothyroidism. The woman had dark urine, but denied chills, fever, respiratory symptoms, bowel or bladder leakage, falls/trauma, or grapefruit juice intake.

Her current medications included oral fluconazole 400 mg/d, simvastatin 20 mg/d, levothyroxine 88 mcg/d, pregabalin 75 mg/d, metformin 1000 mg twice daily, 6 units of subcutaneous insulin glargine at bedtime, and 2 units of insulin lispro with each meal. During the examination, we noted marked proximal muscle weakness, significant tenderness in all extremities, and diminished deep tendon reflexes. The patient had no saddle anesthesia, impaired rectal tone, or sensory abnormalities.

THE DIAGNOSIS

Magnetic resonance imaging of the patient's spine confirmed multilevel discitis and osteomyelitis (T7-T9, L5-S1) with no cord compression. Laboratory data included a creatinine level of 1.42 mg/dL (the patient's baseline was 0.8 mg/dL); a creatine kinase (CK) level of 8876 U/L (normal range, 0-220 U/L); a thyroid-stimulating hormone (TSH) level of 9.35 mIU/L (normal range, 0.4-5.5 mIU/L); and an erythrocyte sedimentation rate of 27 mm/hr (normal range, 0-31 mm/hr).

The patient received aggressive fluid hydration, orally and intravenously. On Day 2, the patient's serum myoglobin level was 14,301 ng/mL (normal range, 30-90 ng/mL) and her aldolase level was 87.6 U/L (normal range, 1.5-8.5 U/L).

■ **Zeroing in on the cause.** There were no signs of drug abuse or use of other non-statin culprit medications that could have caused the patient's rhabdomyolysis. She also did not describe any triggers of rhabdomyolysis, such as trauma, viral infection, metabolic disturbances, or temperature dysregulation. We believed the most likely cause of our patient's signs and symptoms was statin-induced rhabdomyolysis, likely due to an interaction between simvastatin and fluconazole. We considered hypothyroidism-induced rhabdomyolysis, but thought it was unlikely because the patient had a mildly increased TSH level on admission, and one would expect to see levels higher than 100 mIU/L.¹⁻³

We also considered viral myositis in the differential, but it was an unlikely culprit because the patient lacked any history of fever or respiratory or gastrointestinal symptoms. And while paraneoplastic polymyositis could have caused the patient's weakness, the marked muscle pain and acute kidney injury were far more suggestive of rhabdomyolysis.

TABLE 1

Case reports of rhabdomyolysis from a fluconazole-simvastatin interaction

Article	Patient characteristics	Statin and fluconazole doses (mg/d)	Co-administration time	CK peak level (U/L)	Drugs discontinued
Shaukat et al ¹¹	83 y/o man with AML, CHF, hypothyroidism	Simvastatin 40; fluconazole 400	1 week	87,833	Simvastatin, fluconazole
Hazin et al ¹²	79 y/o man with prostate cancer, dementia, DM	Simvastatin N/A; fluconazole N/A	Unknown	~78,000	Simvastatin, fluconazole
Findling et al ¹³	65 y/o woman with CAD, fungal infection of AICD	Simvastatin 40; fluconazole 800	3 weeks	~32,000	Simvastatin only
Present case	76 y/o woman with NHL, hypothyroidism, fungal osteomyelitis	Simvastatin 20; fluconazole 400	12 weeks	32,886	Simvastatin only

AICD, automated implantable cardioverter-defibrillator; AML, acute myeloid leukemia; CAD, coronary artery disease; CHF, congestive heart failure; CK, creatine kinase; DM, diabetes mellitus; N/A, not available; NHL, non-Hodgkin lymphoma.

DISCUSSION

Rhabdomyolysis is a serious complication of statin treatment. Both higher statin doses and pharmacokinetic factors can raise statin levels, leading to this serious muscle-related syndrome.^{4,5} Co-administration of statins with drugs that are strong inhibitors of cytochrome P450 (CYP) 3A4 (the main cytochrome P450 isoform that metabolizes most statins) can increase statin levels several fold.^{6,7} The trigger for our patient's statin-induced rhabdomyolysis was fluconazole, a known moderate inhibitor of CYP3A4, which is comparatively weaker than certain potent azoles like itraconazole or ketoconazole.⁷⁻¹⁰ Doses of fluconazole generally ≥ 200 mg/d are needed to produce clinical interactions with CYP3A4 substrates.⁷ There are only 3 reported cases of fluconazole-simvastatin-induced rhabdomyolysis (TABLE 1).¹¹⁻¹³

The Food and Drug Administration advises against simvastatin co-prescription with itraconazole and ketoconazole, but doesn't mention fluconazole in its Drug Safety communication on simvastatin.¹⁴

Lexicomp places the simvastatin-fluconazole drug interaction into category C, which means that the agents can interact in a clinically significant manner (and a monitoring plan should be implemented), but that the benefits of concomitant use usually outweigh the risks.¹⁵

How our patient's case differs from previous cases

Several features distinguish our patient's scenario from previous cases. First, unlike other cases in which both drugs were stopped, only simvastatin was discontinued in our patient. Simvastatin and fluconazole have a half-life of 3 hours⁶ and 32 hours,⁷ respectively, suggesting that when simvastatin has fully cleared, fluconazole's concentration will not even have halved. Thus, fluconazole was safely continued to treat the patient's osteomyelitis.

Second, compared to previous case reports, our patient was taking a lower dose of simvastatin (20 mg). A 20-mg dose can make the drug interaction easier to miss; pharmacists are more likely to inform the physician of a potential drug interaction when the dose of a statin is ≥ 40 mg compared to when it is < 40 mg (odds ratio=1.89; 95% confidence interval, 0.98-3.63).¹⁶

Researchers involved in the British randomized trial SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) sought to evaluate any added benefit to a higher dose of simvastatin in post-myocardial infarction patients. Among approximately 12,000 patients in the trial, there were 7 cases of rhabdomyolysis for the 80-mg simvastatin group and none for the 20-mg group.⁵ Another large case-control study showed that a 40-mg simvastatin dose was 5 times more likely to cause rhabdomyolysis than a 20-mg dose.¹⁷ Yet, based on

TABLE 2

Main CYP450 isoforms that metabolize statins and the azoles that inhibit them^{6,7,10,19}

CYP450 isoform	Statin metabolized*	Azole inhibitor (in order of decreasing potency)
3A4	Simvastatin; atorvastatin; lovastatin	Ketoconazole, itraconazole, voriconazole, fluconazole
2C9	Fluvastatin; rosuvastatin (minimal); pitavastatin (minimal)	Voriconazole, fluconazole, ketoconazole

*Pravastatin is unique in that it is not metabolized by the CYP450 system, but through sulfation.

➤ Even 20 mg/d simvastatin should not diminish your suspicion for rhabdomyolysis if a patient is taking a CYP3A4 inhibitor.

our patient’s case, even 20 mg/d simvastatin should not decrease physician suspicion for rhabdomyolysis if patients are also taking a CYP3A4 inhibitor.

Third, the simvastatin-fluconazole co-administration time in our patient was 12 weeks, which is longer than previously reported (TABLE 1¹¹⁻¹³). Azole inhibition of CYP450 occurs relatively rapidly, but that does not mean that rhabdomyolysis will always occur immediately. For example, in cases of statin monotherapy, rhabdomyolysis secondary to statin biochemical toxicity can occur up to 1050 (mean=348) days after the drug’s initiation.¹⁸

Avoiding a drug-drug interaction in your patient

Physicians can use pharmacokinetic profiles to choose among different statins and azoles to help avoid a drug interaction (TABLE 2^{6,7,10,19}). Pravastatin’s serum concentration, for example, is not influenced by CYP3A4 inhibitors such as itraconazole¹¹ because pravastatin is metabolized by sulfation⁶ and not by the CYP450 system. Rosuvastatin and pitavastatin are minimally metabolized by the CYP450 system.^{19,20}

Among approximately 2700 statin-treated outpatients,⁴ the prevalence of potentially harmful statin interactions with other drugs (including CYP3A4 inhibitors), was significantly higher among patients treated with simvastatin or atorvastatin (CYP3A4-metabolized statins), than among patients treated with fluvastatin (CYP2C9-metabolized statin) or pravastatin (metabolized by sulfation). Apart from drug-drug interactions, other risk factors for statin-induced rhabdomyolysis include use of

lipophilic statins, advanced age, and female gender.²¹

■ We discontinued our patient’s simvastatin on the day she was admitted to the hospital, but continued with the fluconazole throughout her hospitalization. Her CK level continued to rise, peaked on hospital Day 3 at 32,886 U/L, and then progressively decreased. The patient’s weakness and pain improved and her acute kidney injury resolved with hydration. She was discharged on hospital Day 7 on oral fluconazole, but no statin, and her muscle symptoms have since resolved.

THE TAKEAWAY

When hyperlipidemic patients have to take an azole for an extended period (eg, cancer prophylaxis or chronic osteomyelitis) and the azole is a strong CYP450 inhibitor (eg, itraconazole), switching to a statin that is not primarily metabolized by the CYP450 system (eg, pravastatin, pitavastatin) is wise. If the azole is a moderate CYP450 inhibitor (eg, fluconazole), we suggest that therapy should be closely monitored. In the case of short-term azole treatment (eg, such as for oral candidiasis), the statin should be stopped or the dose reduced by at least 50% (eg, from 40 or 20 mg to 10 mg).⁶

Prescriber knowledge is sometimes a limiting factor in identifying clinically significant interactions.²² This is especially pertinent in a case like this one, where a lower statin dose may result in a lower chance of the pharmacist alerting the prescribing physician¹⁶ and when an azole is used that is a comparatively weaker CYP450 inhibitor than other azoles such as itraconazole.

Even in the era of electronic medical records, approximately 90% of drug interaction alerts are overridden by physicians, and alert fatigue is pronounced.²³

The intricacies and pharmacokinetic principles of this case should contribute to greater provider familiarity with even low-dose simvastatin-fluconazole interactions and help prevent iatrogenic complications such as rhabdomyolysis. **JFP**

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