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Rhabdomyolysis-induced acute renal failure due to itraconazole and simvastatin association

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Abstract

We present the case of an 82-year-old man admitted to our hospital for muscle weakness. He was under simvastatin 20 mg per day and was given pulse itraconazole therapy 8 days before the onset of symptoms for onychomycosis. He developed severe rhabdomyolysis inducing an acute renal failure necessitating renal replacement therapy. He eventually fully recovered. Given the possible concurrent use of simvastatin and itraconazole, awareness of this potential interaction is clinically important.

Keywords: acute renal failure; hepatic metabolism; itraconazole; pharmacological interaction; rhabdomyolysis; simvastatin.

Introduction

We report a case of rhabdomyolysis as a result of a drug interaction between simvastatin and itraconazole. Simvastatin is used for pharmacological management of hypercholesterolemia. Itraconazole is used as an antifungal agent. Given their possible concurrent use, awareness of this potential interaction is clinically important.

Case report

An 82-year-old man presented to the emergency department for weakness and inability to stand up. His medical history included coronary artery disease with three bypasses and a pacemaker in 2008, chronic infection by hepatitis C virus (HCV), chronic arterial hypertension and obesity. His medication included daily administration of amlodipine 10 mg, acenocoumarol 4 mg according to international normalized ratio, simvastatin 20 mg and perindopril 10 mg. A treatment by pulse therapy of itraconazole (200 mg orally, twice daily) was initiated 8 days before the onset of symptoms for onychomycosis. After a few days of treatment he began to feel weak and was forced to call an ambulance to get to the emergency department, being no longer able to walk.

Clinical examination revealed only weakness of lower limbs. Laboratory tests revealed a blood urea nitrogen of 17.1 mmol/L, serum creatinine of 188 μmol/L and serum creatine kinase of 22,294 IU/L. The patient was admitted to hospital for acute rhabdomyolysis and acute renal failure. The patient had normal renal function 8 months before. A computed tomography (CT) scan without contrast showed no obstacles on the urinary track. A heart ultrasound showed a normal systolic function. A search for cryoglobulinemia was negative. The treatment remained unchanged and the renal function, like the rhabdomyolysis, worsened altogether (Figure 1). He was admitted to the intensive care unit (ICU). All medications were stopped except amlodipine and perindopril, but the patient required continuous renal replacement therapy for 9 days. Serum creatine kinase levels fell steeply. The patient slowly recovered from acute renal failure and dialysis could be discontinued (Figure 1).

Discussion

In our case report there seemed no other explanation for the acute rhabdomyolysis and acute renal failure than the drugs taken by the patient, and especially an interaction between simvastatin and the recently started treatment with itraconazole (8 days before the onset of the symptoms). There was no trauma, no fever, no acute infection and no cryoglobulinemia associated with the HCV infection, nor had any toxin been taken (i.e. none of the most common causes of rhabdomyolysis).

Simvastatin alone rarely causes rhabdomyolysis. The reported risk of rhabdomyolysis with simvastatin monotherapy is low and dose related: 0.002% at 20 mg daily, which was the dose taken by the patient (1, 2). The rhabdomyolysis was then unlikely to be caused by simvastatin alone, but by an interaction between simvastatin and the newly initiated itraconazole.

The mechanism by which statins can cause myopathy and then rhabdomyolysis is not completely understood. However, the association appears to be dose dependent, and the risk is known to increase when statins are prescribed in combination with agents that increase the serum concentration of the statin (3). This is exactly what seemed to have happened to our patient. About 80% of simvastatin is metabolized in the liver by CYP3A4. Itraconazole is a potent inhibitor of CYP3A (4, 5). Starting the treatment with itraconazole probably triggered a sharp rise of the simvastatin serum concentration in our patient,

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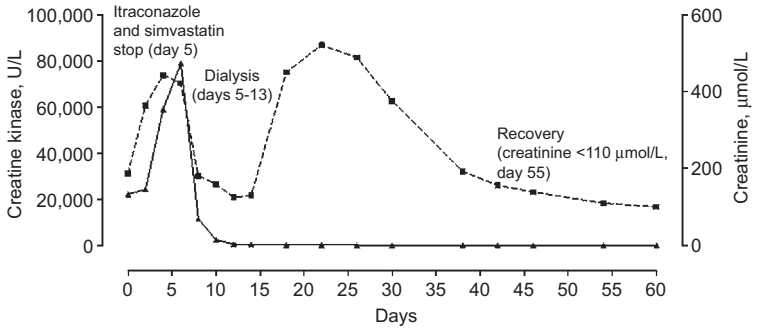

Figure 1 Patient's renal and rhabdomyolysis evolution and treatment history.

causing the acute rhabdomyolysis and finally acute renal failure. This hypothesis was even tested in a hypercholesterolemic volunteer taking chronically 40 mg of simvastatin daily. The trough levels of simvastatin and its metabolite simvastatin acid were 0.5 and 2.1 ng/mL on two determinations at the start of the experiment. When this person was put on itraconazole 200 mg/day, his trough level rose the next day to 6.5 and 5.1 ng/mL, which is nearly a 10-fold rise in just 1 day (6).

Conclusions

Our case report shows that a treatment with itraconazole of a patient already taking simvastatin might cause acute renal failure and if itraconazole remains the drug of choice for the patient, it might be wise to switch from simvastatin to another statin non-dependent on CYP3A4, for example, pravastatin.

Conflict of interest statement

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References

1. Williams D, Freely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clin Pharmakinet 2002;41:343–70.
2. Vasudevan AR, Hamirani YS, Jones PH. Safety of statins: effects on muscle and the liver. Cleve Clin J Med 2005;72:990–3, 996–1001.
3. Ballantyne CM, Corsini A, Davidson MH, Holdaas H, Jacobson TA, Leitersdorf E, et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med 2003;163:553–64.
4. Prueksaritanont T, Ma B, Tu N. The human hepatic metabolism of simvastatin hydroxy acid is mediated primarily by CYP3A, and not CYP2D6. Br J Clin Pharmacol 2003;56:120–4.
5. Watkins PB. Noninvasive tests of CYP3A enzymes. Pharmacogenetics 1994;4:171–84.
6. Segaert MF, De Soete C, Vandewiele I, Verbanck J. Drug-interaction-induced rhabdomyolysis. Nephrol Dial Transplant 1996;11:1846–7.